NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer [ID915]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer [ID915]

Contents:

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

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer [ID915]

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Pfizer (palbociclib) Patient/carer groups • Black Health Agency • Breast Cancer Care • Breast Cancer Now • Breast Cancer UK • Cancer Black Care • Cancer Equality • Haven • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care • Women's Health Concern Professional groups • Association of Breast Cancer Surgery • Association of Cancer Physicians • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society • Cancer Research UK • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association for Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies • Accord Healthcare (anastrazole, letrozole) • Actavis (anastrazole, exemestane, letrozole) • AstraZeneca (anastrazole) • Consilient Health (anastrazole, exemestane) • Novartis (letrozole) • Pfizer (exemestane, tamoxifen) • Sandoz (anastrazole) • Teva UK (exemestane) • Zentiva (anastrazole, exemestane, letrozole) Relevant research groups • Against Breast Cancer • Breast Cancer Hope

Consultees	**Commentators (no right to submit or appeal)**
• Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS Blackpool CCG • NHS England • NHS Harrogate and Rural District CCG • Welsh Government	• Breast Cancer Research Trust • Cochrane Breast Cancer Group • Institute of Cancer Research • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research • Pro-Cancer Research Fund <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

<u>Consultees</u>

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of palbociclib within its marketing authorisation for treating metastatic hormone receptor-positive, HER2-negative breast cancer.

Background

Breast cancer arises from the tissues of the ducts or lobules of the breast. Metastatic breast cancer describes disease that has spread to another part of the body, such as the bones, liver, or lungs.

In 2014 in England, around 46,417 people were diagnosed with breast cancer, and there were approximately 9,554 deaths from breast cancer [1,2]. The 5-year survival rate for people with metastatic breast cancer in England is 15%[3]. Approximately 5% of women with invasive breast cancers have locally advanced or metastatic disease when they are diagnosed[4], and around 35% of people with early or locally advanced disease will progress to metastatic breast cancer in the 10 years following diagnosis[5,6].

Current treatments for metastatic breast cancer aim to relieve symptoms, prolong survival and maintain a good quality of life with few adverse events. Treatment may depend on whether the cancer cells have particular receptors (hormone receptor status or HER2 status), the extent of the disease and previous treatments. NICE Clinical Guideline 81 recommends that endocrine therapy should be offered as first-line treatment for the majority of people with hormone receptor-positive metastatic breast cancer. In clinical practice, people who are post-menopausal with hormone receptor-positive metastatic breast cancer often receive first-line treatment with an aromatase inhibitor (anastrozole or letrozole). People who are pre- or peri-menopausal will receive first-line treatment with tamoxifen and ovarian suppression if they have not previously received tamoxifen. Chemotherapy is usually offered as first-line treatment only for people with hormone-receptor positive advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, providing they understand and are prepared to accept the toxicity.

The technology

Palbociclib (Ibrance, Pfizer) is a selective, small-molecule inhibitor of cyclin-dependent kinases 4 and 6, which prevents DNA synthesis by prohibiting progression of the cell cycle from G1 to S phase. Palbociclib is taken orally.

Palbociclib does not currently have a marketing authorisation in the UK. It has been studied in a clinical trial in combination with letrozole compared with placebo and letrozole in post-menopausal women with previously untreated metastatic hormone receptor–positive, HER2-negative breast cancer. Palbociclib has also been studied in a clinical trial in combination with fulvestrant compared with placebo and fulvestrant in people with metastatic hormone receptor–positive, HER2-negative breast cancer that has relapsed or progressed during prior endocrine therapy.

Intervention(s)	Palbociclib in combination with an aromatase inhibitor
Population(s)	Post-menopausal people with metastatic, hormone receptor-positive, HER2-negative breast cancer previously untreated in the metastatic setting.
Comparators	Aromatase inhibitors (such as letrozole or anastrozole)
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rate • adverse effects of treatment • health-related quality of life.
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.

Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer' (2012). NICE Technology Appraisal guidance 263. Review date June 2015. Review decision, static list. 'Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer' (2011). NICE Technology Appraisal 214. Guidance on static list. 'Fulvestrant for the treatment of locally advanced or metastatic breast cancer' (2011). NICE Technology Appraisal 239. Review date Nov 2014. Review decision, static list 'Gemcitabine for the treatment of metastatic breast cancer' (2007). NICE technology Appraisal 116. Review date, May 2010. Review decision, static list. Appraisals in development (including suspended appraisals): 'Sunitinib in combination with capecitabine within its licensed indication for the treatment of advanced and/or metastatic breast cancer'. NICE Technology Appraisal guidance [ID319]. Suspended. 'Sunitinib in combination with a taxane within its licensed indication for the first line treatment of advanced and/or metastatic breast cancer'. NICE Technology Appraisal guidance [ID58]. Suspended. Related Guidelines: Familial breast cancer: Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer (2013). NICE guideline CG164. Update in progress. 'Advanced breast cancer: diagnosis and treatment' (2009). NICE guideline 81 This guidance replaces previous Technology Appraisals No. 30, 54 and 62. Review date December 2015. Update in progress.

	Related Quality Standards: 'Breast cancer' (2016) NICE quality standard 12. 'Related NICE Pathways: Advanced breast cancer (2015) NICE pathway Familial breast cancer (2015) NICE pathway Early and locally advanced breast cancer (2014) NICE pathway
Related National Policy	Department of Health (2016) 'NHS Outcomes Framework. Domain 1. NHS England (2016) 'Manual for Prescribed Specialised Services'. Chapter 105, Specialist Cancer services (adults)

References

1. Office for National Statistics (2016) Cancer registration statistics, England, 2014. Accessed July 2016.
2. Cancer Research UK (2015) Breast cancer mortality statistics. Accessed July 2016.
3. Cancer Research UK (2014) Breast cancer survival statistics. Accessed July 2016.
4. Cancer Research UK (2015) Breast cancer incidence statistics. Accessed July 2016.
5. NICE (2009) Costing report for clinical guideline 81: advanced breast cancer. Accessed September 2015.
6. Dewis R and Gribbin J (2009) Breast cancer: diagnosis and treatment, an assessment of need. Cardiff: National Collaborating Centre for Cancer. Accessed October 2015.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Palbociclib for Treating Metastatic, Hormone Receptor-positive, HER2-negative Breast Cancer [ID915]

Company Evidence Submission

File name	Version	Contains confidential information	Date
ID915_Pfizer_(27Sep16)	1	Yes	27th Sep '16
ID915_revised redacting 29Nov16	2	Yes	29th Nov '16
ID915_revised redacting 06Jan17	3	Yes	6th Jan '17

Instructions for companies

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

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

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

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1. Executive Summary

1.1. Statement of the decision problem

The decision problem for this appraisal asks if palbociclib in combination with an aromatase inhibitor is clinically and cost effective, within its expected marketing authorisation, for treating locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer, who are post-menopausal and are previously untreated for their advanced or metastatic disease. Further details of the decision problem, its alignment to the final scope issued by NICE,[1] and how it has been addressed in this submission are presented in Table 1 on the following page.

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.[2] In combination with endocrine therapy (ET), palbociclib results in synergistic clinical benefits including increased response rates and prolonged progression-free survival across both ET sensitive and resistant populations.[3-6] In 2015, the MHRA recognised the transformative nature of palbociclib with its potential to address the unmet medical need created by limited 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.[7]

In this submission, palbociclib in combination with an aromatase inhibitor is presented for consideration for treating HR-positive, HER2-negative locally advanced or metastatic breast cancer (ABC), in patients who are previously untreated for their advanced or metastatic disease (as per the licensed indication). This appraisal will not consider the advanced or metastatic breast cancer population eligible for treatment with palbociclib in combination with fulvestrant.

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

Table 1. Summary of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Intervention	Palbociclib in combination with an aromatase inhibitor	Same as final scope issued by NICE (the aromatase inhibitor letrozole)	N/A
Population	Post-menopausal people with metastatic, hormone receptor-positive, HER2-negative breast cancer previously untreated in the metastatic setting.	Evidence submitted is in post-menopausal women	Palbociclib's expected license does not specify menopausal status when combined with an aromatase inhibitor
Comparator(s)	Aromatase inhibitors (such as letrozole or anastrazole)	Same as final scope issued by NICE (the aromatase inhibitor letrozole)	N/A
Outcomes	The outcome measures to be considered include: • overall survival (OS) • progression free survival (PFS) • response rate (RR) • adverse effects of treatment • health-related quality of life (HRQL)	In addition to the outcomes listed in the final scope issued by NICE the decision problem addressed also includes clinical benefit rate (CBR).	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.[8] In this submission, CBR outcomes are presented alongside ORR outcomes in order to demonstrate the superior anti-tumour activity of palbociclib over standard of care.
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	Same as final scope issued by NICE	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	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.		
Subgroups to be considered	N/A	Those treated in the adjuvant setting compared with those who are presenting for the first time with metastatic disease (de novo).	The majority of patients who are treated for ABC in the UK have previously undergone adjuvant therapy.[9, 10] However, a small proportion of patients receive their first diagnosis of breast cancer at the metastatic stage and data suggests the comparative efficacy of these patients may differ.[9]
Special considerations including issues related to equity or equality	No special considerations	No special considerations	N/A

Table 2. Summary of the technology being appraised

UK approved name and brand name	Palbociclib (Ibrance®)
Marketing authorisation/CE mark status	Palbociclib received a positive opinion from the Committee for Human Medicinal Products on 16th September 2016 for the indication detailed in this submission. Marketing Authorisation is expected to be granted on 22nd November 2016.
Indications and any restriction(s) as described in the summary of product characteristics	Palbociclib does not yet have a marketing authorisation in the UK, but has received positive CHMP opinion. Palbociclib is expected to be 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. See draft SPC in appendix 1.
Method of administration and dosage	Palbociclib is administered orally, expected in combination with an aromatase inhibitor, such as letrozole. The expected recommended dosage for women with metastatic HR-positive, HER2-negative ABC is expected to be (license pending) 125mg once daily for 21 consecutive days, followed by 7 days off treatment, repeated in cycles, until disease progression. Letrozole is administered continuously *i.e.* without the 7 days treatment break. A first dose reduction to 100mg daily is allowed as required for the management of AEs. As a second dose reduction, the recommended dose is 75mg daily. See draft SPC in appendix 1.

1.3. Executive summary of clinical effectiveness

Evidence for the clinical efficacy and safety of palbociclib-based combination therapy in previously untreated HR+/HER2-negative breast cancer obtained from the PALOMA-1 and PALOMA-2 randomised clinical trials (RCTs). PALOMA-2 is the pivotal double-blinded phase III RCT and PALOMA-1 is an open–label phase I/II trial. The PALOMA trials have been conducted in patient populations that are applicable to the decision problem.

ABC is an incurable disease, so treatment goals are to delay disease progression while maintaining quality of life, alleviating symptoms, and possibly benefitting overall survival.

Palbociclib offers a double-digit increase in PFS and indeed is the first treatment to break the two-year median PFS barrier in phase III RCTs for ABC. The primary endpoint in the RCTs was progression-free survival (PFS), and treatment with palbociclib plus letrozole resulted in over a 10-month increase in median PFS compared to letrozole alone (24.8 months palbociclib plus letrozole versus 14.5 months for placebo plus letrozole) (see section 4.7.2.1). Importantly, the efficacy observed is not at the expense of safety as it has a well-managed AE profile. This transformative increase in PFS is important for women with ABC for a number of reasons:

- Time spent progression-free is time spent alive as only small number of patients die pre-progression in the first-line.[9]
- PFS has been shown to be correlated with OS.[12-16]
- Progression is associated with an increase in symptoms; staying progression-free maintains quality of life[11]
- Remaining progression-free delays the onset of chemotherapy, which is associated with lowering quality of life[17, 18] and poses a psychological burden on patients, even before it starts.[19, 20]
- Disease progression often causes women to stop work[10], as does chemotherapy;[21] maintaining PFS is important to reduce the chance of this so women can, as much as possible, continue with normal life.
- Maintaining 'normality' is key for patients; the negative effects of ABC can compromise the ability of women to fulfil their caring duties as partners, friends and mothers.[22]

In the UK, there has not been a medicine approved by NICE for use in previously untreated ABC patients since gemcitabine in 2007 (TA116); PFS in ER+, HER2- ABC has therefore not changed for UK patients during this time, which has created a strong unmet need to prolong PFS in patients with ABC.

In addition to the increase in PFS, palbociclib plus letrozole led to a statistically significant improvement in treatment response and a more durable response (DOR) in untreated HR-positive, HER2-negative breast cancer (see section 4.7.2.2).

PALOMA-2 provides direct head-to-head double blind clinical evidence across 666 patients treated with either interventional palbociclib plus letrozole (n = 444), or comparator letrozole in combination with placebo (n = 222), which is the current standard of care in the UK.[23] PFS was the primary endpoint of the RCT, and in the intention-to-treat (ITT) population, median PFS was significantly prolonged in the palbociclib plus letrozole group versus the letrozole plus placebo group (24.8 months versus 14.5 months, respectively; hazard ratio [HR], 0.58; 95% CI, 0.46 to 0.72, p <0.000001, ITT population). Treatment benefit in the palbociclib arm was significant in all subgroups evaluated, including those defined by visceral versus non-visceral versus bone-only disease, those previously treated with adjuvant therapy versus 'de novo' patients (those presenting for the first time in the metastatic setting), and age (>65 vs <65).

Palbociclib plus letrozole was also associated with a significantly higher objective response rate (ORR) (42.1% vs 34.7%, P=0.031) in the intention to treat (ITT) population and (55.3% vs 44.4%, P=0.013) in patients with measurable disease. Clinical benefit rate (CBR), a

measure that incorporates stable disease, was also significantly higher in the palbociclib arm compared to the letrozole only arm (84.9% vs 70.3%, P<0.001).

Point estimates for median DOR favour the palbociclib plus letrozole arm, both for confirmed and unconfirmed tumour response [redacted] and for confirmed tumour response only (22.5 months [95% CI: 19.8, 28.0] versus 16.8 months [95% CI: 14.2, 28.5]). However, these data are not statistically significant.

PALOMA-1 was an open-label phase I/II RCT, involving 84 previously untreated postmenopausal women with ER+/HER2- ABC who received palbociclib-letrozole and 81 who received letrozole alone. The trial confirms the transformative clinical benefit afforded by palbociclib to patients in terms of those described above for PFS and for measures of response.

In PALOMA-1, treatment with palbociclib was associated with numerical improvements in overall survival (OS) for patients with untreated HR-positive, HER2-negative advanced breast cancer but this did not reach statistical significance (see section 4.7.1.2). This trial was not designed to show statistically significant improvements in overall survival.

In PALOMA-1, median OS was numerically longer in the palbociclib plus letrozole group compared to the letrozole alone group (37.5 months versus 33.3 months; HR 0.813, 95% CI 0.492–1.345; p=0.42). Additionally, survival probability in the palbociclib group was higher than in the letrozole group (both plus letrozole) at all time points assessed: 89% vs 87% at 1 year, 77% vs 70% at 2 years, and 53% versus 44% at 3 years. The trial was not powered to demonstrate a statistical difference in overall survival, and indeed the range of subsequent therapies administered in each arm further prevents the attribution of a statistically significant survival advantage to palbociclib.

In PALOMA-2, at the time of PFS data cut-off, survival data were immature and did not meet the pre-specified level of significance for the interim analysis. Of note, at the time of the data cut-off, the median follow-up time in the palbociclib plus letrozole arm was 23.0 months (95% CI: 22.6, 23.4) and in the placebo plus letrozole arm was 22.3 months (95% CI: 21.9, 22.9). Therefore, evidence for OS efficacy for palbociclib is only available from the Phase I/II PALOMA-1 RCT.

Patient reported outcomes (PRO) data from PALOMA-1 and PALOMA-2 support the positive benefit profile of the addition of palbociclib to letrozole in patients with ABC. [redacted] in health-related quality of life or in general health status were observed in patients treated with palbociclib (see section 4.7.2.3).

The addition of palbociclib to letrozole [redacted] as measured by the Functional Assessment of Cancer Therapy-Breast (FACT-B) and EuroQol-5 Dimensions (EQ-5D) questionnaires respectively. In addition, palbociclib [redacted] when measured with the modified Brief Pain Inventory Questionnaire (mBPI-sf). [redacted]

results were observed for general health status as assessed by the EQ-5D index scores

(palbociclib plus letrozole [redacted]. In PALOMA-1 there was no significant deterioration in pain severity and pain inference with palbociclib plus letrozole compared with letrozole alone when measured using the mBPI-sf scale.

The PALOMA trials demonstrated that palbociclib was associated with a generally well-tolerated and manageable side effect profile. The most frequent grade 3 and 4 adverse events were haematological, but typically asymptomatic (see Section 4.12).

In PALOMA-2, permanent discontinuation due to AEs occurred in 9.7% and 5.9% of patients in the palbociclib plus letrozole and placebo plus letrozole groups, respectively.[9] The most frequent grade 3 and 4 adverse events (AEs) in the palbociclib and letrozole arms were neutropenia (66.5% for palbociclib plus letrozole versus 1.4% in the letrozole arm) and leukopenia (24.8% for palbociclib plus letrozole versus 0% in the letrozole arm).[9] Cases of neutropenia associated with palbociclib were rarely febrile and were managed through temporary dose reductions and interruptions without affecting time-on-treatment[4, 24, 25] or PFS benefit.[26] The PALOMA-1 safety analysis was consistent with the safety results reported for PALOMA-2.

In summary, palbociclib in combination with an AI demonstrates a clinically meaningful therapeutic advance in previously untreated ABC by significantly prolonging PFS, with a manageable AE profile and maintenance of HRQL. The transformative nature of palbociclib, with its potential to address the unmet medical need of limited ET efficacy, has been recognised by the MHRA through awarding it the status of Promising Innovative Medicine (PIM).

1.4. Executive summary of cost-effectiveness

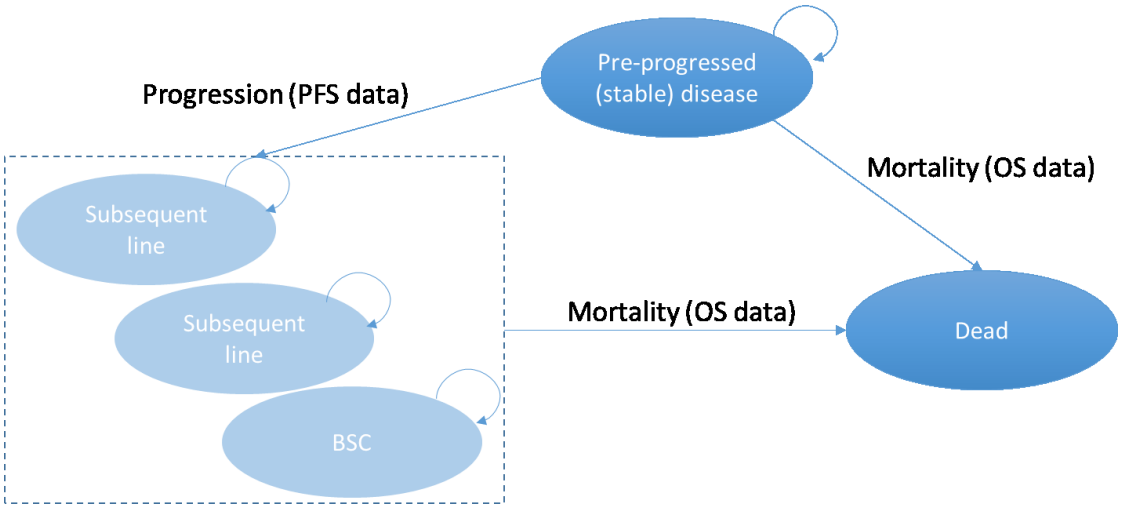
1.4.1. Cost-effectiveness model

The model design was consistent with oncology modelling accepted in previous NICE appraisals, but adapted to best reflect UK clinical practice.

A partitioned survival Markov model was developed for previously untreated advanced or metastatic disease (see section 5.2.2). The structure of the models departs somewhat from the traditional three-state oncology framework of stable disease, progressed disease and death, in that the post-progression state is itself further separated to allow for more granular modelling of subsequent treatment lines (

Figure 1). As patients commonly receive multiple lines of therapy, this avoids the blunted representation of clinical practice created when those who have progressed are grouped into one single post-progression state.

Figure 1. Model schematic



The modelled patient population represents those who present in UK clinical practice, and the comparator in the base case is representative of the standard of care currently in the UK.

The cost-effectiveness analysis considers women with previously untreated, HR+, HER2- ABC, consistent with the decision problem outlined in Table 1, and the expected licensed indication for palbociclib.

Aromatase inhibitors are the standard of care treatment in the UK for patients who would be eligible for palbociclib, with letrozole being the most common.[27] As such, the economic evaluation allows the cost-effectiveness of the combination of palbociclib+letrozole to be evaluated versus the current standard of care using efficacy and safety data directly from PALOMA-1 and PALOMA-2.

These trials have been validated by UK clinical experts as being broadly and sufficiently generalisable to a UK patient population (see section 4.14.1). Of note is the proportion of patients with de novo metastatic disease observed in the trials (37% in PALOMA-2), which was higher than what is seen in UK clinical practice (approximately 5-10%). As such, the base case of the model uses the survival data from PALOMA-2 for patients who were treated in the adjuvant setting only. For completeness, a scenario analysis is provided that uses the whole ITT population, which also includes patients with de novo disease.

1.4.2. Cost-effectiveness results

The cost-effectiveness of palbociclib depends on the pragmatism of the assumptions adopted, with the greatest cost-drivers being PFS (that is, treatment duration and the undervaluation of time spent in PFS), the cost of comparator, and OS. The current cost per QALY approach does not reflect the full value of PFS. In doing so, a disproportionate expectation is placed on overall survival and the resultant ICERs severely underestimate the benefit of palbociclib. As a result, the submission provides a nominal deterministic base case of £150,869 per QALY (using the list price of the medicine).

It is clear that with respect to the cost-effectiveness of palbociclib versus letrozole that the unprecedented gain in PFS is punitive. The large gain in PFS (which equates to a large increase in treatment duration) brings with it a large incremental cost. The issue of increased PFS coupled with increased treatment duration is exemplified when it is considered that decreased treatment duration in both arms of 12 months, whilst holding constant the difference in PFS between arms, would reduce the base case ICER by £64,450 per QALY.

Importantly, the substantial gain in PFS and the resultant range of ways in which this can benefit patients (controlling their disease, controlling their symptoms, remaining alive, maintaining their quality of life, delaying their onset of chemotherapy, being able to stay in work, and their ability to continue a normal life) is not fully captured in the traditional QALY. As an illustrative proxy for the recognition of this benefit, the ICER reduces by £16,735 per QALY if PFS were elicited a 0.1 higher utility to fully reflect the benefit it has to patients.

As opposed to comparing against generic medicine or an add-on therapy, a change to the monthly cost of the comparator such that it is the same as palbociclib, would decrease the base case ICER by £97,795 per QALY. This demonstrates how the introduction of an innovative treatment such as palbociclib as an add-on therapy or into a therapy area with no new treatment or breakthrough (as defined by an exclusively generic treatment space) inherently values that new treatment less than it would do if the therapy area had already benefited from recent innovation.

In the base case, without changes as described above (treatment duration, the value of PFS and the cost of comparator), the overall survival advantage that palbociclib would need to afford to sufficiently offset the increase cost in treatment duration would be 9 years to reach around a £50,000 per QALY threshold, which is not clinically plausible.

The reality is that depending on the assumptions included regarding the value of PFS, comparator cost, and survival benefit, a wide array of results is possible. Despite its double-digit PFS gain, if exclusively pessimistic assumptions are adopted, palbociclib may produce an ICER of above £300,000 per QALY, requiring the monthly cost of palbociclib to be less than the price at which chemotherapies in ABC were approved by NICE in the last decade (TA30, TA54, TA62, TA116).

However, if a more pragmatic approach is adopted, then it is possible to demonstrate cost-effectiveness. If the monthly price of the comparator was comparable to palbociclib, together with an adjusted utility of PFS, the ICER would be £47,187 per QALY. When a 24-month gain is assumed, the ICER would decrease to £36,194 per QALY, falling further still to £26,996 per QALY when removing later-line post-progression costs. As such, we believe that palbociclib can demonstrate value for money to the NHS and be cost-effective treatment option for women with ABC.

Concluding remarks

- ABC is a life-threatening disease that cannot be cured; the clinical goals are to delay disease progression while maintaining quality of life, alleviate symptoms and improve survival outcomes.
- Prolonging progression-free survival is a key goal of treatment:
    - Staying progression-free maintains quality of life
    - Time spent progression-free is time spent alive
    - PFS has been shown to be correlated with OS
    - Remaining progression-free delays the need for of chemotherapy
    - Disease progression causes women to stop work
    - Maintaining the ability to function 'normally' is key for patients
- Existing endocrine treatments for previously untreated ABC are limited by low response rates and resistance, which eventually leads to progression and the need for subsequent treatments.
    - Only around 30% of patients with metastatic disease show objective tumour regression with initial endocrine treatment, and only another 20% show prolonged stable disease. Remaining patients will experience disease progression, usually due to resistance to endocrine therapy.
    - There remains a significant unmet need in increasing the response to treatment and delaying the onset of treatment resistance in order to achieve prolonged PFS.
- Palbociclib in previously untreated HR+/HER2- ABC is a first-in class, transformative medicine demonstrating substantial improvements in efficacy that changes the treatment paradigm:
    - Palbociclib plus letrozole is the first metastatic breast cancer medicine to break the 2-year barrier for PFS within its phase III trial.
    - Palbociclib plus letrozole resulted in a 10.3 month increase in PFS above the standard of care.
    - Increased PFS was associated with improved tumour response and more durable response.
    - Through the postponement of disease progression, palbociclib delays time to subsequent chemotherapy compared to existing treatments in the NHS.
    - The addition of palbociclib to letrozole results in maintenance of HRQL and of health status for a much longer period, allowing patients to have the best life possible with the disease.
    - Palbociclib is generally well tolerated. The most frequent treatment-related grade 3/4 adverse event is neutropenia and this is typically asymptomatic and managed through dose modifications.
- The modelled base-case for palbociclib reflected a significant improvement in median and mean PFS and OS versus the UK standard of care comparator. Despite transformative improvements in efficacy, the value of palbociclib is negatively impacted by its longer treatment duration. This is compounded a comparison versus a comparator regimen priced as a generic, and the undervaluation of utility benefits related to the delay in cancer progression (PFS), versus the value placed on OS. These limitations result in a nominal base case of £150,869/QALY.
- The reality is that a wide array of results is possible dependent upon the assumptions pertaining to the value of PFS, comparator cost, and survival benefit. If exclusively pessimistic assumptions are adopted, palbociclib may produce an ICER of above £300,000 per QALY, requiring palbociclib to cost a near generic price to achieve an ICER within the standard threshold.
- However, if a more pragmatic approach is adopted, then it is possible to demonstrate cost-effectiveness. If the monthly price of the comparator was comparable to palbociclib, together with an adjusted utility of PFS, the ICER would be £47,187 per QALY. When a 24-month gain is assumed, the ICER would decrease to £36,194 per QALY, falling further still to £26,996 per QALY when removing later-line post-progression costs.
    - As such, we believe that palbociclib can demonstrate value for money to the NHS and be cost-effective treatment option for women with ABC.

2. The technology

2.1. Description of the technology

Brand name: IBRANCE®

UK approved name: palbociclib

Therapeutic and pharmacological class: anti-neoplastic agent; protein serine threonine-kinase inhibitor (TKI).

Palbociclib is a first-in-class, orally administered, selective small-molecule inhibitor of cyclin-dependent kinase 4 and 6 (CDKs 4 and 6)[2] as well as the redundant CDK 6/cyclin D1 kinase. Preclinical data indicate that this dual inhibition prevents cellular DNA synthesis and thus inhibits cell division, slowing tumour growth. Preclinical data also indicate that palbociclib causes both growth arrest and potentially secondary cytoreductive effects as well. Palbociclib arrests the cell cycle at G1, inhibits cell proliferation and induces senescence in a broad panel of cancer cell lines.

2.2. Marketing authorisation/CE marking and health technology assessment

Palbociclib received a positive opinion from the Committee for Human Medicinal Products on 16th September 2016 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.[29]

Marketing Authorisation is expected to be granted on 22nd November 2016.

Please refer to Appendix 1 or the (draft) SPC, and Appendix 2 for the (draft) assessment report produced by the European Medicines Authority (EMA), however note that upon initial submission the draft EMA report is not yet available, but can be added to the submission at a later date when available.

This appraisal will only cover the ABC population eligible for palbociclib in combination with an aromatase inhibitor.

The anticipated date of availability of palbociclib in the UK is upon EMA marketing authorisation, expected 22nd November 2016.

Regulatory approval outside the UK includes, on 3rd February 2015, the Food and Drug Administration (FDA), approving palbociclib for the treatment of ER+/HER2- ABC plus letrozole as initial endocrine-based therapy in postmenopausal women.

Palbociclib has also been approved for use in [redacted] countries including in the following countries: [redacted]

[redacted]

2.3. Administration and costs of the technology

Table 3. Costs associated with palbociclib in palbociclib-letrozole combination therapy

	Cost	Source
Pharmaceutical formulation	Palbociclib: hard capsule of 75mg, 100mg, 125mg Letrozole: tablet 2.5mg	PALOMA-1,[3] PALOMA-2,[9] eMIT,[30]
Acquisition cost (excluding VAT) *	Palbociclib £2,950 per pack of 21 capsules (expected list price at launch) Letrozole: average £1.40 (SD: £1.86) per pack of 28 tablet	PALOMA-1,[3] PALOMA-2,[9] eMIT,[30]
Method of administration	Palbociclib: Oral Letrozole: Oral	PALOMA-1,[3] PALOMA-2,[9] Datapharm online[31]
Doses	Palbociclib: 125mg Letrozole: 2.5mg (as per UK clinical practice)	PALOMA-1,[3] PALOMA-2,[9] Datapharm online[31]
Dosing frequency	Palbociclib: daily for 21 consecutive days, followed by 7 days off treatment until disease progression Letrozole: daily (continuously)	PALOMA-1,[3] PALOMA-2,[9] Datapharm online[31]
Average length of a course of treatment	One cycle of palbociclib plus letrozole is 28 days. Within this, the course of treatment is for the first 21 consecutive days.	See appendix 1
Average cost of a course of treatment	£2,950	Pfizer
Anticipated average interval between courses of treatment	There is a 7-day interval between courses. In one 28-days cycle, after a course of 21 consecutive days of treatment with palbociclib plus letrozole, 7 days are spent off palbociclib treatment. Patients continue to receive letrozole.	SPC – see appendix 1
Anticipated number of repeat courses of treatment	Palbociclib plus letrozole will continue as a treatment until progression. Median progression-free survival (PFS) in the pivotal trial was 24.8 months. Treatment for 24.8 months would include 27	PALOMA-1,[3] PALOMA-2,[9]

	courses of palbociclib plus letrozole.	
Dose adjustments	Dose modification of palbociclib is recommended based on individual safety and tolerability concerns. Dose reductions may be required when toxicities above grade 3 occur (CTCAE 4.0). If toxicities are haematological, then withhold palbociclib until recovery to grade ≤2. If non-haematological, then withhold palbociclib until recovery to grade ≤1 or, if the event is not considered a safety risk, until grade ≤2. See Appendix 1 for full details) At the first dose reduction, the recommended dose is 100mg/day. At the second dose reduction, the recommended dose is 75mg/day. If further dose reduction below 75 mg/day is required, discontinue the treatment Dose reductions or dose modifications due to any adverse reaction occurred in 34.4% of patients receiving palbociclib in randomised clinical studies regardless of the combination. Permanent discontinuation due to an adverse reaction occurred in 4.1% of patients receiving palbociclib in randomised clinical studies regardless of the combination	Draft SPC (Appendix 1), PALOMA-1,[3] PALOMA-2,[9]
Anticipated care setting	Secondary care: dispensed by hospital pharmacy	PALOMA-1,[3] PALOMA-2[9]

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events (National Cancer Institute); mg, milligram

2.4. Changes in service provision and management

No additional National Health Service (NHS) infrastructure is expected to be required for the administration of palbociclib; its management is expected to be similar to that of other oral agents implemented in the past.

Table 4. NHS resource use associated with palbociclib combination treatments

	Estimated use
Location of care	Secondary care
Administration costs	Palbociclib is an oral treatment, self-administered and will not incur any additional costs to the NHS besides the cost of pharmacy dispensing, when dispensed from a hospital pharmacy.
Monitoring and testing	Monitor complete blood count prior to start of palbociclib therapy, and at the beginning of each cycle, as well as on day 14 of the first 2 cycles, and as clinically indicated. Absolute neutrophil counts (ANC) of ⩾1000/mm3 and platelet counts of ⩾50,000/mm3 are recommended to receive palbociclib. Infections: Since palbociclib has myelosuppressive properties, it may predispose patients to infections. Patients should be monitored for signs and symptoms of infection and treated as medically appropriate.

Randomised controlled trials (RCTs) of palbociclib suggest greater risk of certain adverse events than with standard endocrine therapy, the most frequent of which are neutropenia and leukopenia.[4, 9] It is important to note, however, that neutropenia and leukopenia associated with palbociclib are rarely symptomatic. The impact of asymptomatic neutropenia and leukopenia is that during the initial treatment phase, patients may need to visit their consultant more often than the three-monthly visits typical of endocrine therapy. More frequent blood monitoring in the first cycles of palbociclib treatment will help clinicians monitor and respond to these issues and optimise the dose, which will reduce the risk of such events in future cycles and associated events e.g. neutropenic sepsis. It is not expected this blood monitoring will significantly impact resources as is costed under HRG tariff DAPS05 at £3.01 per test.[32] Data from PALOMA-1 indicate that neutropenia, especially of more severe grades, tended to occur less with increasing treatment cycles [33, 34] (see section 4.12.3). Once the palbociclib dose has been optimised, visits can likely become less frequent. In the PALOMA-1 trial, patients visited the clinic every two weeks in the first treatment cycle and every four weeks thereafter.[4] No concomitant therapies are administered with palbociclib for the management of adverse events. To ensure appropriate management of palbociclib-induced neutropenia, physicians and nurses will need to be educated on dose-modification guidelines and informed about the fundamental differences between this type of neutropenia, which is asymptomatic and reversible, and chemotherapy-induced neutropenia (see section 4.12.3).

No concomitant therapies are administered with palbociclib plus letrozole for managing adverse reactions.

2.5. Innovation

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

Despite being standard of care in ER+ ABC, progression-free survival (PFS) with currently approved endocrine therapies generally remains less than 1 year.[35-40] Furthermore, significant limitations exist with endocrine therapy with intrinsic resistance in many patients and eventual acquired resistance in initial responders, both of which significantly influencing morbidity and mortality in patients.[28] A medical record review study showed that patients in the UK on first-line endocrine therapies have a median TTP of 12.17 months (see appendix 2). In second line, patients have a median TTP of 7.93 months.[41] 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.[41, 42] These data were not collected in the United Kingdom and Canada. The ability to prolong PFS while maintaining QOL is therefore an important unmet medical need in the ER+/HER2- ABC setting. Therapies to address this would also further benefit patients by postponing subsequent treatment options, which includes chemotherapy and the fear of associated toxicities (see Section 0 for more details).[43, 44]

Palbociclib demonstrates synergistic enhancement of endocrine therapy and in doing so provides unprecedented PFS extension in patients with ER+/HER2- ABC. By extending PFS palbociclib would be expected to postpone the need for potentially burdensome chemotherapy, thereby prolonging time in the progression-free state with a lower pain

burden, stable quality of life, and fewer severe adverse events. Palbociclib therefore represents a change in the first-line ER+/HER2- ABC setting, the likes of which has not been seen since the introduction of AIs over 10 years ago.

Table 5. Summary of PALOMA clinical studies of palbociclib in combination with endocrine therapy in women with ER+/HER2- ABC

	PALOMA-1[4, 24, 45-50]	PALOMA-2[9, 23]	PALOMA-3[5]
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)	0.58 (0.46-0.72; p<0.00001)	0.497 (0.398-0.620; p<0.000001)
Median PFS, mo (95% CI)*	20.2 (13.8-27.5) vs 10.2 (5.7-12.6)	24.8 (22.1-NR) vs 14.5 (12.9-17.1)	11.2 (9.5-12.9) vs 4.6 (3.5-5.6)
PFS gain compared to control (months)*	10.0	10.3	6.6
Most frequent all cause AEs in Palbociclib arm, %			
Neutropenia	75	80	81
Leucopenia	43	39	50
Anaemia	35	24	28
Thrombocytopenia	17	16	22
Infection	55	60	43
Fatigue	41	37	39

*Efficacy summary statistics for PALOMA-2 and PALOMA-3 were updated in October 2015 for the SPC (appendix 1). The values for the two trials are from the SPC.

2.5.2. 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+/HER2− 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.[51] Furthermore in the UK, palbociclib was granted a Promising Innovative Medicine designation by the Medicines & Healthcare Products Regulatory Agency 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.[7]

2.5.3. A first-in-class targeted therapy with a new mechanism of action

The current paradigm of ABC treatment is based on the use of endocrine therapies that prevent oestrogen signalling via the oestrogen receptor (ER), which is the primary driver of breast cancer tumourogenesis.[52, 53] The non-steroidal AIs consist of letrozole and anastrazole; exemestane is a steroidal AI. The mechanisms of action of these endocrine agents are summarised in Table 6.

Table 6. Mechanisms of action of endocrine therapies for the treatment of ABC[28]

Agent	Class	Mechanism of action
Tamoxifen	Anti-oestrogen Selective oestrogen receptor Modulator (SERM)	Binds to ER to prevent oestrogen from stimulating tumour proliferation
Fulvestrant	Anti-oestrogen Selective oestrogen receptor degrader (SERD)	Binds ER to prevent oestrogen from stimulating tumour proliferation and promotes proteasome-mediated degradation of ER
Letrozole, anastrazole	Non-steroidal aromatase inhibitor	Reduces peripheral oestrogen production by inhibiting the aromatase enzyme, effectively depriving breast cancer cells of the required oestrogen drive
Exemestane	Steroidal aromatase inhibitor	

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 (**Error! Reference source not found.**).[2, 4, 6, 34] Through its mechanism of action palbociclib enhances the anti-proliferative efficacy of endocrine treatments through inhibition of the ER receptor in breast cancer cells[2]. This synergistic enhancement was demonstrated in the phase III PALOMA-2 clinical trial in which palbociclib plus letrozole demonstrated a PFS of 24.8 months compared to 14.5 months for letrozole alone (HR 0.58; 0.46-0.72; p<0.000001) in postmenopausal women with ER+/HER2- ABC who had not received prior therapy for their metastatic disease.[23] In addition, evidence suggests that inhibition of CDK4/6 by palbociclib may overcome ET resistance in breast cancer cells[2],[54]. 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 doubled the PFS from 4.6 months for fulvestrant alone to 9.5 months for fulvestrant + palbociclib in women whose ER+/HER2- ABC had progressed on or shortly after endocrine therapy (**Error! Reference source not found.**.[6]

The mechanism by which palbociclib causes cell cycle arrest is important when considering the neutropenia observed in patients treated with palbociclib. In human bone marrow cells cell cycle arrest due to treatment with palbociclib was reversible, such that cellular proliferation resumed to near pre-treatment levels; by contrast cells treated with a chemotherapeutic agent recovered minimally or not at all. The translational significance of this is that the neutropenia caused by CDK4/6 inhibition can be reversed through pro-active

full blood count monitoring and dose interruption on account of the ability of the neutrophils to recover and re-enter the cell cycle. This was seen in the PALOMA studies in which palbociclib plus endocrine-induced G3/4 neutropenia (the most frequent adverse event observed in the study), was largely reversed by dose interruption4, 6, 12 This is in contrast to chemotherapy, which causes neutropenia through irreversible cell death, necessitating recovery by re-population from the original haemopoietic stem cells and raising the possibility that growth factor stimulation (such as the use of GCSF-7) will be required to support bone marrow recovery.[25]

3. Health condition and position of the technology in the treatment pathway

3.1. Overview of ABC

Breast cancer is a heterogeneous disease composed of a growing number of biological subtypes that vary not only in aetiology and prognosis, but also in their responses to current anti-hormonal and chemotherapy treatments. Oestrogen and progesterone drive tumour growth, and tumours that express one or both receptors are typically referred to as hormone receptor positive (HR+). Most HR+ tumours are both ER+ and PR+, while approximately 15-20% are only ER+.[55-57] HR+ breast cancers tend to grow more slowly than HR- tumours and are much more likely to respond to hormonal therapy that lowers the amount of available oestrogen or blocks existing oestrogen from binding its receptor. Determination of HR and HER2 status of breast cancer tumours currently serves as the initial basis for most clinical decisions, and it has both prognostic and predictive importance in breast cancer.

The most common type of ABC is ER+/HER2-. A recent review of more than 152,000 patients in five European countries with metastatic breast cancer at diagnosis or at relapse suggested a prevalence of HR+/HER2- breast cancer ranging from 50.6% (Germany) to 57.3% (France), with the UK falling near the upper end of this range (56.3%).[58]

ABC is a life-threatening disease that cannot be cured; the clinical goals are to delay disease progression while maintaining quality of life, alleviating symptoms and improving survival-related outcomes. The disease is stratified clinically into various stages (Table 7).[59] 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. [9, 10] 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.[60]

Table 7. Clinical stratification of ABC[59]

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 micrometastases only are excluded from stage IIA and are classified stage IB.
See Appendix 3 for further details and abbreviations.

3.2. The effects of ABC on patients, carers and society

With incurable, terminal disease, keeping patients free from disease progression while ideally maintaining quality of life, is a key goal of therapy. Consulted clinical experts have underlined that PFS is a key target for both patients and clinicians when tackling ABC, and the value of prolonging PFS is multi-fold.

3.2.1. The value of progression-free survival (PFS)

- **Progression is associated with an increase in symptoms; staying progression-free maintains quality of life.**

  Patients with ABC may present with general symptoms such as fatigue, difficulty sleeping, depression and pain, as well as symptoms related to the sites of metastatic disease.[61] Patients with ABC show lower physical functioning[62] and lower HRQL than the general population.[17, 63] A study by Lloyd (2006)[11] examining the quality of life in a UK cohort of metastatic breast cancer patients found that disease progression has the largest impact on quality of life.

- **Time spent progression-free is time spent alive.**

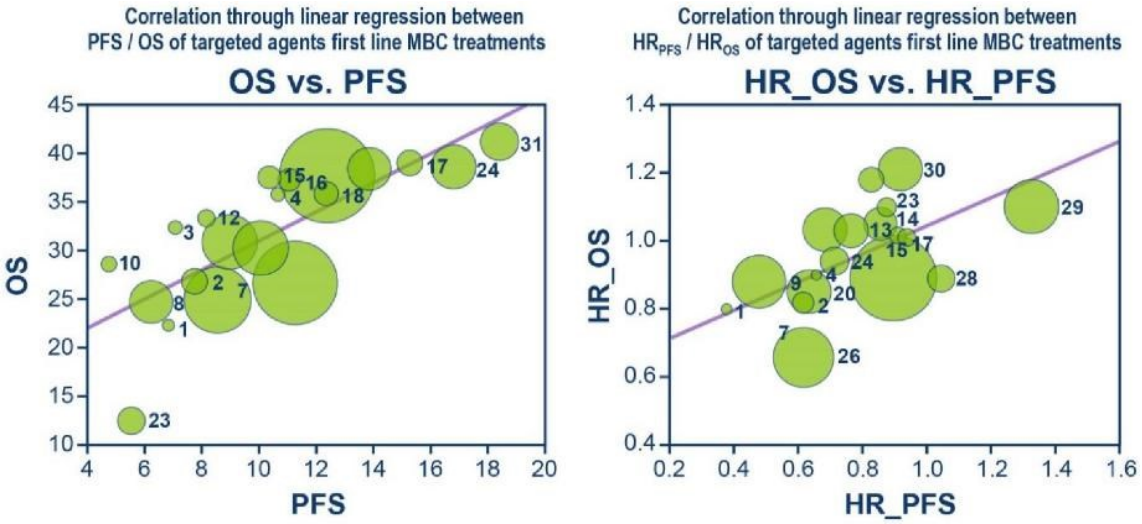
  As well as the quality of life benefits, data suggests the majority of patients remain alive whilst they are progression-free. In palbociclib's pivotal phase III trial (PALOMA-2) 317 patients had experienced objective disease progression at the time of the datacut, with only 14 patients dying without experience disease progression.[9] As such, patients remaining progression-free are likely to remain alive.

- **PFS has been shown to be correlated with OS.**

  The question of whether PFS can be considered an acceptable surrogate end-point for overall survival depends not only on the formal validation studies used to reach that conclusion but also on there being a standardised definition and unbiased ascertainment of disease progression in those clinical trials. A recent publication by Petrilli and Barni (2014)[12] focused on the specific molecular subtypes within metastatic breast cancer while previously analyses focused on general breast cancer without evaluating the subtypes. Randomised phase 3 trials for metastatic breast cancer were identified and correlations between endpoints were evaluated. The Spearman's rank correlation coefficient between hazard ratios in PFS/TTP and hazard ratios in OS was 0.73 (95% CI, 0.719-0.738; P<0.00001); the slope of the regression line was 0.56 ± 0.0034, indicating that an agent producing a 10% risk reduction for PFS will provide a 5.6% risk reduction for OS. Figure 2 presents the correlation between these endpoints.

Additionally, Beauchemin et al (2014) conducted a review of 144 studies involving more than 43,000 patients with metastatic breast cancer and found a statistically significant relationship between median PFS/TTP and OS (r=0.428; P<0.01).[12, 64] Other studies also found such a correlation in ABC.[13-16]

Figure 2. Correlation between progression-free survival and overall survival for first-line targeted agents for metastatic breast cancer



Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
Source: Petrilli and Barni (2014)[12]

- **Remaining progression-free delays the onset of chemotherapy.**

  Chemotherapy can pose a psychological burden on patients with ABC even before it starts. There exists among patients a perceived fear of chemotherapy, which leaves many anxiously contemplating its prospect.[19, 20] The ability of a non-chemotherapy to prolong PFS will lead to a postponement of time to later-line chemotherapy, which is the only treatment option recommended by NICE following the failure of endocrine therapy.[60] Recent technology appraisals have acknowledged this and highlighted the advantage of treatments that may delay the need for chemotherapy, leading to a longer period of high-quality, productive life for a patient;[65, 66] this is a benefit not captured in the QALY.

  Chemotherapy is often associated with severe toxicity and lower quality of life[43, 67,44, 68-70]. The very prospect of chemotherapy induces fear and anxiety in many women with breast cancer,[19, 20] and chemotherapy has also been associated with a reduced ability to work,[21] Among women with locally recurrent or metastatic breast cancer, chemotherapy is associated with lower health-related quality of life than endocrine therapy.[17, 18] 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,[71] and these levels can be persistent.[72]

  A study by Lloyd (2006) examining the quality of life in a UK cohort of metastatic breast cancer patients found their data "underline how important the avoidance of chemotherapy-related side effects is. Each of the toxicities led to a decline in utility of at least 0.103. The study revealed that hair loss is given similar importance, in terms of utility loss, as grade 3/4 side effects such as fatigue and hand-foot syndrome." [11]

See section 4.7.1.1 for data from palbociclib's clinical trial that indeed demonstrate the prolonging of the need for chemotherapy with the more efficacious treatment.

- **Disease progression causes women to stop work; maintaining PFS is important to reduce the chance of this so women can continue with normal life.**

  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 [43, 44] and the ability to work.[21] In European working-age patients with HR+/HER2− advanced breast cancer, 32% of women are working through their first-line chemotherapy, whereas the percentage of women who are able to work through subsequent lines of chemotherapy decreases to 13% when women receive second-line chemotherapy and to 7% when women receive third-line chemotherapy.[21] A study with 19,496 women with breast cancer found that women treated for breast cancer missed between one and two weeks of work every quarter, with rates of absence increasing with disease progression. First-line metastatic patients missed an average of 87 hours per quarter, and at second-line this increased to 112 hours. Further to this, the study found that women whose cancer progressed were more likely to exit employment all together.[10]

- **Maintaining 'normality' is key for patients with incurable disease**

  Diagnosis with ABC and subsequent treatment can negatively affect patients psychologically.[73, 74] UK clinical experts have indicated that in the face of, one of the primary goals of treatment is too 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 many of their remaining months as possible looking after their families, children and continuing to work as 'normal'. 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 then 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.[22]

3.2.2. Effects on carers and society

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 care givers.[75] Diagnosis with ABC and subsequent treatment can negatively affect the caregivers of patients,[76] such carers are at higher risk of depression and reduced quality of life than the general population.[77]

The burden on carers is even greater when the patient's disease progresses as a patient's quality of life falls (Section 3.2.1). 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 potential toxicity, lower quality of life [43, 44] and lower ability to work.[21]

Breast cancer progression is associated with a large increase in healthcare costs, most of which are inpatient costs, such as for aggressive and prolonged chemotherapy.[78] The lifetime cost of managing metastatic breast cancer from diagnosis to death in the UK has been estimated at £12,500 (2004 basis) [79] and at £13,500 (2005 basis) between regional recurrence and metastasis until death.[80] Another study found that the aggregate 5-year cost of treating recurrent breast cancer was £16,640 (2007 basis).[81] These estimates also do not reflect indirect costs related to lost work productivity or burden on families.

Even though treatment acquisition costs for women with ER+/HER2- 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, and a survival of several years leading to accumulation of supportive care costs.[82-84]

Thus, 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 and greater involvement of the health system to support the patient. An innovative treatment for ABC that can prolong survival without progression (and thereby offering a delay to chemotherapy) can significantly mitigate these burdens.

3.3. The clinical pathway of care that shows the context of the proposed use of the technology

3.3.1. Pathway of care for early breast cancer – post-menopausal women

The majority of early breast cancers are diagnosed within the UK National Breast Cancer Screening program.[85] According to NICE Clinical Guideline 80 ('Early and locally advanced breast cancer: diagnosis and treatment'),[85] women diagnosed with early invasive breast cancer, regardless of age, are usually treated with surgery, and may be treated with chemotherapy-based regimens before surgery (neo-adjuvant) to downsize the tumour.

After surgery, most women with early invasive ER+ breast cancer, who are not at low risk of relapse typically receive adjuvant endocrine therapy for at least 5 years.[85]Several endocrine drugs are in clinical use for adjuvant therapy, including tamoxifen and aromatase inhibitors. The aromatase inhibitors anastrazole, exemestane and letrozole are recommended options for the adjuvant treatment of postmenopausal women with early invasive ER+ breast cancer.[85] Women at high risk of disease relapse are offered adjuvant chemotherapy before receiving adjuvant endocrine therapy.[85] Anthracyclines and taxanes are examples of typically used cytotoxic agents. See NICE guidance for further information on risk assessment and treatment of breast cancer. [85]

3.3.2. Pathway of care for advanced breast cancer – post-menopausal women

Patients presenting with ABC who do not have imminently life-threatening disease should preferably be treated with endocrine therapy.[52, 53, 59, 60] This is the target population in the present technology appraisal. Patients who relapse on adjuvant therapy or who suffer recurrence soon after completing adjuvant therapy may be treated with tamoxifen. Such

patients are not within the scope of the present appraisal; indeed, patients resistant to non-steroidal aromatase inhibitors were excluded from the PALOMA-2 RCT described in this appraisal.

For ABC patients whose disease has progressed rapidly and/or has already spread to visceral organs, first-line chemotherapy is recommended, initially with anthracyclines (doxorubicin, epirubicin). If these are ineffective or contraindicated, then sequential systemic monotherapy involving taxanes (paclitaxel and docetaxel), capecitabine, or vinorelbine is recommended. A study of more than 17,000 patients with ER+/HER2- metastatic breast cancer in the UK found that 27.9% were treated initially with chemotherapy.[58]

Some women suffer recurrence or progression following one or more rounds of aromatase inhibitor treatment for their ABC, and they are switched to a second-line treatment such as exemestane (potentially in combination with everolimus). NICE does not recommend the use of exemestane in combination with everolimus for routine care in the NHS, though treatment was available until recently through the Cancer Drugs Fund (CDF), and NHS guidelines are currently being re-appraised.[86] Market research also suggests that although fulvestrant is not recommended in England or Wales for this indication, some NHS trusts may offer it to women who have suffered recurrence or progression following treatment with aromatase inhibitors.[87]

Detailed data are lacking on how many lines of different endocrine therapies are typically administered in the UK. An unpublished survey of more than 70 physicians from the UK and four Western European countries in 2014 found that two-thirds of patients with metastatic breast cancer who receive first-line hormonal therapy go on to receive second-line hormonal therapy, approximately half who receive a second line go on to receive a third, and nearly one third who receive a third line receive a fourth.[88]

3.4. Life expectancy of ABC patients eligible for palbociclib plus letrozole

Prognosis of patients with ABC is poor compared with that of patients with early-stage breast cancer, and survival rates fall as the disease advances: 5-year OS is 99% for women in the UK with stage I breast cancer, 90% for stage II, 60% for stage III, and 15% for stage IV (metastatic).[89] Studies from European countries and the US consistently report average OS for patients with HR+/HER2- ABC as <5 years.[40, 82, 83, 90] Median OS of women receiving their first post-adjuvant systemic therapy can range from 32 to 48 months.[36, 91, 92]

National-level data on ABC incidence in the UK are lacking; regional data suggest that 5% of women with breast cancer have metastatic disease at first diagnosis (de novo disease),[93] or approximately 11,000 women in England. Estimates based on observed frequencies of different breast cancer subtypes and on the incidence of menopause suggest that 48,867 women in England and Wales have breast cancer, of whom almost 7,000 have ER+/HER2- ABC (Table 8). It is estimated that of these women with ER+/HER2- ABC only approximately 5,000 would be eligible to receive palbociclib (Pfizer data on file).

Table 8. Estimation of numbers of women in England and Wales with ER+/HER2- ABC

Definition	Proportion per annum	Population 2013

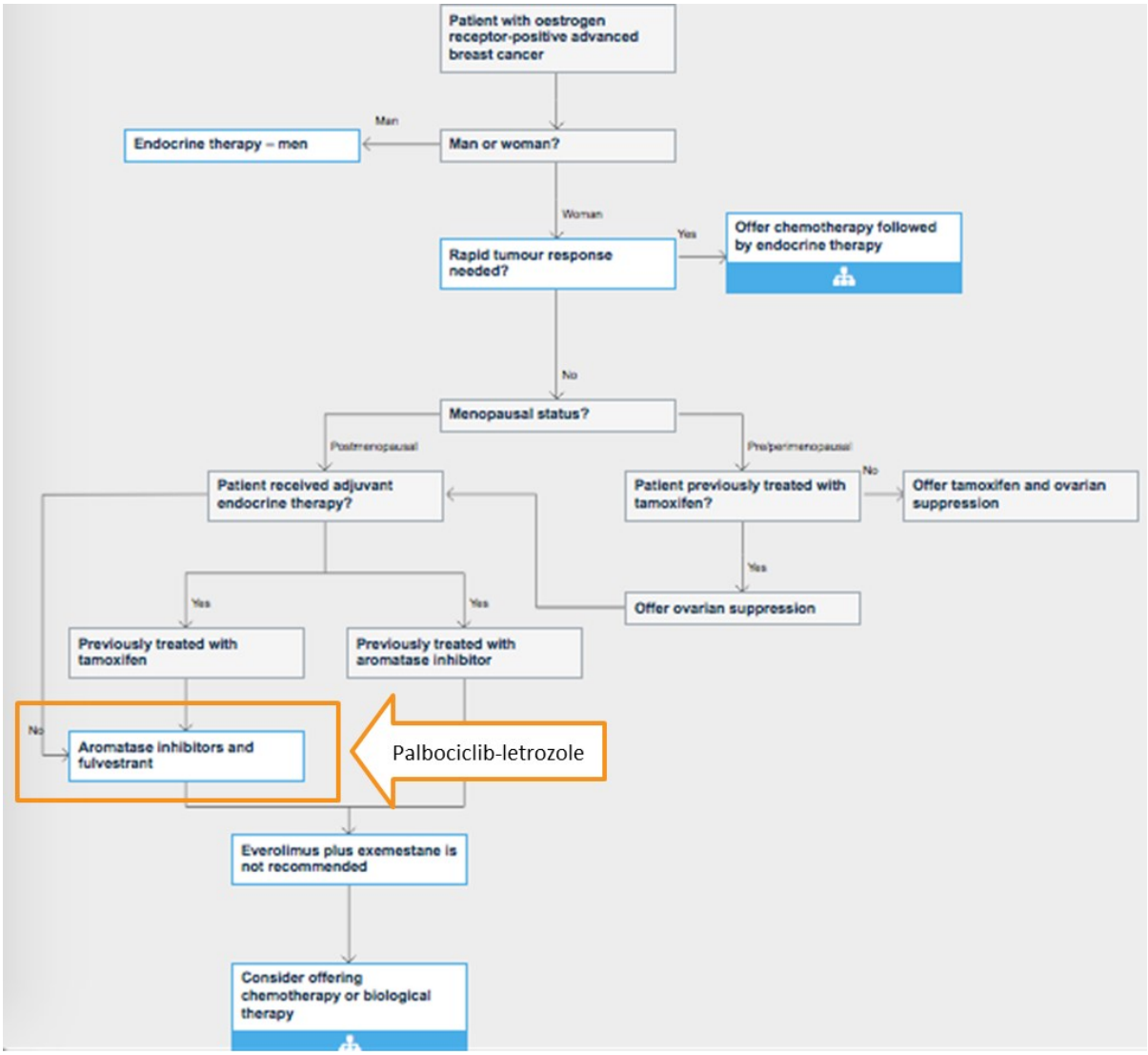
Women with breast cancer in England and Wales	England 46,085 (ONS 2016[94]) Wales 2,782 (Welsh Cancer Intelligence[95])	
Women with invasive breast cancer	90% (NICE 2015[96])	44,061
Women with early and locally advanced invasive breast cancer	95% (NICE 2015[96])	41,858
Women presenting with advanced breast cancer at diagnosis	5% (NICE 2015[96])	2,203
Women presenting with early breast cancer that die before disease progression	30% (NICE 2015[96])	12,557
Women with early and locally advanced breast cancer progressing into advanced stage	35% (NICE 2015[96])	10,255
Total number of women developing advanced BC per year		12,458
Women with ER+/HER2- advanced breast cancer	56% [58]	6,977
Percentage of women who will be postmenopausal	82% [97]	5,721
Percentage women treated with 1st line therapy (*i.e.* previously untreated in the metastatic setting)	95% (Pfizer, data on file)	6,628
Women eligible for palbociclib 1st line (post-menopausal ER+/HER2- ABC)	95% (Pfizer, data on file)	5,435

* Women aged ≥50 years were considered to be postmenopausal

3.5. Relevant guidance and pathways for ABC

The NICE Clinical Guideline 81 on treating ABC is currently undergoing revision, and an updated version is expected in June 2017.[98] Figure 3 based on the current version of NICE CG81 shows the likely positioning for the use of the combination of palbociclib-aromatase inhibitor applies.

Figure 3. The NICE pathway and palbociclib-letrozole treatment (source: [99])



3.6. ESMO and ASCO guidelines, and guidance from the SMC in Scotland

EMSO guidelines [53, 100] for treating ER+/HR2- ABC overlap substantially with those of NICE: both rely heavily on endocrine monotherapy and present chemotherapy as the primary treatment option after progression on such therapies. The ESMO guideline recommends the following treatments:

- In first line:
  - for postmenopausal women, even in the presence of visceral disease not requiring rapid response: aromatase inhibitors or tamoxifen are preferred, unless there is concern or proof of endocrine resistance; fulvestrant HD (500mg, every 4 weeks) is also an option
  - for women who require a more rapid therapeutic response or if doubts exist about endocrine sensitivity: chemotherapy

The ASCO guideline[52] recommends endocrine therapy as initial treatment for patients with HR+ ABC, except for patients with immediately life-threatening disease and patients who

experienced rapid visceral recurrence during adjuvant endocrine therapy. The guideline recommends the following treatments:

- In first line:
    - for postmenopausal women with HR+ ABC: aromatase inhibitors
    - for patients with ABC who have never received adjuvant endocrine therapy: combination therapy of a nonsteroidal aromatase inhibitor and fulvestrant 500mg with a loading schedule

The ASCO guideline also explicitly recognises situations in which palbociclib therapy is appropriate and may be beneficial:

- A nonsteroidal aromatase inhibitor and palbociclib may be offered to postmenopausal women with treatment-naive HR+ ABC (because PFS was improved compared with letrozole alone)

3.7. Variations in established practice

Consistent with the range of biological subtypes of breast cancer and the diversity of patient clinical characteristics, treatment histories and therapeutic responses, the treatment of ABC is complex and strongly dependent on numerous patient-specific factors (discussed in section 3.3). Patient characteristics and treatment history should therefore be considered carefully when assessing the safety and efficacy of ABC treatments in clinical trials, and when prescribing treatments in the clinic. The PALOMA RCTs discussed in Section 4 considered multiple important patient factors through prespecified subgroup analyses.

3.8. Equality issues

We do not believe that this appraisal will exclude or lead to a recommendation that would have a different impact for people protected by equality legislation and/or have a particular disability or disabilities to that of the wider of the population.

4. Clinical effectiveness

Direct head-to-head evidence from PALOMA-2 demonstrates the clinical benefit of palbociclib plus letrozole compared to letrozole alone in women previously untreated for their HR+/HER2- ABC, and is the first phase III trial in metastatic breast cancer to break the two-year barrier with respect to PFS.

- In the ITT population of 666 postmenopausal women with previously untreated HR+/HER2- ABC in the PALOMA-2 phase III RCT, treatment with palbociclib-letrozole resulted in significantly longer median PFS (24.8 months, 95%CI 22.1 to NE) than placebo-letrozole (14.5 months, 95%CI 12.9 to 17.1), corresponding to HR 0.576, 95%CI 0.463 to 0.718 (stratified one-sided $p < 0.000001$).

- Among patients with measurable disease, ORR was significantly higher among patients who received palbociclib-letrozole (55.3%, 95%CI 49.9 to 60.7) than among those received placebo-letrozole (44.4%, 95%CI 36.9 to 52.2), corresponding to an odds ratio of 1.55 (95%CI 1.05 to 2.28, stratified one-sided $p = 0.0132$).

- The proportion of patients showing CBR was significantly higher among patients who received palbociclib-letrozole (84.9%, 95%CI 81.2 to 88.1) than among those who received placebo-letrozole (70.3%, 95%CI 63.8 to 76.2), corresponding to an odds ratio of 2.39 (95%CI 1.58 to 3.59).

- Among patients with measurable disease, median duration of response (DOR) was 22.5 months (95%CI 19.8 to 28.0) for patients who received palbociclib-letrozole, and 16.8 months (95%CI 15.4 to 28.5) for those who received placebo-letrozole.

- In PALOMA-2, the number of OS events did not meet the threshold allowing for an analysis to be conducted. The median follow-up time was 23.0 months (95% CI: 22.6-23.4) for the palbociclib plus letrozole arm and 22.3 months (95% CI: 21.9-22.9) for the placebo plus letrozole arm. The trial was not powered to detect differences in OS, and the current OS data are immature. Although patients will continue to be followed for the final OS analysis on an event-driven basis, however survival estimates are likely to be confounded by the numerous post-progression treatments that patients in both arms will receive.

- Palbociclib was generally well tolerated with a manageable adverse events profile. In PALOMA-2, the most common events overall reported for palbociclib+letrozole were neutropenia, leukopenia and fatigue, however these were often asymptomatic and managed through dose modification, and none of the cases of neutropenia or leukopenia in either treatment group developed into neutropenic fever.

The PALOMA-1 trial of 165 postmenopausal women with previously untreated HR+/HER2- ABC reported a positive trend in OS in favour of palbociclib-letrozole. The observed HR was 0.813 (95%CI 0.492 to 1.345) with a stratified 1-sided p-value of 0.2105. Median OS was 37.5 months (95%CI 28.4 to NE) in the palbociclib-letrozole arm and 33.3 months (95%CI 26.4 to NE) in the letrozole arm. The estimated survival probabilities at 12 months, 24 months, and 36 months between the two treatment arms were 89.0% versus 87.0%, 77.1% versus 70.2%, and 53.0% versus 44.0%, in favour of palbociclib plus letrozole, respectively.

4.1. Identification and selection of relevant studies

A systematic literature review was performed in January 2015 to identify relevant non-randomised controlled trials (non-RCTs) providing evidence on the safety and efficacy of palbociclib for the treatment of postmenopausal women with ER-positive, HER2-negative locally advanced or metastatic breast cancer. The review was subsequently updated to include relevant studies published up to January 2016 in line with NICE guidance.

4.1.1. Search strategy

The systematic review was performed in accordance with the methodological principles of conduct for 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 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting checklist.[101, 102]

The flowing electronic databases were searched for the original systematic review 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 systematic review update. 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

Finally, ClinicalTrials.gov and the International Clinical Trials Registry Platform were searched for relevant RCTs of palbociclib, while the FDA website was searched for the Summary Basis of Approvals.

Full details of the search strategies employed for both the original systematic review and the systematic review update are presented in Appendix 4.

4.1.2. Study selection

Following the database search, duplicate results were excluded. The titles and abstracts of identified sources were assessed against the eligibility criteria presented in Table 9. For those sources considered potentially relevant, or for which the relevance was unclear based on the title or abstract, full texts were obtained and screened for relevance. The screening was performed by two independent reviewers, and disputes relating to eligibility were resolved through discussion between reviewers until consensus, or through consultation with a third reviewer.

Table 9. Eligibility criteria for systematic review of RCTs of palbociclib and endocrine therapies

Domain	Inclusion Criteria	Exclusion Criteria

Domain	Inclusion Criteria	Exclusion Criteria
Population	Postmenopausal women[a] with ER+, HER2- locally advanced or metastatic breast cancer. Studies had to include ≥50% patients with ER+ or HR+ disease, and ≥50% postmenopausal women; alternatively, outcomes had to be reported separately for patients in these subgroups.	Premenopausal women not receiving a luteinising hormone blocker Women with early breast cancer Women with ER- breast cancer Women with HER2+ breast cancer Studies with <50% patients with ER+ or HR+ disease or <50% postmenopausal women were excluded unless outcomes were reported separately in these subgroups.
Intervention	First line: anastrazole, letrozole, palbociclib	Conventional cytotoxic chemotherapy Other therapies not listed (including trastuzumab, ado-trastuzumab, pertuzumab, and lapatinib)
Comparator	As above for "intervention". A study had to have an intervention of interest in at least one study arm to be eligible for inclusion.	As above for "intervention" Studies with the same therapy of interest in both arms ± a failed or obsolete therapy, where "obsolete" means replaced by the comparators of interest.
Outcomes (considered at full-text review only)	Clinical benefit rate Objective response rate Complete response Partial response Overall survival Progression-free survival Time to progression Duration of response Adverse events: Overall rate of AEs Overall treatment-related AEs Overall AEs of grade 3/4 severity Overall treatment-related AEs of grade 3/4 severity Overall serious AEs Overall discontinuations due to AEs Febrile neutropenia Grade 3/4 neutropenia Grade 3/4 arthralgia Grade 3/4 myalgia Other grade 3/4/5 AEs Patient-reported outcomes/utility: EQ-5D EORTC QLQ-C30 EORTC QLQ BR-23 EORTC QLQ FA-13 Fatigue FACT-B BPI	Studies that do not report any relevant outcomes
Study design	Phase 2 and 3 randomised controlled trials	Non-randomised, controlled, prospective clinical trials Long-term follow-up studies (eg. open-

Domain	Inclusion Criteria	Exclusion Criteria
		label follow-up studies) Prospective observational studies (eg. Phase 4 studies) Preclinical studies Phase 1 studies Prognostic studies Retrospective studies Case reports Commentaries and letters (publication type) Consensus reports Non-systematic reviews
	Systematic reviews and meta-analyses were formally excluded at the title/abstract screening stage. However, the full texts of any systematic reviews and meta-analyses on relevant RCTs were acquired and hand-searched to find any additional relevant primary studies not identified through the database searches.	
Language	English	Any other language
Date	No limit	None

[a] Including women who had menopause induced during the study.

Abbreviations: AE, adverse event; BPI, Brief Pain Inventory; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQol 5-dimensions questionnaire; ER, oestrogen receptor; FACT-B, Functional Assessment of Cancer Therapy–Breast; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

Data from included studies were extracted into a pre-specified extraction grid in Microsoft Excel.

4.1.3. Results

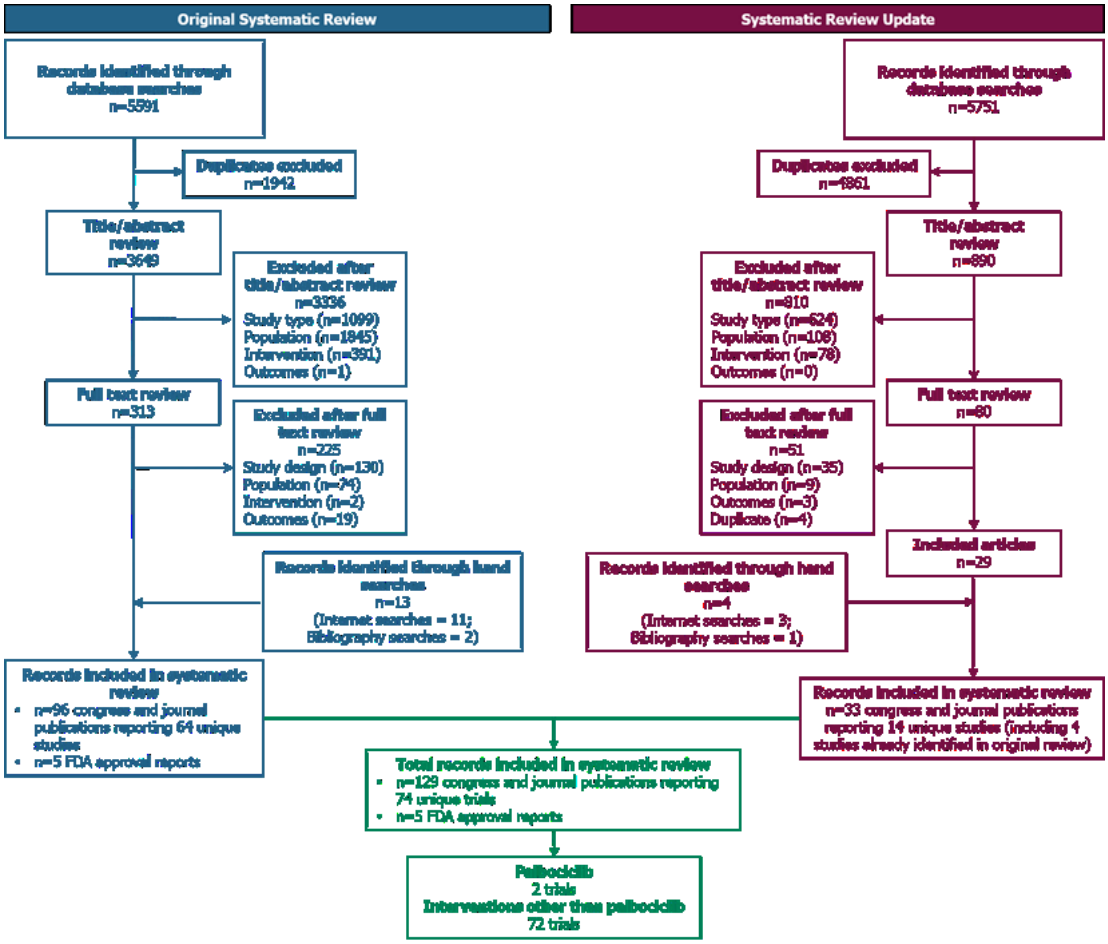
The original systematic review identified 64 unique studies described in 96 congress and journal publications, as well as 5 FDA approval reports. Of these, one study investigated first-line palbociclib plus letrozole compared to placebo-letrozole in women with ER+/HER2- locally advanced or metastatic breast cancer (PALOMA-1).

The systematic review update identified 14 studies, described in 33 congress and journal publications. Ten of the studies were newly identified in the update. One of the newly identified studies investigated second-line palbociclib in combination with fulvestrant in women with ER-positive, HER2-negative locally advanced or metastatic breast cancer (PALOMA-3). Furthermore, the updated search on ClinicalTrials.gov identified one study that investigated palbociclib plus letrozole compared with letrozole for the first line treatment of postmenopausal women with ER+/HER2- ABC (PALOMA-2).

A PRISMA flow diagram of the evidence identified in the original and updated systematic reviews is presented in

Figure 4.

Figure 4. PRISMA flow diagram for the original and updated systematic reviews of RCTs of endocrine therapies



Please refer to Appendix 5 for a full list of palbociclib and comparator publications and studies included in both the original and updated systematic reviews. Records identified from ClinicalTrials.gov are detailed in Appendix 6. A complete list of palbociclib and comparator publications excluded after the full-text review stage of both the original and update systematic reviews is provided in Appendix 7.

4.2. List of relevant randomised controlled trials

Of the studies identified in the original and update systematic reviews, the PALOMA-1 study investigated the use of palbociclib plus letrozole in women with ER+/HER2- locally advanced or metastatic breast cancer (

Table 10).[3, 4, 45] Another relevant RCT is PALOMA-2, a phase III trial designed to confirm and expand on the results of PALOMA-1. PALOMA-2 has not yet been published as a full-length research article in a peer-reviewed journal (expected in December 2016). An abstract presenting partial results[23] was accepted to the 2016 ASCO Annual Meeting after the literature searches described in Section 4.1 were conducted. Some information about PALOMA-2 was also publicly available at clinicaltrials.gov (NCT01740427).

Table 10. List of RCTs involving palbociclib to treat ABC

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference *(Secondary references)*
NCT00721409 (PALOMA-1)	Treatment naïve patients with advanced or metastatic ER+/HER2- breast cancer	Palbociclib plus letrozole	Letrozole	Finn 2015[4] (Bell 2015 Bell 2016, Crown 2015, Finn 2014, Finn 2015a, Finn 2015b, Slamon 2015[24, 45-50]
NCT01740427 (PALOMA-2)	Treatment naïve patients with advanced or metastatic ER+/HER2- breast cancer	Palbociclib plus letrozole	Placebo plus letrozole	Finn 2016[23] and data on file [9]

4.3. Summary of methodology of the relevant randomised controlled trials

4.3.1. PALOMA-1 methodology

PALOMA-1[3, 4] is an international, randomised, multi-centre, open-label Phase 1+2 trial of palbociclib in postmenopausal women with ER+/HER2- ABC who did not receive previous systemic treatment in the advanced or metastatic setting.

Initially, a single-arm Phase 1 study was done to assess the safety of palbociclib given with letrozole in patients with ER+/HER2- ABC and to determine a recommended Phase 2 dose of the combination. The results suggested a dose and schedule consisting of oral palbociclib 125 mg once daily for 3 weeks followed by 1 week off treatment in a 28-day cycle, combined with the standard dose of oral letrozole 2.5 mg once daily. No drug–drug interactions were identified and the most common treatment-related adverse events were neutropenia, leukopenia, and fatigue. Based on these clinical data, a randomised, open-label, Phase 2 study was performed to assess the safety and efficacy of the palbociclib and letrozole combination compared with letrozole alone.

In the Phase 2 part of the study, patients were sequentially enrolled into two cohorts to assess both the activity of palbociclib+letrozole as well as to determine whether selecting patients based on the ABC-associated biomarkers cyclin D1 (CCND1) or p16 might identify subpopulations more likely to benefit from palbociclib (

Figure 5). Cohort 1 was recruited into the study based solely on ER+/HER2- status. Cohort 2 was recruited based on the combination of ER+/HER2- status and amplification of cyclin D1 and/or loss of p16 (*INK4A* or *CDKN2A*) or both. Across both cohorts, a total of 84 patients were randomised to receive palbociclib+letrozole, and 81 were randomised to receive letrozole alone. Accrual to cohort 2 was stopped after an unplanned interim analysis of cohort 1 based on 32 progression-free survival events. The interim analysis was conducted because it was noted that almost twice as many patients in the control group were coming off the study because of disease progression. This interim analysis showed clinically meaningful activity of the palbociclib plus letrozole combination compared with letrozole alone (HR 0·35, 95% CI 0.17-0.72, p=0·006). The statistical analysis plan for the primary endpoint was amended to a combined analysis of cohorts 1 and 2 (instead of cohort 2 alone). Crossover was not allowed at any time.

Details of the PALOMA-1 methodology are summarised in

Table 11.

Table 11. Summary of PALOMA-1 methodology [3]

Trial number (acronym)	PALOMA-1 (study A5481003)
Location	50 sites in Canada, France, Germany, Hungary, Ireland, Italy, Russian Federation, South Africa, South Korea, Spain, Ukraine, US
Trial design	Phase 2, multicentre, randomised, open-label Stopping guidelines: Patients continued on the assigned study treatment until disease progression, unacceptable toxicity, consent withdrawal, or death. Dose interruptions and reductions were allowed for the management of toxic effects. Crossover: Not allowed
Method of randomisation	Patients were randomly allocated in a 1:1 ratio to receive either palbociclib-letrozole or letrozole alone. Randomisation was performed using an interactive web-based randomisation system, stratified by disease site (visceral *vs* only bone *vs* other) and by DFI (>12 *vs* ≤12 months between completion of the last adjuvant treatment and disease recurrence) or *de novo*.
Eligibility criteria for participants	Inclusion criteria: • Patients were women aged 18 years or older. • Patients were classified as postmenopausal and diagnosed with adenocarcinoma of the breast with evidence of (a) locally recurrent disease not amenable to resection or radiation therapy with curative intent, or (b) metastatic disease. • Patients had ER+/HER2- tumours. • Patients had measurable disease according to RECIST version 1.0 or bone-only disease (Phase 2 only). • Patients had an ECOG performance status 0 or 1. • All acute toxic effects in patients due to prior therapy or surgical procedures had resolved to CTCAE Grade ≤1, except alopecia or other toxicities not considered a safety risk. A full list of inclusion and exclusion criteria is presented below in Table 12.
Settings and locations where the data were	The study took place in a clinical trial setting, where the investigator had ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data. Self-administered questionnaires were completed by the patients while in the clinic and

collected	could not be taken home; instruments were to be completed prior to having any tests and to any discussion of their progress with healthcare personnel at the site. Interviewer administration in clinic could be used under special circumstances (e.g., patient had forgotten their glasses or felt too ill). The instruments were given to the patient in the appropriate language for the site.
Trial drugs and method of administration	The palbociclib-letrozole group (n = 84) received: palbociclib, 125mg, oral, once-daily for 3 weeks, followed by a week off in a 28-day cycle; as well as letrozole 2.5mg, oral, once-daily on a continuous daily dosing regimen. On days on which both drugs were to be given, letrozole and palbociclib were to be administered at the same time. The letrozole-placebo group (n = 81) received: letrozole 2.5mg, oral, once-daily on a continuous daily dosing regimen.
Permitted and disallowed concomitant medication	Permitted concomitant medication: • Medication intended solely for supportive care (e.g. analgesics, antidiarrheals, antidepressants) could be used at the investigator's discretion. • Granulocyte Colony Stimulating Factor (GCSF) could be used to treat treatment-emergent neutropenia as indicated by ASCO guidelines [103] • Concomitant medication not recommended: • Drugs known to strongly induce cytochrome P450 3A4, including carbamazepine, dexamethasone, felbamate, omeprazole, primidone, phenobarbital, rifampin, phenytoin, rifabutin, rifapentin, and St. John's Wort • Erythropoietin could be used at the investigator's discretion for the supportive treatment of anaemia. • Bisphosphonates and receptor activator of nuclear factor kappa-B ligand inhibitors could be continued for patients who were already receiving them at the time of study entry. However, the need to commence these therapies while on study therapy was considered indicative of disease progression, unless expressly agreed otherwise by the investigator in consultation with Pfizer. • If neutropenic complications were observed in a cycle in which primary prophylaxis with GCSF was not received, secondary prophylaxis may have been given at the discretion of the investigator, but only if dose reduction or delay were not considered to be a reasonable alternative. Disallowed concomitant medication: • Drugs known to strongly inhibit cytochrome P450 3A4, including ketoconazole, miconazole, itraconazole, posaconazole, clarithromycin, erythromycin, tilithromycin, nefazodone, diltiazem, verapamil, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, delavirdine, and grape fruit juice • Any drug containing "for the treatment of breast cancer" on the product insert • Primary prophylactic use of GCSF • Raloxifene Concomitant radiotherapy and surgery: • Palliative radiotherapy was permitted for the treatment of painful bony lesions, provided the lesions were known to be present at the time of study entry and the investigator had clearly indicated that the need for palliative radiotherapy was not indicative of disease progression. • Palbociclib treatment was to be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment 1 week after. • Caution was advised on theoretical grounds for any surgical procedures during the study, since the appropriate interval of time between surgery and palbociclib required to minimise the risk of impaired wound healing and bleeding has not been determined. Stopping palbociclib was recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate palbociclib treatment was to be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

Primary outcomes	Investigator-assessed PFS, defined as the time from randomisation to radiological disease progression or death on study. Documentation of progression was by objective disease assessment calculated from the lesion measurements, as defined by RECIST 1.0. Disease was assessed by CT or MRI of chest, abdomen, and pelvis; X-ray scans of bone lesions; and clinical evaluation of superficial disease within 28 days of initiation of study treatments, at the end of cycle 2 and on day 1 of every other cycle starting from cycle 4. Disease assessment was repeated at withdrawal or the end of treatment. It was also assessed whenever progression was suspected and to confirm partial or complete response at least 4 weeks after initial documentation of response. Brain CT or MRI was required only when signs and symptoms suggested presence of metastatic brain disease. Post-screening repeat brain scans were required only if metastases were suspected. Bone scans were required within 28 days of initiation of study treatments, and baseline bone lesions were followed every 12 weeks using the most appropriate imaging technique, as well as at withdrawal or end of treatment. A bone scan was required at the time of confirmation of complete response for patients who had bone metastases.
Secondary and other outcomes	• OR, CBR, OS, PROs on the mBPI-sf [46] (in cohort 2), DOR, TTP. See Table 13 for the full definition of these outcomes • Safety – including type, incidence, severity, seriousness and relationship to study medications of adverse events and any laboratory abnormalities
Pre-planned subgroups for PFS	• Age (<65 years, ≥65 years) • Baseline ECOG (0 or 1) • Disease site (visceral, bone only, other) • Previous chemotherapy (yes, no) • Previous endocrine therapy (yes, no) • Previous systemic therapy (yes, no) • Previous chemotherapy only (yes, no) • Previous chemotherapy and endocrine therapy (yes, no) • DFI (≤12 months, ≤12 months + de novo, >12 months; ≤5 years, >5 years) • Biomarker status (positive, negative, unknown) • Region (North America, Europe) • Histopathological grade (1/2, 3) • Progesterone receptor (positive, negative) • Number of disease sites involved (<2, ≥2) • De novo advanced disease (yes, no)
Duration of study and follow-up	Between 22 December 2009 and 12 May 2012, 165 women were randomised to treatment groups. The study achieved its primary endpoint when approximately 95 PFS events had occurred, which was calculated to allow 98% power to detect an HR of 0.50 at one-sided alpha of 0.10, or a 75% power to detect an HR of 0.67. Median duration of follow-up, defined as the months from randomisation to the last contact (if alive) or death was 29.6 months (95%CI 27.9 to 36.0) in the palbociclib-letrozole arm and 27.9 months (95%CI 25.5 to 31.1) in the letrozole arm. All PALOMA-1 data presented in this submission correspond to the data cut-off date of 29 November 2013. [redacted]

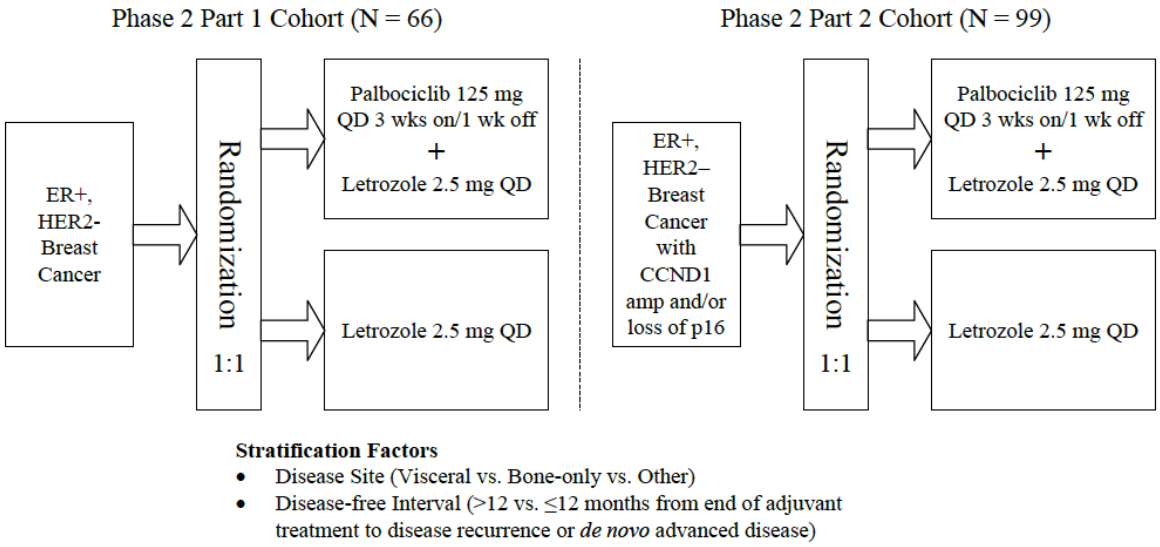
Abbreviations: ABC, advanced or metastatic breast cancer; ASCO, American Society of Clinical Oncology; CBR, complete biological response; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DFI, disease-free interval; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; GCSF, granulocyte colony-stimulating factor; HER2, human epidermal growth factor receptor 2; mBPI-sf, modified Brief Pain Inventory Short Form; MRI, magnetic resonance imaging; OR, objective response; OS, overall survival; PFS, progression-free survival; PRO, patient-

reported outcome; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression; US, United States of America.

The methodology is also depicted graphically in

Figure 5.

Figure 5. PALOMA-1 study design [3]



Abbreviation: QD, Once daily

Table 12. Eligibility criteria for PALOMA-1 [3]

Inclusion criteria	Exclusion criteria
• Patients were women aged 18 years or older. • Patients were classified as postmenopausal because of (a) prior bilateral surgical oophorectomy, (b) amenorrhoea (in women at least 60 years old) or (c) amenorrhoea for at least 12 months in women younger than 60 who had not received chemotherapy, tamoxifen, toremifene, or ovarian suppression and whose follicle-stimulating hormone and estradiol levels were in postmenopausal ranges. • Patients received a histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of (a) locally recurrent disease not amenable to resection or radiation therapy with curative intent, or (b) metastatic disease. • Patients had ER+ tumours. Positivity was defined either as ⩾10 fmol of tritium-oestrogen binding per mg of cytosolic protein based on dextran-coated charcoal and sucrose density assays, or ⩾0.10 fmol of tritium-oestrogen binding per mg of DNA based on immunofluorescence or enzyme-linked immunosorbent assay. In the case of immunohistochemistry determinations, the report had to mention positive receptor status according to the standards of the laboratory. • Patients had HER2- tumours as determined by fluorescent in situ hybridisation or immunohistochemistry. • Patients in cohort 2 had *CCND1* amplification or *p16* loss as determined by the central laboratory. • Paraffin-embedded tumour block(s) for patients were available for centralised assessment of Rb and other cell cycle-related proteins. • Patients had measurable disease according to RECIST 1.0. Previously irradiated lesions were deemed measurable only if progression was documented at the site after completion of radiation therapy. • Patients had an ECOG performance status 0 or 1. • All acute toxic effects in patients due to prior therapy or surgical procedures had resolved to CTCAE Grade ≤1, except alopecia or other toxicities not considered a safety risk. • Patients had adequate organ function as defined by	• Patients had brain metastases (even if treated and stable), history of spinal cord compression, carcinomatous meningitis, or leptomeningeal disease. • Patients had undergone major surgery within 3 weeks of the first study treatment. • Patients had previously received (neo)adjuvant letrozole, followed by disease recurrence within 12 months; any CDK inhibitor; or any anticancer therapies for ABC, with the exception of radiation therapy covering <25% of bone marrow at least 2 weeks prior to study treatment initiation. • Patients were being treated at the time of study enrolment with any anticancer therapies for ABC, any experimental treatment as part of another clinical study, or therapeutic doses of anticoagulant. Low-dose anticoagulants against deep vein thrombosis, low-molecular-weight heparin and aspirin were allowed. • Patients were using or were likely to need food or drugs known to strongly inhibit cytochrome P450 3A4, i.e. grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, posaconazole, erythromycin, clarithromycin, tilithromycin, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, nefazodone, diltiazem, and delavirdine. • Patients had been diagnosed with any secondary malignancy within the last 3 years, except for adequately treated basal cell or squamous cell skin cancer, or in situ carcinoma of the cervix. • Patients had a history of the following conditions during the 6 months prior to study enrolment: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of CTCAE Grade ≥2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accidents including transient ischemic attack, or symptomatic pulmonary embolism. • Patients had active inflammatory bowel disease, chronic diarrhoea, short bowel syndrome, or a history of upper gastrointestinal surgery including gastric resection. • Patients had known hypersensitivity to letrozole or any of its excipients. • Patients had known human immunodeficiency virus infection.

Inclusion criteria	Exclusion criteria
absolute neutrophil count ≥1500/μL platelets ≥100,000/μL serum aspartate aminotransferase and serum alanine aminotransferase within 3 times the upper limit of normal or, in the case of underlying malignancy, within 5 times this limit total serum bilirubin within 1.5 times the upper limit of normal, regardless of liver involvement secondary to the tumour serum creatinine within 1.5 times the upper limit of normal a corrected QT interval ≤470 msec based on the mean value of triplicate electrocardiograms. Inclusion of patients with increased serum indirect bilirubin due to Gilbert's syndrome was permitted • Evidence of signed and dated informed consent documents indicating that patients (or their legal representative) had been informed of all pertinent aspects of the study. • Patients were willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.	• Patients had other severe acute or chronic medical or psychiatric conditions or laboratory abnormalities that might increase risks associated with study participation or investigational product administration or might have interfered with the interpretation of study results and, in the judgment of the investigator, made the patient inappropriate for study entry.

Abbreviations: ABC, advanced or metastatic breast cancer; CDK, cyclin-dependent kinase; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; QT, time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; RECIST, Response Evaluation Criteria in Solid Tumors.

4.3.1.1. Description of outcomes reported in PALOMA-1

The definitions and methods of assessment of the primary and secondary outcomes reported in PALOMA-1 are provided in Table 13.

PFS was the primary outcome in PALOMA-1. It is well-established that prolonged PFS is considered to be of considerable benefit to patients for many different reasons including symptom management, the effect on overall survival, the postponing of later-line chemotherapy, the ability to keep patients functioning normally and remaining in work. For further details on the value of PFS and why treating clinicians regard PFS as a key goal of therapy for ABC, please see Section 3.2.1. PFS is an accepted primary endpoint for RCTs according to the European Medicines Agency guidelines on the evaluation of anticancer medicinal products in humans.[8]

Secondary efficacy outcomes were as described in Table 13. Most secondary outcomes were assessed on the same schedule as disease assessment. PROs were assessed in cohort 2 using the modified Brief Pain Inventory-short form (mBPI-sf).[104-106] These outcomes were assessed on day 1 of each treatment cycle and at withdrawal or end of treatment. Safety was assessed in terms of recording of adverse events within 28 days of initiation of study treatment and then on days 1 and 14 of cycles 1-2 and on day 1 of every subsequent treatment cycle, and finally again at withdrawal or end of treatment.

Table 13. Description of outcomes reported in PALOMA-1 [3]

Outcome	Description
Primary efficacy outcome	
PFS	Time from randomisation to radiological disease progression or death on study. Documentation of progression was by objective disease assessment calculated from the lesion measurements, as defined by RECIST 1.0.
Secondary efficacy outcomes	
OR	Defined according to RECIST 1.0 from the lesion measurements
CBR	Defined as per RECIST 1.0 as complete response, partial response or stable disease lasting at least 24 weeks
OS	Time from the date of randomisation to the date of all-cause death. Patients last known to be alive were censored at date of last contact. Kaplan-Meier analysis was used to estimate OS probability. Survival was assessed up until approximately 28 days from the last dose of study treatment.
DOR	Time from first documentation of complete or partial response to date of first documentation of objective progression or death. This outcome was calculated only for patients who showed complete or partial response.
TTP	Time from the date of randomisation to the date of first documentation of objective progression.
PROs	
mBPI-sf scores	The mBPI-sf is a validated self-report questionnaire consisting of 13 questions that assess the severity and impact of pain on daily function.[104-106] It includes the 4-item Pain Severity Scale (worst pain, least pain, average pain, and pain right now) and the 7-item Pain Interference Scale (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life). Patients were to complete the self-administered questionnaire at baseline (Day 1, Cycle 1), on Day 1 of each subsequent cycle, and at the end of treatment or study withdrawal. They were to complete the mBPI-sf prior to having any tests, receiving

Outcome	Description
	any therapy, and before any discussion of the patient's progress with their physician or other healthcare personnel. [107]
Safety	
Safety	Type, incidence, severity, seriousness of adverse events, their relationship to study medications and any laboratory abnormalities. Adverse events were classified using the MedDRA classification system 16.1. Severity of events was graded according to the CTCAE 3.0 whenever possible. Safety outcomes were assessed until approximately 28 days after the last dose of study treatment.

Abbreviations: CBR, complete biological response; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; mBPI-sf, modified Brief Pain Inventory Short Form; OR, objective response; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression.

4.3.2. PALOMA-2 methodology

PALOMA-2 is an international, randomised, multi-centre, double-blind, and placebo-controlled Phase 3 trial involving 666 patients generally similar to those in PALOMA-1.[9] Key differences in the populations is that compared to the patient population in PALOMA-1, the population in PALOMA-2 is much larger and potentially more homogeneous because it did not contain patients who had relapsed during, or within 12 months after, adjuvant therapy with letrozole or anastrozole.[9] PALOMA-1, in contrast, excluded only patients who had suffered such relapse with letrozole therapy.[3]

Outcomes analysis for HRQL, PFS, OR and OS are presented below. Details of the PALOMA-2 methodology are summarised in Table 14.

Table 14. Summary of PALOMA-2 methodology[9]

Trial number (acronym)	PALOMA-2 (study A5481008)
Location	186 sites in Australia, Belgium, Canada, France, Germany, Hungary, Ireland, Italy, Japan, Republic of Korea, Poland, Russian Federation, Spain, Taiwan, Ukraine, UK (7 sites), US In total there were [redacted] patients from the UK, [redacted] were in palbociclib plus letrozole arm and [redacted] in the placebo plus letrozole arm.
Trial design	Phase 3, multicentre, randomised, double-blind, placebo-controlled Stopping guidelines: Patients were to continue receiving assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. Dose interruptions and reductions were allowed for the management of toxic effects. Crossover: Not allowed
Method of randomisation	Patients were randomly allocated to receive either palbociclib-letrozole or placebo plus letrozole. Patients were randomly assigned 2:1 via an interactive randomization technologysystem, stratified by disease site (visceral *vs* non-visceral), DFI since completion of prior (neo)adjuvant therapy (de novo metastatic *vs* ≤12 months *vs* >12 months), and nature of prior (neo)adjuvant anti-cancer treatment (prior hormonal therapy *vs* no prior hormonal

	therapy).
Eligibility criteria for participants	Inclusion criteria: • Women 18 years or older who had a proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease not amenable to resection or radiation therapy with curative intent, and for whom chemotherapy was not clinically indicated. • Patients had histologically or cytologically confirmed diagnosis of ER+/HER2- breast cancer documented in local laboratory results. • Patients had not received previous treatment with any systemic anti-cancer therapy for their locoregionally recurrent or metastatic ER-positive disease; • Patients were postmenopausal based on prior bilateral surgical oophorectomy, spontaneous cessation of regular menses for at least 12 consecutive months or levels of follicle-stimulating hormone and estradiol in the blood levels within postmenopausal ranges in the absence of alternative pathological or physiological causes. • Patients had measurable disease as defined per RECIST 1.1 or bone-only disease, with bone lesions confirmed by CT, MRI or bone X-ray. • Patients had ECOG performance status of 0-2. A full list of inclusion and exclusion criteria is presented below in Table 15.
Settings and locations where the data were collected	The study took place in a clinical trial setting, where the investigator had ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data. Self-administered questionnaires were completed by the patients while in the clinic and could not be taken home; instruments were to be completed prior to having any tests and to any discussion of their progress with healthcare personnel at the site. Interviewer administration in clinic could be used under special circumstances. The instruments were given to the patient in the appropriate language for the site.
Trial drugs and method of administration	The palbociclib-letrozole group (n = 444) received: palbociclib, 125mg, oral, once-daily for 3 weeks, followed by a week off in a 28-day cycle; as well as letrozole 2.5mg, oral, once-daily on a continuous daily dosing regimen. The placebo plus letrozole group (n = 222) received: placebo, oral, once-daily for 3 weeks, followed by a week off in a 28-day cycle; as well as letrozole 2.5mg, oral, once-daily on a continuous daily dosing regimen.
Permitted and disallowed concomitant medication	Permitted concomitant medication: • Standard therapies for preexisting medical conditions, medical and/or surgical complications, and palliation were permitted. Any medication intended solely for supportive care (e.g. analgesics, antidiarrhaeals, antidepressants) could also be used at the investigator's discretion. • Bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors could be continued for the treatment of osteoporosis or management of existing bone metastases in patients who had been receiving them at a stable dose for at least 2 weeks prior to randomisation. However, the need to initiate or increase the dose of these therapies during the study was considered indicative of disease progression, leading to the discontinuation of the patient from the active treatment phase, unless disease progression could be completely ruled out and the exact reason

	for the use of these therapies was clearly documented. • Primary prophylactic use of granulocyte colony-stimulating factors was not permitted but they could be used to treat treatment-emergent neutropenia, as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.[103] If neutropenic complications were observed in a cycle in which primary prophylaxis with colony-stimulating factors was not received, secondary prophylaxis could be given at the discretion of the investigator, but only if dose reduction or delay were not considered to be reasonable alternatives. Erythropoietin could be used at the investigator's discretion for supportive treatment of anaemia. • If necessary, local antacids could be given at least 2 hours before or after palbociclib/placebo administration. • H2-receptor antagonists, including but not limited to cimetidine, famotidine, nizatidine, and ranitidine could be used, so long as palbociclib/placebo dosing occurred at least 10 hours after the evening dose of H2-receptor antagonist and 2 hours before the morning dose of antagonist. • Concomitant medication not recommended: dexamethasone; herbal medicines; and chronic immunosuppressive therapies, including systemic corticosteroids. In contrast, steroids given for physiological replacement, as anti-emetics or inhaled, as well as short courses of oral/topical steroids given for allergic reactions or asthma flares were allowed. Disallowed concomitant medication: • No additional investigational or commercial anti-cancer agents, including chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy other than letrozole were permitted during the active treatment phase. In general, any drugs containing “for the treatment of breast cancer” on the product insert were not permitted on study. • Strong or moderate CYP3A inhibitors/inducers, including those listed below, were not permitted during the study: amprenavir, atazanavir, boceprevir, carbamazepine, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, felbamate, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, nevirapine, phenobarbital, phenytoin, posaconazole, primidone, rifabutin, rifampin, rifapentin, ritonavir, saquinavir, St. John’s Wort, suboxone, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit, • Drugs known to prolong the QT interval or to predispose to Torsade de Pointes were prohibited during the active treatment phase. • Topical estrogens (including any intra-vaginal preparations), megestrol acetate and selective ER modulators (e.g. raloxifene) were prohibited during the active treatment phase, • Proton-pump inhibitors were prohibited; these included, but were not limited to, the following: dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. Concomitant radiotherapy and surgery: • Any concurrent radiotherapy (except palliative radiotherapy as specified below) or cancer-related surgery was prohibited throughout the active treatment phase of the

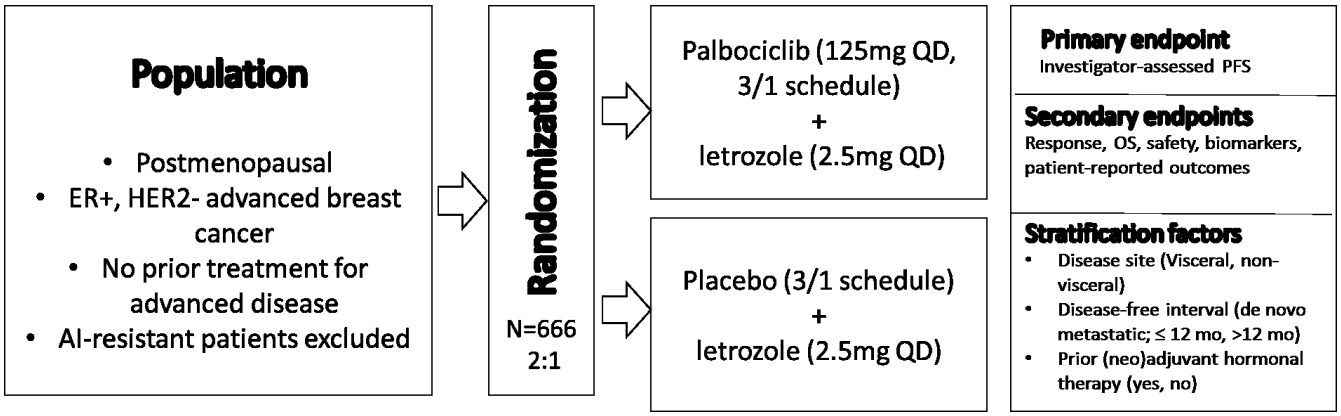
	study. Patients requiring any of these procedures were to be discontinued from the active treatment phase and entered in the follow-up phase. • Palliative radiotherapy was permitted for the treatment of painful bony lesions provided that the lesions were known to be present at the time of study entry and the investigator clearly documented that the need for palliative radiotherapy was not indicative of disease progression. • Palbociclib/placebo treatment was to be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment 1 week after. For patients with bone involvement, it was suggested to institute palliative radiotherapy before study initiation if possible and clinically appropriate (e.g. lesions at risk for spontaneous micro-fractures or painful lesions). Palliative radiotherapy during the active treatment phase was considered alternative cancer therapy and resulted in censoring of the PFS endpoint. • Caution was advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and palbociclib required to minimise the risk of impaired wound healing and bleeding has not been determined. Based on pharmacokinetics data available, stopping palbociclib/placebo was recommended at least 7 days prior to elective surgery. Postoperative decisions to reinitiate palbociclib/placebo treatment were based on clinical assessment of satisfactory wound healing and recovery from surgery.
Primary outcomes	Investigator-assessed PFS, defined as the time from randomisation to radiological disease progression or death on study. Documentation of progression was by objective disease assessment calculated from the lesion measurements, as defined by RECIST 1.1 Disease was assessed by CT or MRI of chest, abdomen, pelvis, bone lesions, and other clinically indicated sites; as well as clinical evaluation of superficial disease. This assessment was performed within 28 days prior to randomisation and every 12 weeks (±7 days) from the date of randomisation. Disease assessment was repeated at withdrawal or the end of treatment. Radiographic tumor assessments could be performed at any time, if deemed necessary by the investigator because of clinical suspicion of disease progression.
Secondary and other outcomes	• OR, DOR, CBR/DCR, OS, biomarker expression *vs* PFS • Patient-reported outcomes assessed using FACT-B and EQ-5D questionnaires • Safety – including type, incidence, severity, seriousness and relationship to study medications of adverse events and any laboratory abnormalities
Pre-planned subgroups for PFS	• Age (<65 years, ≥65 years) • Region (North America, Europe, Asia/Pacific) • Ethnicity (White, Asian) • Baseline ECOG (0 or 1/2) • Bone-only disease at baseline (yes, no) • Measurable disease (yes, no) • Disease site (visceral, non-visceral) • Previous chemotherapy (yes, no) • Previous endocrine therapy (yes, no) • Most recent therapy (aromatase inhibitor, anti-estrogen) • DFI (≤12 months, >12 months, de novo) • Number of disease sites involved (1, 2, ≥3)
Duration of study and follow-up	Between 28 February 2013 and 29 July 2014, 666 women were randomised to treatment groups. The study achieved its primary endpoint when 347 PFS events had occurred, which was calculated to allow 90% power to detect an HR of 0.69 using a one-sided, log-rank test at a

	significance level of 0.025. Median duration of follow-up, defined as the months from randomisation to the last contact (if alive) or death was 23.0 months (95%CI 22.6 to 23.4) in the palbociclib-letrozole arm and 22.3 months (95% CI 21.9 to 22.9) in the placebo plus letrozole arm. All PALOMA-2 data presented in this submission correspond to the data cut-off date of 26 February 2016.

Abbreviations: ABC, advanced or metastatic breast cancer; ASCO, American Society of Clinical Oncology; BCS, breast cancer subscale; CBR, complete biological response; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DFI, disease-free interval; DOR, duration of response; EQ-5D, EuroQoL-5D questionnaire; EQ-VAS, EuroQoL-5D Visual Acuity Scale; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-B, Functional Assessment of Cancer Therapy-Breast; GCSF, granulocyte colony-stimulating factor; HER2, human epidermal growth factor receptor 2; mBPI-sf, modified Brief Pain Inventory Short Form; MRI, magnetic resonance imaging; OR, objective response; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression; US, United States of America.

The methodology is also depicted graphically in Figure 6.

Figure 6. PALOMA-2 study design[9]



Abbreviations: QD, Once daily

Table 15. Eligibility criteria for PALOMA-2[9]

Inclusion criteria	Exclusion criteria
• Women 18 years or older who had a proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease not amenable to resection or radiation therapy with curative intent, and for whom chemotherapy was not clinically indicated. • Patients had histologically or cytologically confirmed diagnosis of ER-positive breast cancer documented in local laboratory results. • Patients had not received previous treatment with any systemic anti-cancer therapy for their locoregionally recurrent or metastatic ER-positive disease; • Patients were postmenopausal based on prior bilateral surgical oophorectomy, spontaneous cessation of regular menses for at least 12 consecutive months or levels of follicle-stimulating hormone and estradiol in the blood levels within postmenopausal ranges in the absence of alternative pathological or physiological causes. • Patients had measurable disease as defined per RECIST 1.1 or bone-only disease, with bone lesions confirmed by CT, MRI or bone X-ray. Tumor lesions previously irradiated or subjected to other locoregional therapy were deemed measurable only if disease progression at the treated site after completion of therapy had been clearly documented. • Patients had ECOG performance status of 0-2. • Patients had adequate organ and marrow function, defined as an absolute neutrophil count ≥1,500/mm^3 (1.5 x 10^9/L), platelet count ≥100,000/mm^3 (100 x 10^9/L), haemoglobin ≥9 g/dL (90 g/L), serum creatinine ≤1.5 times the upper limit of normal (ULN) (or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution), total serum bilirubin ≤1.5 times the ULN (≤3.0 times the ULN if Gilbert's disease present), AST and/or ALT ≤3 times the ULN (≤5.0 times the ULN if liver metastases present), and alkaline phosphatase ≤2.5 times the ULN (≤5.0 times the ULN if bone or liver metastases present). • All acute toxic effects in patients due to prior anti-cancer therapy or surgical procedures had been resolved to National Cancer Institute CTCAE (version 4.0) Grade ≤1, except alopecia or other toxicities not considered by the investigator to pose a safety risk to the patient. • Patients were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. • Patients agreed to provide tumor tissues for centralised retrospective	• Patients had HER2-positive tumours as defined by documentation of erbB-2 gene amplification based on fluorescent in situ hybridisation (FISH) (defined as a HER2/CEP17 ratio ≥2), chromogenic in situ hybridisation (CISH) (defined as per the manufacturer's kit instructions), INFORM HER2 dual in situ hybridisation (defined as per the manufacturer's kit instructions), or documentation of HER2-overexpression by immunohistochemistry (IHC) (defined as IHC3+ or IHC2+ with FISH or CISH confirmation) based on local laboratory results using a Sponsor-approved assay. If HER2 status was unavailable or was determined using a test other than a Sponsor-approved assay, then testing had to be performed using an approved assay prior to randomisation. If tissue samples were available for both primary and recurrent/metastatic tumours, then HER2 assessment from the most recent sample (i.e. recurrent/metastatic sample) was used to define eligibility whenever feasible. • Patients with advanced, symptomatic, visceral spread, who were at risk of life-threatening complications in the short term, including patients with massive uncontrolled effusions (pleural, pericardial, peritoneal), pulmonary lymphangitis, and >50% liver involvement. • Patients with known active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral oedema, and/or progressive growth. Patients with a history of CNS metastases or cord compression were eligible if they had been definitively treated with local therapy (e.g. radiotherapy, stereotactic surgery) and had remained clinically stable off anticonvulsants and steroids for at least 4 weeks before randomisation. • Patients who had previously received prior neoadjuvant or adjuvant treatment with anastrozole or letrozole and who had suffered disease recurrence while on or within 12 months of completing treatment. • Patients who had previously been treated with any CDK4/6 inhibitor. • Patients who had been treated with any of the following within 7 days prior to randomisation: food or drugs known to be CYP3A4 inhibitors (i.e. amprenavir, atazanavir,boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit or

Inclusion criteria	Exclusion criteria
confirmation of ER status and to evaluate correlation among genes, proteins, and RNAs relevant to cell cycle pathways and sensitivity/resistance to investigational agents. Freshly biopsied samples of recurrent/metastatic tumours had to be provided whenever possible. If such a biopsy was not feasible or could not be safely performed, then an archived tumour sample could be accepted. In either case, a formalin-fixed, paraffin-embedded (FFPE) block or 12 unstained FFPE slides were required for patient participation. • Patients had signed and dated an archived informed consent document indicating that the patient (or a legal representative) had been informed of all pertinent aspects of the study before any study-specific activity was performed.	grapefruit juice); drugs known to be CYP3A4 inducers (i.e. carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort); and drugs known to prolong the QT interval • Patients who had undergone major surgery, chemotherapy, or radiotherapy, or who had received any investigational agents or other anti-cancer therapy within 2 weeks before randomisation. Patients who received prior radiotherapy to ≥25% of bone marrow were not eligible, regardless of when it had been administered. • Patients who had been diagnosed with any other malignancy within 3 years prior to randomisation, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix. • Patients who had QTc >480 msec (based on the mean value of triplicate electrocardiograms), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes. • Patients with uncontrolled electrolyte disorders that might compound the effects of a QTc-prolonging drug, such as hypocalcaemia, hypokalaemia, or hypomagnesaemia. • Patients who experienced any of the following within 6 months of randomisation: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of CTCAE (version 4.0) Grade ≥2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism. • Patients with active inflammatory bowel disease or chronic diarrhaea, short bowel syndrome, or any upper gastrointestinal surgery, including gastric resection. • Patients with known hypersensitivity to letrozole or any of its excipients, or to any palbociclib/placebo excipients. • Patients known to be infected with the human immunodeficiency virus. • Patients with other severe acute or chronic medical or psychiatric conditions or laboratory abnormalities that might increase the risk associated with study participation or study drug administration, or that might interfere with the interpretation of study results and that make study participation inappropriate for the patient in the judgment of the investigator. • Patients who were staff members or relatives of staff members at the investigational site, or who were Pfizer employees directly involved in the conduct of the study. • Patients who were participating in phase I-IV studies involving other investigational drug(s) within 2 weeks before randomisation and/or during

Inclusion criteria	Exclusion criteria
	participation in the active treatment phase of the study. • Patients who had recent or active suicidal ideation or behaviour.

Abbreviations: ABC, advanced or metastatic breast cancer; CDK, cyclin-dependent kinase; CDK4/6, cyclin-dependent kinase 4/6; CISH, chromogenic in situ hybridisation; CNS, central nervous system; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; CYP3A4, cytochrome P450 3A4; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; FFPE, formalin-fixed, paraffin-embedded; FISH, fluorescence in situ hybridisation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MRI, magnetic resonance imaging; QT, time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal.

4.3.2.1. Description of outcomes reported in PALOMA-2

The definitions and methods of assessment of the primary and secondary outcomes reported in PALOMA-2 are provided in Table 16.

PFS was the primary outcome in PALOMA-2, and several secondary efficacy outcomes were as described in Table 16. Most secondary outcomes were assessed on the same schedule as disease assessment. Safety was assessed in terms of recording of adverse events within 28 days of initiation of study treatment, on days 1 and 14 of cycles 1-2 and on day 1 of every subsequent treatment cycle, at withdrawal or end of treatment and during follow-up.

Table 16. Description of outcomes reported in PALOMA-2[9]

Outcome	Description
Primary efficacy outcome	
PFS	Time from randomisation to radiological disease progression or death on study. Documentation of progression was by objective disease assessment calculated from the lesion measurements, as defined by RECIST 1.1
Secondary efficacy outcomes	
OR	Defined according to RECIST 1.1 from the lesion measurements
CBR	Defined as per RECIST 1.1 as complete response, partial response or stable disease lasting at least 24 weeks
OS	Time from the date of randomisation to the date of all-cause death. Patients last known to be alive were censored at date of last contact. Kaplan-Meier analysis was used to estimate OS probability.
DOR	Time from first documentation of complete or partial response to date of first documentation of objective progression or death. This outcome was calculated only for patients who showed complete or partial response.
PROs	Breast cancer specific health-related quality of life was assessed using FACT-B. Generic HRQL and general health status was assessed using EQ-5D. Patients were to complete each instrument pre-dose on [redacted]
Biomarkers	Expression of ER, pRb, cyclin D1, p16, and Ki67 were analyzed retrospectively using validated immunohistochemistry assays
Safety	
Safety	Type, incidence, severity, seriousness of adverse events, their relationship to study medications and any laboratory abnormalities. Adverse events were classified using the MedDRA classification system 18.1. Severity of events was graded according to the CTCAE 4.0 whenever possible.

Abbreviations: CBR, complete biological response; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; EQ-5D, EuroQoL-5D questionnaire; EQ-VAS, EuroQoL-5D Visual Acuity Scale; FACT-B, Functional Assessment of Cancer Therapy B questionnaire; mBPI-sf, modified Brief Pain Inventory Short Form; OR, objective response; OS, overall survival; PFS, progression-free survival; pRb, retinoblastoma susceptibility gene product; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression.

4.3.3. Comparative methodology of the PALOMA RCTs

Table 17. Comparative summary of PALOMA-1 and PALOMA-2 methodologies [3, 9]

	PALOMA-1	**PALOMA-2**
Location	50 sites in Canada, France, Germany, Hungary, Ireland, Italy, Russia, South Africa, South Korea, Spain, Ukraine, USA	186 sites in Australia, Belgium, Canada, France, Germany, Hungary, Ireland, Italy, Japan, Republic of Korea, Poland, Russian Federation, Spain, Taiwan, Ukraine, UK (7 sites), USA
Trial design	Phase 2, multicentre, randomised, open-label, placebo-controlled	Phase 3, multicentre, randomised, double-blind, placebo-controlled
Inclusion criteria	Postmenopausal women with ER+/HER2- ABC who did not receive prior systemic treatment for ABC Measurable disease by RECIST or bone-only disease. Adequate organ function and ECOG status of 0 or 1.	Postmenopausal women with ER+/HER2- ABC who did not receive prior systemic treatment for ABC Measurable disease by RECIST or bone-only disease. Adequate organ function and ECOG status of 0-2.
Exclusion criteria	• Previous treatment with letrozole as (neo)adjuvant therapy ≤12 months before study entry • Any previous treatment for advanced breast cancer or previous CDK inhibitor therapy or brain metastasis	• Previous systemic anticancer treatment for advanced disease • DFI ≤12 months after (neo)adjuvant treatment with letrozole or anastrozole
Concomitant medications	None	
Data collection setting	Secondary health care facility (dispensed from hospital pharmacy)	
Intervention and comparators	*Intervention:* Oral letrozole 2.5 mg once daily + oral palbociclib 125 mg once daily for 3-week on/1-week off (n = 84) *Comparator:* Oral letrozole 2.5 mg once daily (n = 81)	*Intervention:* Oral letrozole 2.5 mg once daily + oral palbociclib 125 mg once daily for 3-week on/1-week off (n = 444) *Comparator:* Oral letrozole 2.5 mg once daily (n = 222) + oral placebo once daily for 3-week on/1-week off
Primary outcomes	Investigator-assessed PFS	
Secondary outcomes	OR, CBR, OS, PROs (pain severity and interference using mBPI-sf), DOR, TTP, Safety	OR, CBR, OS, DOR, PROs: breast cancer specific and generic HRQL using FACT-B and EQ-5D), Biomarker expression vs PFS, Safety

	PALOMA-1	PALOMA-2
Pre-planned subgroups for PFS	• Age (<65 years, ≥65 years) • Baseline ECOG (0 or 1) • Disease site (visceral, bone only, other) • Previous chemotherapy (yes, no) • Previous endocrine therapy (yes, no) • Previous systemic therapy (yes, no) • Previous chemotherapy only (yes, no) • Previous chemotherapy and endocrine therapy (yes, no) • DFI (≤12 months, ≤12 months + de novo, >12 months; ≤5 years, >5 years) • Biomarker status (positive, negative, unknown) • Region (North America, Europe) • Histopathological grade (1/2, 3) • Progesterone receptor (positive, negative) • Number of disease sites involved (<2, ≥2) • De novo advanced disease (yes, no)	• Age (<65 years, ≥65 years) • Region (North America, Europe, Asia/Pacific) • Ethnicity (White, Asian) • Baseline ECOG (0 or 1/2) • Bone-only disease at baseline (yes, no) • Measurable disease (yes, no) • Disease site (visceral, non-visceral) • Previous chemotherapy (yes, no) • Previous endocrine therapy (yes, no) • Most recent therapy (aromatase inhibitor, anti-estrogen) • DFI (≤12 months, >12 months, de novo) • Number of disease sites involved 1, 2, ≥3) • Biomarker expression (yes/no *or* low/high)

Abbreviations: ABC, advanced breast cancer; CBR, complete biological response; CDK, cyclin-dependent kinase; DFI, disease-free interval; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HRQL, health-related quality of life; OR, objective response; OS, overall survival; PFS, progression-free survival; pRb, retinoblastoma susceptibility gene product; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumors; mBPI-sf, Modified Brief Pain Inventory.

4.4. Statistical analysis and definition of study groups in the relevant randomised controlled trials

The study populations used for different types of outcomes analysis are summarised for the two PALOMA trials in Table 18.

Table 18. Summary of populations used in PALOMA-1 and PALOMA-2 [3, 9]

Type of analysis	Study population
Efficacy analyses (primary and secondary)	The intention-to-treat population was the primary population for evaluating all efficacy endpoints and patient characteristics. This population included all randomised patients.
Analysis of PROs	PALOMA-1: All analyses were performed on the PRO evaluable population i.e. all randomised patients who completed the baseline PRO assessment, received at least one dose of study treatment, and completed at least one post-baseline PRO assessment. PALOMA-2: Completion rates are reported for the ITT population, all

	other analyses were performed on the PRO evaluable population i.e. patients who completed a baseline assessment and at least one post-baseline assessment. See sections 0 and 4.7.2.3 for the proportion of patients completing PRO assessments in evaluable populations.
Safety analyses	The as-treated 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.
Biomarker analyses	The subset of as-treated patients for which baseline assessment of at least one biomarker was available.

Abbreviation: PRO, patient-reported outcome

Details about statistical analysis in the two RCTs are summarised in Table 19 for the primary outcome of PFS and in Table 20 for secondary outcomes.

Table 19. Summary of statistical analysis and data management for the primary outcome of PFS in PALOMA-1 and PALOMA-2 [3, 9]

PALOMA	Hypothesis	Statistical analysis	Sample size	Data management
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CR, complete response; DFI, disease-free interval; H0, null hypothesis; HA, alternative hypothesis; HR, hazard ratio; PFS, progression-free survival; PR, partial response

Table 20. Summary of statistical analysis for secondary outcomes in PALOMA-1 and PALOMA-2[3, 9]

Trial	Secondary outcome	Statistical analysis
PALOMA-1	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

Trial	Secondary outcome	Statistical analysis
		[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
PALOMA-2	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CBR, clinical benefit response; CR, complete response; DOR, duration of response; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, EuroQol Group 5-Dimension Self-Report Questionnaire; HR, hazard ratio; HRQL, health-related quality of life; OR, objective response; OS, overall survival; PFS, progression-free survival; PR, partial response; pRb, retinoblastoma stability gene product; SD, stable disease; PRO, patient-reported outcome; TTP, time to progression

Details about interim analyses, stopping guidelines and subgroup analyses are reported separately for each of the PALOMA trials in the subsections below.

4.4.1. PALOMA-1

4.4.1.1. Interim analyses and stopping guidelines

At the time enrolment was stopped, 165 patients had been randomised into the trial: 66 to cohort 1 and 99 to cohort 2. This sample size had been estimated to provide 80% power to detect an HR of 0.67 based on 114 PFS events, based on the assumption that palbociclib-letrozole would prolong PFS from 9 months (letrozole alone) to 13.5 months. After 57 PFS events had occurred across both cohorts, the study protocol was amended to include a second interim analysis. This interim analysis was undertaken after 61 events had occurred: HR for PFS in the intention-to-treat population was 0.37 (95%CI 0.21 to 0.63, one-sided $p < 0.0001$). Because events were being observed at a slower pace than anticipated, another protocol adjustment was conducted stipulating that final analysis would be performed after 95 PFS events had accumulated. This would give >98% power to detect an HR of 0.50 at a one-sided α of 0.10, or 75% power to detect an HR of 0.67.

No stopping guidelines were stipulated in PALOMA-1; interim analyses were included for the purposes of obtaining information and to inform phase 3 study design rather than for establishing early stopping of the trial.

4.4.1.2. Statistical methods for between-group comparisons

Based on the interim analyses, the significance level for the final analysis was adjusted using the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary. PFS was compared between treatment groups using a stratified log-rank test with stratification for site of disease, DFI, and study cohort (1 or 2). HRs were estimated using the Cox proportional hazards regression model; the proportionality of hazards assumption was verified as part of the trial analysis, and results were satisfactory.[24] In Section 5.3.1, the proportional hazards assumption is tested as part of the assessment of survival for the economic model (see Figure 19 and Figure 20). Multivariate Cox regression was used to explore the effects of prespecified baseline prognostic factors on PFS (Table 19).

The rate of OR (CR or PR) was reported together with an exact 95% CI calculated based on the Clopper-Pearson method; between-group comparisons were performed using a stratified OR and 95%CI. A similar approach was adopted for the outcome CBR. OS and TTP were compared between groups using the Kaplan-Meier method and log-rank test (one-sided p value).

4.4.1.3. Methods for additional analyses: subgroup analyses

The same methods were used as for the between-group comparisons described above.

4.4.2. PALOMA-2

4.4.2.1. Interim analyses and stopping guidelines

This trial was designed to have one interim analysis, during which the Haybittle-Peto efficacy boundary[1] for rejecting the null hypothesis was used. Interim analysis of PFS was to be performed after at least 226 patients (approximately 65% of total events expected) had documented progressive disease or died. The overall significance level for the efficacy analysis of PFS was preserved at 0.025 (1-sided test). The interim analysis was conducted in October 2015 when 236 PFS events had occurred, corresponding to approximately 68% of the expected events for the study. At this time point, the external data monitoring committee recommended continuation of the study, which Pfizer accepted. Pfizer remained blinded to the results of the interim analysis.

No stopping guidelines were stipulated in PALOMA-2.

4.4.2.2. Statistical methods for between-group comparisons

PFS was analysed in the intention-to-treat population using the Kaplan-Meier method. A stratified log-rank test was used to compare PFS between treatment arms. PFS analyses in subgroup populations were performed to evaluate the consistency across stratification factors and other baseline patient characteristics. Univariate analyses were further conducted to explore the potential influence of baseline factors on primary endpoint of PFS. A multivariate analysis was performed to explore potential prognostic factors, using a Cox proportional hazard model. To protect the family-wise error rate at a level of 0.025, hierarchical group sequential testing was performed with an error spending function at a level of 0.025.

OS was to be hierarchically tested for significance at the time of PFS analysis, provided the primary PFS endpoint was statistically significant at the PFS analysis. As for PFS, hierarchical group sequential testing of OS was performed with an error spending function at a level of 0.025 in order to protect the family-wise error rate at a level of 0.025. A stratified log-rank test using the same stratification factors as for the PFS analysis was to be used to compare OS between the treatment arms.

Blinded independent central review (BICR) of radiology results for all patients was conducted by an external vendor to assess PFS. BICR of CBR, OR and DOR was also conducted for all patients, as well as for the subset of patients with measurable disease at baseline.

4.4.2.3. Methods for additional analyses: subgroup analyses

The same methods were used as for the between-group comparisons described above.

[1] A modification for the interim analysis was proposed to, and agreed with FDA to increase the stringency of the efficacy stopping boundary in the interim analysis to ensure that the results were not only statistically significant but also clinically meaningful. Specifically, the efficacy stopping boundary was changed from O'Brien-Fleming to the Haybittle-Peto approach. A p-value of 0.000013 was to be used as the efficacy boundary for interim analysis. The overall significance level for the efficacy analysis of PFS was preserved at 0.025 for the 1-sided test.

4.5. Participant flow in the relevant randomised controlled trials

The baseline characteristics of patients randomly assigned to treatment arms in the two PALOMA trials are summarised in Table 21. Baseline characteristics were well balanced between the two groups, although there were slight imbalances in disease site, disease-free interval, and previous treatment these difference were not considered to be of clinical significance by consulted UK clinicians at an advisory board. [4, 9].

Table 21. Summary of baseline characteristics of patients in the two PALOMA trials [4, 9]

Trial	Palbociclib treatment	Comparator treatment
PALOMA-1 (A5481003) (n = 165)	**Palbociclib-letrozole (n = 84)**	**Letrozole (n = 81)**
Median age, years	63 (54-71)	64 (56-70)
ECOG performance status		
0	46 (55%)	45 (56%)
1	38 (45%)	36 (44%)
Disease stage		
III	2 (2%)	1 (1%)
IV	82 (98%)	80 (99%)
Disease site		
Visceral	37 (44%)	43 (53%)
Bone only	17 (20%)	12 (15%)
Non-visceral	30 (36%)	26 (32%)
DFI*		
>12 months	25 (30%)	30 (37%)
≤12 months or de novo advanced disease	59 (70%)	51 (63%)
de novo advanced disease only	44 (52%)	37 (46%)
Previous systemic treatment		
None	44 (52%)	37 (46%)
Chemotherapy	34 (40%)	37 (46%)
Hormonal	27 (32%)	28 (35%)
Tamoxifen	24 (29%)	24 (30%)
Anastrozole	8 (10%)	11 (14%)
Letrozole	2 (2%)	1 (1%)
Exemestane	4 (5%)	2 (2%)
PALOMA-2 (A5481008) (n = 666)	**Palbociclib-letrozole (n = 444)**	**Placebo plus letrozole (n = 222)**
Median age, years	62 (range, 30-89)	61 (range, 28-88)
Ethnicity		
White	344 (77.5%)	172 (77.5%)
Black	8 (1.8%)	3 (1.4%)
Asian	65 (14.6%)	30 (13.5%)
Other	27 (6.1%)	17 (7.7%)
Region		
North America	168 (37.8%)	99 (44.6%)
Europe	212 (47.7%)	95 (42.8%)
Asia/Pacific	64 (14.4%)	28 (12.6%)
ECOG performance status		
0	257 (57.9%)	102 (45.9%)
1	178 (40.1%)	117 (52.7%)

2	9 (2.0%)	3 (1.4%)
Disease site		
Visceral	214 (48.2%)	110 (49.5%)
Non-visceral	230 (51.8%)	112 (50.5%)
Measurable disease at baseline		
Yes	338 (76.1%)	171 (77.0%)
No	106 (23.9%)	51 (23.0%)
DFI*		
>12 months	178 (40.1%)	93 (41.9%)
≤12 months	99 (22.3%)	48 (21.6%)
de novo advanced disease	167 (37.6%)	81 (36.5%)
Prior hormonal therapy in (neo)adjuvant treatment		
Yes	249 (56.1%)	126 (56.8%)
No	195 (43.9%)	96 (43.2%)
Prior chemotherapy for primary diagnosis in (neo)adjuvant treatment		
Yes	213 (48.0%)	109 (49.1%)
No	231 (52.0%)	113 (50.9%)
Most recent hormonal therapy		
Aromatase inhibitor	91 (36.5%)	44 (34.9%)
Anti-oestrogen	154 (61.8%)	75 (59.5%)
Other	4 (1.6%)	7 (5.6%)

Unless noted otherwise, data are n (%) or median (interquartile range).

* Defined as time from completion of adjuvant treatment to recurrence

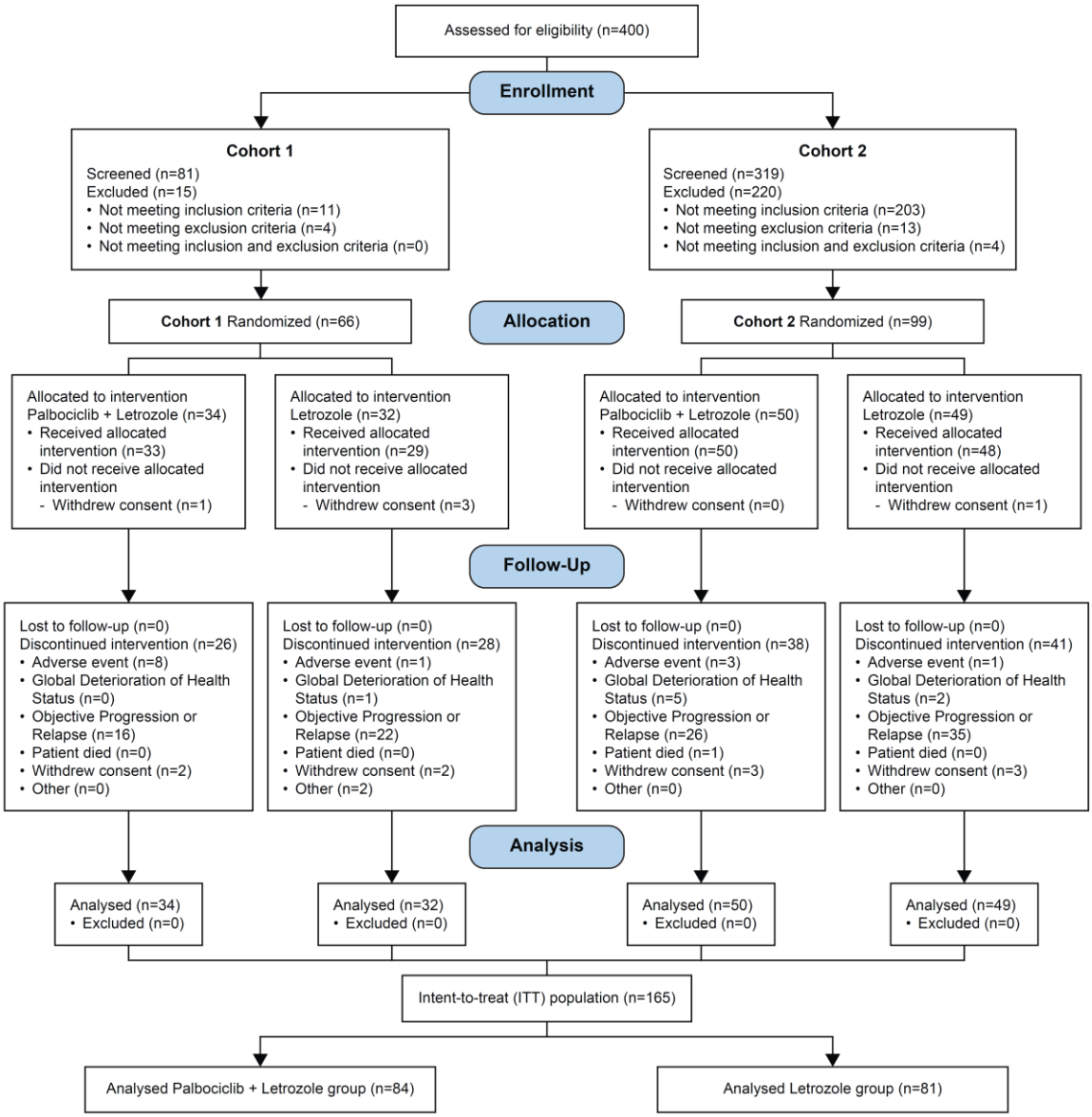
Abbreviations: DFI, disease-free interval; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; IQR, interquartile range; PR, progesterone receptor; SD, standard deviation

In the subsections below, details of participant flow are discussed for each of the PALOMA trials separately.

4.5.1. PALOMA-1

The flow of patients through PALOMA-1 is shown in a CONSORT diagram inFigure 7.[4] Of 400 patients initially assessed for eligibility, 165 were found to meet the inclusion criteria and none of the exclusion criteria and so were randomised into one of the treatment arms and included in the intention-to-treat population. No crossover was allowed in this trial. Nearly all participants who discontinued intervention did so because of objective progression or relapse (n=99/133), and a smaller number did so because of adverse events (n=13/133) or global deterioration of health status (n=8/133). A few patients in each treatment arm withdrew consent (n=10/133).

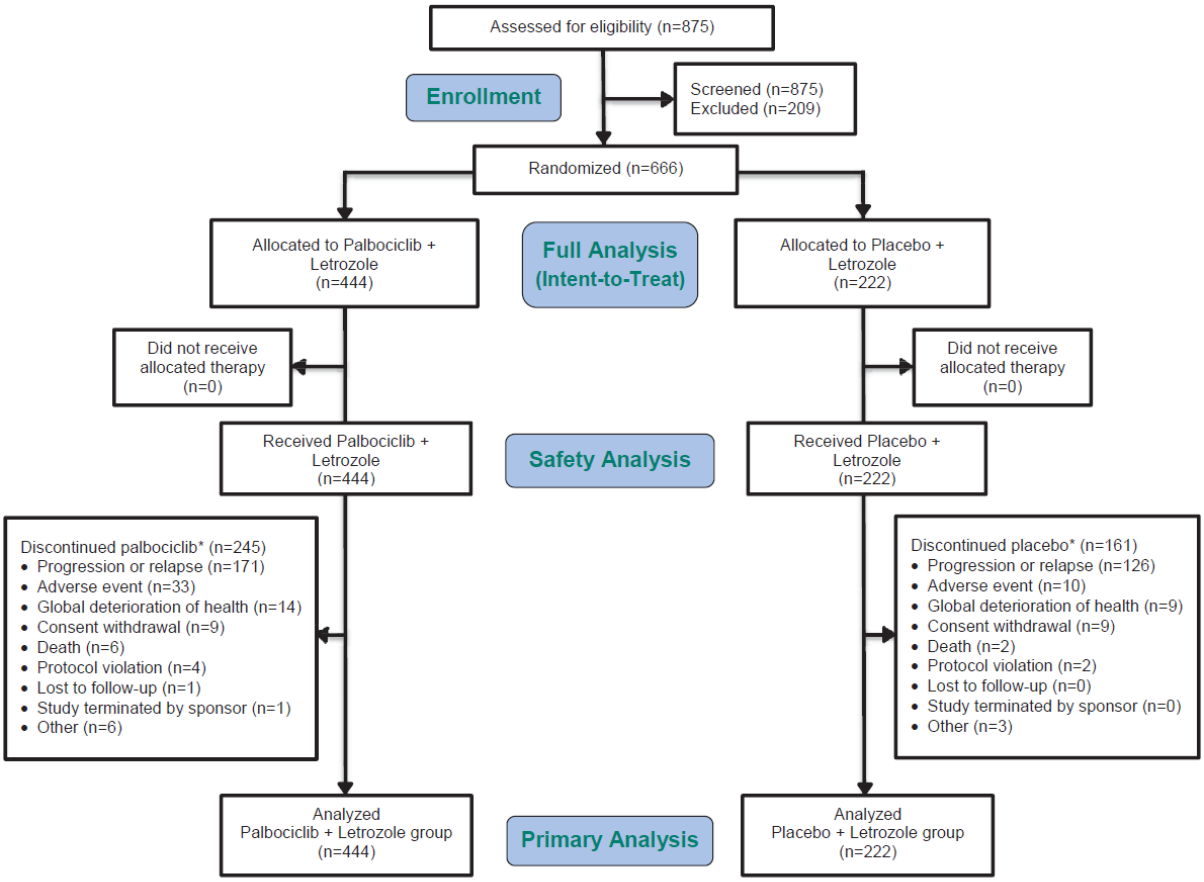
Figure 7. Patient flow through the PALOMA-1 trial [4]



4.5.2. PALOMA-2

The flow of patients through PALOMA-2 is shown in a CONSORT diagram in Figure 8. Of all patients initially assessed for eligibility, 666 were found to meet all the inclusion criteria and none of the exclusion criteria and so were randomised into treatment arms receiving palbociclib-letrozole (n = 444) or placebo plus letrozole (n = 222). No crossover was allowed in this trial. The majority of participants who discontinued intervention did so because of objective progression or relapse (n=297/406), and a smaller number did so because of adverse events (n=43/406) or global deterioration of health status (n=23/406). A few patients in each treatment arm withdrew consent.

Figure 8. Patient flow through the PALOMA-2 trial



*Patients who discontinued palbociclib or placebo could continue to receive letrozole alone.

4.6. Quality assessment of PALOMA-1 and PALOMA-2

The PALOMA trials are rigorously designed RCTs based on pre-specified study protocols. Their quality assessment is summarised in Appendix 8.

4.7. Clinical effectiveness results of the relevant randomised controlled trials

Treatment with palbociclib-letrozole resulted in significantly longer median PFS in women with ABC compared to letrozole alone

- In PALOMA-1 the median PFS in the ITT population for the palbociclib-letrozole group compared to the letrozole group was 20.2 months vs 10.2 months (HR 0.488; 95%CI 0.319 to 0.748; p = 0.0004).

- In PALOMA-2 the median PFS in the ITT population for the palbociclib-letrozole group compared to the placebo-letrozole group was 24.8 months vs 14.5 months (HR 0.576; 95%CI 0.463 to 0.718; p < 0.000001).

Treatment with palbociclib-letrozole resulted in higher OR rate and significantly higher CBR rate in women with ABC than letrozole alone

- In PALOMA-1, OR rate was higher among ITT patients who received palbociclib-letrozole (43%, 95%CI 32 to 54) than among those who received letrozole alone (33%, 95% CI 23 to 45). CBR rate was significantly higher among ITT patients who received palbociclib-letrozole (81%, 95%CI 71 to 89) than among those who received letrozole alone (58%, 95%CI 47 to 69; one-sided p = 0.0009).

- PALOMA-2: OR rate was higher among ITT patients who received palbociclib-letrozole (42.1%, 95%CI 37.5 to 46.9) than among those who received letrozole-placebo (34.7%, 95%CI 28.4 to 41.3). CBR rate was significantly higher among patients who received palbociclib-letrozole (84.9%, 95%CI 81.2 to 88.1) than among those who received placebo-letrozole (70.3%, 95%CI 63.8 to 76.2), corresponding to an odds ratio of 2.39 (95%CI 1.58 to 3.59).

- In PALOMA-2, the number of OS events did not meet the threshold allowing for an interim analysis to be conducted. These data will be analysed on an event driven basis however are unlikely to show differences in OS due to confounding caused by multiple treatment lines following disease progression. In PALOMA-1, treatment with palbociclib+letrozole was associated with a trend toward improved OS in women with ABC compared to letrozole alone. Palbociclib+letrozole showed a trend for improved OS relative to letrozole alone (HR 0.813, 95%CI 0.492 to 1.345) based on analysis of immature OS data (61 deaths among 165 patients).

In the PRO evaluable population, addition of palbociclib to letrozole maintained health-related quality of life with no significant difference compared with letrozole alone.

- In PALOMA-1 palbociclib-letrozole was associated with no decrement in pain severity and pain interference with daily activities (based on the mBPI-sf) relative to letrozole alone, both among all patients as well as in the subgroup of patients with bone metastases at baseline.

[redacted]

The PALOMA-1 and PALOMA-2 trials provide strong evidence that in postmenopausal women with HR+/HER2- ABC not previously treated with systemic therapy for advanced disease, palbociclib acts synergistically with letrozole to provide significantly longer PFS and higher ORR than letrozole alone, a manageable toxicity profile and no significant change in pain compared to letrozole alone. The PFS improvement of 10.3 months associated with adding palbociclib to letrozole is longer than the benefit associated with therapy improvements reported previously for women with ABC or metastatic breast cancer .[35-39, 109, 110] In context, across all other appraisals for metastatic breast cancer that have been appraised by NICE and had final appraisal determination, no intervention has been associated with greater than a 6 month improvement in PFS in its pivotal RCTs (TA23, TA30, TA54, TA62, TA116, TA214, TA239, TA250, TA257, TA263, TA295, TA371). With double-digit improvements in PFS, palbociclib offers truly extraordinary benefits, the likes of which have not been seen before in ABC.

4.7.1. PALOMA-1

An overview of the key clinical effectiveness results reported in PALOMA-1 is presented in Table 22. Primary and secondary efficacy outcomes by treatment group are discussed further in subsequent sections.

Table 22. Overview of clinical effectiveness results in PALOMA-1*[3]

Outcome	Palbociclib-letrozole (n = 84)	Letrozole (n = 81)
PFS		
Median PFS, months (95%CI) – investigator assessment	20.2 (13.8 to 27.5)	10.2 (5.7 to 12.6)
HR (95%CI) for progression or death – investigator assessment	0.488 (0.319 to 0.748, one-sided p = 0.0004)	
Median PFS, months (95%CI) – BICR**	25.7 (17.7 to NE)	14.8 (9.3 to 20.4)
HR (95%CI) for progression or death – BICR	0.621 (0.378 to 1.019, one-sided p = 0.0286)	
Tumour response		
ORR, % (95%CI)	43 (32 to 54)	33 (23 to 45), p between arms = 0.13
ORR, % (95%CI) – patients with measurable disease	55 (43 to 68)	39 (28 to 52), one-sided p between arms = 0.047
CBR, % (95%CI)	81 (71–89)	58 (47–69), p between arms = 0.0009
Stable disease lasting at least 24 weeks	38.1	24.7
TTP		
Median TTP, months – investigator assessment	20.2	10.2
HR (95%CI) for progression – investigator assessment	0.399 (0.265-0.601, stratified log-rank p<0.0001)	
Median TTP, months – BICR	25.7	14.8
HR (95%CI) for progression – BICR	0.621 (95%CI 0.378 to 1.019, stratified log-rank p=0.0286)	
OS		
Median OS, months (95%CI)	37.5 (28.4-not reached)	33.3 (26.4-not reached)
HR (95%CI) for death	0.813 (0.492 to 1.345, stratified 1-sided p = 0.2105)	

p-value <0.001

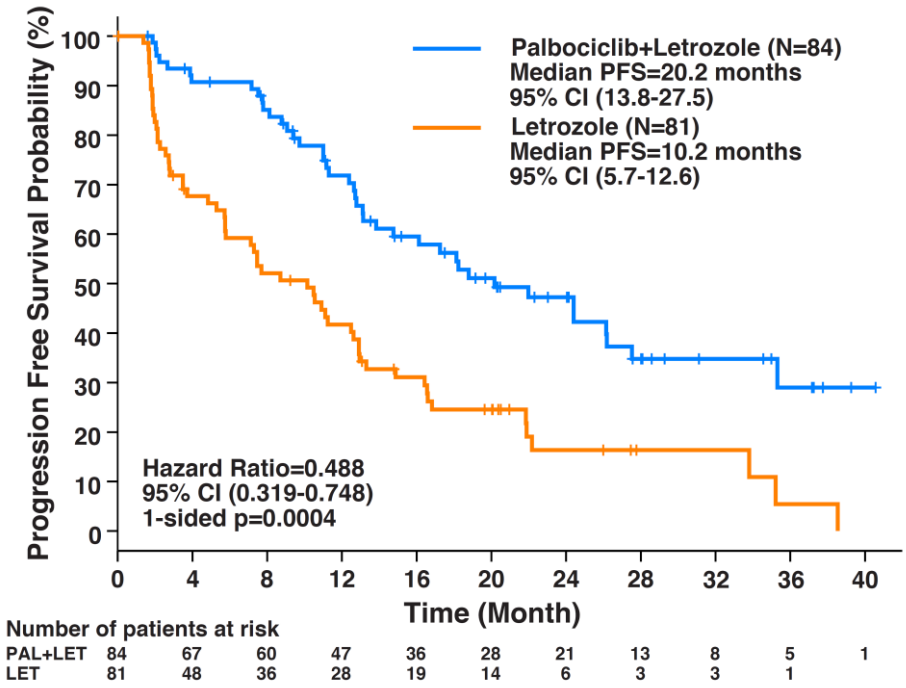
Abbreviations: BICR, blinded independent central review; CBR, clinical benefit response; HR, hazard ratio; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression
*Results refer to the intention-to-treat population unless otherwise noted.
**BICR was conducted on 97% of the intention-to-treat population.

4.7.1.1. Primary efficacy outcome results in PALOMA-1

Progression-free survival (PFS) was significantly prolonged with palbociclib-letrozole versus letrozole alone.

PALOMA-1 met its primary endpoint demonstrating a significant improvement in prolonging PFS with palbociclib-letrozole versus letrozole alone (Table 22). The Kaplan-Meier curve for the analysis of PFS (Figure 9) shows that the curves diverged early for the two treatment arms and was sustained this was considered to be important by clinicians as it demonstrates the early benefit of palbociclib plus letrozole compared to letrozole alone in delaying progression. Treatment with palbociclib-letrozole resulted in significantly longer PFS (20.2 months, 95%CI 13.8 to 27.5) than letrozole alone (10.2 months, 95%CI 5.7 to 12.6), corresponding to HR 0.488, 95%CI 0.319 to 0.748 (one-sided p = 0.0004).[4] This translated to an improvement in median PFS of 10 months for the combination therapy (Figure 9). Retrospective BICR of 97% of patients indicated a similar PFS benefit (Table 22).

Figure 9. Investigator-assessed PFS for the intention-to-treat study population in PALOMA-1 [4]

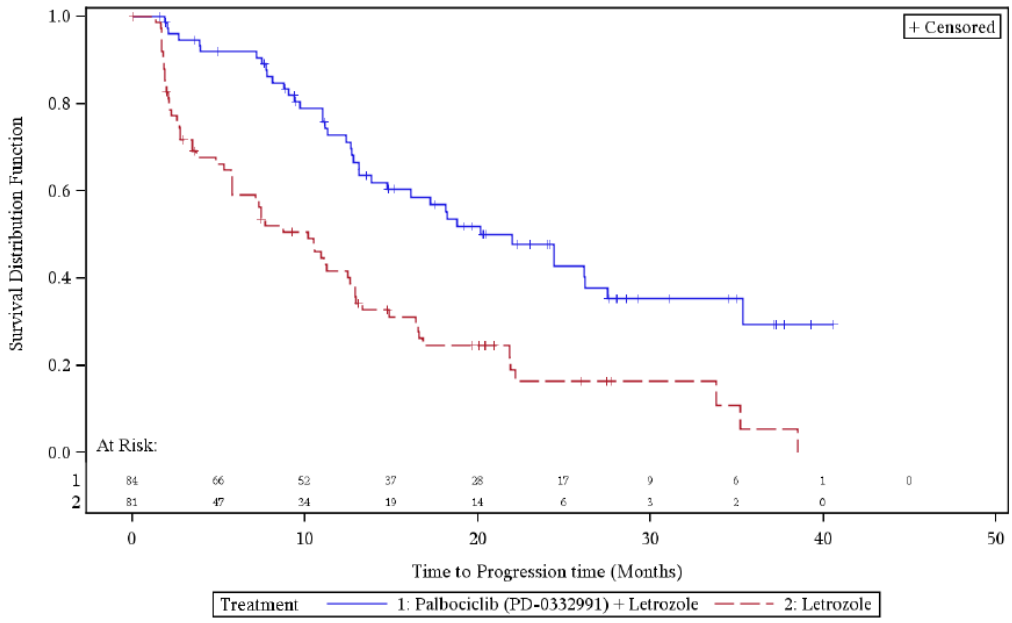


Consistent with this PFS benefit, median TTP was 20.2 months in the palbociclib-letrozole group compared to 10.2 months in the letrozole group, corresponding to HR 0.399 (95%CI 0.265-0.601, stratified log-rank p<0.0001). BICR gave broadly consistent results (palbociclib-letrozole: 25.7 vs. 14.8 months, corresponding to HR 0.621 (95%CI 0.378-1.019, stratified log-rank p = 0.0286). The consistency between PFS and TTP results further supports the potential for palbociclib plus letrozole to delay the onset of subsequent, potentially toxic therapies such as chemotherapy.

As set out in Section 3.2.1, although NICE recommend chemotherapy in ABC after the use of endocrine therapy, delaying chemotherapy has been recognised as being psychologically beneficial to patients in a number of ways. The value of palbociclib in potentially delaying the onset of subsequent therapies is demonstrated by an analysis of treatments given to patients in the PALOMA-1 trial after their disease progressed. This analysis showed that the median time from randomisation to first subsequent treatment was longer in the palbociclib plus letrozole arm than in the letrozole arm when the subsequent treatment was endocrine therapy (428 days [range 239-825] vs. 369 days [65-1102]) and when it was chemotherapy (280 days [69-914] vs. 119 [46-508]). Furthermore, the first subsequent chemotherapy was significantly shorter for patients who had received palbociclib-letrozole than for patients who received letrozole alone (57 days [1-457] vs. 136 days [1-1143]). [111]

Together, these data support the potential for palbociclib to delay the onset of subsequent therapies, including chemotherapy, and the psychological benefits this can bring to patients; this delay to chemotherapy is a benefit not expected to be captured in the QALY.

Figure 10. Kaplan-Meier plot of TTP in the intention-to-treat population of PALOMA-1[3]



Palbociclib's ability to prolong PFS delays the increased challenges associated with the progressed state, whilst offering the benefits of the progression-free state as discussed in section 0. This represents a major advancement in care for patients with ABC.

Section 3.2.1 details how multiple studies have identified that improvements in PFS are likely to be associated with improvements in OS. [12, 64,12,13-16]

The consistent PFS benefit of palbociclib plus letrozole relative to letrozole alone was observed across all analysed sub-groups including those based on stratification factors and baseline characteristics (see section 4.8).

The PFS data from PALOMA-1 are not used for inputs in the economic model, as PFS data from PALOMA-2 is used.

4.7.1.2. Secondary efficacy outcome results in PALOMA-1

Overall response rate in patients with measurable disease and clinical benefit rate in intention-to-treat patients were significantly higher with palbociclib-letrozole than with letrozole.

In the intention-to-treat population, there was a trend towards improved ORR among patients who received palbociclib-letrozole (43%, 95%CI 32 to 54) than among those who received only letrozole (33%, 95%CI 23 to 45; p = 0.13) (Table 23).[4] The ITT population included patients with both measurable and non-measurable disease, the latter of which was comprised principally by bone-only disease, a necessary group to include in the trial owing to their significant representation of the ABC population. As discussed during an advisory board with UK clinicians, there are inherent inaccuracies associated with assessing non-measurable / bone-only disease and this may contribute to the failure of the ITT population to report significant ORR differences between the two trial arms. In the measurable disease population in which assessment by RECIST criteria is more accurate a statistically significant difference in ORR between palbociclib plus letrozole and letrozole alone (55%; 95%CI 43 to 68 *vs* 39%; 95%CI 28 to 52) respectively (one-sided p = 0.047).

As demonstrated above, ORR does not fully capture the ability of a drug to stabilise disease and prevent progression and therefore does not measure the full benefit. In breast cancer CBR is a well-established measure of tumour activity[8] and may be better at capturing the full benefit of a new medicine that has a disease stabilisation component as is a single measure incorporating stable disease for at least 24 weeks and ORR. CBR was significantly higher in patients treated with palbociclib plus letrozole vs letrozole alone for the ITT population [81% (95%CI 71 to 89) vs 58% (95%CI 47 to 69); one-sided p = 0.0009]. Within CBR, the rate of patients showing stable disease for at least 24 weeks was higher in the palbociclib plus letrozole group (38.1%) than in the letrozole group (24.7%). These investigator-assessed outcomes were corroborated by BICR (Table 23).[3]

Table 23. Response to treatment in PALOMA-1 [3]

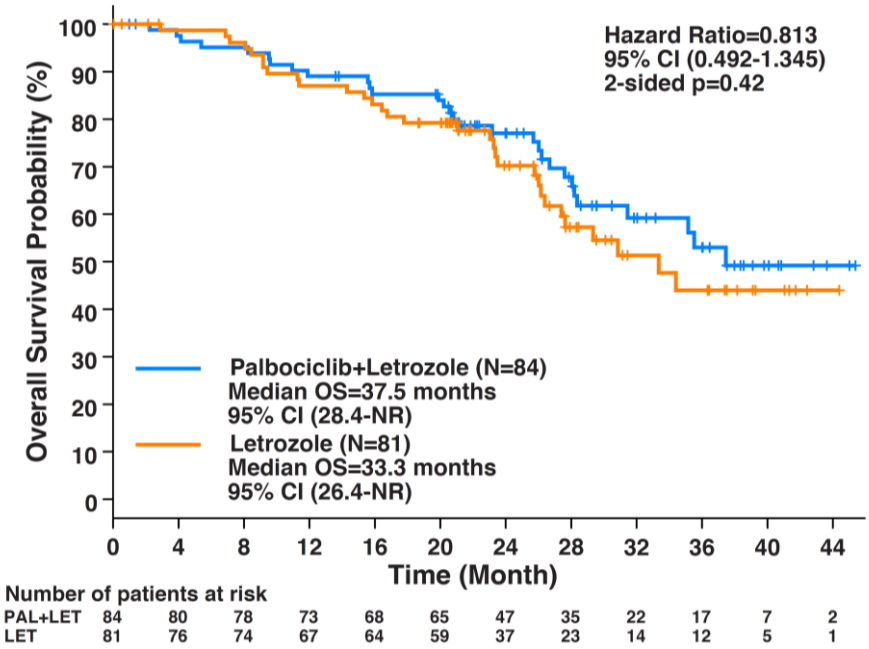
	Palbociclib-letrozole (n=84)	**Letrozole (n=81)**	**p between arms**
ORR in intention-to-treat population, %			
Investigator-assessed	43 (32 to 54)	33 (23 to 45)	0.13
BICR	30 (20 to 41)	21 (13 to 32)	0.1314
ORR in patients with measurable disease, %			
Investigator-assessed	55 (43 to 68)	39 (28 to 52)	0.047
BICR	49 (35 to 63)	32.7 (20 to 47)	0.0728
CBR in intention-to-treat population, %			
Investigator-assessed	81 (71 to 89)	58 (47 to 69)	0.0009
BICR	71 (61 to 81)	51 (39 to 62)	0.0046
Stable disease ≥24 weeks in intention-to-treat population, %			

Investigator-assessed	38.1	24.7	
BICR	41.7	29.6	

p-value <0.001
Rates are shown with 95%CI in parentheses where appropriate.
Abbreviations: BICR, blinded independent central review; CBR, clinical benefit response; ORR, objective response rate

Although the primary outcome in the PALOMA-1 trial was PFS, data on OS were also collected.[4] For overall survival, the median follow-up was 29.6 months (95%CI: 27.9-36.0) in the palbociclib plus letrozole arm and 27.9 months (95% CI: 25.5-31.1) in the letrozole alone arm (Figure 11).[3, 9] Overall survival data reported in PALOMA-1 are immature and demonstrate a trend for improved overall survival with palbociclib plus letrozole versus letrozole.[3] The observed HR was 0.813 (95% CI: 0.492-1.345) with a stratified 1-sided p-value of 0.2105.[3] The median OS in the palbociclib plus letrozole arm was 37.5 months (95% CI: 28.4-NR) and in the letrozole alone arm was 33.3 months (95% CI: 26.4-NR).[3] Survival probability in the palbociclib-letrozole group was 89.0% (95%CI 80.0 to 94.1) at 1 year, 77.1% (95%CI 66.0 to 84.9) at 2 years and 53.0% (95%CI 38.3 to 65.7) at 3 years.[3] The corresponding probabilities in the letrozole group were 87.0% (95%CI 77.2 to 92.8), 70.2% (95%CI 57.7 to 79.7%) and 44.0% (95%CI 28.6 to 58.4%).[3] This analysis was based on only 61 deaths among 165 patients,[3] so the study was substantially underpowered to detect significant differences in OS between the two treatments. Further OS analysis will become available on an event-driven basis therefore we cannot guarantee a date.

Figure 11. Kaplan-Meier analysis of overall survival in the intention-to-treat population of PALOMA-1 [4]



OS data from PALOMA-1 are used to inform the economic model, as data from PALOMA-2 are not currently available.

4.7.1.3. True comparative OS benefit

PALOMA-1 is an RCT in ER+ HER2- ABC where patients survive between a median of 1 to 2 years post-progression. In this time post-progression, patients had a variety of post-progression therapies for which the analyses were not controlled. As patients' health in metastatic cancer deteriorates at varied rates post-progression specific to that individual, patients are more suited to different post-progression therapies. To have a trial powered to detect differences in OS as a primary outcome would mean controlling for post-progression therapies for the entire post-progression period, thus not allowing treating clinicians the necessary flexibility to address individual treatment needs. . As such, it would be difficult to estimate the true comparative OS benefits in metastatic breast cancer trials, such as PALOMA-1, where several lines of post-progression therapies are administered that can confound comparative OS, without controlling for these.

4.7.1.4. PROs in PALOMA-1

Pain severity and interference with daily activities were assessed using the mBPI-sf among all randomized patients who completed the baseline PRO assessment, received at least one dose of study treatment, and completed at least one complete post-baseline PRO assessment (n = 76/84 in the palbociclib-letrozole arm, 74/81 in the letrozole arm).[3] Over 98% of all eligible patients completed over 50% of the questions at each cycle and at the end of treatment, qualifying for inclusion in the mBPI-sf analysis at each cycle and at the end of treatment. Assessments were carried out on day 1 of each treatment cycle and at withdrawal or end of treatment. At least 97% of the questionnaires were evaluable for pain severity, meaning that responses were provided for at least 3 of the 4 relevant items; and all questionnaires were evaluable for pain interference, meaning that responses were provided for at least 4 of the 7 relevant items. Combination therapy was associated with pain severity and pain interference with daily activities that were similar to those of letrozole alone.[3] The mean change in pain severity from baseline was similar for combination therapy as for letrozole alone. Similar pain severity and pain interference were also observed for both treatment arms for the subgroup of patients with bone metastases at baseline.

4.7.2. PALOMA-2

An overview of the key clinical effectiveness results reported in PALOMA-2 is presented in Table 24. Primary and secondary efficacy outcomes by treatment group are discussed further in subsequent sections.

Table 24. Overview of clinical effectiveness results in PALOMA-2[9]*

Outcome	Palbociclib+letrozole (n = 444)	Letrozole+placebo (n = 222)
PFS		
Median PFS, months (95%CI) – investigator-assessed	24.8 (22.1 to NE)	14.5 (12.9 to 17.1)
HR (95%CI) for progression or death – investigator-assessed	0.576 (0.463 to 0.718, one-sided p < 0.000001)	
Median PFS, months (95%CI) – BICR**	30.5 (27.4-NE)	19.3 (16.4 to 30.6)
HR (95%CI) for progression or death – BICR	0.653 (0.505 to 0.844, stratified log-rank one-sided p = 0.000532)	

Outcome	Palbociclib+letrozole (n = 444)	Letrozole+placebo (n = 222)
Tumour response		
ORR, % (95%CI)	42.1% (37.5 to 46.9)	34.7% (28.4 to 41.3), one-sided p between arms = 0.0310
ORR, % (95%CI) – patients with measurable disease	55.3% (49.9 to 60.7)	44.4% (36.9 to 52.2), one-sided p between arms = 0.0132
CBR, % (95%CI)	84.9% (81.2 to 88.1)	70.3% (63.8 to 76.2), one-sided p between arms < 0.0001
Stable disease lasting at least 24 weeks, n (%) – all confirmed cases	[redacted]	[redacted]
DOR		
Median DOR, months (95%CI) – confirmed cases	22.5 (19.8 to 28.0)	16.8 (14.2 to 28.5)
Median DOR, months (95%CI) – all confirmed cases with measurable disease at baseline	22.5 (19.8 to 28.0)	16.8 (15.4 to 28.5)

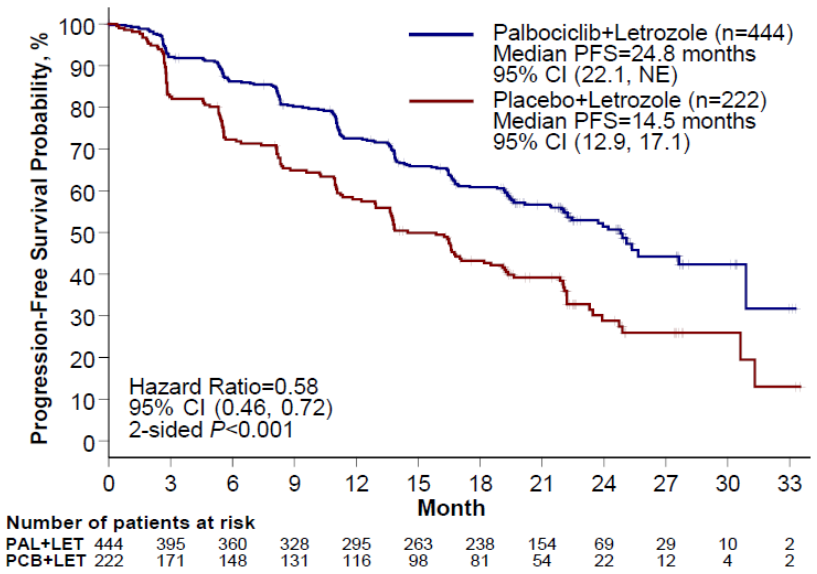
p-value <0.025
Abbreviations: BICR, blinded independent central review; CBR, clinical benefit response; DOR, duration of response; HR, hazard ratio; NE, not estimable; ORR, objective response rate; PFS, progression-free survival
*Results refer to the intention-to-treat population unless otherwise noted.
**BICR was conducted on the entire intention-to-treat population

4.7.2.1. Primary efficacy outcome results in PALOMA-2

The study met its primary endpoint, demonstrating that palbociclib-letrozole significantly prolonged PFS when compared with placebo plus letrozole in postmenopausal women with ER+/ HER2- ABC who had not received prior systemic therapy for their metastatic disease.[9] The primary endpoint was PFS in all randomized patients based on investigator assessment. The observed HR was 0.576 (95%CI 0.463 to 0.718, stratified one-sided p-value <0.000001) in favour of palbociclib plus letrozole. Median PFS was 24.8 months (95%CI 22.1 to NE) in the palbociclib-letrozole arm and 14.5 months (95%CI 12.9 to 17.1) in the placebo plus letrozole arm (Figure 12). BICR analysis of the entire intention-to-treat population corroborated the primary analysis based on investigator-assessed PFS, yielding a largely consistent HR (Table 24).

As detailed in Section 4.8, the relative improvement in treatment effect in PFS with palbociclib plus letrozole versus placebo plus letrozole was observed in PALOMA-2 across all pre-defined subgroups based on stratification factors and baseline characteristics.

Figure 12. Investigator-assessed PFS for the intention-to-treat study population in PALOMA-2[9]



The PFS data from PALOMA-2 are used for inputs in the economic model to inform the rate of progression.

4.7.2.2. Secondary efficacy outcome results in PALOMA-2

In the intention-to-treat population, there was a trend towards improved ORR among patients who received palbociclib+letrozole (42.1%, 95%CI 37.5 to 46.9) than among those who received placebo-letrozole (34.7%, 95%CI 28.4 to 41.3), corresponding to an odds ratio of 1.40 (95%CI 0.98 to 2.01) (Table 25).[9] This difference achieved significance in the population with measurable disease: 55.3% (95%CI 49.9 to 60.7) *vs* 44.4% (95%CI 36.9 to 52.2), corresponding to an odds ratio of 1.55 (95%CI 1.05 to 2.28). The difference also achieved significance in the BICR rate (p-value = 0.0005), which is an advancement on PALOMA-1 (see Table 23). The CBR rate in the intention-to-treat population was significantly higher among patients who received palbociclib-letrozole (84.9% [95%CI 81.2 to 88.1] vs 70.3% [95%CI 63.8 to 76.2]), corresponding to an odds ratio of 2.39 (95%CI 1.58 to 3.59). All these investigator-assessed outcomes were corroborated by BICR.[9] In addition, within CBR, the rate of patients showing stable disease for at least 24 weeks was higher in the palbociclib-letrozole group [redacted] than in the letrozole group [redacted]

Table 25. Response to treatment in PALOMA-2[9]

	Palbociclib-letrozole (n = 444)	**Placebo-letrozole (n = 222)**	**p between arms**
ORR in intention-to-treat population, %			
Investigator-assessed	42.1 (37.5 to 46.9)	34.7 (28.4 to 41.3)	0.0310
BICR	[redacted]	[redacted]	[redacted]
ORR in patients with measurable disease, %			
Investigator-assessed	55.3 (49.9 to 60.7)	44.4 (36.9 to 52.2)	0.0132
BICR	[redacted]	[redacted]	[redacted]
CBR in intention-to-treat population, %			

	Palbociclib-letrozole (n = 444)	Placebo-letrozole (n = 222)	p between arms
Investigator-assessed	84.9 (81.2 to 88.1)	70.3 (63.8 to 76.2)	<0.0001
BICR	[redacted]	[redacted]	[redacted]
DOR in intention-to-treat population, median (months)			
Investigator-assessed	22.5 (19.8-28.0)	16.8 (14.2-28.5)	NA
BICR	[redacted]	[redacted]	[redacted]
DOR in patients with measurable disease, median (months)			
Investigator-assessed	22.5 (19.8-28.0)	16.8 (15.4-28.5)	NA
BICR	[redacted]	[redacted]	[redacted]
Stable disease ≥24 weeks in confirmed cases of the intention-to-treat population, %			
Investigator-assessed	[redacted]	[redacted]	

p-value < 0.025
Rates are shown with 95%CI in parentheses where appropriate.
Abbreviations: BICR, blinded independent central review; CBR, clinical benefit response; DOR, duration of response; NA, not applicable; NE, not estimable; ORR, objective response rate

OS is a secondary outcome in PALOMA-2, but the pre-specified level of significance for assessing OS had not been met at the time of the PFS analysis (data cut-off 01 May 2015). By that time, [redacted] deaths had occurred among 666 study participants, corresponding to only [redacted] of the 390 events pre-specified for final OS analysis. Median follow-up time was 23.0 months (95%CI 22.6 to 23.4) for the palbociclib-letrozole arm and 22.3 months (95%CI 21.9 to 22.9) for the placebo plus letrozole arm. The patients will continue to be followed for OS.

4.7.2.3. Patient reported HRQL in PALOMA-2

Patient reported outcomes were assessed in PALOMA-2 using the breast cancer specific HRQL questionnaire (FACT-B) and generic EQ-5D.[9] Patients completed questionnaires prior to any study or medical procedure on day 1 of cycles 1-3, on day 1 of every other subsequent cycle (i.e. cycles 5, 7, 9…), and at the end of treatment.[9] For all surveys, 95-100% of patients in the intention-to-treat population completed at least 1 question from baseline through cycle 37, except for a response rate of only 80% in the placebo plus letrozole arm in cycle 33 (see Appendix 9).[9]

Health related quality of life was [redacted]

[redacted]

[redacted]

4.8. Subgroup analysis

In PALOMA-1 and PALOMA-2, pre-planned subgroup analyses were conducted based on patient demographics and on stratification factors that were considered to be of particular prognostic importance, with the aim of understanding if any populations might particularly benefit from palbociclib plus letrozole. Clinical experts consulted in the UK have confirmed that these subgroups are of relevance to UK clinical practice. The pre-specified subgroup analyses conducted in the PALOMA trials are summarised in Table 26. The results (Figure 13 and

Figure 14) indicate that a majority of sub-groups analysed across the two studies benefit from the palbociclib combination compared to letrozole alone.

Table 26. Pre-specific subgroup analyses conducted in the PALOMA trials [3, 9]

PALOMA-1	PALOMA-2
Age (<65 years, ≥65 years)	Age (<65 years, ≥65 years)
Baseline ECOG (0 or 1)	Baseline ECOG (0 or 1/2)
Disease site (visceral, bone only, other)	Disease site (visceral, non-visceral)
Region (North America, Europe)	Region (North America, Europe, Asia/Pacific). Note that no specific analyses on UK patients were conducted as the study was not powered for this.
	Ethnicity (White, Asian)
Number of disease sites (<2, ≥2)	Number of disease sites (1, 2, ≥3)
DFI (≤12 months, ≤12 months + de novo, >12 months; ≤5 years, >5 years)	DFI (≤12 months, >12 months, de novo)
Previous chemotherapy (yes, no) Previous chemotherapy only (yes, no) Previous endocrine therapy (yes, no) Previous systemic therapy (yes, no) Previous chemotherapy and endocrine therapy (yes, no)	Previous chemotherapy (yes, no) Previous endocrine therapy (yes, no) Most recent therapy (aromatase inhibitor, anti-estrogen)
Biomarker status (positive, negative, unknown) Histopathological grade (1/2, 3) Progesterone receptor (positive, negative)	Biomarker expression (yes/no *or* low/high)
De novo advanced disease (yes, no)	Bone-only disease at baseline (yes, no) Measurable disease (yes, no)

Abbreviations: DFI, disease-free interval; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; HR, growth hormone receptor; PR, progesterone receptor;

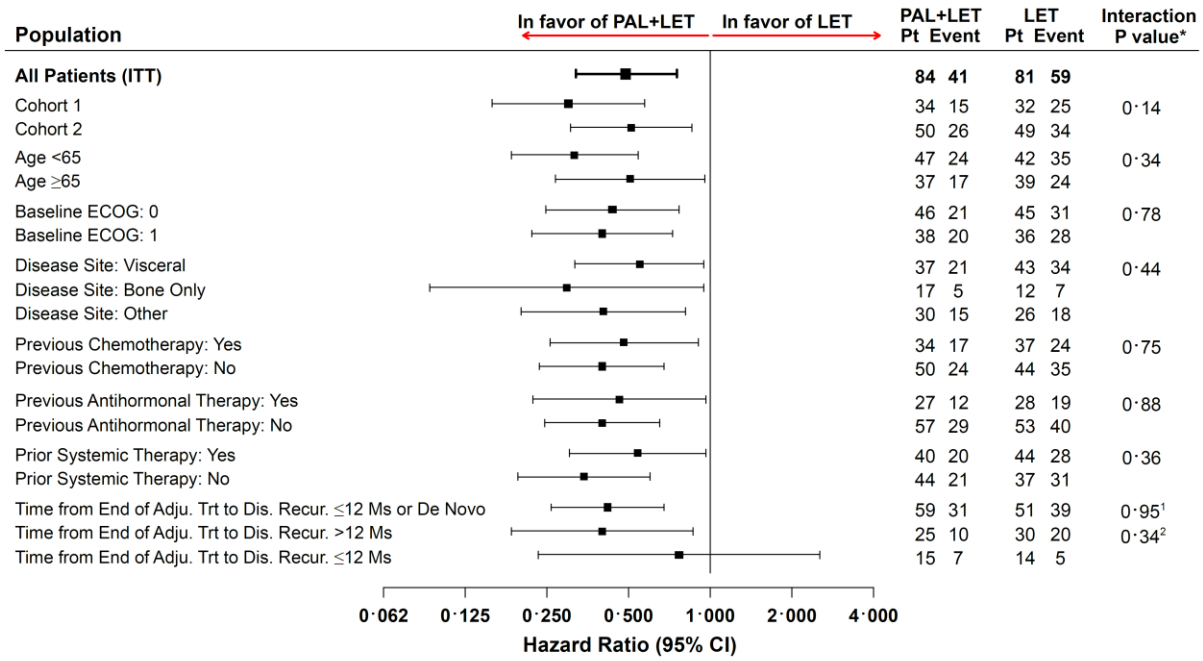
4.8.1. PALOMA-1

Patients in PALOMA-1 were randomised with stratification by disease site (visceral *vs* only bone *vs* other) and by DFI (>12 *vs* ≤12 months between completion of the last adjuvant treatment and disease recurrence or *de novo* ABC). Consistent with the PFS in the ITT population, a pre-planned sub-group analysis indicated that 18 out of the 19 sub-groups derived significant benefit from palbociclib plus letrozole vs letrozole alone [4, 34]. These groups encompassed patient demographics, performance status, disease site, therapy history and for the most part, disease-free interval (DFI). The only exception was the DFI <12 months group (excluding the de novo group) which showed a trend towards benefit with palbociclib but which did not achieve significance. The DFI<12 months group is considered to have more resistant disease and would have likely progressed early on an AI. The non significant difference may be explained by the small sample size (n = 15 in palbociclib-letrozole group, n = 14 in letrozole group), supported by the observation that this group achieved significant benefit in the PALOMA-2 phase III confirmatory study that had a larger

population (although in PALOMA-2 this progressed on tamoxifen and not an AI). The observation of similar PFS benefit between patient subgroups older and younger than 65 is important, since treatment advances for breast cancer have traditionally benefited younger women more than older women.[112]

A recent study provided more evidence on an expanded analyses of PALOMA-1, for subgroups based on age (<65 years and ≥65 years), histological type (ductual carcinoma and lobular carcinoma), and prior systemic therapy.[34] A clinically meaningful improvement in median PFS and clinical benefit response (CBR) rate was seen with palbociclib plus letrozole in every subgroup evaluated. Grade 3–4 neutropenia was the most common AE with palbociclib plus letrozole in all subgroups. Overall, the results suggested that the magnitude of the clinical benefit seen by the addition of palbociclib to letrozole is consistent with that seen in the overall study population. The safety profile of the combination treatment in all subgroups was also comparable to that in the overall safety population of the study.

Figure 13. Investigator-assessed PFS in pre-specified subgroups in PALOMA-1 [4]



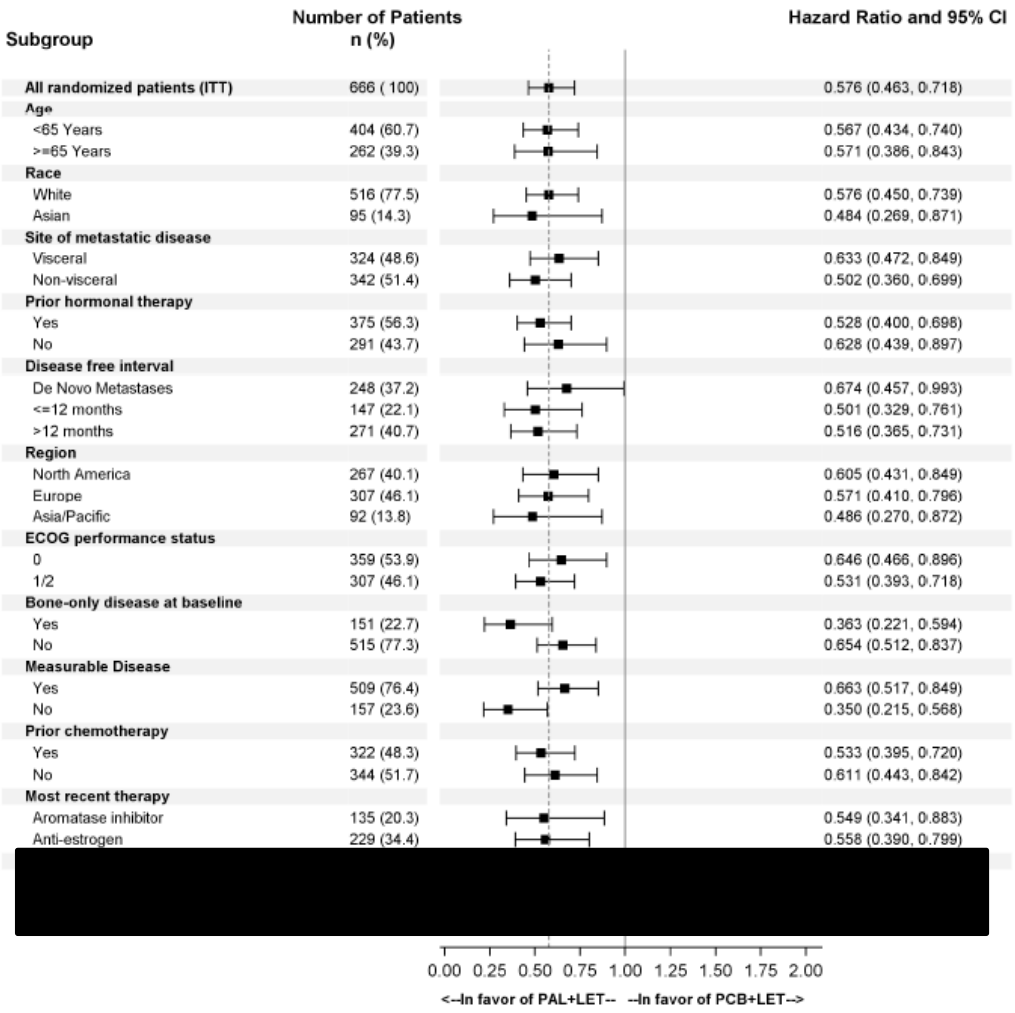
*Two-sided p value. [1]The p value is for the first two subsets. [2]The p value is for the last two subsets.

4.8.2. PALOMA-2

Patients in PALOMA-2 were stratified by site of disease (visceral vs non-visceral), DFI since the end of adjuvant treatment to disease recurrence (de novo metastatic *vs* ≤12 months *vs* >12 months), and nature of prior (neo)adjuvant anticancer therapies (prior hormonal therapy *vs* no prior hormonal therapy). In addition, pre-planned sub-group analyses were also performed on broader patient characteristics of relevance, e.g. age. Consistent with the PALOMA-1 study, a positive trend in clinical benefit for palbociclib was observed in a majority of the pre-specified sub-groups analysed which in addition to others incorporated key prognostic groups of disease site, disease interval and therapy history as per the stratification factors (see section 4.8.1 and

Figure 14).[9] Thus, the PALOMA-2 results confirm, with a much larger population, the PFS benefit observed in PALOMA-1. Among women with de novo metastases the hazard ratio was slightly higher than the ITT, and amongst those who have had adjuvant therapy the hazard ratio is lower than the ITT. Considering that regional data suggest that only 5% of women in the UK with breast cancer have metastatic disease at first diagnosis ('de novo' disease),[93] this suggests the ITT hazard ratio may conservatively reflect palbociclib's efficacy in the context of the UK population.

Figure 14. Investigator-assessed PFS in pre-specific subgroups in PALOMA-2 [9]



These analyses are considered relevant to the decision problem of this appraisal as they demonstrate the broad clinical effectiveness of palbociclib across various subgroups of patients with HR+/HER2- ABC. They have also been identified as treatment effect modifiers in a recent meta-analysis of ABC studies therefore it is reassuring that palbociclib has demonstrated clinical effectiveness in these groups of patients.[113] The demonstration in both PALOMA trials that palbociclib offers PFS benefit to patients older than 65 [9, 34] is important because it may provide additional treatment options for older women with ABC, who have traditionally benefited less than younger patients from therapeutic advances against their disease.[112]

The biomarker analysis is presented in appendix 10.

4.9. Meta-analysis

Not applicable

4.10. Indirect and mixed treatment comparisons

Evidence on the relative efficacy and safety of AIs compared to palbociclib combination with AIs was based on the direct clinical comparisons from the PALOMA 1 and PALOMA 2 clinical trials. No indirect comparison was undertaken.

4.11. Non-randomised and non-controlled evidence

A systematic literature review was performed in January 2015 to identify relevant non-RCTs providing evidence on the safety and efficacy of palbociclib for the treatment of postmenopausal women with ER+/HER2- locally advanced or metastatic breast cancer. The review was subsequently updated to include relevant studies published up to January 2016 in line with NICE guidance.

4.11.1. Search strategy

The systematic review was performed in accordance with the methodological principles of conduct for systematic reviews as detailed in the University of York Centre for Reviews and Dissemination guidance for undertaking systematic reviews in health care, and the PRISMA reporting checklist.[101, 102]

The following electronic databases were searched in the original non-RCT systematic review from their inception date to the following search dates in January 2015:

- 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 electronic databases were searched during the systematic review update on 14 January 2016 to identify new records published since the original systematic review was conducted. The update searches were conducted without a date limit; duplicates from the original systematic review search were removed prior to reviewing titles and abstracts.

To ensure no studies were missed, in the original systematic review search terms were used to identify palbociclib studies for a general locally advanced or metastatic breast cancer population. Studies including data for an ER+/HER2- breast cancer population reporting relevant outcomes were identified during the record screening process. The search did not include terms to denote study types due to the small number of relevant published non-RCTs. The systematic review update searches employed the same search terms wherever

possible, with appropriate translations to search Embase through Ovid SP rather than the Elsevier platform.

In addition, the congress websites reported in the systematic review of RCTs (Section 4.1) were searched for relevant posters and presentations, for 2012-2014 in the original systematic review and for 2015 for the systematic review update.

The following clinical trial registries were also searched to identify ongoing, discontinued, or completed non-RCTs of palbociclib:

ClinicalTrials.gov: clinicaltrials.gov/

International Clinical Trials Registry Platform (ICTRP): www.who.int/ictrp/en/

The bibliographies of systematic reviews and meta-analyses identified after initial review of search results were also searched for references to other potentially relevant studies.

Full details of all search strategies employed are presented in Appendix 11.

4.11.2. Study selection

Following initial record identification, the title and abstracts of identified sources were assessed against the eligibility criteria presented in Table 27. For the sources considered potentially relevant, or for which the relevance was unclear based on the title and abstract, full texts were obtained and screened for relevance. For both the original systematic review and the update, the screening was performed by two independent reviewers, and disputes relating to eligibility were resolved through discussion between reviewers until consensus was reached, or through consultation of a third reviewer.

Table 27. Eligibility criteria for the systematic review of non-RCTs

Domain	Inclusion criteria	Exclusion criteria
Population	Postmenopausal[a] women with ER+/HER2- locally advanced or metastatic breast cancer. Studies had to include ≥50% patients with ER+ or HR+ disease, and ≥50% postmenopausal women; or outcomes had to be reported separately for patients in these subgroups.	Premenopausal women Women with early breast cancer Women with ER- breast cancer Women with HER2+ breast cancer Studies with <50% patients with ER+ or HR+ disease or <50% postmenopausal women were excluded unless outcomes were reported separately in these subgroups.
Intervention	Palbociclib	Any treatment not including palbociclib
Comparator	Any or none	-
Outcomes (considered	Clinical benefit rate	Studies that did not report

Domain	Inclusion criteria	Exclusion criteria
at full-text review only)	Objective response rate Complete response Partial response Stable disease Overall survival Progression-free survival Time to progression Percentage of patients with the following: Overall rate of AEs Rate of serious AEs Discontinuations due to AEs Patient-reported outcomes/utility: EQ-5D EORTC QLQ-C30 EORTC QLQ BR-23 EORTC QLQ FA-13 Fatigue FACT-B Time to treatment discontinuation (duration of treatment)	any relevant outcomes
Study design/publication type	Non-randomised, controlled, prospective clinical trials Long-term follow-up studies (eg. open-label follow-up studies) Prospective observational studies (eg. phase 4 studies) Phase 1 studies Retrospective studies	Randomised, controlled clinical trials Preclinical studies Prognostic studies Case reports Commentaries and letters Consensus reports Non-systematic reviews
	Systematic reviews and meta-analyses were included at the title/abstract screening stage and used for identification of any additional primary studies not identified through the database searches, but were excluded during the full-text review	
Language	English	Any other language
Date	No limit	None

[a] Including women who had menopause induced during the study

Abbreviations: AE, adverse event; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; ER, oestrogen receptor; FACT-B, Functional Assessment of Cancer Therapy–Breast; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

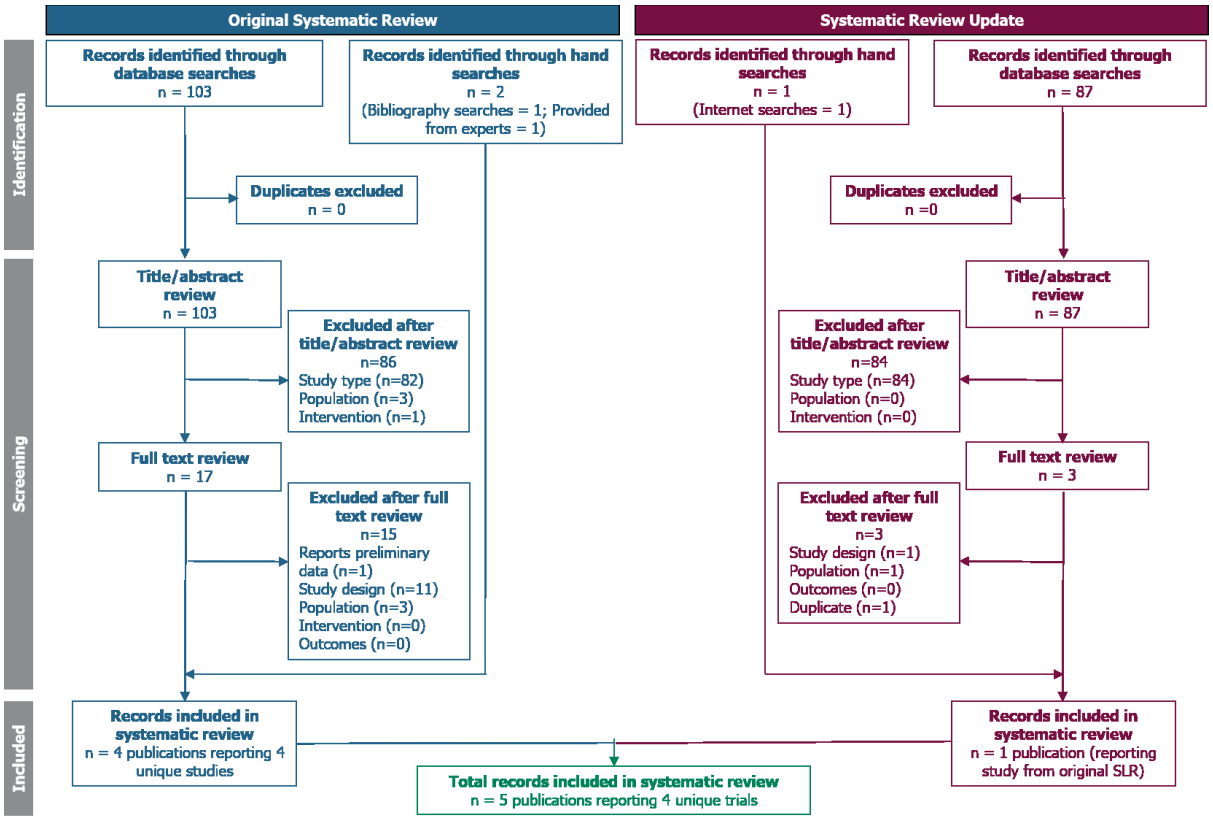
Data from studies included in the systematic review were extracted into a pre-specified extraction grid in Microsoft Excel.

4.11.3. Non-randomised and non-controlled evidence

Database searches in the original systematic review identified 103 unique records. Bibliography searches identified one further record and one study was provided by experts. No relevant studies were identified through ClinicalTrials.gov or the ICTRP. Four publications on 4 unique studies were ultimately considered eligible for inclusion in the original systematic review. The systematic review update identified 88 additional sources through electronic database searches and congress website searches. One publication on a study already identified in the original systematic review was ultimately judged relevant. Therefore, overall, 5 publications reporting on 4 unique studies were included. A PRISMA

flow diagram of the clinical evidence identified in the original and updated systematic reviews is presented in Figure 15.

Figure 15. PRISMA flow diagram for the original and updated systematic reviews of non-RCTs



A complete list of studies excluded after full-text review is presented in Appendix 12.

Details of the 4 relevant non-randomised studies identified in the systematic review are presented in Table 28.

Table 28. Details of relevant non-randomised studies identified in the systematic review

Trial number (acronym)	Objective	Population	Intervention	Comparator	Primary study reference *(Secondary references)*	Rationale for inclusion
NCT01320592	To conduct a dose escalation and dose expansion study investigating the combination of weekly paclitaxel and alternating palbociclib in terms of maximum tolerated dose, safety and preliminary efficacy.	15 patients in the dose escalation cohort and 12 patients in the dose expansion cohort. All patients had metastatic breast cancer tumours expressing retinoblastoma protein, had adequate organ function, and had received ≤ 3 prior cytotoxic metastatic regimens; prior taxane was allowed.	Palbociclib in combination with paclitaxel	None	Clark et al. (2014)[114] *Clark et al. (2015)[115]*	Met eligibility criteria for the systematic review
NCT00141297	To establish the safety profile of palbociclib and to identify the recommended Phase 2 dose of a treatment schedule comprising daily dosing for 21 days followed by 7 days off treatment (3/1 schedule)	41 men and women with retinoblastoma protein-positive solid tumours (except small cell lung cancer or retinoblastoma) or non-Hodgkin lymphoma, that were refractory to standard therapy or for whom no standard-of-care therapy was available. 5 patients had breast cancer.	Palbociclib	None	Flaherty et al. (2012)[116]	Met eligibility criteria for the systematic review
NCT00721409 (phase 1)	To assess the safety and tolerability of palbociclib plus letrozole for advanced breast cancer	Postmenopausal women with ER+/ HER2- advanced breast cancer	Cycle 1: palbociclib Subsequent cycles: palbociclib plus letrozole	Pharmacokinetics were compared for palbociclib alone during cycle 1 (Day 14) compared with palbociclib plus letrozole during cycle 2 (Day 14).	Slamon et al. (2010)[117] *ClinicalTrials.gov (2015)[118]*	Met eligibility criteria for the systematic review

Trial number (acronym)	Objective	Population	Intervention	Comparator	Primary study reference *(Secondary references)*	Rationale for inclusion
				No comparator for response rates.		
UPCC03909; NCT01037790	Primary objectives were to assess disease response and tolerability; secondary objectives included progression-free survival (PFS) and biomarker assessment to determine whether retinoblastoma protein localization, Ki-67 index, p16 loss, or CCND1 amplification were associated with response	37 patients with metastatic breast cancer tumours testing positive for retinoblastoma protein and measurable disease	Palbociclib	None	DeMichele et al. (2015)[119] *ClinicalTrials.gov (2015)*[120]	Met eligibility criteria for the systematic review

Abbreviations: ER, oestrogen receptor; HER2, human epidermal growth factor receptor; N/A, not applicable.

4.11.3.1. Justification of exclusion of trials from further discussion

All identified trials listed above have been considered relevant for inclusion in this submission and for further discussion below.

4.11.3.2. Summary of methodology of the relevant non-randomised and non-controlled evidence

The non-randomised studies identified in the systematic review were all Phase 1 or 2 trials investigating palbociclib for the treatment of breast cancer.

A summary of the methodology employed in the studies identified in the systematic review is presented in Table 29.

Table 29. Methodology of the relevant non-randomised trials identified in the systematic review

Trial number (acronym)	NCT01320592[114, 115]	NCT00141297[116]	NCT00721409 (phase 1)[117, 118]	UPCC03909; NCT01037790[119, 120]
Location	USA	3 sites in USA	109 study locations across USA, Canada, France, Germany, Hungary, Ireland, Italy, Republic of Korea, Russian Federation, South Africa, Spain and Ukraine	Single site in USA
Study design	Phase 1, single-arm, open-label, dose escalation and dose expansion trial. Blinding status of response assessor NR.	Phase 1, open-label, non-comparative, dose escalation trial. Blinding status of response assessor NR.	Phase 1, open-label trial. Blinding status of response assessor NR.	Phase 2, open-label, single-arm trial. Response assessors were blinded to patient identification and dose.
Duration of study	NR	NR	14 months	NR
Trial drugs	Palbociclib: dose-escalated in a standard 3+3 design and taken on days 2-6, 9-14, 16-20 of each 28-day cycle. Patients received paclitaxel 80 mg/m^2 weekly for 3 cycles; thereafter, paclitaxel was administered on Days 1, 8, and 15. After 6 cycles of therapy, patients had the option to stop paclitaxel and continue on palbociclib alone. Starting dose of palbociclib: 50 mg (n=3) 75 mg (n=3) 100 mg (n=6) 125 mg (n=3) Concomitant use of bisphosphonates was allowed.	Palbociclib: cohorts of patients received escalating doses using a standard 3+3 design. Doses were 25, 50, 75, 100, 125, or 150 mg daily for 21 days followed by 7 days off treatment. 5 patients in total had breast cancer; the doses that these particular patients received was not specified. After the first treatment cycle, ancillary supportive medications such as anti-diarrhoea agents were allowed to maintain the full dose of palbociclib.	Palbociclib: During cycle 1, 125 mg daily for 2 weeks, followed by 1 week off treatment (3-week cycle). In subsequent cycles, 125 mg palbociclib daily for 2 weeks followed by 1 week off treatment plus letrozole 2.5 mg daily during the 4-week cycle; no concomitant treatment for advanced breast cancer allowed. N=12	Palbociclib: 125 mg orally on days 1 to 21 of a 28-day cycle, continuing until disease progression or unacceptable toxicity. N=37 Supportive care was allowed at the investigator's discretion, but strong inducers or inhibitors of CYP3A4 were prohibited.
Inclusion criteria	Metastatic breast cancer tumours expressing retinoblastoma protein, adequate organ function, ≤3 prior cytotoxic metastatic regimens (not including cytoxic regimens used in the	Retinoblastoma protein-positive solid tumours refractory to standard therapy or for whom no standard-of-care therapy was available	Postmenopausal women, advanced, inoperable ER+/HER2- breast cancer; no prior or concomitant anticancer therapy for advanced disease	Metastatic breast cancer tumours expressing retinoblastoma protein, measurable disease. There was no limit to the number of prior

Trial number (acronym)	NCT01320592[114, 115]	NCT00141297[116]	NCT00721409 (phase 1)[117, 118]	UPCC03909; NCT01037790[119, 120]
	adjuvant setting)			therapies allowed.
Exclusion criteria	Chemotherapy, radiotherapy or hormonal therapy within the last 3 weeks (6 weeks for nitrosoureas, mitomycin C or bevacizumab), or failure to recover from adverse events due to previous agents administered more than 4 weeks prior to study day 1; a major surgical procedure less than 4 weeks previously (all surgical wounds had to be fully healed); known active CNS metastases and/or carcinomatous meningitis (although patients with CNS metastases who had completed a course of radiotherapy were eligible for the study if they were clinically stable)	Cytotoxic chemotherapy within 3 weeks prior to first treatment (8 weeks for mitomycin C or nitrosoureas); hormone therapy, radioimmunotherapy, immunotherapy, or other biologic therapy within 14 days prior to treatment	Other major cancer in the past 3 years or important cardiovascular events in the past 6 months	Uncontrolled intercurrent illness; a baseline QTcB interval >470 ms; pregnancy; breastfeeding; or human immunodeficiency virus infection
Primary outcomes (including scoring methods and timings of assessments)	Adverse events associated with palbociclib The maximally-tolerated dose and safety of palbociclib in combination with paclitaxel during the first 3 cycles of therapy. Toxicity was assessed weekly.	The safety profile of palbociclib, including the identification of: DLT The maximum administered dose The MTD The RP2D of a treatment schedule comprising daily dosing for 21 days followed by 7 days off-treatment (3/1 schedule) Safety and physical status were assessed at baseline, at regular intervals throughout the study, and within 1 week following treatment discontinuation. AE severity was graded using the NCI CTCAE v3.0.	Number of patients with treatment emergent AEs; number of patients with treatment related AEs; number of patients with dose limiting toxicities	Disease response, RECIST 1.0 measured after every 2 cycles. Assessments were reduced to every 3 cycles for patients on treatment for >18 months. Tolerability, with toxicity assessed using the NCI CTCAE v3.0 in cycle 1 on days 1, 8, 15, and 21 and then on day 1 of subsequent cycles
Secondary outcomes (including scoring	MTD in an expanded cohort of breast cancer patients	Characterisation of single-dose and steady-state pharmokinetics or oral palbociclib	Objective response rate, RECIST 1.0; percentage of participants with clinical benefit rate, RECIST	PFS Biomarker analysis

Trial number (acronym)	NCT01320592[114, 115]	NCT00141297[116]	NCT00721409 (phase 1)[117, 118]	UPCC03909; NCT01037790[119, 120]
methods and timings of assessments)		Evaluation of preliminary antitumour activity Tumour measurements derived from CT or MRI scans were obtained at baseline, after every 2 cycles during the study, and at the end of treatment/study withdrawal. Tumour responses were evaluated on the basis of RECIST v1.0.	1.0; pharmacokinetics	
Other outcomes (eg. exploratory; including scoring methods and timings of assessments)	The relationship between selected biomarkers and efficacy, tolerability and safety outcomes. Response was assessed every 2 cycles using RECIST 1.0.	NR	NR	NR
Pre-planned subgroups	Subgroups of response by hormone receptor status were reported, but it is not clear whether these were pre-planned.	NR	NR	Subgroups of response by hormone receptor status were reported, but it is not clear whether these were pre-planned.

Abbreviations: AE, adverse event; CNS, central nervous system; CT, computed tomographic; DLT, dose-limiting toxicities; ER, oestrogen receptor; HER2, human epidermal growth factor receptor; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; PFS, progression free survival; RECIST, response evaluation criteria in solid tumours; RP2D, recommended phase II dose.

4.11.3.3. Statistical analysis of the non-randomised and non-controlled evidence

Details of any statistical analyses performed in the relevant non-RCTs identified in the systematic review are presented in Table 30. Only study UPCC03909 (NCT01037790) reported statistical analyses,[119] and this was for a secondary endpoint (PFS) among subgroups by HR status and numbers of prior lines of therapy.

Table 30. Statistical analyses employed in the relevant non-randomised trials identified in the systematic review

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT01320592[114, 115]	NR	NR	27 (15 in dose escalation group;12 in dose expansion group) No power calculations reported	NR
NCT00141297[116]	NR	NR	5 with breast cancer No power calculations reported	NR
NCT00721409[117, 118]	NR	NR	12 No power calculations reported	NR
UPCC03909; NCT01037790[119, 120]	NR	Statistical comparison of median PFS between HR-positive and HR-negative population	37 No power calculations reported	NR

4.11.3.4. Participant flow in studies

The baseline characteristics of patients across treatment groups in the identified non-RCTs are presented below from Table 31 to Table 34.

Table 31. Baseline characteristics of patients in NCT01320592[114, 115]

Baseline characteristic	Palbociclib + paclitaxel dose escalation (n=15)[a]	Palbociclib + paclitaxel combined dose escalation and dose expansion cohort (n=27)[b]
Median age (range), years	52 (33-68)	53 (33-70)
Hormone receptor status	ER+, HER2-: 66.7% ER+, HER2+: 6.7% ER-, HER2-: 26.7%	ER+/HER2-, 16 (59.3%) ER-/HER2-, 9 (33.3%) ER any/HER2+, 2 (7.4%)
Prior therapies	Prior taxane: Any, 66.7%	Prior chemotherapy regimens (metastatic), n (%):

Baseline characteristic	Palbociclib + paclitaxel dose escalation (n=15)[a]	Palbociclib + paclitaxel combined dose escalation and dose expansion cohort (n=27)[b]
	Adjuvant, 53.3% Metastatic, 13.3% None, 33.3%	0 or 1 lines of therapy, 16 (59) 2 or 3 lines of therapy, 11 (41) Prior taxane, n (%): Any, 21 (77.8) Adjuvant, 19 (70.4) Metastatic, 5 (18.5) None, 6 (22.2)
Site of metastatic disease, n (%)	NR	Visceral, 21 (77.8) Bone, 9 (33.3) Soft tissue/lymph nodes, 4 (15.4)
Postmenopausal	NR	NR

[a] Dose escalation baseline characteristics presented in Clark et al. (2014).[114]
[b] Combined dose escalation and dose expansion baseline characteristics reported in Clark et al. (2015).[115] Baseline characteristics for dose expansion cohort only NR in either publication.
Abbreviations: ER, oestrogen receptor; HER2, human epidermal growth factor receptor; NR, not reported.

Table 32. Baseline characteristics of patients in NCT00141297[116]

Baseline characteristic	Palbociclib (N=41[a])
Median Age, Years (Range)	54 (22-77)
Performance Status, n (%)	• ECOG PS 0, 21 (51%) • ECOG PS 1, 19 (46%) • ECOG PS NR for one patient

Prior Therapies, n (%)	• Any chemotherapy, 34 (83%)
	  ○ 1-2 regimens chemotherapy, 21 (51%)
	  ○ 3 regimens chemotherapy, 12 (29%)
	  ○ >3 regimens chemotherapy, 1 (2%)
	• Hormonal therapy, 4 (10%)
	• Immunotherapy/biologic therapy, 7 (17%)
	• Radiotherapy, 17 (42%)
	• Surgery, 37 (90%)

Postmenopausal	NR

[a] In this study, 5 of 41 patients with tumours positive for retinoblastoma protein had breast cancer. Patient characteristics were not reported separately for the breast cancer subset; the data reported here represent all 41 patients in the trial.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; NR, not reported.

Table 33. Baseline characteristics of patients in NCT00721409 (Phase 1)[117, 118]

Baseline characteristic	Palbociclib + Letrozole (N=12)
Median Age (Range)/ Years	61 (43-74)
Performance Status	ECOG PS 0, 92% ECOG PS 1, 8%
Hormone Receptor Status	ER+, HER2-: 100%
Prior Therapies	Chemotherapy, 67% Anthracycline, 50% Anastrozole, 33% Letrozole, 8% Tamoxifen, 25% Radiotherapy, 58% None, 17%
Postmenopausal	Yes

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2.

Table 34. Baseline characteristics of patients in UPCC03909 (NCT01037790)[119, 120]

Baseline characteristic	Palbociclib (N=37)
Median Age (Range)/ Years	59 (39-88)
Hormone Receptor Status, n (%)	• ER+ and/or PR+: 33 (89%) • ER+, PR−: 7 (19%) • ER−, PR+: 4 (11%) • ER+, PR+: 22 (60%) • HR+, HER2−: 31 (84%) • HR+, HER2+: 2 (5%) • HR−, HER2−: 4 (11%)

Prior Therapies, n (%)	Prior hormonal therapy:
	• Adjuvant, 22 (59%)
	• Advanced, 31 (84%)
	  ○ Number of advanced lines (median, range), 2 (0-5)
	  ○ 0 or 1 line of therapy, 13 (35%)
	  ○ ≥ 2 lines of therapy, 24 (65%)
	
	Prior chemotherapy:
	• Adjuvant, 26 (70%)
	• Advanced, 34 (92%)
	  ○ Number of advanced lines (median, range), 2 (0-13)
	  ○ 0 or 1 line of therapy, 9 (24%)
	  ○ ≥ 2 lines of therapy, 28 (76%)

Postmenopausal	NR

Abbreviations: ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PR, progesterone receptor; NR, not reported.

4.11.3.5. Quality assessment of the relevant non-randomised and non-controlled evidence

The non-randomised studies identified as relevant for inclusion were assessed using the checklist from Downs and Black (1998).[121] None of the studies scored full marks on the assessment. As two of the studies (NCT01320592;[114, 115] NCT00721409 [phase 1][117]) were only available as posters or ClinicalTrials.gov records with limited information available, their scoring may reflect limited reporting rather than the study quality.

Full quality appraisals for each study identified in the systematic review are presented in Appendix 13.

4.11.3.6. Clinical effectiveness results of the relevant non-randomised and non-controlled evidence

NCT01320592

In NCT01320592, patients received weekly paclitaxel and alternating palbociclib, with palbociclib escalated in a 3+3 design. During the dose escalation phase, the best observed response (as measured by RECIST 1.0) was partial response (PR) recorded in 6 patients, stable disease (SD) in 5 patients and progressive disease (PD) in 4 patients. Among 11

patients with PR or SD, 8 patients continued on therapy for more than 6 months and 4 patients continued on therapy for more than 1 year. Equivalent data were not presented for the dose expansion part of the trial.

The efficacy data reported in Clark et al. (2014)[114] and Clark et al. (2015)[115] are summarised in Table 35.

Table 35. Summary of clinical effectiveness data for NCT01320592[114, 115]

Dose escalation cohort (Clark et al. 2014)[114]				
Study arm	Paclitaxel + palbociclib, starting dose of palbociclib 50 mg (N=3)	Paclitaxel + palbociclib, starting dose of palbociclib 75 mg (N=3)	Paclitaxel + palbociclib, starting dose of palbociclib 100 mg (N=6)	Paclitaxel + palbociclib, starting dose of palbociclib 125 mg (N=3)
Best response[a]				
Complete response, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Partial response, n (%)	1 (NR)	2 (NR)	2 (NR)	1 (NR)
Stable disease, n (%)	1 (NR)	1 (NR)	1 (NR)	2 (NR)
Progressive disease, n (%)	1 (NR)	0 (0)	3 (NR)	0 (0)
Dose escalation and dose expansion cohorts (Clark et al. 2015)[115]				
Paclitaxel + palbociclib, starting doses of palbociclib 50 mg, 75 mg, 100 mg and 125 mg				
Best response (N=23)[a]				
Waterfall plot of best RECIST response by palbociclib dose, prior taxane and receptor subtype (HR+/HER2-; HR any/HER2+; HR-/HER2-)				
PFS (N=NR)				
KM plot for PFS by receptor subtype (ER+; HER2+; TN)				

[a] Waterfall plot of best RECIST response by palbociclib dose and receptor subtype (ER+/HER2-; ER+/HER2+; ER-/HER2-) also presented.
[b] 3/27 patients had clinical progressive disease prior to the end of cycle 2, while 1 additional patient was unevaluable for response due to toxicity.
Abbreviations: ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; KM, Kaplan Meier; NR, not reported; PFS, progression free survival; RECIST, response evaluation criteria in solid tumours; TN, triple negative.

NCT00141297[116]

NCT00141297 evaluated the safety of palbociclib at escalating doses of 20, 50, 75, 100, 125 and 150 mg. Of the 41 patients enrolled, 5 had breast cancer and the only outcome presented separately for this subgroup was response rate.[116]

The efficacy data as reported in Flaherty et al. (2012) are presented in Table 36.[116] It should be noted that only 37 patients were evaluable for RECIST response. It was reported that no patients achieved partial response, and one breast cancer patient achieved stable disease. It was not reported whether the remaining breast cancer patients had progressive disease or were not evaluable for RECIST response.

Table 36. Summary of clinical effectiveness data presented in NCT00141297[116, 120]

Study arm	Palbociclib (N=5)
Best response	
Complete response, n (%)	NR (NR)

Partial response, n (%)	0 (0)
Stable disease, n (%)	1 (20)
Progressive disease, n (%)	NR (NR)

NCT00721409 (Phase 1)

This Phase 1/2 study, reported in Slamon et al. (2010),[117] assessed the safety and tolerability of palbociclib in postmenopausal women with ER+/HER2- ABC who had not received any prior anticancer therapy for advanced disease. The best overall response was assessed by RECIST 1.0. Efficacy data from the non-randomised, Phase 1 portion of the trial are presented in Table 37.[117]

Table 37. Summary of clinical effectiveness data presented in NCT00721409 (Phase 1)[117, 118]

Study arm	Palbociclib + Letrozole (N=12)
Best response	
Complete response, n (%)	0
Partial response, n (%)	3 (25)
Stable disease, n (%)	9 (75)
Stable disease ≥ 6 months, n (%)	5 (42)
Progressive disease, n (%)	0
Objective response rate, % (95% CI)	33.3 (9.9-65.1)
Clinical benefit rate,[a] % (95% CI)	83.3 (51.6-97.9)

[a] Clinical benefit rate was defined as a confirmed CR, confirmed PR or SD for at least 24 weeks on study. Confirmed responses are those that persisted on repeat imaging ≥4 weeks after initial response.
Abbreviations: CI, confidence interval; NR, not reported

UPCC03909 (NCT01037790)

In this Phase 2 study, primary endpoints were response to therapy (as measured by RECIST version 1.0) and tolerability. Other endpoints included PFS. Efficacy endpoints were analysed in sub-groups based on hormone receptor and human epidermal growth factor status. A median PFS of 3.8 months (95%CI 1.9 to 5.8) was reported for patients with HR+/HER2- breast cancer. Median PFS was significantly longer for the HR+ population than for the HR- population (4.5 vs 1.5 months, p = 0.03).[119]

Efficacy data reported in UPCC03909 are presented in Table 38.[119]

Table 38. Summary of clinical effectiveness data presented in UPCC03909[119, 120]

Study arm	Palbociclib	Subgroup: All HR+ disease	Subgroup: All HR- disease	Subgroup: HR+/HER2- disease	Subgroup: HR+/HER2+ disease	Subgroup: HR-/HER2- disease
	N=37	N=33	N=NR	N=NR	N=NR	N=NR
Best response						
Complete response, n (%)	0 (0)	0 (0)	-	-	-	-
Partial response, n (%)	2 (5)	2 (6)	-	-	-	-
Stable disease <6 months, n (%)	14 (38)	13 (39)	-	-	-	-

Study arm	Palbociclib	Subgroup: All HR+ disease	Subgroup: All HR- disease	Subgroup: HR+/HER2- disease	Subgroup: HR+/HER2+ disease	Subgroup: HR-/HER2- disease
	N=37	N=33	N=NR	N=NR	N=NR	N=NR
Stable disease ≥6 months, n (%)	5 (14)	5 (16)	-	-	-	-
Stable disease, n (%)	19 (51)	18 (55)	-	-	-	-
Progressive disease, n (%)	16 (43)	13 (39)	-	-	-	-
CBR (PR + ≥6 months SD)	7/37 (19%)	7/33 (21%)	-	-	-	-
CBR by prior metastatic hormonal therapy: 0 or 1 prior lines hormone ≥2 prior lines hormone Fisher exact test, *P*	N/A	 0/9 (0%) 7/24 (29%) 0.081	-	-	-	-
CBR by prior metastatic chemotherapy: 0 or 1 prior lines chemotherapy ≥2 prior lines chemotherapy Fisher exact test, *P*	N/A	 4/9 (44) 3/24 (13%) 0.068	-	-	-	-
Median duration of response (range)/ months	4 (2-5)	5 (2-6)	-	-	-	-
Median PFS (95% CI)/ months	3.7 (1.9-5.1)	4.5	1.5	3.8 (1.9-5.8)	5.1 (5.1-infinity)	1.5 (0.62-infinity)

Abbreviations: CBR, clinical benefit rate; N/A, not applicable; PFS, progression free survival; PR, partial response.

Overall, the identified studies do not provide additional information to be considered with regard to the decision problem. This is because the studies investigated palbociclib in combinations that are not included within the scope for this appraisal (Clark et al. (2014)[114] and Clark et al. (2015)[115]) or the study populations are not large enough to enable conclusions to be drawn on efficacy (Flaherty et al. (2012)[116]; DeMichele et al. (2015)[119]) or safety (Slamon et al. (2010),[117]).

4.12. Adverse reactions

The two PALOMA RCTs indicate that palbociclib is associated with generally manageable and reversible adverse events, and were most commonly haematological events.

- In PALOMA-1, rates of all-cause serious adverse events were 21.7% in the palbociclib-letrozole group and 6.3% in the letrozole group. The corresponding rates in PALOMA-2 were 19.6% in the palbociclib-letrozole group and 12.6% in the placebo plus letrozole group.
- The most frequent adverse events in the palbociclib-letrozole group were neutropenia and leukopenia: in PALOMA-1, neutropenia of any grade occurred in 75% of patients in the palbociclib-letrozole group but in only 5% of patients in the letrozole group. Grade 3/4 neutropenia was also more frequent in the palbociclib-letrozole group (54% vs. 1.3%). In the PALOMA-2 trial, neutropenia of any grade occurred in 79.5% of patients in the palbociclib-letrozole group but in only 6.3% of patients in the placebo plus letrozole group. Grade 3/4 neutropenia was also more frequent in the palbociclib-letrozole group (66% vs. 1.4%).
- Palbociclib-associated neutropenia and leukopenia were rarely associated with febrile neutropenia: no such cases were observed in PALOMA-1; in PALOMA-2, it occurred in only 8 of 444 patients (1.6%) in the palbociclib-letrozole arm and none of the patients in the placebo plus letrozole arm. Incidence of neutropenia decreased with increasing treatment cycle in PALOMA-1, indicating that dose optimisation during initial cycles can reduce risk of this adverse event. Non-haematological AEs were mainly grade 1 or 2, with few grade 3 or 4.
- Grade 3/4 AEs for both haematological and non-haematological AEs were managed by dose interruption or reduction as advised by the trial protocol. This did not negatively impact time on treatment and overall dose intensity. Neutropenia and leukopenia were the most frequent causes of dose modification. Nevertheless, median treatment duration in the palbociclib group was longer than in the control group, indicating that these adverse events are manageable allowing time on treatment to remain unaffected. Further supporting this was that discontinuations due to AEs was generally low in both palbociclib plus letrozole and letrozole alone arms (PALOMA-1, 7% vs 2% respectively; PALOMA-2, 10% vs 6%).

4.12.1. PALOMA-1

Safety was assessed in all patients who received at least one dose of study treatment (n = 83 in the palbociclib-letrozole arm, 77 in the letrozole arm). Adverse events were recorded within 28 days of initiation of study treatment and then on days 1 and 14 of cycles 1-2, on day 1 of subsequent treatment cycles, and finally at withdrawal or end of treatment. Rates of all-cause serious adverse events were 21.7% in the palbociclib-letrozole group and 6.3% in the letrozole group. Grade 3/4 adverse events were also more frequent for palbociclib-letrozole (75.9 vs. 20.8%), and the most frequent grade 3 or 4 events with palbociclib-letrozole were neutropenia and leukopenia. The most common events overall reported for palbociclib-letrozole were neutropenia, leukopenia and fatigue [4] (Table 39). None of the cases of neutropenia or leukopenia in either treatment group developed into neutropenic fever. Other common adverse events included anaemia, nausea, arthralgia, and alopecia, but most of these were G1-2. There was one death on study in PALOMA-1: one patient in the palbociclib-letrozole group died of disease progression, and this was considered unrelated to study treatment.[4]

A summary of treatment-emergent adverse events reported in PALOMA-1 is presented in Table 39. Adverse events were coded according to MedDRA (version 17.1), with severity grades defined by CTCAE 3.0.

Table 39. All-cause, treatment-emergent adverse events [n, (%)] with incidence of at least 10% among patients in PALOMA-1 who received at least one dose of study treatment [3]

	Palbociclib-letrozole (n=83)			Letrozole (n=77)		
	All grades	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
Any adverse event	83 (100)	49 (59.0)	14 (16.9)	65 (84.4)	16 (20.8)	0
Neutropenia	62 (74.7)	40 (48.2)	5 (6.0)	4 (5.2)	1 (1.3)	0
Leukopenia	36 (43.4)	16 (19.3)	0	2 (2.6)	0	0
Fatigue	34 (41.0)	2 (2.4)	2 (2.4)	18 (23.4)	1 (1.3)	0
Anaemia	29 (34.9)	4 (4.8)	1 (1.2)	5 (6.5)	1 (1.3)	0
Nausea	21 (25.3)	2 (2.4)	0	10 (13.0)	1 (1.3)	0
Arthralgia	19 (22.9)	1 (1.2)	0	12 (15.6)	2 (2.6)	0
Alopecia	18 (21.7)	NA	NA	2 (2.6)	NA	NA
Diarrhoea	17 (20.5)	3 (3.6)	0	8 (10.4)	0	0
Hot flush	17 (20.5)	0	NA	9 (11.7)	0	NA
Thrombocytopenia	14 (16.9)	2 (2.4)	0	1 (1.3)	0	0
Decreased appetite	13 (15.7)	1 (1.2)	0	5 (6.5)	0	0
Dyspnoea	13 (15.7)	2 (2.4)	0	6 (7.8)	1 (1.3)	0
Nasopharyngitis	13 (15.7)	0	0	8 (10.4)	0	0
Back pain	12 (14.5)	0	1 (1.2)	12 (15.6)	1 (1.3)	0
Headache	12 (14.5)	0	0	8 (10.4)	0	0
Vomiting	12 (14.5)	0	0	3 (3.9)	1 (1.3)	0
Asthenia	11 (13.3)	2 (2.4)	0	3 (3.9)	0	0
Bone pain	10 (12.0)	1 (1.2)	1 (1.2)	3 (3.9)	0	0
Constipation	10 (12.0)	0	0	7 (9.1)	0	0
Cough	10 (12.0)	0	0	8 (10.4)	0	0
Stomatitis	10 (12.0)	0	0	2 (2.6)	0	0
Epistaxis	9 (10.8)	0	0	1 (1.3)	0	0
Influenza	9 (10.8)	1 (1.2)	0	1 (1.3)	0	0
Musculoskeletal pain	9 (10.8)	1 (1.2)	0	5 (6.5)	0	0
Upper respiratory tract infection	9 (10.8)	1 (1.2)	0	2 (2.6)	0	0

Abbreviations: NA, Not applicable

Adverse events led to significantly more dose interruptions and reductions in the palbociclib plus letrozole group than in the letrozole group [3] (Table 40). In the palbociclib plus letrozole arm, neutropenia was the most frequent cause of dose reduction (30%) and of temporary discontinuation (51%). The 6-month interval analysis of the most common (>15%) AEs indicated that they tend to occur with greater frequency within the first 6 months with some decrease in incidence over time.[33] Nevertheless, treatment duration was longer in the palbociclib arm (Table 40), indicating that temporary dose interruptions and reductions can keep patients on effective treatment despite neutropenia and leukopenia.

Subgroup analysis based on whether patients were younger or older than 65 [34] indicated similar rates of grade 3/4 adverse events, and in both groups the most frequent events were

neutropenia, leukopenia, fatigue and anaemia. The two groups were also similar in terms of rates of dose reductions and discontinuations. These results further support the ability of palbociclib to benefit younger and older patients.

Table 40. Treatment duration and dose intensity among patients in PALOMA-1 who received at least one dose of study treatment [3]

	Palbociclib-letrozole (n = 83)		**Letrozole (n = 77)**
	Palbociclib	**Letrozole**	**Letrozole**
Median duration of treatment, days	420.0	428.0	231.0
Number (%) of patients with at least one:			
Cycle delay	70 (84.3)	--	--
Dose reduction	33 (39.8)	--	--
Dose interruption	47 (56.6)	32 (38.6)	23 (29.9)
Relative dose intensity*, %			
Mean (SD)	94.1 (26.2)	99.5 (1.1)	99.5 (2.2)
Median	95.4	100.0	100.0

Abbreviations: SD, standard deviation

* Defined as (actual dose / intended dose) x 100%

4.12.2. PALOMA-2

Safety was assessed in all patients who received at least one dose of study treatment, and this as-treated population was identical to the intention-to-treat population.[9] Adverse events were recorded within 28 days prior to randomisation, on days 1 and 14 of cycles 1-2, on day 1 of subsequent treatment cycles, and finally at withdrawal or end of treatment. For serious adverse events (SAEs), the active reporting period began from the time that the patient provided informed consent until 28 calendar days after the last administration of the study drug. Rates of all-cause serious adverse events were 19.6% in the palbociclib-letrozole group and 12.6% in the placebo plus letrozole group. Grade 3 or 4 adverse events were also more frequent for palbociclib-letrozole (77.5 vs 25.2%), and the most frequent grade 3/4 events with palbociclib-letrozole were neutropenia and leukopenia.[9] Infections occurred at high rates in both treatment arms (all grades = 59.7 vs 42.3% for palbociclib vs letrozole respectively), with nearly all of these being grade 1 or 2 (.93% v 97% respectively). Despite the frequency of neutropenia in the palbociclib arm, only 7 of 444 patients (1.6%) developed febrile neutropenia compared to 0% in the placebo plus letrozole arm. Other common adverse events included anaemia, nausea, arthralgia, and alopecia, but most of these were low-grade. In the palbociclib-letrozole arm, 2.3% of patients died during the study treatment period (within 28 days after the last dose of palbociclib or placebo), while 1.8% of patients in the placebo plus letrozole arm died. Similar proportions of patients died in the following period (19.1% of patients in the palbociclib-letrozole arm and 15.3% of patients in the placebo plus letrozole arm), as of the data cut-off date of 26 February 2016. Nearly all deaths were attributed to ABC.

A summary of treatment-emergent adverse events reported in PALOMA-2 is presented in Table 41. Adverse events were coded according to MedDRA (version 18.1), with severity grades defined by CTCAE 4.0.

Table 41. All-cause, treatment-emergent adverse events [n, (%)] with incidence of at least 10% among patients in PALOMA-2 who received at least one dose of study treatment [9]

	Palbociclib-letrozole (n=444)			Placebo-letrozole (n=222)		
	All grades	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
Any adverse event	439 (98.9)	276 (62.2)	60 (13.5)	212 (95.5)	49 (22.1)	5 (2.3)
Neutropenia[(1)]	353 (79.5)	249 (56.1)	46 (10.4)	14 (6.3)	2 (0.9)	1 (0.5)
Neutropenia	294 (66.2)	207 (46.6)	38 (8.6)	7 (3.2)	1 (0.5)	1 (0.5)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia[(2)]	173 (39.0)	107 (24.1)	3 (0.7)	5 (2.3)	0	0
Fatigue	166 (37.4)	8 (1.8)	0	61 (27.5)	1 (0.5)	0
Nausea	156 (35.1)	1 (0.2)	0	58 (26.1)	4 (1.8)	0
Arthralgia	148 (33.3)	3 (0.7)	0	75 (33.8)	1 (0.5)	0
Alopecia	146 (32.9)	0	0	35 (15.8)	0	0
Stomatitis[(3)]	135 (30.4)	4 (0.9)	0	30 (13.5)	0	0
Diarrhoea	116 (26.1)	6 (1.4)	0	43 (19.4)	3 (1.4)	0
Cough	111 (25.0)	0	0	42 (18.9)	0	0
Anaemia[(4)]	107 (24.1)	23 (5.2)	1 (0.2)	20 (9.0)	4 (1.8)	0
Leukopenia	106 (23.9)	63 (14.2)	3 (0.7)	1 (0.5)	0	0
Anaemia	103 (23.2)	23 (5.2)	1 (0.2)	20 (9.0)	4 (1.8)	0
Back pain	96 (21.6)	6 (1.4)	0	48 (21.6)	0	0
Headache	95 (21.4)	1 (0.2)	0	58 (26.1)	4 (1.8)	0
Hot flush	93 (20.9)	0	0	68 (30.6)	0	0
Neutrophil count decreased	87 (19.6)	59 (13.3)	8 (1.8)	7 (3.2)	1 (0.5)	0
Constipation	86 (19.4)	2 (0.5)	0	34 (15.3)	1 (0.5)	0
Rash[(5)]	79 (17.8)	4 (0.9)	0	26 (11.7)	1 (0.5)	0
Asthenia	75 (16.9)	10 (2.3)	0	26 (11.7)	0	0
White blood cell count decreased	72 (16.2)	46 (10.4)	0	4 (1.8)	0	0
Thrombocytopenia	69 (15.5)	6 (1.4)	1 (0.2)	3 (1.4)	0	0
Vomiting	69 (15.5)	2 (0.5)	0	37 (16.7)	3 (1.4)	0
Pain in extremity	68 (15.3)	1 (0.2)	0	39 (17.6)	3 (1.4)	0
Stomatitis	68 (15.3)	1 (0.2)	0	13 (5.9)	0	0
Decreased appetite	66 (14.9)	3 (0.7)	0	20 (9.0)	0	0
Dyspnoea	66 (14.9)	5 (1.1)	0	30 (13.5)	3 (1.4)	0
Insomnia	66 (14.9)	0	0	26 (11.7)	0	0
Dizziness	63 (14.2)	2 (0.5)	0	33 (14.9)	0	0
Nasopharyngitis	62 (14.0)	0	0	22 (9.9)	0	0
Rash	61 (13.7)	2 (0.5)	0	22 (9.9)	0	0
Upper respiratory tract infection	59 (13.3)	0	0	25 (11.3)	0	0
Dry skin	55 (12.4)	0	0	13 (5.9)	0	0
Pyrexia	55 (12.4)	0	0	19 (8.6)	0	0
Myalgia	53 (11.9)	0	0	20 (9.0)	0	0
Urinary tract infection	53 (11.9)	5 (1.1)	0	17 (7.7)	0	0
Abdominal pain	50 (11.3)	4 (0.9)	0	12 (5.4)	0	0
Oedema peripheral	50 (11.3)	0	0	14 (6.3)	0	0
Dysgeusia	45 (10.1)	0	0	11 (5.0)	0	0

[(1)] Includes neutropenia and decreased neutrophil count.

[(2)] Includes leukopenia and decreased white blood cell count.

(3) Includes aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, or stomatitis.
(4) Includes anaemia, decreased haematocrit, and decreased haemoglobin.
(5) Includes dermatitis, acneiform dermatitis, rash, erythematous rash, maculo-papular rash, papular rash, pruritic rash, and toxic skin eruption.

Adverse events led to significantly more dose interruptions and reductions in the palbociclib plus letrozole group than in the placebo plus letrozole group (Table 42).[9] However, these analyseswere not adjusted for the longer median duration of treatment in the palbociclib plus letrozole arm (603 days) than in the placebo plus letrozole arm (413 days).[9] In the palbociclib plus letrozole arm, neutropenia was the most frequent cause of dose reduction (29.3%) and of temporary discontinuation (64.4%). Nevertheless, treatment duration was longer in the palbociclib plus letrozole arm, indicating that temporary dose interruptions and reductions can keep patients on effective treatment despite neutropenia and leukopenia.

Table 42. Treatment duration and dose intensity among patients in PALOMA-2 who received at least one dose of study treatment[9]

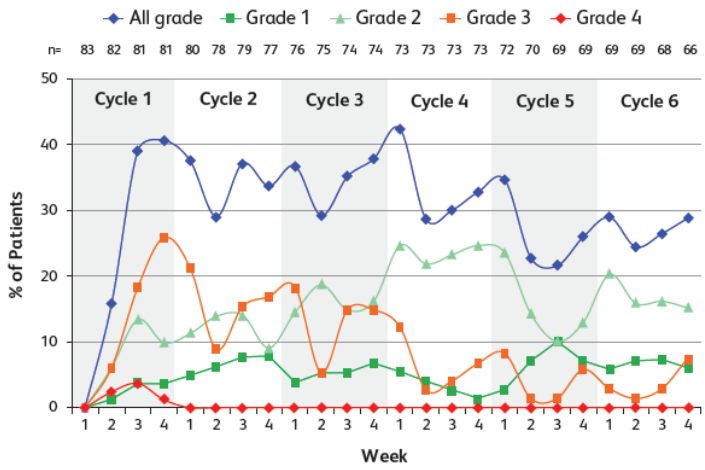
	Palbociclib-letrozole (n = 444)		**Placebo-letrozole (n = 222)**	
	Palbociclib	**Letrozole**	**Placebo**	**Letrozole**
Median duration of treatment, days	603	617	413	420
Number (%) of patients with at least one:				
Cycle delay	[redacted]	[redacted]	[redacted]	[redacted]
Dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
Dose interruption	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity*, %				
Median (range)	93.0 (40.3-109.5)	99.9 (73.4-100.2)	99.6 (56.1-104.5)	100.0 (79.0-100.0)

4.12.3. Asymptomaticity and clinical manageability of neutropenia

In the PALOMA trials, symptomatic neutropenia or leukopenia, indicated by neutropenic fever, was either not observed (PALOMA-1) or rare (PALOMA-2). Subgroup analysis from PALOMA-1 indicates that grade 3/4 neutropenia tended to occur less often with increasing treatment cycles (

Figure 16).[33, 34]

Figure 16. Neutropenia prevalence during first 6 cycles of palbociclib-letrozole treatment in PALOMA-1 [34]



The neutropenia associated with palbociclib-based combination therapy appears to be a cytostatic effect reversible upon dose interruption, in contrast to the cytotoxic neutropenia associated with chemotherapy.[122] Indeed, detailed molecular studies in which human bone marrow mononuclear cells were exposed to palbociclib or chemotherapeutic agents (paclitaxel, doxorubicin) indicate that palbociclib triggers reversible bone marrow suppression, in contrast to the apoptosis caused by chemotherapy.[25] The primary toxicity of asymptomatic neutropenia was effectively managed by dose modification without affecting overall time on treatment. Follow-up subgroup analyses of PFS in PALOMA-3[26] showed that neutropenia did not affect the therapeutic efficacy of palbociclib. Median PFS was similar between patients who experienced grade ≥3 neutropenia *vs* grade ≤2 (11.1 vs 11.0 months; HR 0.98, 95%CI 0.64 to 1.51), between patients who experienced 1 *vs* 0 dose reductions because of neutropenia (9.5 vs 9.5 months; HR 0.87, 95%CI 0.61 to 1.25), or between patients who experienced a dose interruption or cycle delay because of neutropenia *vs* those who did not (9.5 vs 9.9 months, HR 0.84, 95%CI 0.61 to 1.17).

The greater risk of neutropenia and leukopenia with palbociclib likely means that during the initial treatment phase, patients will need to visit the hospital for clinical review more frequently than for endocrine monotherapy. The current prescribing information for palbociclib in the USA recommends checking the absolute neutrophil count on days 1 and 14 of the first two therapy cycles, on day 1 of each subsequent cycle, and as clinically indicated.[123] Once the palbociclib dose has been optimised, visits can likely become less frequent since the likelihood of severe neutropenia decreases with treatment cycle. This management plan was used during the PALOMA-1 trial (see section 2.4).

Table 43 reports the adverse reactions from the pooled dataset of the three randomised studies.[3, 5, Pfizer, 2016 #145] The adverse reactions are listed by system organ class and frequency category. Frequency categories are defined as: very common (≥1/10), common (≥1/100 to <1/10), and uncommon (≥1/1,000 to <1/100).

Table 43. Adverse reactions based on pooled dataset from 3 randomised studies (N=872)[3, 5, 9]

System Organ Class Frequency Preferred Term	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections and infestations			
Very common			
Infections[b]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders			
Very common			
Neutropenia[c]	703 (80.6)	482 (55.3)	88 (10.1)
Leukopenia[d]	394 (45.2)	228 (26.1)	5 (0.6)
Anaemia[e]	241 (27.6)	38 (4.4)	2(0.2)
Thrombocytopenia[f]	166 (19.0)	14 (1.6)	3 (0.3)
Common			
Febrile neutropenia	14 (1.6)	10 (1.1)	1 (0.1)
Metabolism and nutrition disorders			
Very common			
Decreased appetite	138 (15.8)	7(0.8)	0 (0.0)
Nervous system disorders			
Common			
Dysgeusia	74 (8.5)	0 (0.0)	0 (0.0)
Eye disorders			
Common			
Vision blurred	38 (4.4)	1 (0.1)	0 (0.0)
Lacrimation increased	50 (5.7)	0 (0.0)	0 (0.0)
Dry eye	31 (3.6)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders			
Common			
Epistaxis	73 (8.4)	0 (0.0)	0 (0.0)
Gastrointestinal disorders			
Very common			
Stomatitis[g]	252 (28.9)	6 (0.7)	0 (0.0)
Nausea	298 (34.2)	3 (0.3)	0 (0.0)
Diarrhoea	214 (24.5)	9 (1.0)	0 (0.0)
Vomiting	149 (17.1)	4 (0.5)	0 (0.0)
Skin and subcutaneous tissue disorders			
Very common			
Rash[h]	144 (16.5)	6 (0.7)	0 (0.0)
Alopecia	226 (25.9)	N/A	N/A
Common			
Dry skin	82 (9.4)	0 (0.0)	0 (0.0)
General disorders and administration site conditions			
Very common			
Fatigue	342 (39.2)	20 (2.3)	2 (0.2)
Common			
Asthenia	112 (12.8)	12 (1.4)	0 (0.0)
Pyrexia	108(12.4)	1 (0.1)	0 (0.0)
Investigations			
Common			
ALT increased	70 (8.0)	15 (1.7)	1 (0.1)
AST Increased	75 (8.6)	22 (2.5)	0 (0.0)

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; N/n=number of patients; N/A=not applicable.

[a] Preferred Terms (PTs) are listed according to MedDRA 17.1.

[b] Infections includes all PTs that are part of the System Organ Class Infections and infestations.

[c] Neutropenia includes the following PTs: Neutropenia, Neutrophil count decreased.

[d] Leukopenia includes the following PTs: Leukopenia, White blood cell count decreased.

[e] Anaemia includes the following PTs: Anaemia, Haemoglobin decreased, Haematocrit decreased.

System Organ Class Frequency Preferred Term	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)

[f] Thrombocytopenia includes the following PTs: Thrombocytopenia, Platelet count decreased.
[g] Stomatitis includes the following PTs: Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis.
[h] Rash includes the following PTs: Rash, Rash maculo-papular, Rash pruritic, Rash erythematous, Rash papular, Dermatitis, Dermatitis acneiform, Toxic skin eruption.

4.13. Interpretation of clinical effectiveness and safety evidence

The PALOMA-1 and PALOMA-2 trials provide strong evidence that palbociclib acts synergistically with letrozole to provide significantly longer PFS and higher ORR and CBR than letrozole alone in postmenopausal women with HR+/HER2- advanced or metastatic breast cancer not previously treated with systemic therapy for advanced disease while maintaining health related quality of life.

4.13.1. PFS

Both RCTs indicate significantly longer PFS with the palbociclib combination compared to letrozole alone. In PALOMA-1, palbociclib was also associated with significantly longer TTP (data for PALOMA-2 not available). Prolonged PFS and TTP indicate that palbociclib extends the time before patients may require subsequent therapies, including chemotherapy. Indeed, follow-up analysis of treatments given to patients in the PALOMA-1 trial after their disease progressed[111] showed that the addition of palbociclib to letrozole delayed initiation of endocrine therapy and chemotherapy as the first treatment after progression (see section 4.7.1.2). In addition, prolonged PFS allows patients to experience the benefits of being progression-free, as discussed in section 3.2.1.

This transformative clinical benefit is not limited to a particular sub-group of women within the trial. Extensive pre-specified subgroup analyses in PALOMA-1 and PALOMA-2 demonstrate a significant PFS benefit for palbociclib-based combination therapy over existing therapies in women with HR+/HER2- ABC naïve to post-adjuvant systemic therapy or with a history of multiple lines of endocrine therapy.

4.13.2. Response rate

In both PALOMA-1 and PALOMA-2 trials, palbociclib was associated with a trend towards improved ORR in the ITT populations and with a significant improvement in the measurable disease subgroup. Given that many drugs for breast cancer are associated with only modest ORRs, those responses observed with palbociclib provide further evidence of the improved efficacy associated with its use. Both PALOMA trials showed that palbociclib increased the proportion of patients who experienced stable disease lasting at least 24 weeks. These results, together with the observed PFS and TTP benefit, indicate that palbociclib offers improved disease control compared to letrozole alone, with the benefit of a longer experience of the un-progressed state and delaying the requirement for subsequent therapies in women with HR+/HER2- ABC.

4.13.3. Patient reported outcomes – Well-being, pain and QoL

The demonstrated ability of palbociclib to prolong PFS in a range of women with HR+/HER2- ABC is especially beneficial because the extended survival period is associated maintenance of patient wellbeing and HRQL with not significant deterioration in pain. An anonymous, Internet-based survey of 1,072 patients diagnosed with breast cancer[124] 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. Both PALOMA trials indicated that palbociclib maintains patient's experience of function and quality of life with no statistically significant difference relative to letrozole alone. Results of a post-hoc within-treatment arm analysis 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 letrozole (see appendix 9). It was also demonstrated that neutropenia does not have a significant negative impact on EQ-5D index scores in the patients treated with palbociclib plus letrozole (see section 4.13.3).

Across the PALOMA-1 and -2 trials, the addition of palbociclib to letrozole demonstrated a largely consisted AE profile with neutropenia and leukopenia being the most common AEs reported. Around 60% of these were severity grade 3 or 4, but were generally manageable with dose modifications as per the protocol guidance. Indeed, the management of AEs is reflected in the number of dose interruptions, reductions and cycle delays compared to letrozole alone. As such, there were very few episodes of febrile neutropenia and no deaths attributed to this adverse event. The finding that palbociclib-associated neutropenia is relatively uncomplicated may be due to the mechanism by which palbociclib causes cell cycle arrest which permits recovery in neutrophil numbers following dose modification, contrasts with the apoptosis-dominated mechanism associated with chemotherapy-induced neutropenia.[25, 122] Other AEs, including alopecia,[9] anaemia, diarrhoea, fatigue, and nausea,[3] were principally grade 1 or 2 with little if any grade 3 or 4. SAE frequency was higher for palbociclib in both PALOMA-1 and -2 studies compared to letrozole (

Table 44 and

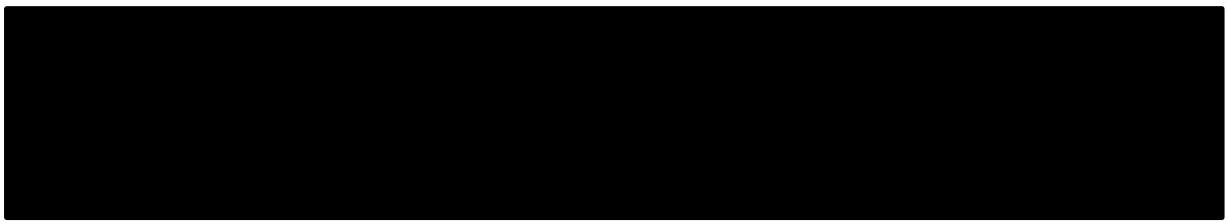
Table 45). There were no deaths due to AEs in PALOMA-2. In PALOMA-1, one patient in the palbociclib plus letrozole arm of the second phase died due to a non-treatment-related SAE of disease progression on Day 68 (Day 12 of Cycle 3).

Table 44. PALOMA-1: Treatment-Emergent Serious Adverse Events by Preferred Term and Maximum CTCAE Grade by Descending Frequency (All Causalities) - both phases: As Treated Set

MedDRA Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Palbociclib + Letrozole (N=83)						
Patients with at least 1 SAE	0	1 (1.2)	9 (10.8)	7 (8.4)	1 (1.2)	18 (21.7)
Pulmonary embolism	0	0	0	3 (3.6)	0	3 (3.6)
Back pain	0	1 (1.2)	0	1 (1.2)	0	2 (2.4)
Diarrhoea	0	0	2 (2.4)	0	0	2 (2.4)
Abdominal pain	0	0	1 (1.2)	0	0	1 (1.2)
Alanine aminotransferase increased	1 (1.2)	0	0	0	0	1 (1.2)
Aspartate aminotransferase increased	0	1 (1.2)	0	0	0	1 (1.2)
Asthenia	0	1 (1.2)	0	0	0	1 (1.2)
Blood alkaline phosphatase increased	1 (1.2)	0	0	0	0	1 (1.2)
Bone pain	0	0	0	1 (1.2)	0	1 (1.2)
Chest pain	0	0	0	1 (1.2)	0	1 (1.2)
Colitis ischaemic	0	0	1 (1.2)		0	1 (1.2)
Disease progression	0	0	0	0	1 (1.2)	1 (1.2)
Fallopian tube cancer	0	0	1 (1.2)	0	0	1 (1.2)
Fractured sacrum	0	0	1 (1.2)	0	0	1 (1.2)
Gamma-glutamyltransferase increased	0	0	1 (1.2)	0	0	1 (1.2)
Gangrene	0	0	0	1 (1.2)	0	1 (1.2)
Gastrointestinal disorder	0	0	1 (1.2)	0	0	1 (1.2)
Humerus fracture	0	0	0	1 (1.2)	0	1 (1.2)
Influenza	0	0	1 (1.2)	0	0	1 (1.2)
Intervertebral disc protrusion	0	0	1 (1.2)	0	0	1 (1.2)
Nephrolithiasis	0	0	1 (1.2)	0	0	1 (1.2)
Neuralgia	0	0	1 (1.2)	0	0	1 (1.2)
Pain	0	0	1 (1.2)	0	0	1 (1.2)
Pneumonia	0	1 (1.2)	0	0	0	1 (1.2)
Renal disorder	0	0	1 (1.2)	0	0	1 (1.2)
Staphylococcal bacteraemia	0	0	1 (1.2)	0	0	1 (1.2)
Upper respiratory tract infection	0	0	1 (1.2)	0	0	1 (1.2)
Urethral obstruction	0	0	1 (1.2)	0	0	1 (1.2)
Letrozole (N=77)						
Patients with at least 1 SAE	0	0	5 (6.5)	0	0	5 (6.5)
Anaemia	0	0	1 (1.3)	0	0	1 (1.3)
Cardiac failure	0	0	1 (1.3)	0	0	1 (1.3)
Erysipelas	0	1 (1.3)	0	0	0	1 (1.3)
Hip fracture	0	0	1 (1.3)	0	0	1 (1.3)
Ileus	0	0	1 (1.3)	0	0	1 (1.3)
Oesophageal achalasia	0	0	1 (1.3)	0	0	1 (1.3)
Pleural effusion	0	0	1 (1.3)	0	0	1 (1.3)
Subcutaneous emphysema	0	0	1 (1.3)	0	0	1 (1.3)

Includes data up to 28 days after last dose of study drug.
MedDRA (v16.1) coding dictionary applied.
Abbreviations: AE, Adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SAE, Serious adverse event.

Table 45. PALOMA-2: Summary of All-Causality Serious Adverse Events by CLUSTER of Preferred Terms and Maximum CTCAE Grade Reported by ≥1% of Patients in Either Treatment Arm (All Cycles) - As Treated Population



4.14. Strengths of the evidence

The two PALOMA RCTs examine large size, international, multi-centre populations totalling 831 women with clinical profiles of ABC largely typical of populations seen in the UK as confirmed by UK KOLs. Treatment groups were largely similar across all baseline characteristics with some imbalances in PALOMA-1 as described in Table 21. The trials focused on PFS as the primary outcome, since prolonging PFS means postponing the need for subsequent therapies including chemotherapy with its associated burden.[17, 21, 43, 44]

The size of each PALOMA trial meant that extensive pre-planned subgroup analyses could be performed to assess the clinical efficacy of palbociclib in various patient subpopulations. This is essential because the target populations for palbociclib therapy are likely to present with a diverse range of characteristics (visceral, bone only, other; recurrent disease or de novo), number of disease sites, treatment histories [none, previous chemotherapy, previous endocrine therapy; as (neo)adjuvant or in metastatic context], and response histories (previous progression on endocrine therapy with short or long DFI). The extensive subgroup analyses across the PALOMA trials build a strong case that all these populations can experience significantly longer PFS than with standard therapy alone. Equally important as extending PFS, palbociclib-based combination therapy is at least equivalent to standard endocrine therapy alone in terms of PROs such as pain, interference with daily activities and QoL.

4.14.1. External validity and generalisability of the PALOMA trials to patients in the UK

The trials have high external validity because they have been designed to encompass key patient characteristics that are of clinical relevance when treating patients with ABC. This population includes but is not restricted to the stratification factors of disease site, disease free interval, and prior hormonal therapy. Whilst there were slight imbalances in these in the phase II PALOMA-1 study, they were broadly balanced in the PALOMA-2 study, the efficacy and safety outcomes of which were consistent with PALOMA-1 suggesting the imbalance was not detrimental to the outcome.

Clinical opinion has also supported the high external validity of the trial populations. The overall patient demographic profiles in the trials were believed to be largely similar to those expected for UK clinical practice, based on consultations with UK breast oncologists in advisory boards.[125, 126] Limitations of the population are discussed in section 4.15.

The comparator in the clinical trials was a nonsteroidal AI which is UK standard of care for women with untreated HR+HER2- ABC. Furthermore, most women received 5 years of adjuvant ET therapy (+/- CT for high risk patients) following curative surgery, which is also consistent with SOC.

4.15. Limitations

It is not currently possible to isolate the effects of palbociclib on OS, given that OS usually requires following a cohort for several years. During this time, patients with ABC would be expected to receive a range of treatments after palbociclib, which could confound direct measurement of OS benefit (see section 3.3.2). Indeed, analysis of treatments given to patients in the PALOMA-1 trial after their disease progressed revealed a range of endocrine therapies, chemotherapies and other therapies.[111] For these reasons, PFS may offer a suitable surrogate end-point for OS for palbociclib.

PFS may be a suitable surrogate end-point for OS for palbociclib. A review of 144 studies involving more than 43,000 patients with metastatic breast cancer showed that PFS or TTP correlated strongly with OS.[12, 64] While biases in the modelling performed in that work call into question whether OS can be directly predicted from the PFS observed for a breast cancer drug, the evidence suggests that drugs associated with longer PFS than a comparator treatment are highly likely to be associated with longer OS as well.[8, 127]

The results of PALOMA-2 were discussed at a UK advisory board with 10 clinical experts; feedback was that the trial was robust and the results were impressive. Although the patient populations in the PALOMA trials are largely similar to the relevant population in the UK, the clinical experts have indicated that the proportion of patients with de novo ABC in PALOMA-1 (49%) and PALOMA-2 (38%) is higher than that typically seen in UK clinical practice (5-10%).[125, 126] Importantly, however, this is not thought to render the results of the trial ungeneralisable to the UK given that subgroup analyses demonstrated consistency in relative treatment effect.

4.16. Ongoing studies

The subject of this HTA has been the evaluation of palbociclib plus letrozole in HR+/HER2- ABC patients with no prior treatment for their advanced disease. In addition to this, PALOMA-3, a phase III double-blinded, randomised RCT evaluating palbociclib plus fulvestrant versus fulvestrant alone in endocrine resistant HR+/HER2- ABC has also completed.[6, 128] The primary end-point was met giving a PFS of 9·5 months (95% CI 9·2–11·0) in the fulvestrant plus palbociclib group and 4·6 months (3·5–5·6) in the fulvestrant plus placebo group (hazard ratio 0·46, 95% CI 0·36–0·59, p<0·0001). The AE profile consistent with that seen in PALOMA-2 and QOL was maintained or improved in certain domains compared to fulvestrant alone. Details of the study are given in Table 58. PALOMA-2 is also given for reference.

The clinical program to further understand the value of palbociclib in the treatment of breast cancer is ongoing. Currently, there are three phase III RCTs. In the HR+/HER2- ABC setting, PEARL will evaluate palbociclib in combination with exemestane vs capecitabine to understand the potential role in treating non-steroidal AI-resistant patients. In the early

breast cancer setting, PENELOPE and PALLAS evaluate palbociclib in combination with endocrine therapy post-neo-adjuvant treatment of high and intermediate risk respectively with view to understanding if this could improve DFS. These studies are described in Table 46. The phase III RCT, PALOMA-2 is also given for reference. A diverse number of international phase II and earlier collaborative and investigator led studies are also in progress.

Table 46. Ongoing Phase III studies of palbociclib in breast cancer

	Advanced Breast Cancer			Early Breast Cancer	
Study	**PALOMA-2**	**PALOMA-3**	**PEARL**	**PENELOPE**	**PALLAS**
Population	Endocrine sensitive	Endocrine resistant	Endocrine resistant	High risk	Intermediate Risk
Histology	ER+/HER2-	ER+/HER2-	ER+/HER2-	ER+/HER2 normal	ER+/HER2-
Menopausal Status	Post-menopausal	Pre- and post-menopausal	Post-menopausal	Pre- and post-menopausal	Pre- and post-menopausal
No. of Patients	666	521	348	1,100	4,600
Treatment Arms	Palbociclib + letrozole vs. placebo + letrozole	Palbociclib + fulvestrant vs. placebo + fulvestrant	Palbociclib + exemestane vs. capecitabine	Palbociclib + SOC vs. SOC	Palbocilib + endocrine Therapy vs. endocrine Therapy
Primary Endpoint	PFS	PFS	PFS	iDFS	iDFS
Sites	International including UK	International including UK	International excluding UK	International including UK	International including UK
Current Status	Completed	Completed	Recruiting	Recruiting	Recruiting
www.clinicaltrials.gov reference	NCT01740427	NCT01942135	NCT0202850	NCT01864746	NCT01864746

Abbreviations: CBR, clinical benefit response; iDFS = invasive disease-free interval; PII, phase II; PFS, progression-free survival; TBD, to be determined

5. Cost effectiveness

De novo cost-effectiveness model

- The cost-utility of palbociclib was assessed with a partitioned Markov survival model, comparing palbociclib plus letrozole to letrozole alone.
- PFS estimates for both treatment arms were derived directly from patient-level data in PALOMA-2 and extrapolated beyond the trial period, in each case using Weibull parametric functions chosen on the basis of statistical fit and external validation.
- OS estimates for both treatment arms were based on phase I/II data from PALOMA-1 (as no phase III data were available) and adjusted to reflect an OS gain of the same magnitude as the observed PFS gain. This adjusted OS was extrapolated beyond the end of the trial using Weibull parametric functions for each of the two arms.
- Health-state utilities in the progression-free state were elicited from EQ-5D scores collected in the PALOMA-2 phase III trial, specific to each treatment arm. Utilities for the post-progression state were taken from the literature. Disutilities for adverse events were considered already accounted for in the on-treatment utility.
- Resource use inputs were derived from NICE guidelines (CG81), which were then validated through consultation with UK clinical experts.

Base case results

- Despite palbociclib plus letrozole's measurable clinical benefit over letrozole alone, in the nominal base case, the deterministic ICER was £150,869 per QALY at list price.
- One-way sensitivity analyses indicated that the key drivers of the model are covariates attributed to the OS and PFS. The probabilistic ICER was very similar to the deterministic.

Exploratory scenarios

- Despite transformative improvements in efficacy, if exclusively pessimistic assumptions are adopted, palbociclib may produce an ICER which would require its monthly cost to a near generic price.
- However, if a more pragmatic approach is adopted, then it is possible to demonstrate cost-effectiveness.
- If the monthly price of the comparator was comparable to palbociclib, together with an adjusted utility of PFS, the ICER would be £47,187 per QALY. When a 24-month gain is assumed, the ICER would decrease to £36,194 per QALY, falling further still to £26,996 per QALY when removing later-line post-progression costs.
- As such, we palbociclib can demonstrate value for money to the NHS and be cost-effective treatment option for women with ABC.

5.1. Published cost-effectiveness studies

5.1.1. Identification of studies

5.1.1.1. Search strategy

A *de novo* systematic literature review was conducted to identify economic evaluations of palbociclib for the treatment of postmenopausal women with ER-positive, HER2-negative locally advanced or metastatic breast cancer with the objective of identifying estimates of the cost-effectiveness of palbociclib within this subtype of patients. The systematic review was performed in accordance with the methodological principles of conduct for systematic reviews as detailed in the University of York Centre for Reviews and Dissemination's (CRD) "Guidance for Undertaking Reviews in Health Care".[101]

The following electronic databases were searched on the 20th January 2016:

- MEDLINE and MEDLINE In-Process
- Embase
- The Cochrane Library, specifically the following:
    - Health Technology Assessment (HTA) Database
    - NHS Economic Evaluation Database (NHS-EED)
- EconLit

Searches of MEDLINE, MEDLINE In-Process and Embase were run simultaneously via the Ovid SP platform. Cochrane Library databases were searched via the Wiley Online platform, and EconLit was searched using the EBSCO platform.

A manual search of abstracts from conference proceedings of the following major conferences was also performed on 16th, 17th and 22nd March 2016:

- European Breast Cancer Conference (EBCC)
- European Society of Medical Oncology (ESMO) Congress
- International Health Economics Association (iHEA) Conference
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) – Annual European and International Meetings

Manual searches for conference abstracts were limited to those published a maximum of two years prior to the search date, as it was assumed that high-quality studies reported in abstract form before this time would have since been published in a peer-reviewed journal.

The bibliographies of included articles (including systematic reviews and meta-analyses identified during the abstract review stage) were hand-searched for references to other potentially relevant studies for inclusion in the systematic review.

Finally, the following HTA websites were hand-searched on 18th and 21st March 2016 for any previous, relevant HTA submissions:

- National Institute for Health and Care Excellence (NICE)
- Scottish Medicines Consortium (SMC)

The search strategies used in the literature review are presented in Appendix 14.

5.1.1.2. Study selection

To be included in the review, articles had to meet the pre-defined eligibility criteria detailed in Table 47.

The citations found through the searches were first assessed against the eligibility criteria by two independent reviewers based on abstract and title. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. Full-text copies of publications potentially meeting the eligibility criteria were then obtained and reviewed in more detail by the two independent reviewers. At both the title/abstract and full-text review stages, any disagreements between the reviewers were resolved by discussion until a consensus was met, with a third reviewer making the final decision if necessary. For studies meeting the eligibility criteria after the second (full-text) screening stage, data were extracted by a single reviewer into a pre-specified data extraction grid and verified by a second individual.

Table 47. Eligibility criteria for the cost-effectiveness systematic review

Domain	Inclusion	Exclusion	Rationale
Population	First-line population: Postmenopausal women with ER-positive, HER2-negative locally advanced or metastatic breast cancer who have not received any prior systemic anticancer treatment for advanced disease	Population not relevant, or outcomes not reported separately for the population of interest	This is the patient population relevant to the NICE decision problem for this submission.
Intervention	Palbociclib	Studies not evaluating palbociclib	This is the intervention specified in the NICE decision problem for this submission.
Comparator	Any pharmacological intervention	Non-pharmacological comparators	This encompasses all relevant comparators specified in the NICE decision problem for this submission.
Outcomes	The outcomes of relevant study designs, including: Costs Life years Quality-adjusted life years (QALYs) Incremental costs and QALYs Incremental cost-effectiveness ratios (ICERs)	Studies presenting irrelevant outcomes only	These outcomes encompass the economic outcomes specified as relevant in the NICE decision problem for this submission.

Domain	Inclusion	Exclusion	Rationale
Study design	Economic evaluations, specifically one of the following analysis types: Cost-effectiveness Cost-utility Cost-benefit Cost-minimisation Cost-consequence	Any other study design	The study designs and publication types specified as eligible for inclusion were those considered most likely to report relevant data for this systematic review.
Publication type	Economic evaluations and HTAs	Any other publication type, including non-systematic reviews, editorials and case reports	
	Systematic reviews of economic evaluations were included at the title/abstract screening stage and used for identification of any additional primary studies not identified through the database searches, but were excluded during the full-text review stage.		
Language	English	Any other language	The review team did not have the linguistic capability to review non-English language articles; however, studies were not limited to those conducted in specific geographical locations.

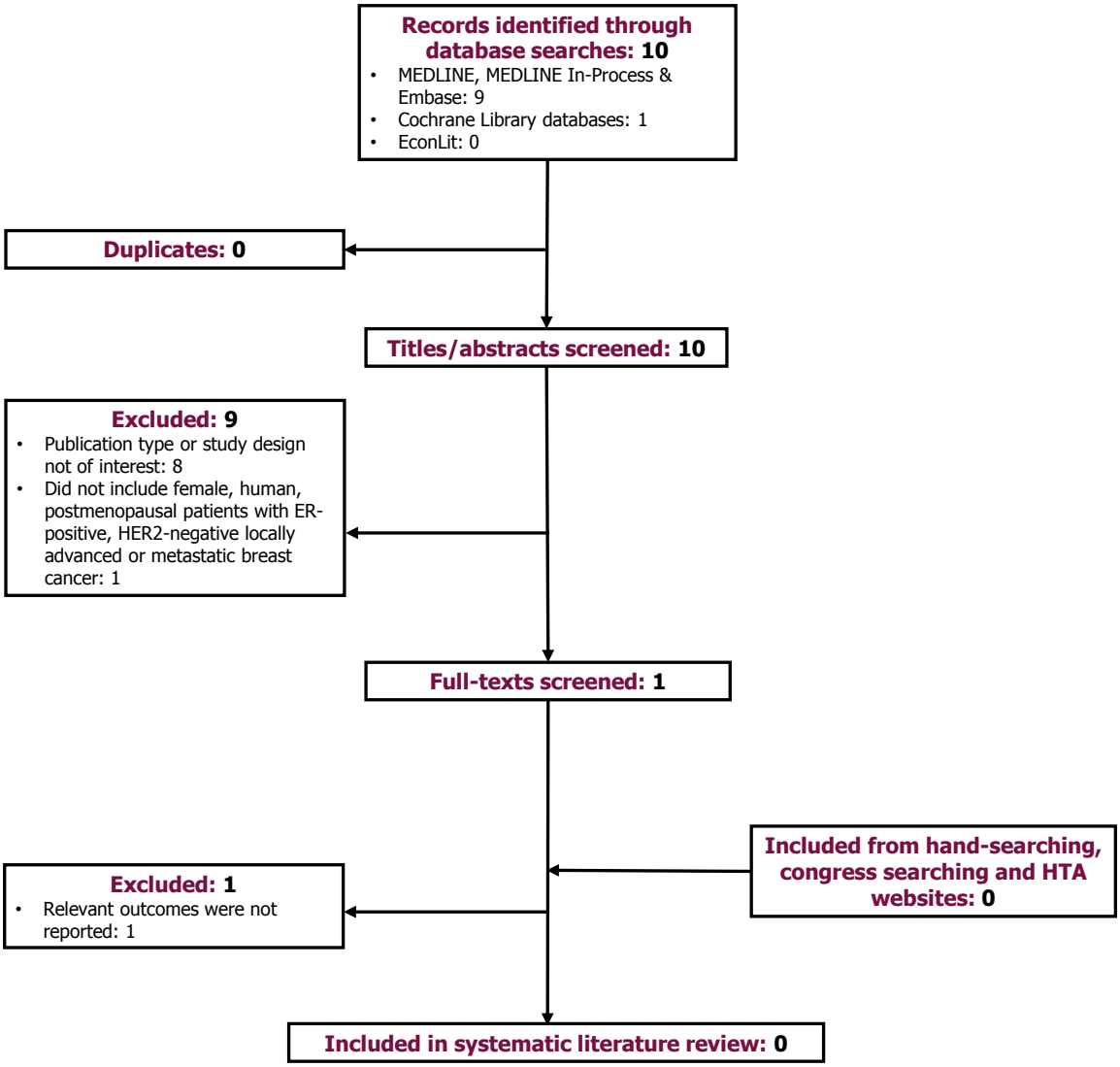
Abbreviations: ER, endocrine resistant; HER, human epidermal growth factor receptor; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

5.1.2. Description of identified studies

At the time of the search, a total of 10 articles were identified from the electronic database searches, all of which were reviewed at the title/abstract review stage. A single article was identified as being potentially relevant; however, this article did not meet the eligibility following full-text review. No additional articles to those captured through the database searches were identified through congress searching, the HTA website searches and through through hand searching of bibliographies. The flow of studies through the systematic review process is presented in

Figure 17.

Figure 17. PRISMA flow diagram of identified studies in the cost-effectiveness systematic review (March 2016)



A complete list of studies excluded after the full-text review stage is presented in Appendix 15.

5.1.3. Quality assessment of identified studies

As no studies were eligible for inclusion in the systematic review, no quality assessments were conducted.

5.2. De novo analysis

5.2.1. Patient population

The *de novo* economic analysis was designed to reflect the stated decision problem, and as such considered the populations from PALOMA-1[3,4] and PALOMA-2[9,23]: that is, postmenopausal women with HR+/HER2- ABC who have never received systemic therapy in the advanced/metastatic setting (i.e. first-line treatment).

5.2.2. Model structure

A partitioned survival Markov model was developed, with its structure validated by clinical experts. On the basis of discussions with UK clinical experts, the model was structured such that it departs somewhat from the more traditional three-state framework of stable disease, progressed disease and death, in that the post-progression state is itself further divided to allow for more granular modelling of the treatments received after progression. After patients received a first-line pre-progression treatment, the model allowed patients up to four lines of further active therapy, followed by best supportive care (BSC) (

Figure 18). In ER+ HER2- ABC, patients commonly receive multiple lines of therapy and so grouping those who have progressed into one single post-progression state is a blunted reflection of clinical practice. By allowing the model to specify subsequent treatment lines independently, and validating these through UK clinical expert opinion, this partitioned survival model better reflects the clinical care pathway of women in the UK with ABC.

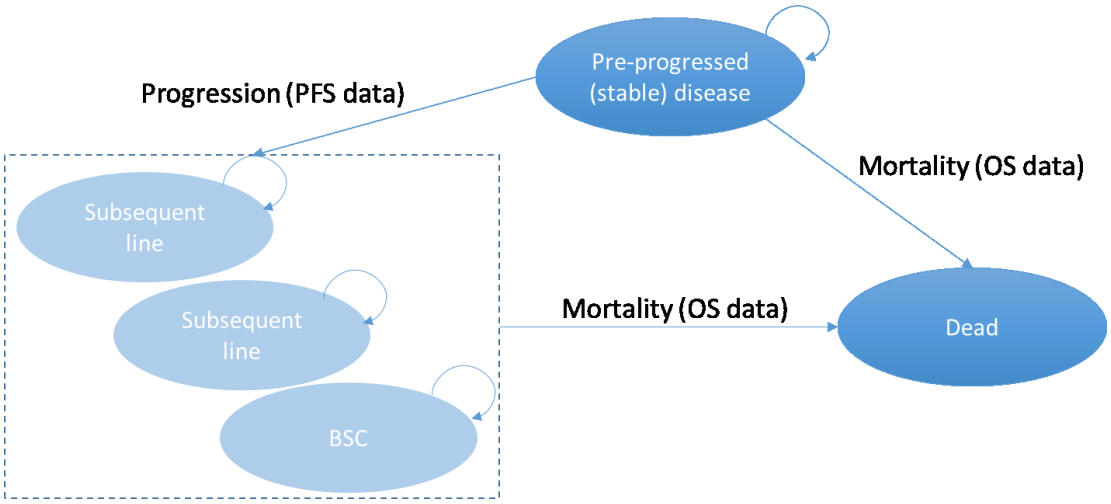
The model health states are described in Table 48.

Table 48. Description of the model health states

Health state	Treatment sequence
Pre-progression: main comparison of treatments	1st line (no previous systemic treatment in the metastatic setting)
Post-progression: subsequent treatments	2nd line (75%) or BSC (25%)
	3rd line (75%) or BSC (25%)
	4th line (75%) or BSC (25%)
	BSC (100%)
Death (absorbing state)	Death

Abbreviations: BSC, best supportive care
*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).

Figure 18. Model schematic



It was assumed that all patients enter the model in the "pre-progression" state (equivalent to stable disease) and receive treatment with either palbociclib plus letrozole, or letrozole monotherapy. Patients could either remain stable, progress or die. Patients were not assumed to change medication before disease progression.

Following progression, patients stopped the current treatment and moved to the post-progression state. The model assumed that each post-progression treatment sequence/line lasts for up to six cycles, drawn from data reported in a recent study in the UK looking at treatment patterns in ER+/HER2– ABC patients in the UK (see Section 5.3.3 for further details).[42] After completing up to four 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.[60] The probability of death was time-dependent and based upon the OS Kaplan-Meier of the respective treatment arm.

The cycle length was 28 days, in line with the administration regimen of both the intervention and the comparator. Each year in the model therefore included 13 cycles. Due to the short length of the treatment cycle, the half-cycle correction was not implemented; the inclusion of a half-cycle correction with such a short cycle length would be expected to have minimal impact on the results.

5.2.3. Intervention technology and comparators

The intervention and the comparators were included in the model in line with their marketing authorisations.[65] The final scope notes an aromatase inhibitor as the specified comparator. Letrozole monotherapy was used as the representative aromatase inhibitor, as this is the most widely used aromatase inhibitor in the UK for these patients, and clinical equivalence among aromatase inhibitors is widely accepted among treating clinicians. This also allowed the use of head-to-head clinical trial data for the intervention and comparator to be drawn directly from the pivotal trials.

Table 49. Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Life-time (40 years)	To ensure the analysis captures all relevant costs and HRQL impairment
Were health effects measured in QALYs; if not, what was used?	Measured in QALYs	QALYs allow comparison of effectiveness across a range of disease areas
Discount of 3.5% for utilities and costs	3.5%	NICE reference case[86]
Perspective (NHS/PSS)	NHS/PSS	NICE reference case[86]

Abbreviations: HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years

5.3. Clinical parameters and variables

5.3.1. Progression-free survival for palbociclib plus letrozole and letrozole

As presented in Table 24, PALOMA-2 reported a median PFS of 24.8 months for the palbociclib+letrozole arm and 14.5 months for the letrozole monotherapy arm. Survival regression modelling was used to fit parametric curves to patient-level data (PLD) from the trial. The following models were considered: exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma. The selection of the best distribution for use in the cost-effectiveness model was made using a combination of standard statistical criteria (such as the Akaike and Bayesian information criteria (AIC and BIC, respectively)) and external clinical validation (that is, consultation with clinical experts and comparison with previously published survival curves).[129]

The AIC and BIC for all models fit to the data are presented in Table 50 and

Table 51. The log-logistic and Weibull had the best relative model fit (AIC, BIC) for palbociclib plus letrozole, whilst the log-normal had the best relative model fit (AIC, BIC) for letrozole plus placebo. Although the AIC and BIC were clearly able to exclude particular distributions, the estimates across the remaining distributions were too similar to rely exclusively on statistical criteria. Face validity and the visual fit of these models were therefore explored.

Table 50. AIC and BIC for the palbociclib plus letrozole parametric models (PFS)

Measure	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
AIC	1786.50	1779.18	1782.87	1777.87	1783.80	1779.37
BIC	1790.60	1787.37	1791.06	1786.06	1792.00	1791.66

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival

Table 51. AIC and BIC for the placebo plus letrozole parametric models (PFS)

Measure	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
AIC	1110.85	1110.19	1107.10	1110.06	1111.80	1108.53
BIC	1114.25	1117.00	1113.91	1116.86	1118.60	1118.74

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival

Consideration of the extrapolated mean (Table 52) and median (Table 53) values of the analysed models showed that the log-normal and log-logistic models would produce the highest mean values (long distribution tails).

Table 52. Estimated mean PFS (months)

Measure	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
Palbociclib plus letrozole	36.6	32.4	58.9	67.3	27.3	36.2
Letrozole	21.1	20.6	29.1	40.0	19.0	24.8

Abbreviations: PFS, progression-free survival

Table 53. Estimated median PFS (months)

Measure	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Kaplan Meier estimate
Palbociclib plus letrozole	25.3	24.1	25.5	24.5	24.2	24.4	24.8
Letrozole	14.6	14.9	13.8	14.1	15.0	14.0	14.5

Abbreviations: PFS, progression-free survival

The visual fit of the distributions with respect to the raw Kaplan-Meier data was similar across parametric models (Appendix 16). However, visual inspection was aided by comparisons with previous literature. In a published study for lapatinib in an ER+ HER2- population which included letrozole as the comparator arm,[130] letrozole achieved a median PFS of 14.7 months. This is similar to its median PFS in PALOMA-2 of 14.5 months. Letrozole was again the comparator in a study for bevacizumab[131], but for ER+ patients with mixed HER2 status; its median PFS was 15.6 months. Again in ER+ patients, letrozole was associated a median time to progression of 9.4 months,[38] when compared with tamoxifen. Due to letrozole's PFS in PALOMA-2 being within the range of previous studies, the curves in these studies were used to help select the most suitable distribution.

At 30 months in the lapatinib study, around 20% of ER+ HER2- patients were progression-free in the letrozole arm on the Kaplan-Meier plot; similarly, at 30 months in the bevacizumab study, around 20% of the letrozole arm on the Kaplan-Meier were progression-free. Lastly, in the study comparing letrozole to tamoxifen that had a TTP of under 10 months, the percentage of patients still without progression at 30 months was, again, 20%. Across the range of parametric distributions fit to PALOMA-2, the log-logistic, the log-normal and the gamma all showed over 25% of patients progression-free at 30 months in the letrozole arm, suggesting the tails of these curves may produce mean survival estimates for

letrozole that are too high. The percentage of patients progression free at 30 months with the exponential distribution was around 24%, whilst the Weibull and Gompertz curves produced values of around 21% (more similar to the three external studies[38, 130, 131]). Visually, the shapes of the letrozole curve in all three external studies are similar to the Weibull and the Gompertz curves fit to the letrozole arm PALOMA-2, confirming these are curves as most plausible when compared with previously published literature.

In conclusion, the Weibull distribution was chosen to model PFS in the letrozole arm, on the basis of both statistical fit and external validation; sensitivity analyses explored alternative models. The proportional hazards assumption was tested to help guide the choice of distribution for palbociclib, as a similar comparison to data outside the trial was not possible. The difference is median OS in these distributions is 9.2 months, which is 1.1 months less than observed in PALOMA-2 (10.3 months). This allows the selection of distributions to provide conservative PFS gains for palbociclib in comparison to the Kaplan-Meier data.

Although Cox proportional hazard models are semi-parametric and cannot provide extrapolated survivor functions, they are useful in testing the proportional hazards assumption. The log-cumulative hazard plot in Figure 19 shows parallel lines suggesting the proportional hazards assumption holds. Furthermore, in Figure 20 the Schoenfeld residuals form an almost horizontal line when plotted against time, further supporting proportional hazards. Consequentially, the same distribution was chosen for the palbociclib arm as was chosen for the letrozole arm (the Weibull). However, guidance in TSD14[129] (referred to by NICE in a recent appraisal in lung cancer, ID865), suggests that when patient level data are available, distributions should be fit independently to each arm. In line with this, the Weibull distributions were fitted independently to each treatment arm in the model and showed a 24.9 month median PFS for palbociclib and a 15.7 month median PFS for letrozole (9.2 month difference).

Figure 19. Log-cumulative hazard plot for PALOMA-2 (PFS)

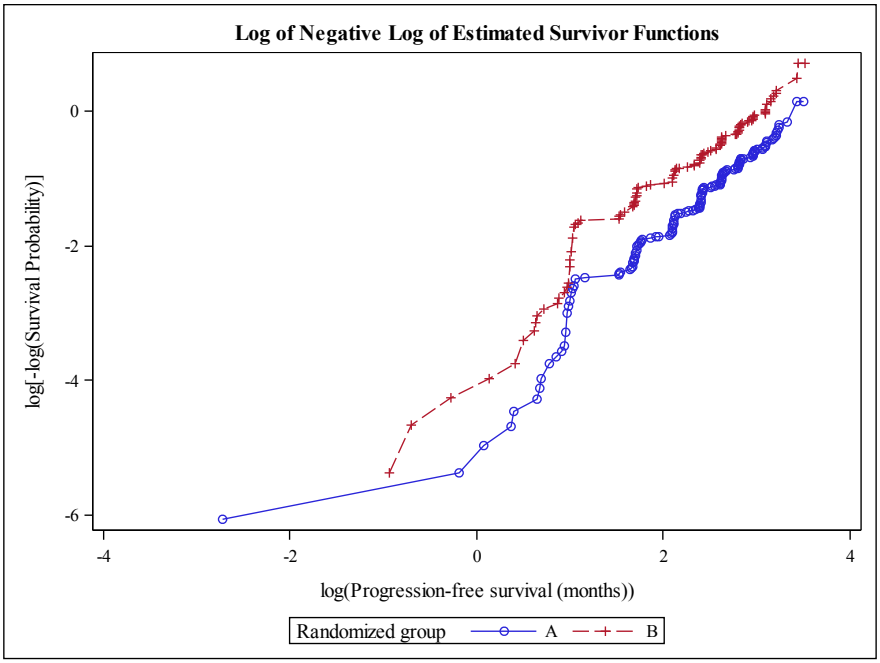
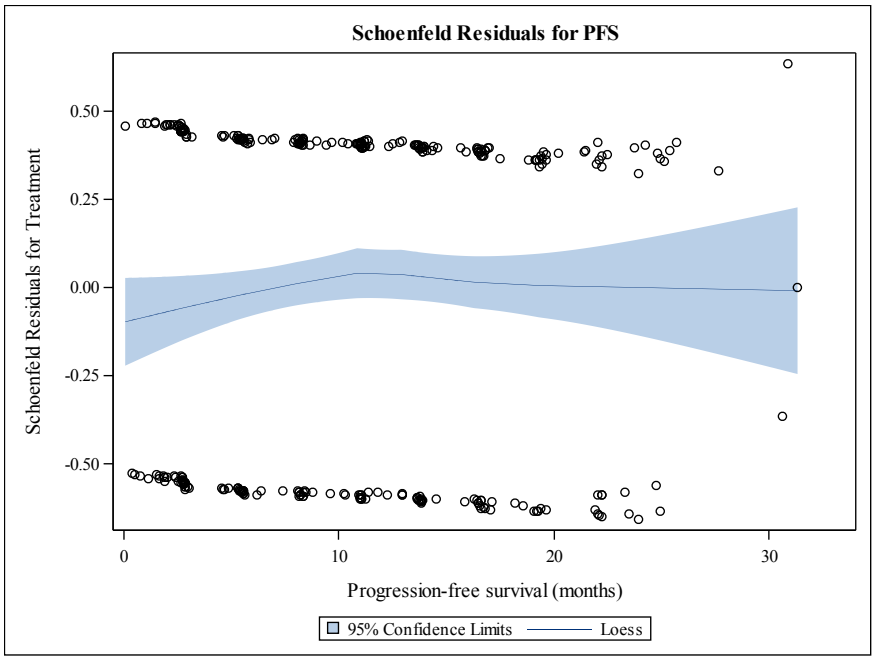


Figure 20. Schoenfeld residual plot for PALOMA-2 (PFS)



5.3.2. Overall survival for palbociclib plus letrozole and letrozole

Using regression analysis, patient level data from PALOMA-1 were extrapolated for inclusion in the economic model. The AIC and BIC for all parametric models fitted to the data are presented in Table 54 and Table 55. The Weibull, log normal and log logistic had the best relative statistical model fit (AIC, BIC) for letrozole (Table 55). Consideration of the extrapolated mean (Table 57) and median (Table 58) values of the analysed models showed that the log-normal and log-logistic models produce higher mean values (longer distribution tails).

Table 54. AIC and BIC for the palbociclib plus letrozole parametric models (OS)

Measure	Exponential	Weibull	Log Normal	Log-logistic	Gompertz	Gen. Gamma
AIC	317.57	312.08	314.76	312.81	312.6	313.90
BIC	320.00	316.94	319.62	317.67	317.4	321.19

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

Table 55. AIC and BIC for the letrozole parametric models (OS)

Measure	Exponential	Weibull	Log Normal	Log-logistic	Gompertz	Gen. Gamma
AIC	318.48	310.05	310.05	309.75	313.1	311.63
BIC	320.88	314.84	314.84	314.54	317.8	318.82

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

Table 56. Survival curve parameters on PFS from the PLD analysis (PALOMA-2)

	Exponential			Weibull			Log-normal			Log-logistic			Gompertz			Generalised gamma		
	Mean	**Low**	**High**	**Mean**	**Low**	**High**	**Mean**	**Low**	**High**	**Mean**	**Low**	**High**	**Mean**	**Low**	**High**	**Mean**	**Low**	**High**
Palbociclib plus letrozole																		
μ	7.02	6.87	7.16	**6.89**	6.76	7.03	6.66	6.5	6.82	6.61	6.48	6.75	7.25	6.99	7.52	6.81	6.63	7
σ				**0.81**	0.72	0.92	1.29	1.16	1.44	0.7	0.62	0.8	-7.22	-8.12	-6.31	1.01	0.76	1.34
δ																0.58	0.05	1.11
Placebo plus letrozole																		
μ	6.46	6.3	6.63	**6.44**	6.29	6.59	6.04	5.86	6.22	6.06	5.88	6.23	6.59	6.29	6.88	6.16	5.82	6.5
σ				**0.88**	0.77	1.02	1.22	1.08	1.38	0.71	0.62	0.82	-7.77	-9.66	-5.88	1.15	0.91	1.44
δ																0.26	-0.42	0.95

Visual fit and external validation are also important components of curve selection. The visual fit to the raw Kaplan Meier plot was very similar across all models (Appendix 17), apart from the exponential distribution, which did not have a good fit. Median OS for letrozole in PALOMA-1 was 33.3 months, which is consistent with previously published estimates of OS for aromatase inhibitors. Median OS for letrozole in a study comparing to tamoxifen in ER+ patients (HER2 status not measured) was 34 months, with around 30% of patients were still alive at 48 months in this study.[38] A study including another aromatase inhibitor, anastrozole, reported a median OS of 38.2 months (following TTP of 10.2 months), with around 35% of patients alive at 48 months.[92] A third aromatase inhibitor, exemestane, was associated with a 37.2 month median OS in a study of ER+ patients (HER2 status not recorded), with just below 35% still alive at 48 months.[36]

Examining the parametric models fit to letrozole's PALOMA-1 data, around 30% of patients in the Weibull distribution were alive at 48 months, 35% in the log-logistic and gamma, and 25% in the Gompertz. The exponential (10%) and log-normal (38%) were furthest away. When comparing these against the previously published literature listed above,[36, 38, 92] the Weibull, log-logistic and gamma appeared the most plausible.

Table 57. Estimated mean OS (months)

Treatment	Exponential	Weibull	Log Normal	Log-logistic	Gompertz	Gen. Gamma
Palbociclib + letrozole	70.8	50.1	79.4	72.4	38.3	41.4
Letrozole	60.6	43.0	54.9	54.3	37.7	43.3

Abbreviations: OS, overall survival

Table 58. Estimated median OS (months)

Treatment	Expon-ential	Weibull	Log Normal	Log-logistic	Gompertz	Gen. Gamma	*KM*
Palbociclib + letrozole	49.1	40.0	45.1	41.9	39.0	39.5	***37.5***
Letrozole	42.0	34.9	36.6	35.4	35.2	35.5	***33.3***

Abbreviations: OS, overall survival; KM, Kaplan Meier

Considering statistical fit, visual fit, and external validity, the log-logistic was the preferred distribution choice for the letrozole arm, with the Weibull curve also valid for consideration.

When considering palbociclib's relative OS versus letrozole, it is important to recall both the issues of potential confounding in the PALOMA trials (see Section 4.7.1.2), and literature identifying a correlation between PFS and OS in ABC (see Section 3.2.1). In light of this, the base case assumes an adjusted OS for palbociclib that reflects a difference in OS between arms that is of the same magnitude as the observed difference in PFS. This assumption implies the same time is spent in the post-progression period for a patient in either treatment arm, *i.e.* the patients begin the progressed disease state at the same level of health, and progress towards death with the same probabilities.

In the base case, the patient level Kaplan-Meier OS data from PALOMA-1 were taken for the two treatment arms, and Weibull distributions were fitted to each; the median OS of these

distributions were 40.6 months in the palbociclib arm (compared with 33.3 in PALOMA-1) and 34.9 months in the letrozole arm (compared with 37.5 in PALOMA-1. The difference in PALOMA-2 PFS was a median of 10.3 months, but this decreased to 9.2 months once Weibull distributions were fitted to PFS estimates. To enable the model to assume a 9.2 month median OS gain, the 'scale' parameter of palbociclib's Weibull curve was adjusted so that the median OS of this curve was 44.1 months (=9.2 months higher); the shape of the curve remained the same. The formula used for adjusting the scale parameter of the Weibull curve based upon a specified median OS was:

$$scale\__{PAL\text{-}LET} = \frac{\ln(2)}{MedianTime^{shape}}$$

The survival curve of palbociclib plus letrozole was then calculated:

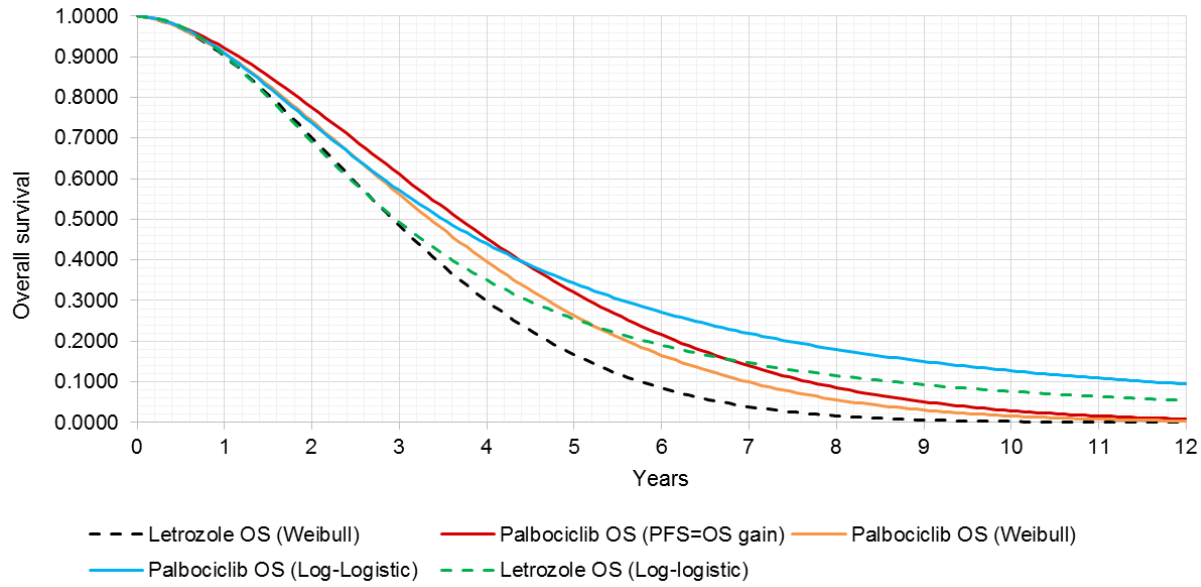
$$S(t)_{PAL\text{-}LET} = exp\ (\ -\ scale\__{PAL\text{-}LET} \times Time\text{^}shape)$$

The following alternative sensitivity analyses were performed around OS (see Section 5.8). The rationale for these were exploring distributions that fit the PALOMA-1 data best, exploring a method identified in the literature for estimating true OS, and to examine the impact of removing OS completely (the pessimistic extreme):

1. Log-logistic distributions fit to the unadjusted PALOMA-1 data
2. Weibull distributions to the unadjusted PALOMA-1 data
3. An alternative target median OS that was derived from a study by Beauchemin et al.[64]
4. No OS benefit in the absence of data from PALOMA-2

Figure 21 below presents the unadjusted survival curve of the palbociclib arm (estimated using parametric modelling (Weibull) of PALOMA-1 PLD) and the curve adjusted such that it estimated the same OS gain as seen with PFS.

Figure 21. Comparison of adjusted base case overall survival (PFS=OS) versus unadjusted PALOMA-1 distributions (log-logistic and Weibull)



5.3.3. Efficacy of subsequent treatments

As described in Section 5.2.2, subsequent lines were modelled to allow for a more detailed reflection of UK clinical practice. Progression from subsequent lines was implemented in the model as a fixed duration on treatment to control the effect between arms, but this is varied in a sensitivity analysis.

In the base case, after patients had progressed on either the intervention or the comparator, they incurred health state costs related to subsequent lines. A targeted literature review for cost studies identified a Pfizer study which examined the medical records of 41 physicians in the UK to report the patient characteristics with and treatment received for ABC (Table 59).[42] From this study, the number of mean cycles ranged from 5.8 to 11.1, dependent on line and treatment; no evidence on fourth line was available. For consistency, the duration of time spent in subsequent lines in the model was assumed as 6 cycles per line for both treatment arms; it was found that varying this number had minimal impact on the ICER (Figure 28).

As different patients would have different treatments post-progression, and furthermore, it was found that the introduction of later line drug acquisition costs did not vary the ICER significantly. As such, only the health state management costs and a health state specific utility for later lines were included. How these costs changed between lines was elicited from interviews with clinical specialists (

Table 76), and the utility estimates were identified through a literature search (see section 5.4.3.5).

A range of 4 to 9 cycles was used in sensitivity analyses, and rates of progression from subsequent treatment lines were assumed fixed between the two treatment arms.

Table 59. Mean duration (months) by treatment regimen received in Kurosky 2015[42]

	Second line	Third line
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 in combination with 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)

At each line of progression, it was assumed in the base case that 25% of patients would not switch to a subsequent line, and would instead receive BSC until death (see also Table 48}. This was based on clinical expert opinion, and reflects that not all surviving patients continue active treatment (either by choice or for health reasons). Sensitivity analyses were conducted to explore both different treatment durations in these later lines and different proportions of patients remaining on active treatment; neither significantly impact the ICER. After patients had completed subsequent therapies, they incurred costs related to by best supportive care.

The model bases OS on the Kaplan-Meier survival data from the relevant treatment arm (section 5.3.2), which necessarily incorporates the influence of subsequent treatments on survival. Therefore, the model assumes that subsequent treatments do not influence OS.

5.3.4. Treatment safety

When selecting adverse events for the economic analysis we considered the likely impact of these events on the total costs and QALYs. The incidence of grade 5 severity events was low: 2.3% in the palbociclib plus letrozole arm vs. 1.8% in the placebo plus letrozole arm. Hence, grade 5 events were not considered. All other events with severity ≥3 grade were included in the analysis, assuming that they would have a likely measurable impact on costs and QALYs (Table 59).

It was assumed that the risk of an event would remain the same while on treatment. In the model, the risk for each event was adjusted for the exposure to treatment. For the palbociclib plus letrozole arm in PALOMA-2 the median exposure to treatment was 603 days (range: 1 to 1037 days) for letrozole and 618 days (range: 1 to 1037 days) for palbociclib. In the placebo plus letrozole arm, the median exposure was 413 days (range: 10 to 1071 days) for placebo and 420 days (range: 10 to 1075 days) for letrozole. The probability of any grade 3 and any grade 4 events were calculated based on the incidence but also the respective median exposure. For example, a palbociclib event with an incidence of 50% would be

adjusted for 603 days on treatment to be 30.3% per year (365 days), allowing a cyclical probability in the model.

Comprehensive, multi-disciplinary input was sought from clinical experts (oncologists, nurse specialists and pharmacists) from centres across the UK regarding the patient and resource impact of adverse events. On the basis of this feedback, the model assumed that all adverse events occurring (and therefore treated) together would incur one healthcare resource use cost in relation to time with a healthcare professional, rather than cumulative.

It was assumed that patients continued to experience adverse events if they were on treatment. However, only events incurred in the first-line (specific to either the intervention or the comparator) were included in the analysis. This followed the assumption that only treatment-line resource use was considered for subsequent treatments. The alternative approach of including these was considered when building the model but were found to have minimal impact on the ICER as their inclusion would have a comparable impact on both treatment arms.

The risk for each event was adjusted for the exposure to treatment. For the palbociclib plus letrozole arm the median exposure to treatment was 603 days (range: 1 to 1037 days) for letrozole and 618 days (range: 1 to 1037 days) for palbociclib. For the placebo plus letrozole arm the median exposure was 413 days (range: 10 to 1071 days) for placebo and 420 days (range: 10 to 1075 days) for letrozole. The probability of any grade 3 and any grade 4 events were calculated based on the respective median exposure. For instance, the 62% grade 3 incidence was adjusted to 44% per year (365 days).

Table 60. Adverse events in the economic model[9]

	Palbociclib plus letrozole	Placebo plus letrozole
Number patients in arm	444	222
Any grade 3 event	276	49
Any grade 4 event	60	5
Exposure to treatment (days)	603	420
Duration adjustment (months)	20	14
Any event / total number of patients		
Any grade 3 event	62%	22%
Any grade 4 event	14%	2.2%
Probabilities used in the model		
Any grade 3 event	44.38%	19.44%
Any grade 4 event	8.39%	1.95%

5.4. Measurement and valuation of health effects

5.4.1. Health-related quality-of-life data from clinical trials

EuroQol five-dimensions questionnaire (EQ-5D^{TM}) was part of the PALOMA-2 clinical trial data.

The EQ-5D questionnaire consists of 5 descriptors of current health state: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients completed questionnaires prior to any study or medical procedure on Day 1 of Cycles 1, 2 and 3 and then Day 1 of every other cycle thereafter starting with Cycle 5 (ie, Cycle 5, 7, 9, etc), and at the end of treatment visit. Of the 666 patients in the PALOMA-2 ITT population, 98.4% of the palbociclib-letrozole arm and 98.2% of the letrozole arm reported EQ-5D index scores.

[redacted] differences in baseline EQ-5D index scores were found between the palbociclib plus letrozole and the placebo plus letrozole arm. Furthermore, [redacted] differences were observed in the overall EQ-5D index score on treatment between the two comparators ([redacted]).[9] These results demonstrate that the improved PFS with palbociclib does not come at the expense of HRQL. Moreover, there are benefits to HRQL from palbociclib that may not captured in the EQ-5D and thus not included in the QALY calculation. These relate to the numerous benefits of remaining progression-free as listed in Section 3.2.1.

Since the EQ-5D is the preferred measure of HRQL in adults as per the NICE reference case [86] the clinical trial EQ-5D data from PALOMA-2 were used in the economic evaluation, that is [redacted] for the baseline utility of the palbociclib plus letrozole arm and [redacted] for the baseline utility of the letrozole arm in the stable disease state.

5.4.2. Mapping

Not applicable since EQ-5D data were available for palbociclib plus letrozole and placebo plus letrozole from PALOMA-2.[9]

5.4.3. Health-related quality-of-life studies

5.4.3.1. Search strategy

EQ-5D data was available from PALOMA-2 to be used in the pre-progression health state. A systematic literature review was conducted to identify health state utility values (HSUVs) for adult patients with advanced or metastatic breast cancer, in order to identify alternate values, but also to identify values that could be used in the post-progression states. The systematic review was performed in accordance with the methodological principles of conduct for systematic reviews as detailed in the University of York CRD's "Guidance for Undertaking Reviews in Health Care".[101]

The following electronic databases were searched on the 16th January 2016:

- MEDLINE and MEDLINE In-Process
- Embase
- The Cochrane Library, including the following:
- Health Technology Assessment (HTA) Database
- NHS Economic Evaluation Database (NHS-EED)
- EconLit

Searches of MEDLINE, MEDLINE In-Process and Embase were run simultaneously via the Ovid SP platform. The Cochrane Library databases was searched via the Wiley Online platform, and EconLit was searched using the EBSCO platform.

The bibliographies of systematic reviews and meta-analyses identified during the abstract review stage were additionally hand-searched for references to other potentially relevant studies for inclusion in the systematic review.

5.4.3.2. Study selection

To be included in the review, articles had to meet the pre-defined eligibility criteria detailed in Table 61.

The citations found through the searches were first assessed against the eligibility criteria by two independent reviewers based on abstract and title. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. Full-text copies of publications potentially meeting the eligibility criteria were then obtained and reviewed in more detail by the two independent reviewers. At both the title/abstract and full-text review stages, any disagreements between the reviewers were resolved by discussion until a consensus was met, with a third reviewer making the final decision if necessary. For studies meeting the eligibility criteria after the second (full-text) screening stage, data were extracted by a single reviewer into a pre-specified data extraction grid and verified by a second individual.

Table 61. Eligibility criteria for the HSUV systematic review

Domain	Inclusion Criteria	Exclusion Criteria	Rationale
Population	Adult, female patients (≥18 years old) with advanced or metastatic breast cancer	Population does not include adult, female, metastatic/advanced breast cancer patients; alternatively, relevant outcomes are not presented separately for this patient population	Only studies on adult, female, advanced/metastatic breast cancer patients are relevant for the purposes of this submission
Intervention On	Any or none	NA	Both non-treatment specific and treatment specific utility values are relevant for the purposes of this submission
Comparator	Any or none	NA	
Outcomes	Original health state utility data, obtained using any methodology (eg. TTO, SG, VAS, EQ-5D, SF-6D, HUI, QWB, or disease-specific utility instruments)	HSUV data not reported No useful HSUV data reported. For example: Article presents only previously published data Study is methodological only	A broad approach was taken with regard to the methodology for obtaining HSUVs, in case insufficient studies were identified using the methodology specified in the NICE reference case (EQ-5D measured in the patient population of interest and valued using the UK general population)
Study design	Experimental studies	Comments, letters,	The study designs specified

	including RCTs and non-RCTs, observational studies, economic evaluations	editorials and non-systematic or narrative reviews, case studies, case reports or case series	as eligible for inclusion were those considered most likely to report relevant data for this submission
	Systematic reviews were included at the title/abstract screening stage and used for identification of any additional primary studies not identified through the database searches, but were excluded during the full-text review if not presenting a novel analysis		
Language	English	Any other language	The review team did not have the linguistic capability to review non-English language articles; however, studies were not limited to those conducted in specific geographical locations

Abbreviations: EQ-5D, EuroQoL-5 Dimension; HSUV, health state utility value; HUI, Health Utilities Index; NICE, National Institute for Health and Care Excellence; QWB, Quality of Well-Being; RCT, randomised controlled trial; SF-6D, Short Form-6 Dimension; SG, standard gamble; TTO, time trade-off; VAS, visual analog scale.

5.4.3.3. Summary of identified studies and results

The systematic literature review identified 46 publications meeting the eligibility criteria, corresponding to 40 studies. A PRISMA flow diagram of studies identified in the review is presented in Figure 22, while a summary of the studies excluded at the full-text review stage, and the reasons for their exclusion, is given in Appendix 19.

Of the 40 studies identified, 39 were original research studies. Of these, 12 presented utilities derived using EQ-5D while the remainder reported only utilities derived by other methods, such as the Health Utilities Index Mark 3 (HUI-3) or direct elicitation with standard gamble (SG), time trade-off (TTO) or visual analogue scale (VAS). The remaining study identified in the review was a systematic review and meta-regression analysis of utility data derived from both EQ-5D and alternative methodologies.

Of the 12 original research studies that reported HSUV obtained through the EQ-5D, 3 reported utilities that were entirely consistent with the NICE reference case in terms of collecting EQ-5D health state descriptions directly from patients, and valuing these health states using the preferences of a representative sample of the UK general population.[132-134] Two of these studies were conducted in Europe,[132, 133] while the third was a clinical trial conducted in an unspecified, multicentre setting.[134] The health states considered in these 3 studies were as follows:

- Farkkila et al. (2011): metastatic disease and terminal care.
- Lidgren et al. (2007): overall metastatic breast cancer (MBC), MBC with hormone therapy, MBC with chemotherapy, MBC with distant recurrence after 1 month of the first recurrence and MBC with no new distant recurrences after 1 month of the first recurrence.

- Zhou et al. (2009) considered three health states in a population of MBC patients treated with either lapatinib plus capecitabine chemotherapy or capecitabine monotherapy: tumour response, stable disease or progressive disease.

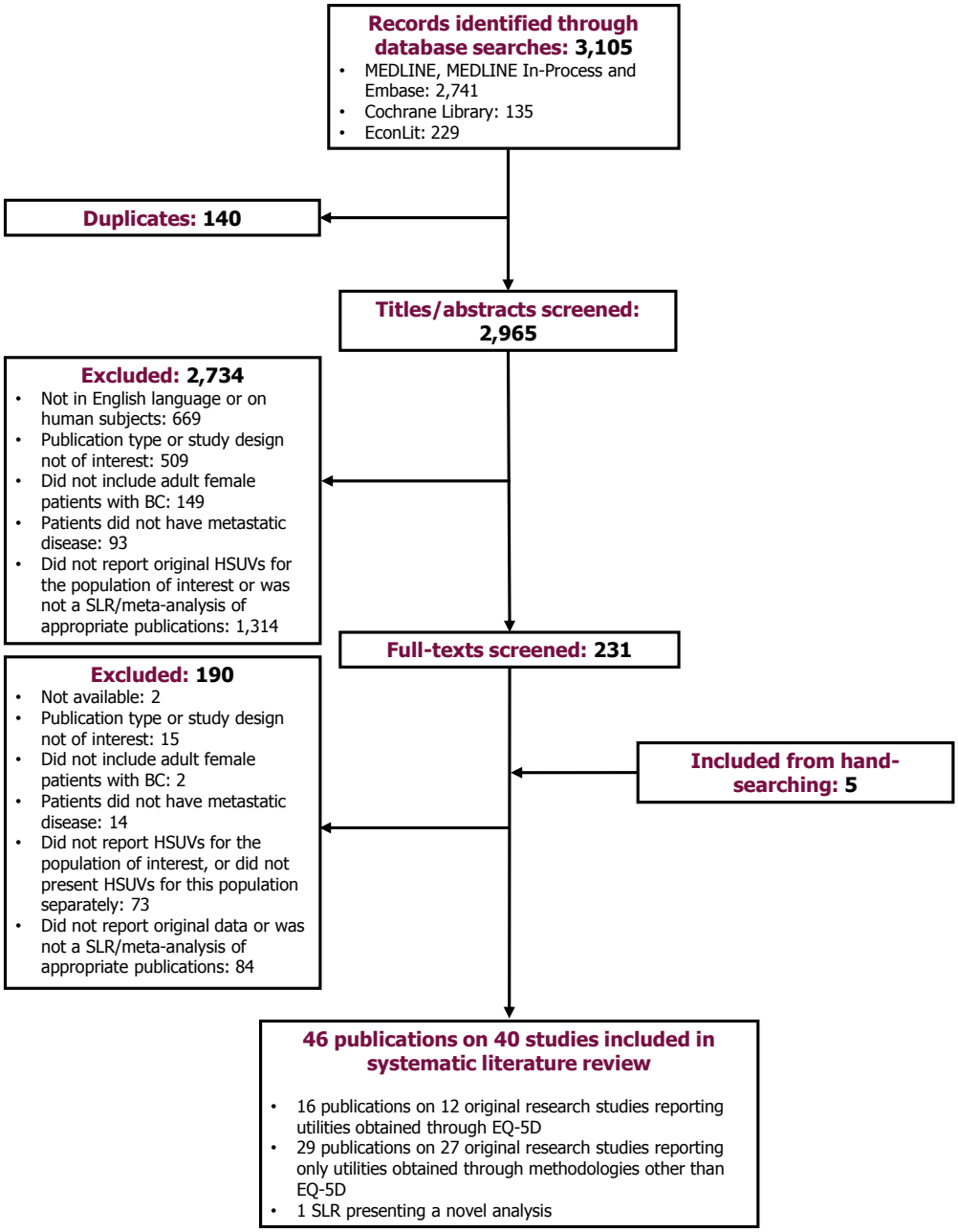
Of the original research studies that reported utility values obtained using methods other than EQ-5D, 2 were conducted in the UK and elicited the preferences of the UK general population.[11, 135] The latter is in line with NICE's viewpoint that, as the UK NHS is tax-funded, the preferences of the UK general population should be taken into account when deciding how limited NHS resources should be spent. Both studies recruited 100 members of the UK general public to rate a series of relevant health states directly using the SG methodology. These health states included:

- Lloyd et al. (2006): Stable MBC with no toxicity, treatment response, disease progression, febrile neutropenia, diarrhoea and vomiting, hand-foot syndrome, stomatitis, fatigue, and hair loss.

- Walker et al. (2006): one state of MBC.

A summary of all included studies is presented in Appendix 20, and references for the associated publications are provided in Appendix 21.

Figure 22. PRISMA flow diagram of studies identified in the HSUV systematic review



Abbreviations: BC, breast cancer; EQ-5D, EuroQol 5 dimensions; HSUV, health state utility value; SLR, systematic literature review

5.4.3.4. Adverse events

The EQ-5D HRQL estimates included in the PALOMA-2 trial are estimates taken from patients whilst on treatment. Consequently, they reflect the health status of the patients incorporating the effect on HRQL of the adverse event profiles associated with the palbociclib and the letrozole regimens in PALOMA-2. Hence, the utility estimates included in the economic model for the palbociclib and the letrozole regimens are already expected to include any disutility associated with adverse events. Therefore, in the base case, no disutility due to adverse events is applied as it would be double-counting. This approach has been previously accepted by NICE in oncology (ID865). A sensitivity analysis is presented where adverse events disutility is included whilst on first-line treatment.

5.4.3.5. Health-related quality-of-life data used in cost-effectiveness analysis

In the pre-progression health state, patients were assumed to be treated with one of the comparators and therefore experience the baseline utilities obtained from the PALOMA-2 EQ-5D analysis.

The baseline utility values for all subsequent post-progression states (three subsequent treatments and BSC) were assumed to be equal. Considering palbociclib had a higher utility pre-progression, this is a conservative assumption as it ignores any beneficial utility 'overhang' from the pre-progression state that patients may have with palbociclib versus letrozole alone. The values were based on the Lloyd 2006 disease progression decrement applied on the stable disease baseline utility value [11] as explained below:

- Stable disease with no toxicity in Lloyd 2006: 0.715 [11]
- Disease progression: -0.272 [11]
- A multiplier for the progressed disease health state was estimated based on the difference of the base utility and the decrement for progression:

$$Multiplier = 1 + \frac{-0.272}{0.715} = 0.620$$

- The multiplier was then applied to the pre-progressed average utility values for palbociclib plus letrozole and letrozole arms (EQ-5D values from PALOMA-2).

$$Utility_{post-progressed} = Multiplier \times Average\_Utility_{pre-progresed}$$
$$= 0.620 \times average([redacted]) = 0.4492$$

The summary of the baseline utility values used in the cost-effectiveness model is presented in Table 62.

Table 62. Summary of utility values for cost-effectiveness analysis

Health state	Letrozole		Palbociclib-letrozole		Source
	Mean value	95% CI	Mean value	95% CI	
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]	PALOMA-2 EQ-5D analysis (data on file) [9]
Post-progression: all lines	0.4492		0.4492		Based on PALOMA-2 EQ-5D analysis (data on file) and the disease progression multiplier from Lloyd 2006 [11]

Abbreviations: CI, confidence interval

5.5. Cost and healthcare resource use identification, measurement and valuation

5.5.1. Resource identification, measurement and valuation studies

5.5.1.1. Search strategy

A *de novo* systematic review was conducted to identify costs and resource use studies published since 2012 in a patient population with advanced/metastatic breast cancer. The systematic review was performed in accordance with the methodological principles of conduct for systematic reviews as detailed in the University of York CRD's "Guidance for Undertaking Reviews in Health Care".[101]

The search was carried out on 21st January 2016 using the following databases:

- MEDLINE and MEDLINE In-Process
- Embase
- The Cochrane Library, specifically the following:
- Health Technology Assessment (HTA) Database
- NHS Economic Evaluation Database (NHS-EED)
- EconLit

Searches of MEDLINE, MEDLINE In-Process and Embase were run simultaneously via the Ovid SP platform. Cochrane Library databases were searched via the Wiley Online platform, and EconLit was searched using the EBSCO platform.

The bibliographies of included articles (including systematic reviews and meta-analyses identified during the abstract review) were hand-searched for references to other potentially relevant studies for inclusion in the systematic review.

A manual search of abstracts from conference proceedings of the following major conferences was also performed on 16th and 17th March 2016:

- EBCC
- ESMO Congress
- iHEA Conference
- ISPOR Annual European and International Meetings

Manual searches for conference abstracts were limited to those published a maximum of two years prior to the search date, as it was assumed that high-quality studies reported in abstract form before this time would have since been published in a peer-reviewed journal.

In addition, the following HTA websites were searched for previous, relevant HTAs on 18th and 21st March 2016:

- NICE
- SMC

The search strategies used in the literature review are provided in Appendix 22.

5.5.1.2. Study selection

To be included in the review, articles had to meet the pre-defined eligibility criteria detailed in Table 63.

The citations found through the searches were first assessed against the eligibility criteria by two independent reviewers based on abstract and title. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. The full-texts of studies meeting the eligibility criteria were obtained and reviewed in more detail by the two independent reviewers. At both the title/abstract and full-text review stages, any disagreements between the reviewers were resolved by discussion until a consensus was met, with a third reviewer making the final decision if necessary. For studies meeting the eligibility criteria after the second (full-text) screening stage, data were extracted by a single reviewer into a pre-specified data extraction grid and verified by a second party.

Table 63. Inclusion and exclusion criteria for the cost and healthcare resource use systematic review

Domain	Description	Exclusion	Rationale
Population	Adult, female patients (≥18 years old) with advanced or metastatic breast cancer	Irrelevant population, or outcomes not reported for the population of interest specifically	This is the patient population relevant to the NICE decision problem for this submission.
Intervention	Any or none	NA	Non-treatment specific cost and resource use data as well as treatment-specific cost and resource use data are relevant for the purposes of this systematic review.
Comparator	Any or none	NA	
Outcomes	Costs and resource use relevant to the UK National Health Service (NHS) and Personal Social Services (PSS), that would be of relevance to a cost-effectiveness model for palbociclib: Frequency and/or duration of costs and resource use associated with administration of drugs (outpatient visits, general practice nurse visits, hospital nurse visits) Wastage of non-oral drugs Premedication Frequency of monitoring tests	No relevant outcomes presented	This list of outcomes encompassed the inputs required for a cost-effectiveness model for palbociclib from a UK perspective.

	(computed tomography [CT] scans, magnetic resonance imaging [MRI], bone scans, ultrasound scans, chest X-rays, Granulocyte colony-stimulating factor [G-CSF], nadir blood count), including whether this varies over time or by type of therapy Frequency and/or duration of costs and resource use associated with best supportive care in both pre-progression and post-progression health states (community nurse, general practitioner visit, GP home visit, clinical nurse specialist, social worker, therapist) Costs associated with terminal care		
Study design	Cost of illness studies, observational studies, RCTs collecting cost and/or resource use data, HTAs reporting primary research	Non-systematic reviews, editorials, case reports	The study designs and publication types specified as eligible for inclusion were those considered most likely to report relevant data.
	Systematic reviews, meta-analyses and previous HTAs were included at the title/abstract screening stage and used for the identification of additional primary studies not identified through the database searches. These were excluded during the full-text review unless they reported any primary research.		
Geographic region	Studies conducted in the UK	Studies not conducted in the UK	Only those studies which presented data relevant to the UK NHS/PSS aligned with the NICE decision problem for this submission.
Language	English	Any other language	The review team did not have the linguistic capability to review non-English language articles, and it was considered unlikely that data relevant to the UK NHS/PSS would have been published in a language other than English.

Date of publication	Studies published since 2012	Studies published prior to 2012	Studies were limited to post-2012 to avoid inclusion of cost and resource use data that were not representative of the current clinical situation.

Abbreviations: CT, computed tomography; GP, general practitioner; G-CSF, granulocyte colony-stimulating factor; MRI, magnetic resonance imaging; NA, not applicable; NHS, National Health Service; PSS, Personal Social Services.

5.5.1.3. Summary of identified studies and results

The systematic literature review did not identify any relevant studies performed in England, but 1 relevant study was identified which was conducted in a single centre in West Wales.

The PRISMA flow diagram of studies identified in the cost and healthcare resource systematic literature review is presented in Figure 23.

A summary of the identified study is presented in Table 64. A summary of the studies excluded at the full-text review stage, and the reasons for their exclusion, is given in Appendix 23.

Figure 23. PRISMA flow diagram of identified studies in the cost and healthcare resource use SLR

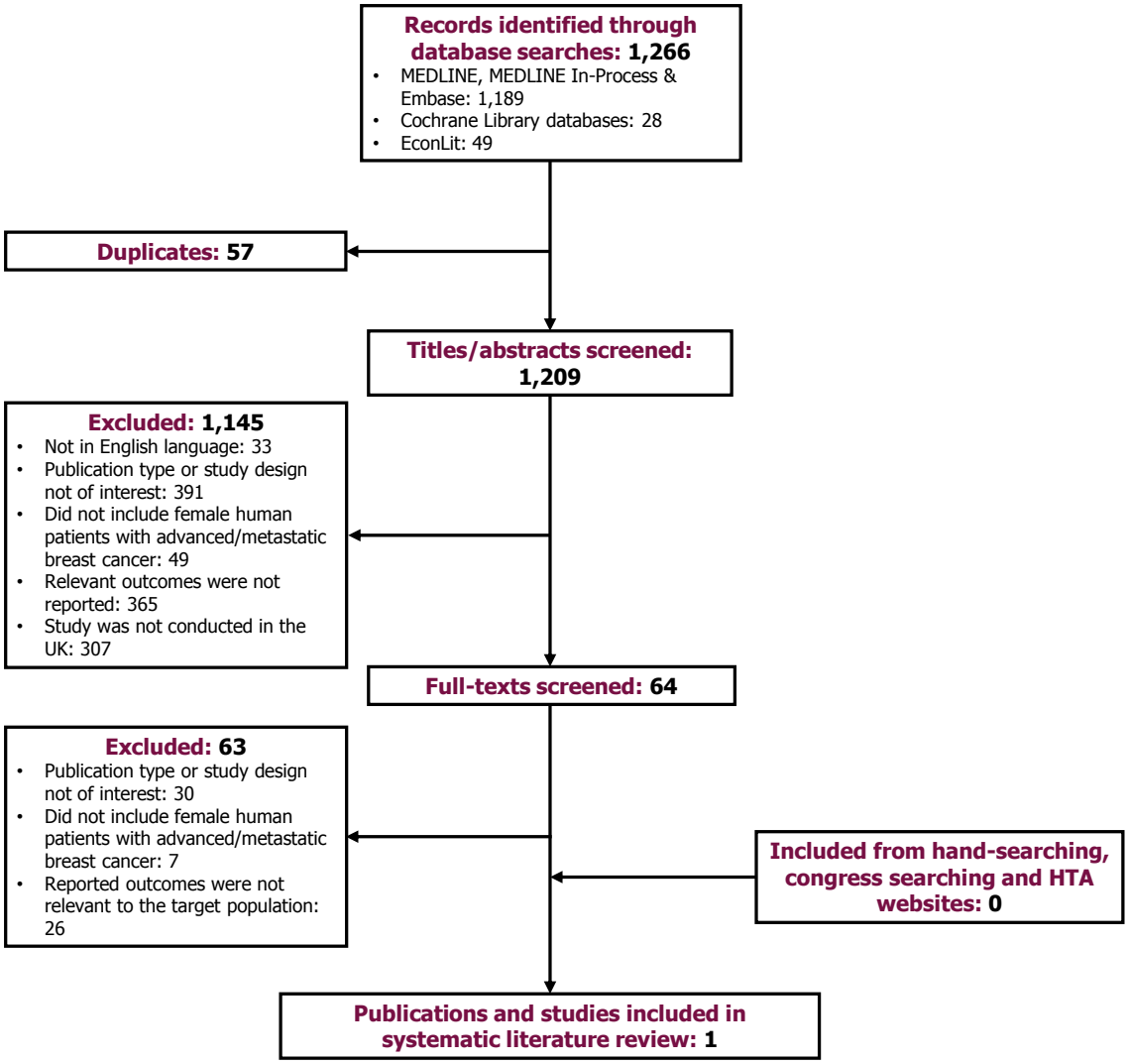

Records identified through database searches: 1,266
MEDLINE, MEDLINE In-Process & Embase: 1,189
Cochrane Library databases: 28
EconLit: 49
Duplicates: 57
Titles/abstracts screened: 1,209
Excluded: 1,145
Not in English language: 33
Publication type or study design not of interest: 391
Did not include female human patients with advanced/metastatic breast cancer: 49
Relevant outcomes were not reported: 365
Study was not conducted in the UK: 307
Full-texts screened: 64
Excluded: 63
Publication type or study design not of interest: 30
Did not include female human patients with advanced/metastatic breast cancer: 7
Reported outcomes were not relevant to the target population: 26
Included from hand-searching, congress searching and HTA websites: 0
Publications and studies included in systematic literature review: 1

Table 64. Summary of the cost and healthcare resource use study identified in the systematic review

<table>
<tr><th>Study</th><th>Objective and patient population</th><th>Country and cost year</th><th>Valuation methods</th><th colspan="3">Technology and other costs</th><th>Resource use</th><th>Applicability to UK clinical practice</th></tr>
<tr><td>Holt et al. 2013[136]</td><td>Objective:
To model the cost-effectiveness of routine Oncotype DX testing in the UK for women with node-negative or minimal node involvement ER+ breast cancer.

Patient population:
146 patients were enrolled in the study, 142 patients were included in the final analysis. All patients were female with excised ER+ and node-negative (pN0, pN0i+) invasive breast cancer or with minimal node involvement (pN1mi).

Study design:
Non-interventional</td><td>Wales

Cost year: 2010</td><td>All patients maintained a diary of medical interactions during the 6 months following inclusion in the study.

<u>Chemotherapy costs</u>
Hospital notes and electronic chemotherapy prescription records were used as well as the patient diaries in order to estimate the total cost of chemotherapy.

<u>Other treatment costs</u>
All other treatment costs were derived from UK-specific sources (not specified).

Treatment costs</td><td colspan="3"><table><tr><th>Cost type</th><th>Chemotherapy mean cost, £ (SD) n=35</th><th>No chemotherapy mean cost, £ (SD) n=107</th></tr><tr><td>GP</td><td>67 (94)</td><td>68 (107)</td></tr><tr><td>GP home visit</td><td>3 (20)</td><td>1 (12)</td></tr><tr><td>GP phone consultation</td><td>1 (4)</td><td>1 (6)</td></tr><tr><td>GP nurse</td><td>4 (19)</td><td>23 (120)</td></tr><tr><td>District nurse</td><td>398 (721)</td><td>29 (151)</td></tr><tr><td>Hospital nurse</td><td>53 (200)</td><td>15 (68)</td></tr><tr><td>Lymphoedema clinic</td><td>16 (52)</td><td>38 (117)</td></tr><tr><td>Hospital doctor</td><td>236 (246)</td><td>218 (294)</td></tr><tr><td>Counsellors</td><td>0 (0)</td><td>11 (85)</td></tr><tr><td>Physiotherapist</td><td>1 (6)</td><td>3 (14)</td></tr><tr><td>Plastic surgeon</td><td>14 (46)</td><td>8 (46)</td></tr><tr><td>Hospital stay</td><td>596 (1689)</td><td>90 (482)</td></tr><tr><td>Herceptin</td><td>2,241 (8,509)</td><td>0 (0)</td></tr><tr><td>Consultant</td><td>79 (107)</td><td>82 (95)</td></tr><tr><td>CT SIM planning</td><td>1,312 (1,158)</td><td>1,212 (1,065)</td></tr></table></td><td>Not reported</td><td>Applicable. The study was conducted in a Welsh cancer centre and medical interactions directly within the patient population were recorded.</td></tr>
</table>

			were inflated where necessary using the Hospital and Community Health Services pay and price inflation index (2010).	Radiotherapy	6,987 (4,171)	6,680 (4,286)		
				Radiotherapy review	138 (89)	135 (103)		
				Radiotherapy boosts	1,433 (2,299)	768 (1,799)		
				Mould room	6 (21)	5 (20)		
				FEC	1,119 (892)	0 (0)		
				TAC	1,465 (2,116)	0 (0)		
				Pre-chemotherapy assessment	60 (44)	0 (0)		
				Pre-chemotherapy blood tests	27 (8)	0 (0)		
				Oncologist appointment	157 (150)	0 (0)		
				MUGA	4 (16)	0 (0)		
				ECHO	9 (28)	0 (0)		
				CDU doctor	46 (84)	0 (0)		
				CDU triage nurse	42 (71)	0 (0)		
				Bone scan	26 (64)	56 (84)		
				GCSF	3,510 (8,246)	0 (0)		
				Total	20,418 (13,052)	9,568 (6,087)		

5.5.2. Intervention and comparators' costs and resource use

Drug administration-related costs for the model consisting of drug acquisition, pack wastage for oral tablets and capsules, administration, and monitoring costs, were considered for inclusion. The assumptions and inputs behind each type of cost are presented in the following sections.

5.5.2.1. Drug acquisition costs

The source of drug acquisition costs for letrozole was the electronic market information tool eMIT,[30] and the licensed dose was obtained from the Summary of Product Characteristics (SPC).[31] Data on drug acquisition cost inputs, licensed dose values, and available drug formulations are reported in Table 65.

Table 65. Drug acquisition cost inputs

Technology	Licensed dose (mg)	Package information	Cost (£) per package	Source
Palbociclib	125mg daily used in model (100mg and 75mg also available)	125mg tablets, 21 tablets in pack	Proposed list price: £2,950	Unpublished. Note, the same price for all mg
Letrozole	2.5mg daily	2.5mg tablets, 28 tablets in pack	£1.52 (SD: £1.47)	eMIT 2016[30]

Abbreviations: eMIT, electronic market information tool; SD, standard deviation

5.5.2.2. Wastage costs

For both palbociclib and letrozole, each pack contains 28 days' treatment (see section 2.3). It was assumed that once a model cycle was started, the full cost of a pack is incurred and any wastage is inherently costed in that cycle. No additional drug wastage costs were considered in the model for either arm.

5.5.3. Monitoring costs

The model considers a number of treatment-related monitoring costs, which are presented in Table 66 for each treatment. The unit costs for each monitoring resource are listed in Table 67.

Resource use was guided by NICE CG81,[60] and then further scrutinised by clinical nurse specialists (CNSs), whose opinions were solicited in April 2016 via telephone interviews conducted by a third party, to inform the frequency of several resources (Table 66).

Table 66. Monitoring costs assumptions for each drug

Drug	Monitoring resource use assumption	Source
Palbociclib	1 full blood count (FBC) every month	Draft SPC in Appendix 1
Letrozole	No monitoring resource use	Assumption

Abbreviations: FBC, full blood count; FDA, Food and Drug Administration; KOL, key opinion leader

Table 67. Unit costs for monitoring resource use

Resource use	Unit cost (£)	Note about unit cost	Source
FBC	£3.01	DAPS05 Haematology	NHS reference costs 2014/15[32]

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

5.5.4. Administration costs

The treatments considered in the model are self-administered orally by the patient, and therefore are assumed to incur no administration costs.

5.5.5. Health-state unit costs and resource use

Resource use considered in the model was both health-state and treatment-line dependent. Data to inform estimates of resource use for each line of treatment was based upon the packages of resource use in the NICE Clinical Guideline 81, published in 2009.[60]

To accurately reflect clinical practice in 2016 and to accurately estimate the change in resource use as patients progress through lines of therapy, the CNSs were consulted to update and to increase the specificity of these package of care descriptions. Key issues from the CNSs' evaluation of the packages, along with any areas of remaining uncertainty, were discussed with a multi-disciplinary team responsible for treating metastatic breast cancer patients at a centre in England, which including oncologists, a pharmacist, and another clinical nurse specialist. The model therefore uses the most appropriate elements of healthcare resources that best reflect clinical practice. Details on the resource use included in the model for the 'pre-progression' state (i.e. first-line) and then for the 'progressed' state (i.e. second-, third- and fourth-line, and then also best supportive care) are presented in Table 68, while unit costs are listed in Table 69.

In addition to the above, terminal care costs are implemented in the model for patients with progressed disease for the last 2 weeks of the patient's life and consist of time spent at the hospital, hospice, and home. The proportion of patients distributed to each setting was based on data from the NICE CG 81 Package 3: 40% at the hospital, 10% at the hospice, and 50% at home.[60] The resource use and unit costs for terminal care are shown in Table 70.

Table 68. Background health state resource use

Line of treatment	Resource use	Frequency / length of visit	Travel time cost? (i.e. home visit)
1st line (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	
	GP contact (surgery visit)	Once every month, visit lasting 11.7 min	
	Clinical nurse specialist	Once every month, visit lasting 1 hour	
2nd line (post-	Community nurse home visit	Once every quarter, visit lasting 20	Yes

Line of treatment	**Resource use**	**Frequency / length of visit**	**Travel time cost?** (i.e. home visit)
progression, subsequent treatment 1)		min	
	Consultant visit (oncologist)	Once every 6 months, visit lasting 1 hour	
	GP contact (surgery visit)	Once every month, visit lasting 11.7 min	
	Clinical nurse specialist	Once every month, visit lasting 1 hour	
	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	
	CT scan	Once every 3 months	
3rd line (post-progression, subsequent treatment 2)	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	
	GP contact (surgery visit)	Thrice every 2 months, visit lasting 11.7 min	
	Clinical nurse specialist	Twice in a month, visit lasting 1 hour	
	Social worker home visit	Once every 2 months, visit lasting 30 min	Yes
	Palliative care (outpatient setting)	Once every month, visit lasting 20 min	
	CT scan	Once every 3 months	
	Therapist	Once every 2 months, visit lasting 30 min	
	Physiotherapist	Once every 2 months, visit lasting 30 min	
4th line (post-progression, subsequent treatment 3)	Community nurse home visit	Once every month, visit lasting 20 min	Yes
	Consultant visit (oncologist)	Once every month, visit lasting 1 hour	
	GP contact (surgery visit)	Twice every month, visit lasting 11.7 min	
	Clinical nurse specialist	Thrice every month, visit lasting 1 hour	
	Social worker home visit	Once every month, visit lasting 30 min	Yes
	Palliative care (outpatient setting)	Once every month, visit lasting 15 min	
	CT scan	Twice every 3 months	
	Therapist	Once every 2 months, visit lasting 30 min	
	Physiotherapist	Once every month, visit lasting 30 min	

Line of treatment	Resource use	Frequency / length of visit	Travel time cost? (i.e. home visit)
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	
	Social worker home visit	Once every month, visit lasting 30 min	
	Palliative care (outpatient setting)	Three times every month, visit lasting 15 min	
	Therapist	Once every 2 month, visit lasting 30 min	
	Physiotherapist	Once every month, visit lasting 30 min	
	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 69. Unit costs for background health state resource use

Resource use	Raw unit cost (£)	Note about unit cost	Source
Community nurse visit	£55.50	Average between per hour, without qualifications (£44) and per hour of patient-related work, with qualifications (£67).	PSSRU 2015, p. 169[137]
Community nurse travel time	£27.75	Assume half of the community nurse visit unit cost to reflect half an hour of travel.	Assumption
Consultant visit (oncologist) – first visit	£177.83	WF01A service code 800 Clinical Oncology (Previously Radiotherapy) Non-Admitted Face to Face Attendance, First	NHS Reference costs 2014/15[32]
Consultant visit (oncologist) – follow-up visit	£131.97	WF01A service code 800 Clinical Oncology (Previously Radiotherapy) Non-Admitted Face to Face Attendance, Follow-up	NHS Reference costs 2014/15[32]
GP contact (surgery visit)	£38.50	11.7 minutes visit, average between excluding staff time, no qualifications (£33) and including staff time, with qualifications (£44)	PSSRU 2015, p. 177[137]
GP contact (home visit)	£198.00	Average between per hour of patient contact, without qualifications (£171) and with qualifications (£225). Travel cost is included.	PSSRU 2015, p. 177[137]
Clinical nurse specialist	£86.00	Average between per hour of client contact cost, without qualifications (£81) and with qualifications (£91)	PSSRU 2015, p. 175[137]

Resource use	Raw unit cost (£)	Note about unit cost	Source
Social worker visit	£67.00	Average between per hour of client-related work, without qualifications (£55) and with qualifications (£79)	PSSRU 2015, p. 188[137]
Social worker travel time	£33.50	Assume half of the social worker visit unit cost to reflect half an hour of travel.	Assumption
Palliative care	£55.50	Assume same cost as community nurse.	Assumption
CT scan	£121.68	RD24Z Computerised Tomography Scan of two areas, with contrast	NHS Reference costs 2014/15[32]
Therapist	£39.00	Average between per hour hospital occupational therapist, without qualifications (£34) and per hour community occupational therapist, with qualifications (£44)	PSSRU 2015, p. 191 (community occupational therapist), 218 (hospital occupational therapist)[137]
Physiotherapist	£36.00	Average between per hour without qualifications (£34) and with qualifications (£38)	PSSRU 2015, p. 218 (hospital occupational therapist)[137]
Lymphoedema nurse	£55.50	Assume same cost as community nurse home visit and travel time to reflect half an hour of travel.	Assumption

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

Table 70. 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 CG 81 Package 3[60]	£5,521.73	NICE CG 81 Package 3 unit costs, [60] inflated from 2006/07 to 2014/15 values[137]
Hospice	10%		£6,883.98	
Home	50%		£2,848.87	

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

5.5.6. Adverse event unit costs and resource use

As discussed in 5.3.4, comprehensive, multi-disciplinary input was sought from clinical experts (oncologists, nurse specialists and pharmacists) from centres across the UK regarding the patient and resource impact of adverse events. On the basis of this feedback, the model assumed that all adverse event occurring together would incur one disutility (rather than cumulative disutility) and that events occurring together would incur one cost (again, rather than cumulative.) The resource use costs associated with the adverse events are listed in Table 71.

Neutropenia was the most common event for both grade 3 and grade 4 severity, and it was used as indicative of the resource use for managing patients on palbociclib plus letrozole and letrozole alone. The model assumed that the cost of the event was incurred once as opposed to a repeated cost.

Along with the assumptions around resource use required to treat the event, Table 71 also presents sourced unit costs for the management from NHS Reference Costs and the PSSRU. The model assumed that the duration of the event and its management costs would last for less than a cycle.

Table 71. Resource use assumptions and unit costs for grade 3 or 4 adverse events

Adverse event	Resource use assumption	Unit cost (£)	Note about unit cost	Source
Neutropenia (grade 3)	1 oncologist visit per event (20 min visit) for patient management and dose modification	£43.99	WF01A service code 800 Clinical Oncology (Previously Radiotherapy) Non-Admitted Face to Face Attendance, Follow-up	NHS Reference costs 2014/15[32]
Neutropenia (grade 4)	1 oncologist visit per event (30 min visit) for patient management and dose modification	£65.99		

5.5.7. Miscellaneous unit costs and resource use

None applicable.

5.6. Summary of base case de novo analysis inputs and assumptions

5.6.1. Summary of base case de novo analysis inputs

Table 72. Summary of variables applied in the economic model

Category	Variable	Value	Variance	Source/assumption
General settings of the model				
General settings of the model	Cycle length (days)	28	Fixed	Assumption based on the duration of each treatment sequence
	Time horizon	Lifetime (40 years)	Fixed	To ensure the analysis captures all relevant costs and HRQL impairment
	Discount rate – effect	3.50%	Fixed	NICE reference case[86]
	Discount rate - cost	3.50%	Fixed	NICE reference case[86]
	WTP	£30,000	Fixed	NICE reference case[86]
Sequences				
Number of cycles spent in each sequence	PPS – first treatment	6	5 - 7	See section 5.2.2
	PPS – second treatment	6	5 - 7	
	PPS – third treatment	6	5 - 6	
Proportion patients on treatment	PPS – first treatment	75%	50% - 100%	See section 5.2.2
	PPS – second treatment			
	PPS – third treatment			
Efficacy probabilities				

Category	Variable	Value	Variance	Source/assumption
LET_PBO and PAL_LET	PFS	Time-dependent	N/A	Based on PFS survival analysis of PALOMA-2 data (see section 5.3.1)
	OS	Time-dependent	N/A	Assuming the PFS gain is equal to the OS gain (base-case); Based on OS survival analysis of PALOMA-1 data (sensitivity analysis); based on the Beauchemin linear regression method (sensitivity analysis). See section 5.3.2.
Safety probabilities				
Duration on treatment	PAL_LET arm	603 days	Fixed	PALOMA-2 CSR[9]
	LET_PBO arm	420 days	Fixed	PALOMA-2 CSR[9]
Annualised probabilities for duration on treatment	Any grade 3 event (PAL_LET arm)	44.38%	Fixed	PALOMA-2 CSR[9], number any grade 3 events = 276, number patients in arm = 444
	Any grade 3 event (LET_PBO arm)	19.44%	Fixed	PALOMA-2 CSR[9], number any grade 3 events = 49, number patients in arm = 222
	Any grade 4 event (PAL_LET arm)	8.39%	Fixed	PALOMA-2 CSR[9], number any grade 4 events = 60, number patients in arm = 444
	Any grade 4 event (LET_PBO arm)	1.95%	Fixed	PALOMA-2 CSR[9], number any grade 4 events = 5, number patients in arm = 222
Line-related utilities				
Baseline utility (pre-progressed state)	LET_PBO arm	[redacted]	[redacted]	PALOMA-2 CSR[9]
	PAL_LET arm	[redacted]	[redacted]	
Disease progression multiplier	Same multiplier for both arms	0.62	0.35 – 0.42	Calculated from Lloyd et al. 2006[11] using the base-state utility value and the disease progression value
AE multiplier	(For sensitivity analysis)	0.83	0.012	Calculated from Lloyd et al. 2006[11] by taking the average of all adverse event decrements
Duration of AE (proportion of 28-day cycle) (for sensitivity analysis)				
Duration of event	Any grade 3 event	0.5	0.45 – 0.55	Assumption
	Any grade 4 event			
Treatment cost				
Palbociclib cost/pack	125mg tablet, 21 tablets in pack	£2,950	Fixed	Internal, unpublished
Letrozole cost/pack	2.5mg tablet, 28 tablets in pack	£1.52	SD = £1.47	eMIT[30]
Monitoring costs				
PAL_LET arm	Full blood count –	1.0	0.5 – 2.0	Draft SPC Appendix 1

Category	Variable	Value	Variance	Source/assumption
	frequency			
Adverse events costs				
Cost of managing most prevalent AEs	Neutropenia (grade 3)	£44	£29 - £53	Assume 1 oncologist visit per event (20 min)[138]
	Neutropenia (grade 4)	£66	£44 - £80	Assume 1 oncologist visit per event (30 min)[138]
Health state-dependent resource use frequency and length of stay				
1st line frequency of resource use (per cycle)	Community nurse home visit – frequency	0.3	0.0 – 1.0	See section 5.5.5
	Community nurse home visit – length of visit (hour)	0.3	0.2 – 0.5	
	Consultant visit (oncologist) – frequency	0.2	0.1 – 0.3	
	Consultant visit (oncologist) – length of visit (163pt)	1	0.8 – 1.3	
	GP contact (surgery visit) – frequency	1.0	0.5 – 1.5	
	Clinical nurse specialist – frequency	1.0	0.3 – 2.0	
	Clinical nurse specialist – length of visit (hour)	1.0	0.8 – 1.3	
2nd line frequency of resource use (per cycle)	Community nurse home visit – frequency	0.3	0.0 – 1.0	See section 5.5.5
	Community nurse home visit – length of visit (hour)	0.3	0.2 – 0.5	
	Consultant visit (oncologist) – frequency	0.2	0.1 – 0.3	
	Consultant visit (oncologist) – length of visit (hour)	1.0	0.8 – 1.3	
	GP contact (surgery visit) – frequency	1.0	0.5 – 1.5	
	Clinical nurse specialist – frequency	1.0	0.3 – 2.0	
	Clinical nurse specialist – length of visit (hour)	1.0	0.8 – 1.3	
	Social worker – frequency	0.5	0.0 – 1.0	
	Social worker – length of visit (hour)	0.5	0.3 – 0.7	
	Palliative care (e.g. change of analgesia pump, outpatient) – frequency	0.5	0.0 – 1.0	
	Palliative care – length of visit (hour)	0.3	0.2 – 0.5	
	CT scan – frequency	0.3	0.0 – 0.5	
3rd line frequency of resource use (per cycle)	Community nurse home visit – frequency	0.7	0.3 – 1.0	See section 5.5.5
	Community nurse home visit – length of visit (hour)	0.3	0.2 – 0.5	
	Consultant visit (oncologist) – frequency	0.5	0.3 – 1.0	
	Consultant visit (oncologist) – length of	1.0	0.8 – 1.3	

Category	Variable	Value	Variance	Source/assumption
	visit (hour)			
	GP contact (surgery visit) – frequency	1.5	1.0 – 2.0	
	Clinical nurse specialist – frequency	2.0	1.0 – 3.0	
	Clinical nurse specialist – length of visit (hour)	1.0	0.8 – 1.3	
	Social worker – frequency	0.5	0.0 – 1.0	
	Social worker – length of visit (hour)	0.5	0.3 – 0.7	
	Palliative care (e.g. change of analgesia pump, outpatient) – frequency	1.0	0.5 – 1.5	
	Palliative care – length of visit (hour)	0.3	0.2 – 0.5	
	CT scan – frequency	0.3	0.0 – 0.5	
	Therapist – frequency	0.5	0.0 – 1.0	
	Therapist – length of visit (hour)	0.5	0.3 – 0.7	
	Physiotherapist – frequency	0.5	0.0 – 1.0	
	Physiotherapist – length of visit (hour)	0.5	0.3 – 0.7	
4th line frequency of resource use (per cycle)	Community nurse home visit – frequency	1.0	0.5 -1.5	See section 5.5.5
	Community nurse home visit – length of visit (hour)	0.3	0.2- 0.5	
	Consultant visit (oncologist) – frequency	1.0	0.5 – 1.5	
	Consultant visit (oncologist) – length of visit (hour)	0.5	0.0 -1.0	
	GP contact (surgery visit) – frequency	2.0	1.5 – 2.5	
	Clinical nurse specialist – frequency	3.0	2.0 – 3.0	
	Clinical nurse specialist – length of visit (hour)	1.0	0.8 – 1.3	
	Social worker – frequency	1.0	0.5 – 1.5	
	Social worker – length of visit (hour)	0.5	0.3 -0.7	
	Palliative care (e.g. change of analgesia pump, outpatient) – frequency	1.0	0.5 – 1.5	
	Palliative care – length of visit (hour)	0.25	0.2 – 0.3	
	CT scan – frequency	0.7	0.0 – 1.0	
	Therapist – frequency	0.5	0.0 – 1.0	
	Therapist – length of visit (hour)	0.5	0.3 – 0.7	
	Physiotherapist – frequency	1.0	0.5 – 1.5	
	Physiotherapist – length of visit (hour)	0.5	0.3 – 0.7	

Category	Variable	Value	Variance	Source/assumption
BSC frequency of resource use (per cycle)	Community nurse home visit – frequency	3.0	2.0 – 4.0	See section 5.5.5
	Community nurse home visit – length of visit (hour)	0.3	0.25 – 0.4	
	GP contact (home visit) – frequency	2.0	1.0 – 4.0	
	Clinical nurse specialist – frequency	3.0	2.0 – 4.0	
	Clinical nurse specialist – length of visit (hour)	1.0	0.8 – 1.3	
	Social worker – frequency	1.0	0.5 – 2.0	
	Social worker – length of visit (hour)	0.5	0.3 – 0.7	
	Palliative care (e.g. change of analgesia pump, outpatient) – frequency	3.0	2.0 – 4.0	
	Palliative care – length of visit (hour)	0.25	0.2 – 0.3	
	Therapist – frequency	0.5	0.3 – 0.8	
	Therapist – length of visit (hour)	0.5	0.3 – 0.7	
	Physiotherapist – frequency	1.0	0.5 – 2.0	
	Physiotherapist – length of visit (hour)	0.5	0.3 – 0.7	
	Lymphoedema nurse (community nurse cost home visit) – frequency	1.0	0.0 – 2.0	
	Lymphoedema nurse (community nurse cost home visit) – length of visit (hour)	0.3	0.2 – 0.5	
Health state-dependent resource use – unit costs				
Health-care professional and diagnostic services unit costs	Community nurse visit	£55.50	£44.00 - £67.00	PSSRU 2015, p. 169[137]
	Community nurse home visit – travel time	£27.75	£22.00 - £33.50	PSSRU states “no information is available for average mileage covered per visit.” Hence, it is assumed that an appointment would carry 30 minutes of travel time there and back.
	Clinical nurse specialist	£86.00	£81.00 - £91.00	PSSRU 2015, p. 175[137]
	Social worker	£67.00	£55.00 - £79.00	PSSRU 2015, p. 188[137]
	Social worker – travel time	£33.50	£27.50 - £39.50	Assume half of social worker consultation time.
	Oncologist – first visit	£177.83	£127.57 - £200.37	NHS Reference costs 2014/15: WF01B service code 800 Clinical Oncology (Previously Radiotherapy) Non-Admitted Face to Face Attendance, First[138]
	Oncologist – follow-up visit	£131.97	£87.72 - £159.94	NHS Reference costs 2014/15: WF01A service

Category	Variable	Value	Variance	Source/assumption
				code 800 Clinical Oncology (Previously Radiotherapy) Non-Admitted Face to Face Attendance, Follow-up[138]
	GP contact (per surgery visit)	£38.50	£33.00 - £44.00	PSSRU 2015, p. 177[137]
	GP contact (home visit)	£198.00	£171.00 - £225.00	PSSRU 2015, p. 177[137]
	Therapist	£39.00	£34.00 - £44.00	PSSRU 2015, pp. 191, 218[137]
	Physiotherapist	£36.00	£34.00 - £38.00	PSSRU 2015, p. 218, £34 (£38) per hour.[137]
	Full blood count	£3.01	£1.87 - £3.67	NHS Reference costs 2014/15: DAPS05 Haematology[138]
Terminal care – resource use				
Terminal care cost (last 2 weeks) by setting	At hospital	0.4	Fixed	NICE CG81 2009[60]; NICE TA295[86]
	At hospice	0.1	Fixed	
	At home	0.5	Fixed	
Terminal care – unit costs				
Terminal care cost (last 2 weeks) by setting	At hospital	£5,521.7	£3,865.2 - £7,178.3	NICE CG81 2009[60]; NICE TA295[86]
	At hospice	£6,884.0	£4,818.8 - £8,949.2	
	At home	£2,848.9	£1,994.2 - £3,703.5	

Abbreviations: AE, adverse event; BSC, best supportive care; CT, computed tomography; GP, general practitioner; HRQL, health-related quality of life; LET_PBO, letrozole arm; N/A, not applicable; OS, overall survival; PAL_LET, palbociclib plus letrozole arm; PFS, progression-free survival; PPS, post-progressed state; WTP, willingness to pay

5.6.2. Assumptions

Table 73. Key model assumptions

Model input	Assumption	Source / rationale
Model duration	Lifetime	See section 5.2.2
Cycle length	28 days	This is the length of a treatment cycle for both the intervention and comparator, and is short enough to model outcomes accurately. Drug acquisition cost is incurred at the start of the cycle so pack wastage is included.
Half-cycle correction	No half-cycle correction	No correction was implemented due to the short cycle length (see section 5.2.2)
Discounting	3.5% for costs and benefits	NICE reference case[86]
Perspective	NHS and PSS	NICE reference case[86]
Cost inputs	NHS Reference costs; PSSRU; eMIT for generic drug costs	Implicitly in line with reference case; eMIT provides the most conservative acquisition costs for generic therapies.
Progression-free survival	PFS was extrapolated using Weibull distributions and curves were fit independently. These	PALOMA-2 phase III clinical data provided head-to-head evidence, and as patient level data were available, independent curves were

Model input	Assumption	Source / rationale
	distributions were the best fit and provided a more conservative median PFS gain (9.2 months) for palbociclib than was observed in PALOMA-2 (10.3 months)	fit. The Weibull distribution was selected as the best fit curves for each of the two arms. However, it is likely the proportional hazards assumptions holds. See section 5.3.1.
Overall survival	Adjusted OS to reflect median PFS gain translating to median OS gain (9.2 months)	PALOMA-2 phase III clinical data provided head-to-head evidence, and as patient level data were available, independent curves were fit. The Weibull distribution was selected as the best fit curves for each of the two arms. However, it is likely the proportional hazards assumptions holds. See section 5.3.2
Safety	The base case includes the cost of grade 3 and 4 events in any arm that exceed incidence of >5%.	Event incidence was sourced from the head-to-head PALOMA-2 RCT, and, in line with previous oncology modelling, only grade 3 and 4 adverse events were considered. See section 5.3.4.
	Any events of grade 5 were not considered	Due to the low incidence (2.3% in the palbociclib arm and 1.8% in the letrozole arm), grade 5 events were not considered.
Administration cost	No administration costs for either regimen	Both regimens are orally self-administered by patients at home, and are not chemotherapies. It has been assumed that administration costs are thus not incurred.
Adverse events costs	AE costs were assumed to be those of neutropenia grade 3 (20 min oncologist visit) and grade 4 (30 min oncologist visit).	See section 5.5.6
Health state-dependent resource use	The model assumes an increasing health state-dependent resource use based on visits to several health professionals (differing in frequency per cycle and length of visit depending on the health state requirements).	See section 5.5.5
Terminal care resource use	Assumed the same resource use split (40% hospital/10% hospice/50% home).	In line with NICE CG package 3.[60] See section 5.5.5
Terminal care unit costs	Inflated the NICE CG81 terminal care resource use unit costs to 2014/15 values from 2006/07 values.	The inflation indices were obtained from PSSRU 2015[137]
Treatment duration	Both regimens are administered until progression	Both the intervention and comparator are treatments that are not restricted to a pre-defined number of cycles, but rather ore offered as treatments until disease progression. It is assumed that treatment costs

Model input	Assumption	Source / rationale
		are incurred up to the point the patient leaves the pre-progressed state.
Subsequent treatment lines	Considering up to 4 lines of therapy, followed by best supportive care	In ER+ HER2- ABC, patients commonly receive multiple lines of therapy and so grouping those who have progressed into one single post-progression state is less accurate and less reflective of clinical practice. By considering evidence to model subsequent treatment lines independently, and validating these through UK clinical expert opinion, the model better reflects the clinical care pathway of women in the UK with ABC (see section 5.3.3).
Sequences	Allowing 25% of the patients to move to BSC instead of remaining in subsequent lines of active therapy	See section 5.2.2 and 5.3.3
Utility values	Utility values were taken from the EQ-5D in the head-to-head clinical trial for the pre-progression states, and from the literature for post-progression.	The 'gold standard' source of utility data were available from PALOMA-2 for the pre-progression state. In the post-progression state, utilities were reduced accordingly, based upon data from a study by Lloyd.[11]
Disease progression multiplier	The model assumes the same disease progression multiplier for both arms, calculated from Lloyd et al. 2006[11] using the Lloyd base-state utility value and the disease progression value.	See section 5.4.3.5
Adverse events utility decrement	It was assumed that there would be no explicit decrements of disutility associated with adverse events, beyond existing on-treatment EQ-5D utility. A sensitivity analysis included disutility.	The utility estimates included in the economic model for both arms are taken directly from patients on treatment in the PALOMA-2 trial, and hence this HRQL reporting is expected to already reflect the negative changes in utility incurred through the adverse event profiles of the treatments. The impact of including a disutility due to adverse events is perceived to be 'double-counting', however its inclusion was explored in a sensitivity analysis.
Duration of adverse events in the sensitivity analysis	Grade 3 and grade 4 neutropenia were assumed to last for half the cycle length (2 weeks).	See section 5.8.2.2

Abbreviations: ABC, advanced breast cancer; AE, adverse event; BSC, best supportive care; CG, Clinical Guideline; HRQL, health related quality of life; LET_PBO, letrozole only arm; NHS, National Health Service; OS, overall survival; PAL_LET, palbociclib plus letrozole arm; PFS, progression-free survival; PPS, post-progressed state; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit

5.7. Base case results

5.7.1. Base case incremental cost effectiveness analysis results

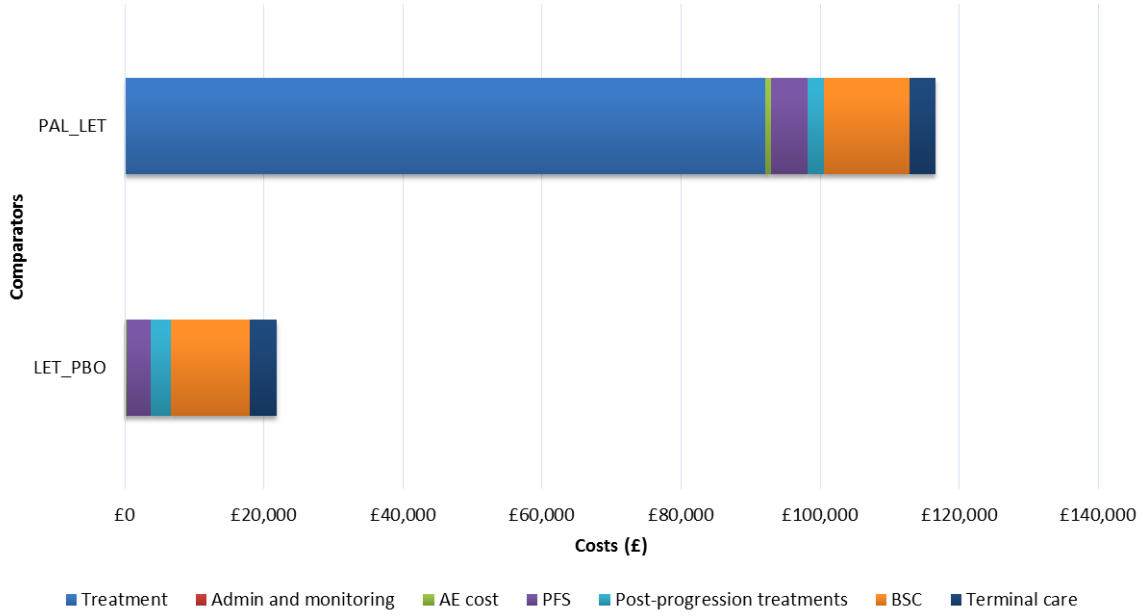
Nominal base case deterministic results of palbociclib plus letrozole versus the letrozole alone are presented in Table 74. The base case deterministic ICER was £150,869 per QALY. The breakdown of the total costs is reported in Figure 24 below, whilst the breakdown of total QALYs is presented in Figure 25. Owing to the limitations of the current analytical framework, these do not comprehensively reflect the value of palbociclib.

Table 74. Base case deterministic results for palbociclib+letrozole vs letrozole (palbociclib at list price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental			ICER (£ per QALY)
				Costs (£)	LYGs	QALYs	
Letrozole alone	£21,843	3.02	1.77				
Palbociclib+ letrozole	£116,696	3.79	2.40	£94,853	0.78	0.63	£150,869

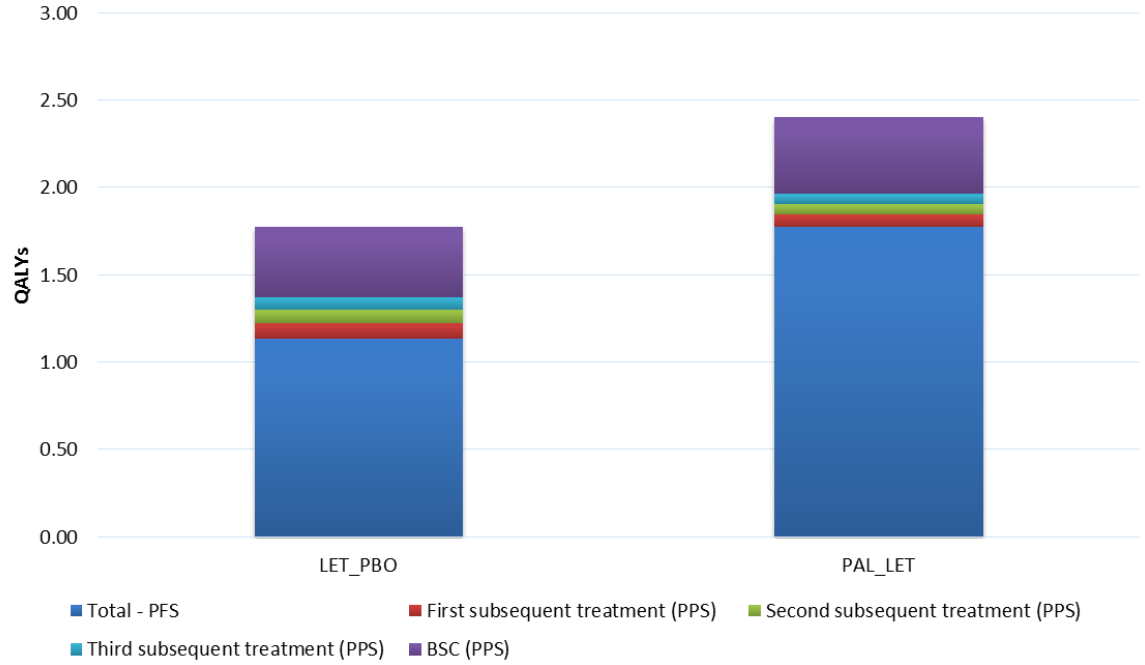
Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; LYG, life year gained; QALY, quality-adjusted life year

Figure 24. Breakdown of total costs (palbociclib list price)



Abbreviations: AE, adverse event; BSC, best supportive care; LET_PBO, letrozole only arm; PAL_LET, palbociclib plus letrozole arm; PFS, progression-free survival

Figure 25. Breakdown of total QALYs (palbociclib list price)



Abbreviations: BSC, best supportive care; LET_PBO, letrozole only arm; QALY, quality-adjusted life year; PAL_LET, palbociclib plus letrozole arm; PFS, pre-progressed state; PPS, post-progression state

5.7.2. Clinical outcomes from the model

The clinical outcomes from the modelled base case are presented in Table 75 for palbociclib plus letrozole, and

Table 76 for letrozole alone. For the letrozole alone comparison, the model's clinical outcomes are externally validated via a comparison versus previously published literature.

Table 75. Clinical outcomes (in months) from the model versus published first-line studies – palbociclib+letrozole

Outcome	Palbociclib plus letrozole	
	Model result (adjusted OS)	**Head-to-head RCTs: PALOMA-2 (PFS) PALOMA-1 (OS)**
Median PFS (months)	24.9 months	24.8 months
Patients progression-free at 30 months	40%	40%
Mean PFS	30.9 months	*Not reached, not reported*
Median OS (months)	44.3 months	37.5 months
Patients alive at 48 months	45%	41%
Mean OS (months)	50.1 months	*Not reached, not reported*

Abbreviations: OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial

Table 76. Clinical outcomes (in months) from the model versus published first-line studies – letrozole

Outcome	Letrozole alone		
	Model result	**Head-to-head RCTs: PALOMA-2 (PFS) PALOMA-1 (OS)**	**Previously published literature**
Median PFS (months)	15.7 months	14.5 months	14.7 months in ER+ HER2- [130]
Patients progression-free at 30 months	21%	20%	20% [38, 130, 131]
Median OS (months)	35.1 months	33.3 months	34 to 38.2 months [38, 92]
Patients alive at 48 months	30%	33%	30% to 35% [36, 38, 92]
Mean OS (months)	38.9 months	*Not reached, not reported*	-

Abbreviations: OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial

5.7.3. Disaggregated results of the base case incremental cost effectiveness analysis

Table 77. Summary of QALY gain by health state

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	% absolute increment
Pre-progressed state	1.7763	1.1383	0.6380	0.6380	101.47%
Post-progressed state (1st subsequent treatment)	0.0699	0.0882	-0.0184	0.0184	2.92%
Post-progressed state (2nd subsequent treatment)	0.0625	0.0775	-0.0150	0.0150	2.39%
Post-progressed state (3rd subsequent treatment)	0.0552	0.0664	-0.0112	0.0112	1.79%
Post-progressed state (BSC)	0.4380	0.4027	0.0354	0.0354	5.63%
Total	**2.4018**	**1.7731**	**0.6287**	**0.6287**	**100.00%**

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year

Table 78. Summary of costs by health state (palbociclib at list price)

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	% absolute increment
Pre-progressed state	£98,268	£3,771	£94,497	£94,497	99.63%
Post-progressed state (1st subsequent treatment)	£495.84	£626.26	-£130.42	£130.42	0.14%
Post-progressed state (2nd subsequent treatment)	£791.83	£982.17	-£190.35	£190.35	0.20%
Post-progressed state (3rd subsequent treatment)	£1,016.85	£1,223.99	-£207.14	£207.14	0.22%

Post-progressed state (BSC)	£12,365.25	£11,366.38	£998.86	£998.86	1.05%
Terminal care	£3,758.38	£3,873.67	-£115.29	£115.29	0.12%
Total	**£116,696.13**	**£21,843.16**	**£94,852.97**	**£94,852.97**	**100.00%**

Abbreviations: BSC, best supportive care

Table 79. Summary of predicted resource use by category of cost

Item	Cost intervention	Cost comparator	Increment	Absolute increment	% absolute increment
Drug acquisition costs	£92,101.27	£31.68	£92,069.59	£92,069.59	97.07%
Within cycle wastage costs	£0.00	£0.00	£0.00	£0.00	0.00%
Drug administration costs	£0.00	£0.00	£0.00	£0.00	0.00%
Drug monitoring costs	£93.79	£0.00	£93.79	£93.79	0.10%
AE costs	£782.02	£205.10	£576.92	£576.92	0.61%
Bckg health state costs (stable disease)	£5,290.91	£3,533.90	£1,757.01	£1,757.01	1.85%
1st subsequent treatment bckg HS cost	£495.84	£626.26	-£130.42	£130.42	0.14%
2nd subsequent treatment bckg HS cost	£791.83	£982.17	-£190.35	£190.35	0.20%
3rd subsequent treatment bckg HS cost	£1,016.85	£1,223.99	-£207.14	£207.14	0.22%
BSC	£12,365.25	£11,366.38	£998.86	£998.86	1.05%
Terminal care	£3,758.38	£3,873.67	-£115.29	£115.29	0.12%
Total	**£116,696.13**	**£21,843.16**	**£94,852.97**	**£94,852.97**	**100.00%**

Abbreviations: AE, adverse events; bckg, background, BSC, best supportive care; HS, health state

5.8. Sensitivity analyses

5.8.1. Probabilistic sensitivity analysis

In order to explore uncertainty around the model key variables in the base case, probabilistic sensitivity analysis (PSA) was performed for 1,000 iterations. This number of iterations was deemed sufficient due to the close proximity of the deterministic and probabilistic results. Appendix 25 presents the parameters included in the PSA along with their assumed distributions and standard error or range.

Table 80 presents a comparison between the deterministic and average PSA results. The deterministic and average PSA results for incremental costs, incremental QALYs and ICER value are very similar, suggesting either deterministic or probabilistic results can be considered for decision making purposes in the knowledge they produce very similar results.

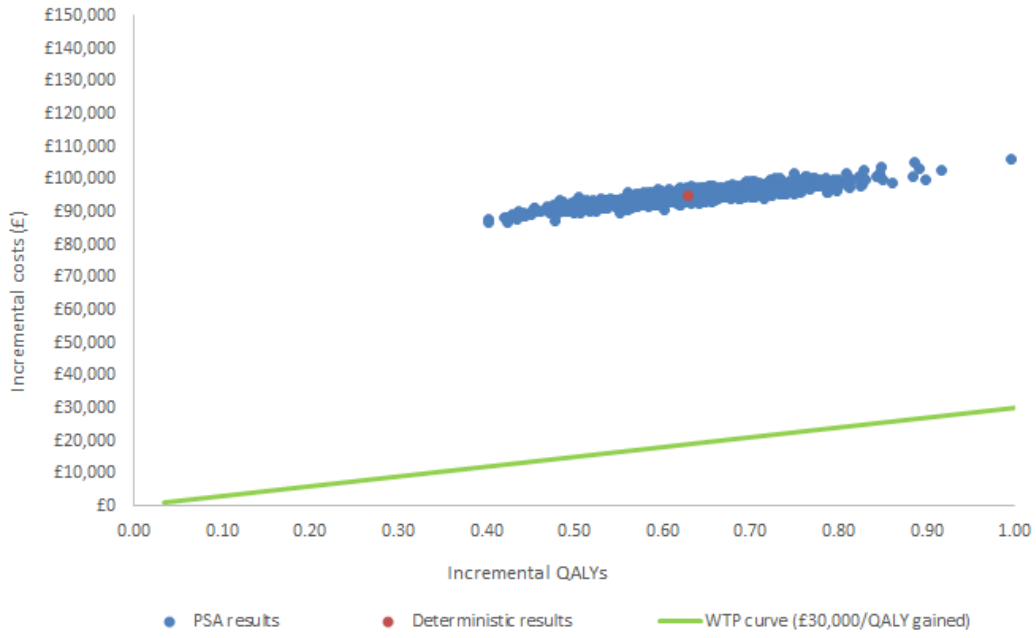
Table 80. PSA results for palbociclib plus letrozole vs letrozole (palbociclib at list price)

	Incremental costs (£)	Incremental QALYs	ICER (per QALY)
Deterministic result	£94,853	0.63	£150,869
Average value from PSA	£94,951	0.63	£151,058

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PSA, probabilistic sensitivity analysis

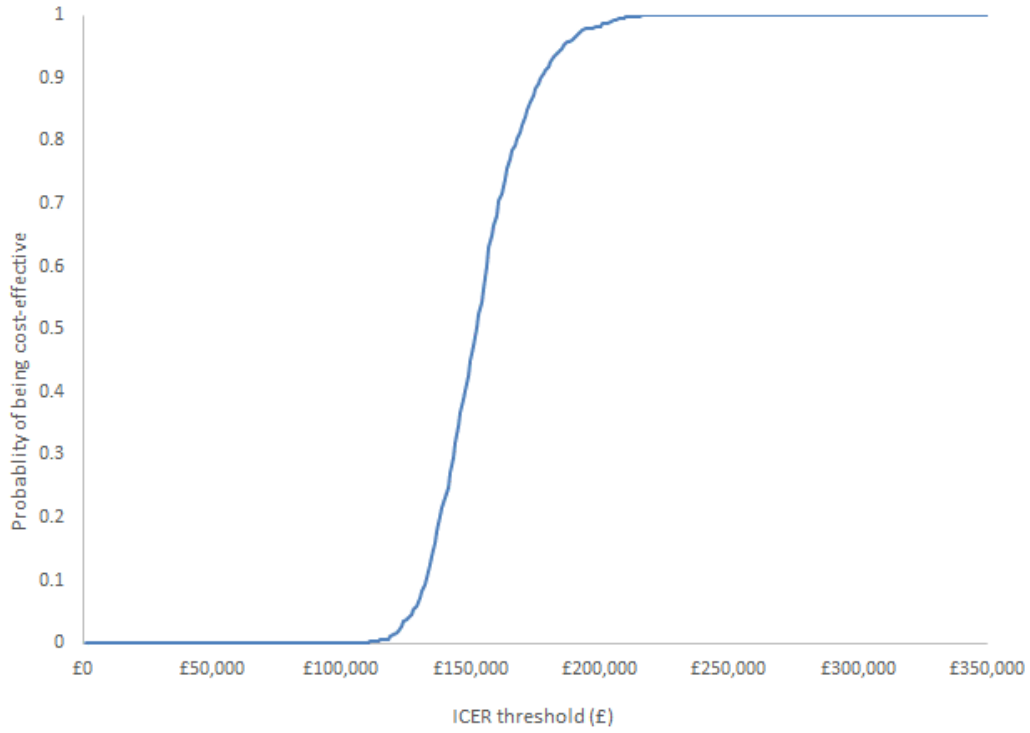
The result of the PSA (1,000 samples) is presented in Figure 26. The scatter-plot indicates that the palbociclib+letrozole vs letrozole sampled results are above the £30,000 WTP threshold. The cost-effectiveness acceptability curve (CEAC) is presented in Figure 27.

Figure 26. Cost-effectiveness plane (palbociclib+letrozole vs letrozole; palbociclib at list price)



Abbreviations: QALY, quality-adjusted life year; PSA, probabilistic sensitivity analysis, WTP, willingness to pay

Figure 27. CEAC (palbociclib+letrozole vs letrozole; palbociclib at list price)



Abbreviations: ICER, incremental cost-effectiveness ratio

5.8.2. Deterministic sensitivity analysis

5.8.2.1. One-way sensitivity analyses using confidence intervals

The sensitivity of the model results and the drivers of cost-effectiveness were explored with one-way sensitivity analysis (OWSA). Tests were performing around the 95% confidence interval values of all model parameters (scenarios 1-12) (Table 81).

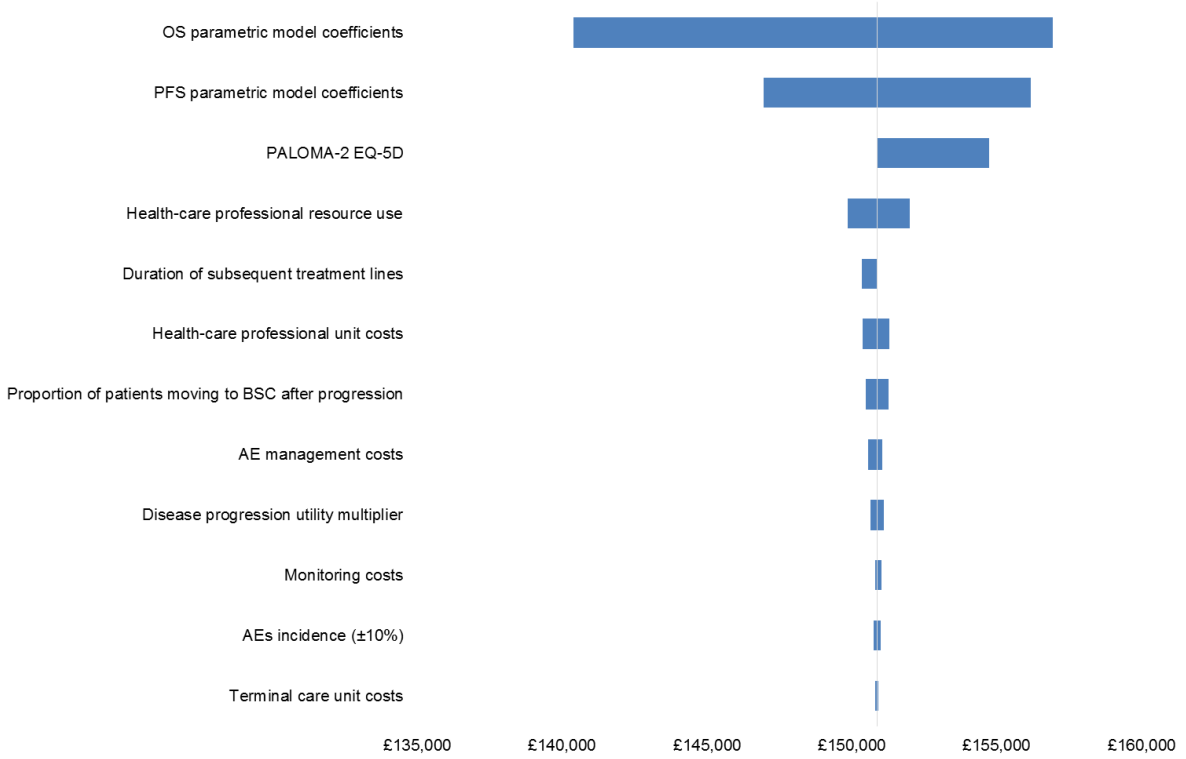
Table 81. List of OWSAs testing parameters between the limits of their 95% CI

Scenario	Parameter varied	CIs reported in:
1	OS parametric model coefficients	Section 5.3.2
2	PFS parametric model coefficients	Table 56
3	Disease progression utility multiplier	Section 5.4.3.5
4	Duration of subsequent treatment lines	Section 5.3.3
5	Proportion of patients moving to BSC after progression	Table 48
6	AE incidence	Section 5.3.4
7	Monitoring costs	Section 5.5.3
8	AE management costs	Table 71
9	Health-care professional unit costs	Table 69
10	Health-care professional resource use	Table 68
11	Terminal care unit costs	Table 70
12	PALOMA-2 EQ-5D	Table 62

Abbreviations: AE, adverse event; BSC, best supportive care; CI, confidence interval; OS, overall survival; PFS, progression-free survival

Sensitivity analysis around the 95% confidence interval values of model parameters shows that the OS and PFS parameters were very strong drivers of the model results. Results were also sensitive to baseline utility values, health-care professional resource use estimates and unit costs, duration of subsequent treatment lines and the proportion of patients moving to BSC after progression, although the effect of these on the ICER were marginal. A tornado diagram for scenarios 1-12 is shown in Figure 28.

Figure 28. Tornado diagram of the most influential parameters (palbociclib at list price)



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

5.8.2.2. One-way sensitivity analyses varying assumptions in the model

Ten model assumptions were varied to investigate the degree of change in the ICER. These are presented in Table 82.

Table 82. List of OWSAs testing model assumptions

Scenario	Parameter varied
13	Use the Beauchemin linear regression method
14	Use unadjusted OS from PALOMA-1 – Weibull for both arms
15	Use unadjusted OS from PALOMA-1 – Log-logistic for both arms
16	PFS parametric models – Gompertz for both arms
17	AEs: include AE disutility values
18	Model horizon: 5 years
19	Model horizon: 10 years
20	Model horizon: 15 years

Scenario	Parameter varied
21	Exclude discounting costs and benefits at 3.5%
22	Baseline utility (pre-progressed state): assume same value
23	Disease progression multiplier: use Nafees value [139]
24	Assume gradual utility decrease with every line of progression
25	Assume no post-progression sequential modelling: direct move to BSC
26	Use the health state costs from the NICE TA295 submission

Abbreviations: AE, adverse event; BSC, best supportive care; CI, confidence interval; OS, overall survival; PFS, progression-free survival

Whilst the analyses in Table 82 have been described previously in the submission, or are self-explanatory, several sensitivity analyses deserve further explanation:

Scenario 13: the Beauchemin method

This analysis uses the 'Beauchemin linear regression method'. This method is presented in the light of a lack of phase III OS data. However, as previously explained in section 5.3.2, even if it were available, the true comparative OS may not be clear due to confounding factors such as a variety of post-progression therapies. Beauchemin et al.[64] suggested a linear regression to estimate the median OS gain if the PFS gain was known (in months):

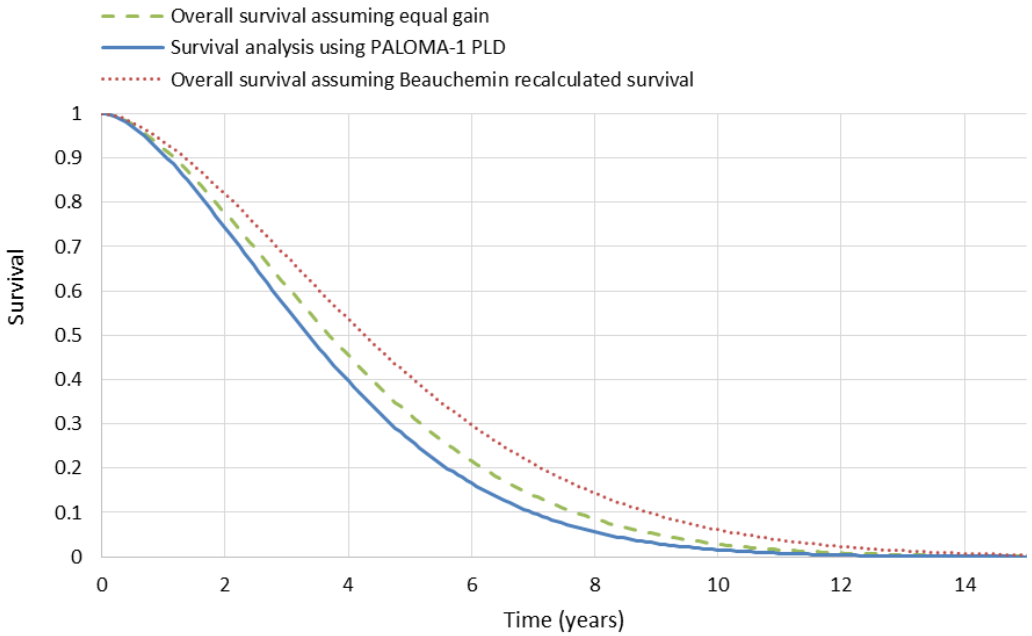
$$\Delta\_OS = -0.088 + 1.753 \times \Delta\_PFS,$$

where Δ is the incremental value between the intervention and control (in this case, difference between the palbociclib plus letrozole and letrozole arms). Based on the Beauchemin formula, the new Δ_OS was calculated from the PFS gain in the model (a Weibull distribution fit to PALOMA-2 data, resulting in 9.22 months median gain):

$$\Delta\_OS = -0.088 + 1.753 \times 9.22 \text{ months} = 16.09 \text{ months OS gain}$$

Using the same methodology as in section 5.3.2 for adjusting the scale parameter of the Weibull curve, the OS of the palbociclib plus letrozole arm was adjusted to fit the results of Beauchemin's formula. For comparison, the OS distributions for the palbociclib plus letrozole arm estimated using the Weibull model are presented in Figure 29 for PALOMA-1 which was not powered to detect differences in OS, the base case where the PFS gain translates into an OS gain, and the Beauchemin method of estimating OS.

Figure 29. Comparison of survival curves (PALOMA-1 IPD vs Beauchemin vs OS adjusted to meet PFS gain)



Abbreviations: IPD, individual patient data; OS, overall survival; PFS, progression-free survival

Scenario 17: adverse event disutility values

While in the base case analysis no disutility due to adverse events is applied to avoid double-counting, scenario 18 considers a disutility values of the grade 3/4 events listed in Table 71.

A secondary source was used to provide evidence on the HRQL impairment of several adverse events.[11] The Lloyd et al. study has been previously utilised in ABC economic evaluations and has been accepted by NICE for a recent submission in the disease area.[86] The utility of the base state in Lloyd et al. (stable ABC on treatment with no toxicity) and the utility decrements associated with departures from this health state were used to calculate a multiplier of the utility decrement for each adverse event (Table 83). For types of adverse events not reported in Lloyd et al. the average multiplier was used from the adverse events that did have disutility estimates. The precision for all multiplier decrements was assumed to be 0.01 (calculated based on the SD of the multipliers).

The multiplier for those grade 3 and 4 events is:

$$\mu_{3/4} = \frac{U_B + U_{dis\_AE}}{U_B}$$

where:
$\mu_{3/4}$ is the multiplier for the AEs of grade 3 and 4
U_B is the base state
U_{dis_AE} is the utility decrement

Table 83. Standard gamble utility from Lloyd et al. 2006[11] and the calculated multiplier

Description of HS/event	SG utility	Multiplier ($\mu_{3/4}$)
Base state - stable disease with no toxicity	0.715	
Febrile neutropenia (grade 3/4)	-0.15	0.790
Diarrhoea and vomiting (grade 3/4)	-0.103	0.856
Hand-foot syndrome (grade 3/4)	-0.116	0.838
Stomatitis (grade 3/4)	-0.151	0.789
Fatigue (grade 3/4)	-0.115	0.839
Hair loss*	-0.114	0.841
Average multiplier (grade 3/4)		**0.825 (standard error 0.01)**

Abbreviations: HS, health state; SG, standard gamble

* Note Lloyd et al. does not report severity for hair loss

It is important to note that this analysis will produce an overly conservative ICER as the 'average multiplier' disutility in Table 83 is applied to neutropenia. Neutropenia is prevalent in the palbociclib arm, however it is typically asymptomatic and managed through blood monitoring with no negative impact to a patient's HRQL. As such, the inclusion of adverse events not only double-counts on top of the already valued EQ-5D, but overly impacts the palbociclib arm due to the neutropenia not being expected to result in disutility.

Scenario 22: assume the same values for the baseline utility values of the pre-progressed state

This analysis assumes the same baseline utility value for both arms, taking the average of the PALOMA-2 EQ-5D values[9]:

Average baseline utility (both arms) = average ([redacted]*) =* [redacted]

Scenario 23: use the Nafees value for the disease progression multiplier

A 2016 poster by and colleagues assessed the health-state utilities in ABC in the UK. It predicted a utility value of 0.83 for stable disease, and 0.39 for progressive disease.[139] A disease progression multiplier was calculated as shown below and its impact was assessed in the model.

Disease progression multiplier (Nafees) = $\frac{0.39}{0.83} = 0.47$

Scenario 24: assume a gradual utility decrease with every line of progression

This analysis assumed a gradual decrease in the utility values of each line of progression following the pre-progressed state. The values for the post-progressed first and second subsequent treatments were assumed to be 0.6 and 0.5, respectively. The post-progressed third subsequent treatment utility value was not changed (i.e. remained 0.4492).

Scenario 25: assume no post-progression sequential modelling

Scenario 26 assumes that all progressed patients move directly to BSC, without going through any rounds of subsequent active treatments.

Scenario 26: use the health state costs from the NICE TA295 submission

Following on from Scenario 26 where patients cannot be transferred to other active treatments following progression, Scenario 27 uses the health-state costs employed in a previous advanced breast cancer submission, NICE TA295[86]. The health state costs used were:

- Stable disease: £202.38
- Progressed disease: £802.28
- Terminal care: £3,785

Table 84 displays the results of the deterministic sensitivity analyses performed to identify the drivers of the model (scenarios 13 to 27). The sections below describe the findings of the sensitivity analysis. The choice of OS parametric curve causes the highest degree of change in the ICER, along with the assumption behind the method used to estimate OS. The increase in OS from the PALOMA-1 Weibull estimate to the base case reduces the ICER around £35,000 per QALY, and moving to the Beauchemin estimate reduces the ICER around an additional £32,000 per QALY. Adding disutility values in addition to the already elicited EQ-5D risks double-counting, and it also considers neutropenia as a disutility whereas typically neutropenia in the PALOMA-2 trial was asymptomatic and thus would not have resulted in disutility for the patient. As the paper that was used to source this disutilities was published in 2006, it is likely the neutropenia would have been neutropenia associated to chemotherapy, which experts have stated is would be different to that associated with palbociclib. The other scenarios considered did not impact the results of the analysis significantly.

Table 84. List of sensitivity analyses varying model assumptions (palbociclib at list price)

Scenario	Parameter varied	Incremental costs	Incremental QALYs	Deterministic ICER
13	Use the Beauchemin linear regression method	£100,711	0.86	£116,806
14	Use unadjusted OS from PALOMA-1 – Weibull for both arms	£91,384	0.49	£187,881
15	Use unadjusted OS from PALOMA-1 – Log-logistic for both arms	£95,112	0.63	£150,273
16	PFS parametric models – Gompertz for both arms	£84,696	0.44	£193,312
17	AEs: include AE disutility values	£94,853	0.57	£166,954
18	Model horizon: 5 years	£84,718	0.42	£199,943
19	Model horizon: 10 years	£94,201	0.61	£153,485
20	Model horizon: 15 years	£94,834	0.63	£150,934
21	Exclude discounting costs and benefits	£102,608	0.73	£140,954
22	Baseline utility (pre-progressed state): assume same value	£94,853	0.57	£166,802
23	Disease progression multiplier: use Nafees value	£94,853	0.63	£150,334
24	Assume gradual utility decrease with every line of progression	£94,853	0.62	£152,781
25	Assume no post-progression sequential modelling: direct move to BSC	£94,121	0.63	£149,704
26	Use the health state costs from the NICE TA295 submission	£94,522	0.63	£150,342

Abbreviations: AE, adverse event; BSC, best supportive care; CI, confidence interval; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year

The base case assumed an adjusted OS gain that is relative to the median PFS gain. However, Section 5.3.2 details that the log-logistic curves for OS should be selected to explore the ICER when the data are unadjusted and distributions are fit to PALOMA-1. The ICER in scenario 15 is £150,273 per QALY with the unadjusted OS data, which is comparable to the base case adjusted ICER of £150,869 per QALY. It is important to note that PALOMA-2 OS data is not currently available, and scenarios 27 and 28 (in the following section, 5.8.3) explore more extreme assumptions behind OS and the impact to the ICER.

The largest increase to the ICER was seen in scenario 18 where the model's time horizon is reduced. However, in order to accurately capture the full costs and benefits to a patient in line with NICE's reference case, this scenario should only be considered as illustrative. Scenario 22 demonstrated that the ICER is sensitive to the pre-progression utilities, with the ICER increasing once palbociclib's [redacted] utility gain (elicited from the EQ-5D in PALOMA-2) was removed. The ICER was equally sensitive to the incorporation of disutilities in scenario 17 however two issues arise behind this increase: firstly that this scenario likely double-counts as utility impact from adverse events are already inherently captured in on-treatment EQ-5D, but also that this is heavily driven by a symptomatic utility for neutropenia whereas in PALOMA-2 it was typically asymptomatic.

5.8.3. Exploratory scenario analyses

Gemcitabine in combination with paclitaxel was the last technology to be recommended by NICE in ABC (TA116). This chemotherapy offered less than a 2-month improvement in time to progression versus the standard of care paclitaxel, at a cost of £11,848 for 6 cycles (not including additional administration costs).[140] Despite palbociclib offering an improvement in PFS in excess of 10 months, the nominal base-case ICER does not capture the transformative value of the medicine. Indeed, it would be considered not cost-effective if judged using the most pessimistic assumptions and without the full value of PFS benefit taken into account.

This section presents an array of ICERs spanning all possible interpretations of the major areas of uncertainty and drivers of the model. These include pessimistic assumptions adopted in the context of previous breast cancer appraisals, with respect to OS gain for example, which would highlight how low the price would need to be to achieve cost-effectiveness. These also the effect of 'modifying' the ICER calculation to illustrate what a proxy correction for issues that otherwise prevent cost-effectiveness may look like.

The following scenarios explore reasons for the ICER not being within the current threshold:

Scenario 27: Only PFS gain, with pessimistically no OS gain.

A pessimistic assumption of OS benefit would be to consider that the 10.3 months improvement in PFS leads to no improvements in OS, due to the lack of data from PALOMA-2 and the confounded data from PALOMA-1 being not statistically significant. This assumption implies a negative effect from palbociclib as a first-line therapy on patient health and thus life expectancy post-progression, despite it being a well-tolerated therapy that does not deteriorate HRQL. This assumption assumes the OS distribution for letrozole from PALOMA-1 is also applied to the palbociclib arm (*i.e.* identical OS).

Scenario 28: Increased overall survival gain

The current cost per QALY approach does not reflect the full value of PFS, and in doing so, a disproportionate expectation is placed on overall survival and the resultant ICERs severely underestimate the benefit of palbociclib. This scenario adjusts OS to reflect a 5-year gain with palbociclib, with modelled median OS for letrozole of months and for palbociclib. This is implemented in the model using the same functionality as was used in the base case (see Section 5.3.2).

Scenario 29: Increase in the value of PFS

Lloyd (2006) presents pre-progression utility of 0.72 (PALOMA-2 is [redacted] for the two arms) and post-progression utility of 0.49.[11] The value of keeping a patient progression free is thus a utility benefit of 0.23.

We believe the value of PFS to society and to patients is greater than this, and this does not reflect the benefits of remaining progression-free to women with ABC as detailed in section 3.2.1. As such, a scenario has been conducted that examines the impact on the ICER should a utility benefit of remaining progression-free be greater than just controlling the disease. More specifically these include delaying the onset of chemotherapy, the

psychological benefits from being on a successful treatment, being able to stay in work and continue with normal life, and the ability to continue a family life at home and care for a family as before. In this scenario, the utility estimate for both treatment arms is increased by 0.1 in the progression-free state, as a proxy reflection of a more comprehensive valuation of the benefits of PFS.

Scenario 30: A comparator with similar costs

Palbociclib is an add-on therapy, resulting in 100% of the drug acquisition costs contributing towards the incremental costs. Even if it were not an add-on therapy, the comparator arm acquisition costs are minimal accounting for only £1.52 per cycle due to letrozole being generic, bringing a similar situation where almost all of the intervention's acquisition costs are incremental. This scenario examines the impact on the ICER should the comparator arm monthly acquisition costs be the same as the intervention and consistent with other newer oncology medical innovations which are approved by NICE.

Scenario 31: Reduced treatment duration

With a medicine that treats until progression, a larger gain in PFS is, to its detriment, accompanied by a larger treatment duration. If a treatment provides the same incremental benefit (*e.g.* 10 months PFS), but does so with a shorter treatment duration, the incremental costs are reduced without impact to the incremental QALYs. Over time, as advances have been made in medical innovation to improve PFS and ultimately OS benefit, there has been a natural trend towards drug treatment durations becoming longer resulting in increased costs to offer greater benefits. This scenario examines the same incremental benefit to patients, but with an absolute lower treatment duration, and likewise PFS duration, reduced by 1 year in each arm.

Table 85. Exploratory scenario analyses varying model assumptions (palbociclib at list price)

#	Assumptions varied	Change in ICER from base case
Base case deterministic ICER		**£150,869 per QALY**
27	Only PFS gain for palbociclib (10.3 months) No OS gain for palbociclib (0 months)	+ £161,766
28a	Increased OS improvements with palbociclib: a 5-year incremental gain	- £89,047
28b	Increased OS improvements with palbociclib: a 5-year incremental gain, *but removing post-progression costs*	- £108,075
29	Increase in utility of +0.1 for patients in the PFS state	- £16,735
30	A comparator with the same monthly acquisition costs *(i.e. fixed cost of £2,951.52 per month, but only for respective treatment durations)*	- £97,795
31	Reduced treatment duration by 12 months in each arm *(PFS reduced from 15.7 to 3.7 months for letrozole, and from 24.9 to 12.9 months for palbociclib)*	- £64,450

Abbreviations: AE, adverse event; BSC, best supportive care; CI, confidence interval; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year

If assumptions pertaining to OS benefit are pessimistic as shown in scenario 27, a willingness to pay threshold of between £20,000 and £30,000 per QALY dictates that the acquisition cost of a pack palbociclib must be between £220 to £300 per 4-week cycle. This is a near generic price and is lower monthly cost than that at which a range of chemotherapies were approved by NICE for ABC in the last decade (lower than the monthly cost of gemcitabine [TA116], vinorelbine [TA54], capecitabine [TA62], and taxanes [TA30]). This does not reflect the value of an exceptional 10.3 month extension of PFS.

Scenarios 28 and 29 demonstrate the impact on the ICER of improvements in the QALY gain, coming from changes to the overall survival assumptions and from a higher valuation of PFS to patients. Scenario 28 demonstrates that OS is an important driver in influencing the ICER, and an assumed 5-year survival gain with no change to PFS or treatment duration results in a lowering of the basecase ICER by approximately £100,000 per QALY. However, this is still not sufficient to meet the £30,000 per QALY threshold.

The acquisition cost of the comparator arm has a major impact on the ICER, with scenario 30 illustrating a reduction in the base case ICER of £97,795 per QALY. This sizeable reduction in the ICER demonstrates how the introduction of an innovative treatment such as palbociclib as an add-on therapy or into a therapy area with no new treatment or breakthrough (as defined by an exclusively generic treatment space) inherently values that new treatment less than it would do if the therapy area had already benefited from recent innovation.

It is important to keep in mind that as treatments continue to improve and efficacy is increased, therapies that treat until progression naturally must treat for longer time periods. This will make cost-effectiveness increasing harder to establish, especially if the adoption of innovative technologies is stymied to the point where all standard of care treatments are generic. Scenario 31 illustrates that should the duration of treatment be lower in both arms, the base case ICER would fall by £64,450 per QALY.

The reality is that depending on the assumptions included regarding the value of PFS, comparator cost, and survival benefit, a wide array of results is possible. Despite its double-digit PFS gain, if exclusively pessimistic assumptions are adopted, palbociclib may produce an ICER of above £300,000 per QALY.

However, if more pragmatic assumptions are adopted which serve to mitigate the limitations of the cost per QALY calculation in this instance, then it is possible to demonstrate cost-effectiveness. For example, if the monthly price of the comparator was comparable to palbociclib, together with an adjusted utility of PFS, the ICER would be £47,187 per QALY. When a 24-month gain in OS is assumed, the ICER would decrease to £36,194 per QALY, falling further still to £26,996 per QALY when removing later-line post-progression costs.

Table 86. Combining scenarios to evaluate exploratory ICERs (palbociclib at list price)

#	Assumptions changed	Incremental costs	Incremental QALYs	ICER (per QALY)
32	• Comparative monthly acquisition costs • Value of PFS utility increase (+0.1) • *No change to base case OS assumption*	£33,013	0.82	£47,187
33	• Comparative monthly acquisition costs (#30) • Value of PFS utility increase (+0.1) • Incremental OS gain of 12 months	£35,734	0.82	£43,819
34	• Comparative monthly acquisition costs • Value of PFS utility increase (+0.1) • Incremental OS gain of 12 months • Removal of post-progression costs	£33,013	0.82	£40,482
35	• Comparative monthly acquisition costs (#30) • Value of PFS utility increase (+0.1) • Incremental OS gain of 24 months	£45,963	1.27	£36,194
36	• Comparative monthly acquisition costs • Value of PFS utility increase (+0.1) • Incremental OS gain of 24 months • Removal of post-progression costs	£33,013	1.27	£26,996

5.9. Subgroup analysis

The forest plot for PALOMA-2 (

Figure 14) demonstrated that palbociclib plus letrozole was associated with statistically significant improvements in PFS versus letrozole alone across all subgroups. As palbociclib demonstrated such a consistent measurable benefit, no subgroups have been analysed as part of the cost-effectiveness evaluation.

5.10. Validation

5.10.1. Clinical validation

The observed clinical benefit for palbociclib plus letrozole versus letrozole alone was consistent across both PALOMA-1 (10.0 months benefit) and PALOMA-2 (10.3 months benefit). The patient numbers in PALOMA-2 (n=666) render it a well-sized trial upon which to base judgments of efficacy.

In the phase III trial, PALOMA-2, the letrozole alone arm was associated with a PFS of 14.5 months. This is similar to a previous study in a likewise ER+ HER2- population which included letrozole as the comparator arm, in which letrozole achieved a median PFS of 14.7 months.[130] OS was not available in PALOMA-2, but in PALOMA-1 letrozole was associated with a median 33.3 months OS, similar to published literature (34 to 38.2 months [36, 38, 92]).

The results of PALOMA-2 have been reviewed at a UK advisory board of 10 clinical experts; feedback was that the trial was robust and the results were impressive in terms of PFS. The patient population in PALOMA-2 was perceived to be generalisable to the women with the disease in the UK, however experts noted that the proportion of patients with *de novo* ABC in PALOMA-2 (38%) is higher than that typically seen in UK clinical practice (5-10%).[125, 126] However, this is not thought to render the results of the trial any less generalisable to the UK given that subgroup analyses demonstrated consistency in relative treatment effect. Indeed, it should be noted that the hazard ratio for PFS was higher in the de novo patients in PALOMA-2, which may suggest using the ITT data to represent UK women (95% of whom have had adjuvant therapy) would lead to a conservative estimation of palbociclib's benefit and thus a potentially conservative ICER in the model.

Clinical experts underlined that PFS is a key target for patients and clinicians when tackling ABC, and the value of prolonging PFS to patients is multi-fold (see Section 3.2.1). They confirmed that comparative effectiveness in OS is difficult to demonstrate given the prolonged follow-up of patients and the effects of multiple lines of therapy, following progression from first line ABC treatment. In light of those potential biases, experts believed that PFS is a valid and meaningful endpoint for the clinical trial and a reasonable outcome upon which to base decision-making.

5.10.2. Validation of de novo cost-effectiveness analysis

The analysis builds on methods from previous appraisals and translates effectively the clinical trial evidence into the economic model. A partitioned survival model that reflects cancer progression and mortality is the most typical mathematical framework and has been followed by recent NICE TAs.[86, 87] As presented in Section 5.2.2, the model is adapted to allow a more accurate reflection of the post-progression patient pathway with multiple subsequent lines of later progression. This was consistent with advice from clinical experts

on the likely escalation of costs as patients progress through several treatments before they exhaust all options and receive BSC. These assumptions were tested in a sensitivity analysis (Scenario 25).

The model input data for PFS and OS were validated and compared with external sources for credibility (as explained above in Section 5.10.1), but further to a comparison of median values, the tails of previously published survival curves and the visual shape of the curves were used to aid the choice of survival distributions in the de novo model.

Extensive clinical expert opinion was sought to estimate, validate, and guide assumptions pertaining to the healthcare resource use inputs, as well as using data from NICE guidelines for breast cancer. With regards to estimating resource use for health state management costs, adverse event management, and patient monitoring requirements, clinical opinion was obtained from multiple UK experts during interviews, and at an advisory board with a multi-disciplinary breast cancer team. Costing input data came from the latest NHS Reference Costs, PSSRU, and eMIT databases to provide results that can be validated as suitable to a UK context.

5.10.3. Quality control

Several quality control measures were undertaken to validate the model findings included in this submission. Internal quality control was undertaken by the developers of the model on behalf of the manufacturer. In addition, the model was critiqued by an external independent health economist with a full review of model structure, parameter inputs, and core assumptions. Simplistic crude modelling was also undertaken that showed that the estimates of costs and QALYs were intuitive.

5.11. Interpretation and conclusions of economic evidence

ABC is a terminal and devastating disease for these women, their families and caregivers. PALOMA-2 is the first phase III RCT in ABC in which the intervention has demonstrated over 2 years median PFS. As such, palbociclib plus letrozole in previously untreated women is a treatment with truly transforms the treatment paradigm. An increase of 10.3 months in PFS versus the standard of care therapy is a genuine step change in the treatment of these women. To put this in context, across 12 previous submissions in ABC to NICE that have a final appraisal determination (FAD), new therapies have only offered a 1 to 6 month gain in PFS within their respective pivotal RCTs (TA23, TA30, TA54, TA62, TA116, TA214, TA239, TA250, TA257, TA263, TA295, TA371).

Gemcitabine in combination with paclitaxel was the last technology to be recommended by NICE in ABC, offering less than a 2 month improvement in time to progression and less than a 3 month improvement in OS versus the standard of care,[140] at an acquisition cost of £1975 per 3-week cycle.[141] Since this, the last seven appraisals with a FAD in ABC have been not recommended by NICE (TA214, TA239, TA250, TA257, TA263, TA295, TA371). NICE have, at the time of submission, never recommended a treatment for first-line ER+ HER2- ABC. A medical need exists for the development of additional therapeutic alternatives.

Despite its double-digit PFS gain, if exclusively pessimistic assumptions are adopted, palbociclib cannot achieve an ICER below the required threshold without reducing the price

to below that of ABC chemotherapies when they were approved in ABC. However, if pragmatic assumptions are adopted which in part allow for a more comprehensive valuation of PFS benefit, then palbociclib can demonstrate value for money to the NHS and be cost-effective treatment option for women with ABC.

6. Assessment of factors relevant to the NHS and other parties

Table 8 estimates the total eligible woman patient population in England and Wales who are ER+, HER2-, and are previously untreated in the metastatic setting, thus being eligible for palbociclib plus an aromatase inhibitor. From the 5,435 potential women, 5,116 are in England and 319 in Wales.

It is important to note that these estimates are for *all* eligible women, however it is not expected that all eligible women will receive palbociclib hence the actual numbers treated will be less. This is due to a significant proportion of women presenting with aggressive symptoms and therefore being eligible for chemotherapy, as well as the availability of more treatment options expected to launch over the coming years.

The forecast uptake of palbociclib over the next 3 years is presented in Table 87; this is based upon current market research data on file that indicates aromatase inhibitors are prescribed in around [redacted] of the ER+HER2- market in previously untreated women, and it is anticipated [redacted] of these women would be switched to a palbociclib regimen, if available, due to its superior efficacy.[27] These estimates also consider an increasing annual incidence of 0.6% per annum, based on statistics from Cancer Research UK that have identified a 6% rise in incidence over the last 10 years in the UK.[142]

Table 87. Forecast number of women expected to be treated with palbociclib

	2017	2018	2019
Women eligible for first-line palbociclib	5,435	5,468	5,500
Uptake of palbociclib	[redacted]	[redacted]	[redacted]
Women treated with palbociclib	[redacted]	[redacted]	[redacted]

Abbreviations: BC, breast cancer
*considers that palbociclib will not receive a NICE recommendation until part way through the year

The cost of administering palbociclib is negligible as it is an oral therapy that is self-administered at home. There are no companion diagnostic testing costs associated with palbociclib, and tests to determine the subtype of a patient's breast cancer are already routine practice and are conducted regardless of the availability of palbociclib.

It is anticipated that there will be costs associated with full blood counts, which allow for the monitoring of neutropenia, leukopenia, anaemia, and thrombocytopenia. In the previously presented clinical evidence, the incidence of neutropenia and leukopenia in particular were higher with palbociclib than with letrozole alone. Full blood counts are reimbursed at £3.01 each in accordance with NHS Reference Costs (DAPS05 Haematology),[138] twice in the first month, then once per month after. It is assumed the HRG tariff encompasses all costs for the test in an outpatients setting. There is no significant cost expected in the management of adverse events as dose reduction is the standard approach to the most prevalent, haematological toxicities.

Table 88 presents the estimated budget impact for women who will be expected to receive palbociclib, at list price. In practice, women will begin palbociclib across all months, but for simplicity, the calculations assume half of the year's new patients begin at the start of the year, and half mid-way through the year. Each patient incurs 2 years of cost (based upon a median PFS from PALOMA-2 [24.8 months]). For example, new patients starting in January 2017 will incur a full year's worth of cost in 2017, then a second full years' worth of cost in 2018. Those starting in July 2017 will incur half a year's cost in 2017, a full year's cost in 2018, then a final half a year's cost in 2019. The budget impact is split in the table by palbociclib acquisition, combination letrozole acquisition, and additional monitoring.

Table 88. Forecast budget impact using median treatment duration

	2017	2018	2019
New ABC women treated with palbociclib	[redacted]	[redacted]	[redacted]
Total palbociclib drug acquisition* budget impact	[redacted]	[redacted]	[redacted]
Cost of new patients in the current year	[redacted]	[redacted]	[redacted]
Cost of patients starting in previous year (now in their 2nd year of treatment)	£0	[redacted]	[redacted]
Total letrozole drug acquisition⁺ budget impact	[redacted]	[redacted]	[redacted]
Cost of new patients in the current year	[redacted]	[redacted]	[redacted]
Cost of patients starting in previous year (now in their 2nd year of treatment)	£0	[redacted]	[redacted]
Blood monitoring budget impact˜	[redacted]	[redacted]	[redacted]
Cost of monitoring new patients in the current year	[redacted]	[redacted]	[redacted]
Cost of monitoring patients starting in previous year (now in their 2nd year of treatment)	£0	[redacted]	[redacted]
Total budget impact per year	[redacted]	[redacted]	[redacted]

Abbreviations: ABC, advanced breast cancer

*List price of palbociclib is £2,950 per 28 days, equating to £3,207 per calendar month, and £38,482 per annum
⁺Letrozole price is £1.52 per 28 days, equating to £1.65 per calendar month, and £19.73 per annum
˜FBC cost is £3.01 per patient, per count (13 counts in year 1, then 12 counts in year 2)

The current treatment that would be displaced by a palbociclib plus letrozole combination is letrozole monotherapy. Letrozole monotherapy is administered till progression with a median PFS of 14.5 months.[9] Displaced costs are in line with the previous assumptions (half of patients begin at the start of the year and half mid-way through the year). These alleviated cost savings are displayed below in Table 89.

Table 89. Cost savings from replacement of current treatment

	2017	2018	2019
New ABC women treated with palbociclib	[redacted]	[redacted]	[redacted]
Total cost savings from letrozole monotherapy	[redacted]	[redacted]	[redacted]
Savings from new patients in the current year	[redacted]	[redacted]	[redacted]
Savings from patients starting in previous year (now in their final 2.5 months of treatment)	£0	[redacted]	[redacted]

Abbreviations: ABC, advanced breast cancer

Due to palbociclib have a longer treatment duration than current therapy (estimated from median PFS of 24.8 months versus 14.5 months), palbociclib also displaces subsequent "second-line" treatment for a period of 10.3 months. Market research suggests that this subsequent treatment is either everolimus plus exemestane (monthly acquisition cost of around £2,712), exemestane monotherapy (monthly acquisition cost of around £6) or fulvestrant monotherapy (monthly acquisition cost of around £568).[27, 143] The average of these treatment costs, for a period of 10 months, is considered in Table 90 as an estimate of potential cost displacement from the current budget year due to prolonging of PFS with first-line palbociclib. Only list price acquisition costs are considered; administration, monitoring and adverse event costs are not considered.

Furthermore, health state management costs increase as a patient progresses to the following line of treatment from £169.56 per month to £245.22 per month (see Table 68), so when considering budget impact within these final 10.3 months of palbociclib therapy, higher management costs are also being alleviated.

Table 90. Costs alleviated/displaced from current year's budget due to palbociclib prolonging disease progression

	2017	2018	2019
New ABC women treated with palbociclib	[redacted]	[redacted]	[redacted]
Second-line costs alleviated/displaced from current budget year (i.e. displaced costs during the final 10 months of the palbociclib regimen)	£0	[redacted]	[redacted]
*10 months of second-line drug costs alleviated from current year due to continued treatment with palbociclib **	-	[redacted]	[redacted]
10 months of health state costs alleviated from current year due to continued treatment with palbociclib	-	[redacted]	[redacted]

Abbreviations: ABC, advanced breast cancer

**Second-line treatment costs are an average of list prices of everolimus+ exemestane, exemestane, and fulvestrant (=£1,095 per calendar month); no discounts or patient access schemes are reflected here for these medicines*

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Single technology appraisal

Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer [ID915]

Dear Rachel,

The Evidence Review Group, Liverpool Reviews & Implementation Group, and the technical team at NICE have looked at the submission received on 27 September 2016 from Pfizer. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

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

Please provide your written response to the clarification questions by **5pm** on **4 November 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals https://appraisals.nice.org.uk/request/20130

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

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

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

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

If you have any queries on the technical issues raised in this letter, please contact [redacted], Technical Lead [redacted] Any procedural questions should be addressed to [redacted], Project Manager [redacted]

Yours sincerely

[redacted]

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Technical Adviser – Appraisals
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Section A: Clarification on clinical effectiveness data

A1. **Priority request:** Please provide the statistical analysis plans for the PALOMA-1 trial and the PALOMA-2 trial.

A2. **Priority request: Overall survival data for the PALOMA-2 trial:**

a. The company states that, at the time of the progression-free survival analysis in the PALOMA-2 trial (01 May 2015), the number of overall survival events did not meet the threshold allowing for an interim analysis to be conducted (p.74 of the company submission), and also that the pre-specified level of significance for assessing overall survival had not been met (p.12 and p.83 of the company submission). Please clarify which of these statements was the reason for not conducting an analysis of overall survival at this time and whether this reason was pre-specified.

b. The ERG notes that in Table 14 of the company submission, it is stated: "All PALOMA-2 data presented in this submission correspond to the data cut-off date of 26 February 2016." Since more events (deaths) would have occurred in the 8 months following the time of the progression-free survival analysis in the PALOMA-2 trial (01 May 2015), please provide the overall survival data, including Kaplan-Meier plots, for the PALOMA-2 trial for the latest data cut.

A3. **Priority request: Subgroup analyses (progression-free survival):**

a. For the PALOMA-1 trial, please provide the median progression-free survival (and 95% confidence intervals) in each treatment arm and hazard ratio (and 95% confidence intervals) between arms for:

    i. Patients with de novo disease.

    ii. Patients who have received previous adjuvant/neoadjuvant therapy.

b. For the PALOMA-2 trial, please provide the median progression-free survival (and 95% confidence intervals) in each arm and hazard ratio (and 95% confidence intervals) between arms for:

    i. Patients with de novo disease.

    ii. Patients who have received previous adjuvant/neoadjuvant therapy.

c. Pre-specified subgroup analyses are reported for the PALOMA-1 trial in Figure 13 and for the PALOMA-2 trial in Figure 14 of the company submission. However, hazard ratios (and 95% confidence intervals) are only reported in

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Figure 14. Please provide hazard ratios (and 95% confidence intervals) for Figure 13.

A4. **Priority request: Proportional hazard assumptions for progression-free survival and overall survival:**

a. In the company submission, it is stated that the assumption of proportional hazards was tested for progression-free survival data from the PALOMA-1 trial by reference to Figures 19 and 20. However, these figures show the PALOMA-2 trial data. Please clarify whether any testing of proportional hazards was conducted for progression-free survival or overall survival using data from the PALOMA-1 trial.

b. Please clarify the methodology used to generate hazard ratios for the PALOMA-2 trial.

c. The proportional hazards assumption appears to be violated for overall survival in the PALOMA-1 trial (where it can be seen that the Kaplan-Meier curves for each treatment arm cross in Figure 11 of the company submission). Please clarify whether the progression-free survival data from the PALOMA-2 trial and the overall survival data from the PALOMA-1 trial can therefore be justifiably correlated (as stated in Section 3.2 of the company submission) given that the proportional hazards assumption is likely to hold for the PALOMA-2 trial progression-free survival data but not for the PALOMA-1 trial overall survival data.

A5. Disease progression:

a. Table 13 and Table 16 define progression as ‘radiological’ progression (i.e. that progression must be determined by radiological scanning) in both the PALOMA-1 trial and the PALOMA-2 trial, however the permitted and disallowed concomitant medications reported in Tables 11 and 14 of the company submission imply that increased used of bisphosphonates / other treatments will also be treated as progression in both trials. Please clarify the exact definitions used for ‘progression’ in the analyses of both the PALOMA-1 and PALOMA-2 trial.

b. Please provide the results of the univariate and multivariate analyses for both investigator-assessed and blinded independent review progression-free survival for the PALOMA-2 trial as described in Table 19 of the company submission (i.e. Table 14.2.1.10.1, Table 14.2.2.10.1, Table 14.2.1.10.2, Table 14.2.2.10.2 of the PALOMA-2 clinical study report).

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A6. Subsequent treatment received on disease progression: For PALOMA-1, the following poster reports subsequent treatment received by patients in the PALOMA-1 trial following disease progression: Finn RS, Crown JP, Ettl J, Pinter T, Thummala A, Shparyk Y, et al. Treatment patterns of post-disease progression in the PALOMA-1/TRIO-18 trial. 38th Annual San Antonio Breast Cancer Symposium December 8-12; San Antonio, TX2015. If available, please provide the equivalent data for the PALOMA-2 trial.

A7. Pooled data:

a. Please clarify whether the company considered performing a meta-analysis of the data from the PALOMA-1 trial and the PALOMA-2 trial. Please outline the rationale for not performing a meta-analysis.

b. Please clarify whether the company considered pooling adverse event data from the PALOMA-1 trial and the PALOMA-2 trial. Please outline the rationale for not pooling these data.

A8. Design (trial conduct and analysis) of the PALOMA-1 trial:

a. Please clarify whether the 12 patients included in the Phase I stage of the NCT00721409 trial were also included in the Phase 2 PALOMA-1 trial.

b. Following the first interim analysis of the PALOMA-1 trial, accrual to cohort 2 was stopped (Section 4.3.1 of the company submission).

i. Please provide justification for this amendment, considering that the trial was not designed with stopping rules.

ii. Please clarify how the decision was made to stop recruitment when there was not a pre-specified level of significance to stop recruitment based on this analysis.

c. Following the first interim analysis of the PALOMA-1 trial, the statistical analysis plan for the primary endpoint was amended to a combined analysis of cohorts 1 and 2, instead of just cohort 2 (Section 4.3.1 of the company submission).

i. Please clarify whether the analysis plan was amended so that the analyses of secondary outcomes could also use the combined dataset of both cohorts 1 and 2.

ii. Please provide the rationale for changes to the planned analysis of both primary and secondary outcomes.

d. In Section 4.4.1.2 it is stated that based on the interim analyses of the PALOMA-1 trial, the significance level for the final analysis was adjusted using the Lan-

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DeMets procedure with an O'Brien-Fleming stopping boundary. Please clarify what the adjusted significance level was.

e. Please clarify what significance levels were used for testing the PALOMA-1 trial secondary outcomes: overall survival, time to progression, objective response, and clinical benefit rate.

f. Please explain the rationale for the use of one sided hypothesis tests for the outcomes of progression-free survival, overall survival, time to progression, objective response, and clinical benefit rate for the PALOMA-1 trial.

A9. Design (trial conduct and analysis) of the PALOMA-2 trial:

a. Please explain the rationale for using a 2:1 randomisation ratio in the PALOMA-2 trial.

b. Please clarify why the sample size calculation for the PALOMA-2 trial was based on an [redacted] (Table 19 of company submission and p.90 of the clinical study report), when it is a stratified log rank test that is performed to analyse the progression-free survival data from the PALOMA-2 trial.

c. Please explain the rationale for the use of one sided hypothesis tests for the outcomes of progression-free survival, objective response, and clinical benefit rate for the PALOMA-2 trial.

d. Please clarify if one sided hypothesis tests were used for the patient-reported outcomes for the PALOMA-2 trial, and please explain the rationale if this is the case.

A10. Eastern Cooperative Oncology Group performance status in the PALOMA-1 and PALOMA-2 trials:

a. Please provide a summary of Eastern Cooperative Oncology Group status by treatment arm at time of progression for patients in the PALOMA-1 trial, i.e. the numbers of patients with each performance status score at this point in time.

b. Please provide a summary of Eastern Cooperative Oncology Group status by treatment arm at time of progression for patients in the PALOMA-2 trial, i.e. the numbers of patients with each performance status score at this point in time.

A11. Health-related quality of life data:

a. Please clarify whether the health-related quality of life data reported for the PALOMA-1 trial in the company submission are derived from pre-specified or

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post-hoc analyses.

b. Please clarify whether the health-related quality of life data reported for the PALOMA-2 trial in the company submission are derived from pre-specified or post-hoc analyses.

c. Appendix 9 Table 15 to the company's submission provides EQ-5D scores for patients with and without neutropenia. Please provide the same data for patients in the placebo plus letrozole arm of the PALOMA-2 trial.

Section B: Clarification on decision model parameters and cost effectiveness data

B1. **Priority request: the PALOMA-2 trial population used in model.** Table 1 of the company submission states that subsequent to the scope issued by NICE a subgroup will be investigated for "those treated in the adjuvant setting compared with those who are presenting for the first time with metastatic disease (de novo)".The final paragraph in Section 1.4.1 states that the "…base case of the model uses the survival data from the PALOMA-2 trial for patients who were treated in the adjuvant setting only. For completeness, a scenario analysis is provided that uses the whole intention-to-treat population, which also includes patients with de novo disease." No further mention is made in the company submission of a subpopulation of patients from the PALOMA-2 trial being used to model the base case and no scenario analysis is given that specifically relates to the whole intention-to-treat population. Additionally, there does not appear to be any difference between the progression-free survival Kaplan-Meier curves from the intention-to-treat population given in Figure 12 and those used to fit the parametric models (Appendix 16). Please clarify and justify which population of the PALOMA-2 trial is used to model the base case and the scenarios.

B2. **Priority request: the PALOMA-1 trial population used to model overall survival**. Given the issues raised in Question B1, please clarify which population from the PALOMA-1 trial was used to inform modelling of overall survival in the base case and scenarios.

B3. **Priority request: Remodel using intention-to-treat populations.** If the intention-to-treat populations from the PALOMA-1 trial and the PALOMA-2 trial have not been used in the base case, please fit progression-free survival and overall survival models using the intention-to-treat populations.

B4. **Priority request: Kaplan-Meier data.** Please provide the following Kaplan-Meier analyses (listed in a to h below) to the following specification:

Populations: Including all patients lost to follow-up or withdrawing from trial.

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Censoring: Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be ***censored at the date of data cut-off****; i.e. not when last known to be alive (overall survival/post-progression survival), and not at the date of last tumour assessment.*

Format: Please present analysis outputs in Microsoft Excel using the format of the sample table shown at the end of this request.

Requested Kaplan-Meier analyses

ID	Trial data set	Population	Kaplan-Meier data requested
a	*The PALOMA-2 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
e	*The PALOMA-1 trial, latest data cut*	*intention-to-treat population*	Time to death from any cause stratified by treatment arm
f			Time to disease progression or death based on investigator assessment, stratified by treatment arm
g			Time from disease progression by investigator assessment to death from any cause (post-progression survival) stratified by treatment arm
h			Time to treatment discontinuation stratified by treatment arm

* The ERG is aware that the pre-specified level of significance for assessing overall survival had not been met at the time of the original progression-free survival analysis (data cut-off 01 May 2015) (company submission p.83). However, the ERG believes that any analysis of overall survival in PALOMA-2 that can be made available would be of central importance to this appraisal.

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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
SKIP…		……	……	……	…	…
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

B5. **Priority request: EQ-5D.** Please clarify what is meant in Section 4.7.2.3 of the company submission by the statement “For all surveys, 95-100% of patients in the intention-to-treat population completed at least 1 question from baseline through cycle 37”. Please explain what this means in terms of missing data included in the calculation of utility scores from the PALOMA-2 trial and how these missing data were dealt with. Specifically:

a. How many records included in the baseline utility calculation contained at least one missing value? And how many in the calculation of mean utilities per cycle?
b. How many records included in the baseline utility calculation were complete (i.e. no missing responses in the five 3-level questions)? And how many in the calculation of mean utilities per cycle?
c. Were records with missing values subject to imputation? If so, what proportion at each cycle, and how was this carried out?

B6. **Priority request: EQ-5D.** Please provide results for EQ-5D utility scores (using the UK value set) in the PALOMA-2 trial (most recent data-cut) showing the number of valid patient responses, and the mean and standard deviation of the EQ-5D values at each observation cycle stratified by treatment for the intention-to-treat population and each of three subgroups defined by country of origin:

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a. intention-to-treat population (319 sites)
b. USA and Canada (167 sites)
c. Europe, including Russia (109 sites)
d. Other (43 sites with patients from Asia and Australia).

Please present the results in Microsoft Excel using a format similar to the example table below:

Cycle	Number of valid responses	Mean utility estimate	Standard deviation of estimated utility
.	.	.	.
.	.	.	.

B7. EQ-5D. Please provide the number of patients in the PALOMA-2 trial who completed the EQ-5D, stratified by treatment arm, for the following age ranges: 25–34; 35–44; 45–54; 55–64; 65–74; 75+.

B8. The PALOMA-2 trial clinical study report tables and figures. Please include the tables and figures from the PALOMA-2 trial clinical study report that are referred to but not included in the text (Section 14 of the clinical study report)

B9. **Dose reductions:** Table 36 of the PALOMA-2 clinical study report shows a total of [redacted] dose reductions of palbociclib. Please provide an analysis of these dose reduction events by treatment cycle, indicating how many during a treatment period (e.g. days 2-13 of cycle 1 or days 2-20 of subsequent cycles) and how many at other time (days 14 of cycle 1 to day 1 of cycle 2, or days 21 to day 1 for subsequent cycles).

Cycle	Dose reduction events in active treatment period	Dose reduction events in 'rest' period	Total dose reduction events
1	.	.	.
2, etc.	.	.	.

Section C: Textual clarifications and additional points

C1. Please clarify if median exposure to treatment data in the PALOMA-2 trial are academic in confidence data. The data are marked as such in the last paragraph in Section 5.3.4 and in Table 60 but not in the second paragraph of the same section.

C2. Please confirm that publication of the PALOMA-2 data currently marked academic in confidence throughout the company submission is still expected to be published in December 2016.

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Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer [ID915]

Friday 4th November 2016

Company response to ERG clarification questions (received 21st October 2016)

Dear Joanna,

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. An Excel file accompanies this document relating to data specifically requested in Excel, and the Statistical Analysis Plans (SAPs) for the PALOMA-1 and PALOMA-2 clinical trials will be sent through separately (in response to question A1).

Responses to questions B4 (the provision of additional Kaplan-Meier data) and B9 (the breakdown of dose reductions) are not included in this version but will be sent to NICE separately next week.

Sincerely,

[redacted]

Section A: Clarification on clinical effectiveness data

A1. **Priority request:** Please provide the statistical analysis plans for the PALOMA-1 trial and the PALOMA-2 trial.

These documents have been sent separately. Please note that the information included in the Statistical Analysis Plans (SAPs) are confidential, unless presented unmarked elsewhere in the submission.

A2. **Priority request: Overall survival data for the PALOMA-2 trial:**

a. The company states that, at the time of the progression-free survival analysis in the PALOMA-2 trial (01 May 2015), the number of overall survival events did not meet the threshold allowing for an interim analysis to be conducted (p.74 of the company submission), and also that the pre-specified level of significance for assessing overall survival had not been met (p.12 and p.83 of the company submission). Please clarify which of these statements was the reason for not conducting an analysis of overall survival at this time and whether this reason was pre-specified.

The two reasons noted in the submission are linked to one another. A pre-specified number of PFS events were required in the two arms of the study to have sufficient power to detect a hazard ratio in favour of the intervention using a one-sided, unstratified log-rank test. In accordance with the SAP, OS was to be tested for significance when interim PFS analyses were performed, *provided* PFS was statistically significant at this time. The interim PFS analysis was conducted on data from 01 May 2015; however, PFS had not reached the pre-specified efficacy boundary. As such, an OS analysis was not conducted. Please see Section 4.2 in the supporting PALOMA-2 SAP document for additional detail.

When the number of PFS events was sufficient for the final PFS analyses to be conducted (26 February 2016), an interim OS analysis was conducted, in accordance with the SAP. This OS analysis was based on [redacted] deaths from 666 patients; however, this was only [redacted] of the required 390 total deaths needed for the final OS analysis. While Pfizer were blinded to this interim OS analysis, the results were reviewed by the External Data Monitoring Committee (E-DMC). The E-DMC did not inform Pfizer about early stopping for efficacy or express any safety concerns, but indicated that the pre-specified level of significance had not been met and that the OS data should continue to be collected for the final analysis. Currently, investigators, patients, and Pfizer remain blinded to the OS data.

b. The ERG notes that in Table 14 of the company submission, it is stated: "All PALOMA-2 data presented in this submission correspond to the data cut-off date of 26 February 2016." Since more events (deaths) would have occurred in the 8 months following the time of the progression-free survival analysis in the PALOMA-2 trial (01 May 2015), please provide the overall survival data, including Kaplan-Meier plots, for the PALOMA-2 trial for the latest data cut.

As set out above in the response to *A2a*, the analysis of OS could not be performed on 01 May 2015, as PFS had not reached the pre-specified efficacy boundary at this time. This rule was pre-specified in the SAP.

At the time of the final PFS analysis (26 February 2016), the interim OS analysis that was conducted showed that an insufficient number of deaths had occurred to allow for the final OS analysis. Since Pfizer remains blinded to the interim OS analysis, the Kaplan-Meier OS curves and censoring information as part of the interim OS analysis cannot be provided at this time.

A3. **Priority request: Subgroup analyses (progression-free survival):**

a. For the PALOMA-1 trial, please provide the median progression-free survival (and 95% confidence intervals) in each treatment arm and hazard ratio (and 95% confidence intervals) between arms for:

i. Patients with de novo disease.

In PALOMA-1, the median PFS for patients with de novo advanced disease was [redacted] months (95% CI: [redacted]) in the palbociclib plus letrozole arm, and [redacted] months (95% CI: [redacted]) in the letrozole plus placebo arm. The hazard ratio for PFS in these de novo patients was 0.341 (95% CI: 0.194, 0.599).[2]

ii. Patients who have received previous adjuvant/neoadjuvant therapy.

In PALOMA-1, the median PFS for patients who had previous systemic therapy was [redacted] months (95% CI: [redacted]) in the palbociclib plus letrozole arm, and [redacted] months (95% CI: [redacted]) in the letrozole plus placebo arm. The hazard ratio for PFS in these de novo patients was 0.539 (95% CI: 0.302, 0.962).[2]

b. For the PALOMA-2 trial, please provide the median progression-free survival (and 95% confidence intervals) in each arm and hazard ratio (and 95% confidence intervals) between arms for:

i. Patients with de novo disease.

In PALOMA-2, the median PFS for patients with de novo advanced disease was [redacted] months (95% CI: [redacted]) in the palbociclib plus letrozole arm, and [redacted] months (95% CI: [redacted]) in the letrozole plus placebo arm. The hazard ratio for PFS in these de novo patients was 0.674 (95% CI: 0.457, 0.993).[3]

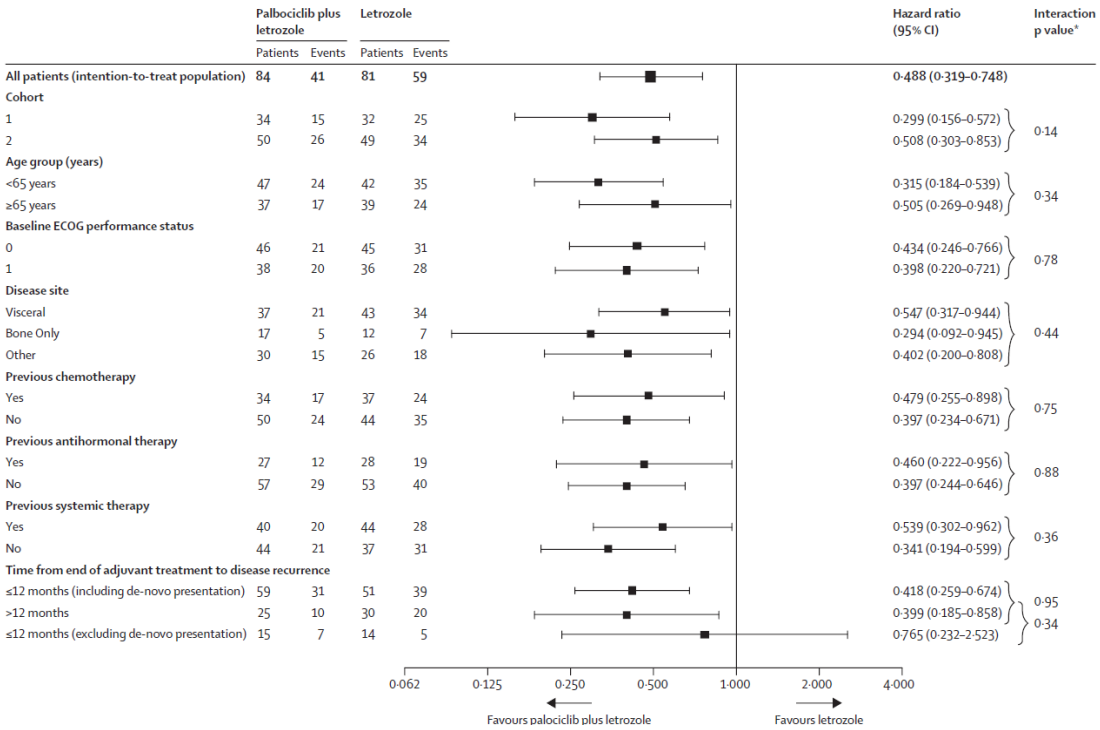
ii. Patients who have received previous adjuvant/neoadjuvant therapy.

In PALOMA-2, the median PFS for patients with de novo advanced disease was [redacted] months (95% CI: [redacted]) in the palbociclib plus letrozole arm, and [redacted] months (95% CI: [redacted]) in the letrozole plus placebo arm. The hazard ratio for PFS in these de novo patients was [redacted] (95% CI: [redacted]).[3]

c. Pre-specified subgroup analyses are reported for the PALOMA-1 trial in Figure 13 and for the PALOMA-2 trial in Figure 14 of the company submission. However, hazard ratios (and 95% confidence intervals) are only reported in Figure 14. Please provide hazard ratios (and 95% confidence intervals) for Figure 13.

Figure 1 below (taken from Finn et al. 2015[4]) details the hazard ratios and 95% confidence intervals across the subgroups presented in Figure 13 of the company's evidence submission.

Figure 1. Investigator-assessed PFS in pre-specified subgroups in PALOMA-1[4]



A4. **Priority request: Proportional hazard assumptions for progression-free survival and overall survival:**

a. In the company submission, it is stated that the assumption of proportional hazards was tested for progression-free survival data from the PALOMA-1 trial by reference to Figures 19 and 20. However, these figures show the PALOMA-2 trial data. Please clarify whether any testing of proportional hazards was conducted for progression-free survival or overall survival using data from the PALOMA-1 trial.

The question refers to text in in Section 4.4.1.2 (page 63) of the company's evidence submission. This section is where methods related to PALOMA-1 are discussed. The reference to Figures 19 and 20 is incorrectly placed in this section, and should instead be placed in Section 4.4.2.2 on the following page, where methods related to PALOMA-2 are discussed.

Figures 19 and 20 in the company's evidence submission present tests for proportional hazards related to PFS in PALOMA-2, with the objective to inform assumptions behind the survival modelling in the economic evaluation. Corresponding figures (a log-cumulative hazard plot and a Schoenfeld residual plot) are not presented for PFS for PALOMA-1 in the evidence submission. This is because PFS from PALOMA-1 was not used in the economic evaluation, due to the availability of phase III data from PALOMA-2.

b. Please clarify the methodology used to generate hazard ratios for the PALOMA-2 trial.

Hazards ratios and 2-sided 95% confidence intervals were estimated using Cox proportional hazards regression. Time-to-event endpoints between the two treatment arms were compared with a 1-sided stratified log-rank test, adjusting for the site of disease, and/or a 1-sided unstratified log-rank test at the α=0.025 overall significance level. Cox proportional hazards models were also used to explore the potential influences of the baseline stratification factors on time-to-event endpoints.[5]

c. The proportional hazards assumption appears to be violated for overall survival in the PALOMA-1 trial (where it can be seen that the Kaplan-Meier curves for each treatment arm cross in Figure 11 of the company submission). Please clarify whether the progression-free survival data from the PALOMA-2 trial and the overall survival data from the PALOMA-1 trial can therefore be justifiably correlated (as stated in Section 3.2 of the company submission) given that the proportional hazards assumption is likely to hold for the PALOMA-2 trial progression-free survival data but not for the PALOMA-1 trial overall survival data.

As the base case ICER does not rely on a correlation between differences in OS in PALOMA-1 and differences in PFS in PALOMA-2, a violation of the proportional hazards assumption for OS in PALOMA-1 does not impact the assumptions supporting the economic base case.

Section 3.2 in the evidence submission highlights a range of published studies which have identified a correlation between PFS and OS in advanced/metastatic breast cancer.[6-10] The company's base case model does not use this evidence as support for a correlation between PALOMA-2 PFS and PALOMA-1 OS, but rather as support for a correlation between PALOMA-2 PFS and the expected "true" OS benefit (i.e., unconfounded OS).

Importantly, the PALOMA-1 study was not powered to detect differences in OS.[4] This must be taken into account when considering that the OS curves crossed. Due to this lack of statistical power in the analyses and the likely confounding of OS (for example, through differences in post-progression therapies between arms), it should not be assumed that violation of the proportional hazards assumption, or the lack of a statistically significant OS advantage, is robust evidence to conclude that palbociclib is not associated with an OS benefit. Furthermore, the OS from PALOMA-1 is not

mature. Palbociclib plus letrozole did show a numerical improvement in median OS versus letrozole alone in PALOMA-1, which is consistent with palbociclib's large statistically significant improvement in PFS that is observed across both PALOMA-1 and PALOMA-2.

A5. Disease progression:

a. Table 13 and Table 16 define progression as 'radiological' progression (i.e. that progression must be determined by radiological scanning) in both the PALOMA-1 trial and the PALOMA-2 trial, however the permitted and disallowed concomitant medications reported in Tables 11 and 14 of the company submission imply that increased used of bisphosphonates / other treatments will also be treated as progression in both trials. Please clarify the exact definitions used for 'progression' in the analyses of both the PALOMA-1 and PALOMA-2 trial.

PFS was defined as the time from the date of randomisation to the date of the first documentation of objective tumour progression as per RECIST v1.1 or death due to any cause in the absence of progressed disease, whichever occurred first, based on investigator assessment.[1] If a patient is initiating bisphosphonate post-baseline and progression was not ruled out, in the absence of radiographic evidence this would be reported as "Global Deterioration of Health Status".

b. Please provide the results of the univariate and multivariate analyses for both investigator-assessed and blinded independent review progression-free survival for the PALOMA-2 trial as described in Table 19 of the company submission (i.e. Table 14.2.1.10.1, Table 14.2.2.10.1, Table 14.2.1.10.2, Table 14.2.2.10.2 of the PALOMA-2 clinical study report).

Univariate analyses, palbociclib plus letrozole versus letrozole plus placebo:

- BICR: HR [redacted] (95% CI: [redacted])[3]
- Investigator assessed: HR [redacted] (95% CI: [redacted])[3]

Multivariate analyses, palbociclib plus letrozole versus letrozole plus placebo:

- BICR: HR [redacted] (95% CI: [redacted])[3]
- Investigator assessed: HR [redacted] (95% CI: [redacted])[3]

The full tables are provided as separate documents.

A6. Subsequent treatment received on disease progression: For PALOMA-1, the following poster reports subsequent treatment received by patients in the PALOMA-1 trial following disease progression: Finn RS, Crown JP, Ettl J, Pinter T, Thummala A, Shparyk Y, et al. Treatment patterns of post-disease progression in the PALOMA-1/TRIO-18 trial. 38th Annual San Antonio Breast Cancer Symposium December 8-12; San Antonio, TX2015. If available, please provide the equivalent data for the PALOMA-2 trial.

A full list of follow-on therapies is provided in a separate document.[3] In the palbociclib plus letrozole arm, [redacted] had received follow-up systemic therapy at the time of data-cut (26 February 2016). Of these [redacted], the most common administered therapies were:

[redacted]

In the letrozole plus placebo arm, [redacted] had received follow-up systemic therapy at the time of data-cut (26 February 2016). Of these receiving follow-up therapy, the most common therapies were:

[redacted]

**Note that the above data are not specific to the first follow-on therapy (i.e. second-line therapy) but encompass the use of all follow-on therapies across all subsequent lines at the time of data-cut, which is why it does not sum to 100%. Although listed individually, these do necessarily not reflect monotherapy use but are merely the most prevalent treatments.*

A7. Pooled data:

a. Please clarify whether the company considered performing a meta-analysis of the data from the PALOMA-1 trial and the PALOMA-2 trial. Please outline the rationale for not performing a meta-analysis.

PALOMA-1 was a phase I/II RCT with 165 patients, whereas PALOMA-2 was a confirmatory phase III RCT with 666 patients. As PFS data from PALOMA-2, the larger, confirmatory, later phase trial were available, this was the most robust data source to inform PFS. Pooling data with PALOMA-1 was thus deemed not necessary. Furthermore, the follow-up time between the two studies currently varies, which impacts the proportion of patients who are off study treatment. As such, pooling would be expected to increase heterogeneity between the two studies.

The absolute difference in median PFS between treatment arms in PALOMA-1 and PALOMA-2 are very similar (median 10.0 months and 10.3 months, respectively). As a consequence, there should be negligible impact on the estimated QALY gain due to only very minor differences in incremental benefit. However, it is important to note that, in PALOMA-1, this incremental benefit was observed with a slightly lower absolute PFS than observed in PALOMA-2 (palbociclib PFS was 20.2 months in PALOMA-1 and 24.8 months in PALOMA-2). As the economic model assumes palbociclib treatment continues until progression, including PALOMA-1 (or pooling PALOMA-1 with PALOMA-2) would be expected to maintain the incremental benefit, yet reduce the treatment duration (thus reducing incremental costs). As a result, it is anticipated that the pooling of PALOMA-1 and PALOMA-2 PFS would lower the ICER, suggesting the current base case is a conservative estimate of palbociclib's cost-effectiveness.

b. Please clarify whether the company considered pooling adverse event data from the PALOMA-1 trial and the PALOMA-2 trial. Please outline the rationale for not pooling these data.

Pooled safety data for palbociclib are presented in Table 43 of the evidence submission. For reasons detailed previously in the response to *A7a*, PALOMA-2 was the most robust source of clinical evidence; pooling data with PALOMA-1 was not deemed necessary for the economic modelling. Furthermore, Figure 28 in the company's evidence submission shows that the impact on the ICER of varying adverse event incidence is minimal.

The economic model considers the impact of grade 3 and 4 adverse events with an incidence of >5% in either treatment arm. Key events included were neutropenia, leukopenia, infections and anaemia. Table 1 below shows the similarity in the incidence of these grade 3 and 4 events across the two studies, supporting the assumption that pooling would have negligible impact on the ICER.

Table 1. Key G3/4 events associated with palbociclib plus letrozole (extracts from Tables 39 and 41 of evidence submission)

Adverse event	PALOMA-1	PALOMA-2
Any event (G3/4)	76%	76%
Neutropenia (G3/4)	54%	55-66%*
Leukopenia (G3/4)	25%	19%
Infections (G3/4)	*<5%*	7%
Anaemia (G3/4)	5%	6%

**range depending on inclusion of patients with decreased neutrophil count*

A8. Design (trial conduct and analysis) of the PALOMA-1 trial:

a. Please clarify whether the 12 patients included in the Phase I stage of the NCT00721409 trial were also included in the Phase 2 PALOMA-1 trial.

No, these 12 patients from Phase I were not included in the Phase 2 analyses.

b. Following the first interim analysis of the PALOMA-1 trial, accrual to cohort 2 was stopped (Section 4.3.1 of the company submission).

i. Please provide justification for this amendment, considering that the trial was not designed with stopping rules.

In an unplanned interim analysis of cohort 1 based on 32 PFS events, it was noted that almost twice as many patients in the control group were coming off the study because of disease progression.[4] These preliminary results from cohort 1 suggested that further patient selection based upon CCND1 amplification or p16 loss was unlikely to further improve patient outcome over the use of oestrogen receptor and HER2 status alone. As a result, further enrolment was stopped into cohort 2 and the SAP was amended such that the primary endpoint would be analysed in cohort 1 and 2 combined instead of cohort 2 alone.[4]

ii. Please clarify how the decision was made to stop recruitment when there was not a pre-specified level of significance to stop recruitment based on this analysis.

The study changes were made without any efficacy results from cohort 2 and were overseen by the Study Steering Committee.[4] In addition to stopping recruitment to cohort 2 considering the observations set out above in *A7bii*, it was decided prospectively to combine the analyses of cohorts 1 and 2.[4] Stopping of enrolment would not affect the pre-specified level of significance.

c. Following the first interim analysis of the PALOMA-1 trial, the statistical analysis plan for the primary endpoint was amended to a combined analysis of cohorts 1 and 2, instead of just cohort 2 (Section 4.3.1 of the company submission).

    i. Please clarify whether the analysis plan was amended so that the analyses of secondary outcomes could also use the combined dataset of both cohorts 1 and 2.

The amended SAP was applied to all efficacy analyses (including both primary and secondary endpoints).

    ii. Please provide the rationale for changes to the planned analysis of both primary and secondary outcomes.

Please see the response to question *A8bi*.

d. In Section 4.4.1.2 it is stated that based on the interim analyses of the PALOMA-1 trial, the significance level for the final analysis was adjusted using the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary. Please clarify what the adjusted significance level was.

The adjusted level of significance for PFS was 0.0938 based on the study design.

e. Please clarify what significance levels were used for testing the PALOMA-1 trial secondary outcomes: overall survival, time to progression, objective response, and clinical benefit rate.

No formal testing was performed for those endpoints. Nominal p-values were reported but no multiplicity adjustments were made for the secondary analyses.

f. Please explain the rationale for the use of one sided hypothesis tests for the outcomes of progression-free survival, overall survival, time to progression, objective response, and clinical benefit rate for the PALOMA-1 trial.

In this study, one-sided hypothesis tests were deemed suitable due to there being sufficient confidence that the intervention was more efficacious than the comparator. Further, it was more efficient statistically, considering an expected small sample size, under the hull hypothesis to use one-sided testing.

A9. Design (trial conduct and analysis) of the PALOMA-2 trial:

a. Please explain the rationale for using a 2:1 randomisation ratio in the PALOMA-2 trial.

Given the preliminary efficacy observed in PALOMA-1 and the confidence in the intervention, there was a desire to not to want to expose more patients to a (likely) less efficacious treatment. Further, this also permitted the collection of additional safety data for the intervention.

b. Please clarify why the sample size calculation for the PALOMA-2 trial was based on an [redacted] (Table 19 of company submission and p.90 of the clinical study report), when it is a stratified log rank test that is performed to analyse the progression-free survival data from the PALOMA-2 trial.

The sample size determination is typically based on an unstratified log-rank test. The intention of using a stratified log-rank test was to potentially gain power to show a treatment effect. However, in this study, the unstratified analysis actually has a higher power than the stratified analysis (that is, a better estimated hazard ratio).

c. Please explain the rationale for the use of one sided hypothesis tests for the outcomes of progression-free survival, objective response, and clinical benefit rate for the PALOMA-2 trial.

As set out in the response to question *A8f,* one sided hypothesis tests were deemed suitable due to there being sufficient confidence that the intervention was more efficacious than the comparator. Further, it was more efficient given the small sample size under the hull hypothesis to use one-sided testing.

d. Please clarify if one sided hypothesis tests were used for the patient-reported outcomes for the PALOMA-2 trial, and please explain the rationale if this is the case.

Two-sided hypothesis tests were used for patient-reported outcome analyses (except for time to deterioration analyses).

A10. Eastern Cooperative Oncology Group performance status in the PALOMA-1 and PALOMA-2 trials:

a. Please provide a summary of Eastern Cooperative Oncology Group status by treatment arm at time of progression for patients in the PALOMA-1 trial, i.e. the numbers of patients with each performance status score at this point in time.

Table 2. ECOG status at the time of progressed disease (PD), PALOMA-1[11]

ECOG PS at PD	Palbociclib + letrozole (n=84)		Letrozole + placebo (n=81)	
	n	%	n	%
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b. Please provide a summary of Eastern Cooperative Oncology Group status by treatment arm at time of progression for patients in the PALOMA-2 trial, i.e. the numbers of patients with each performance status score at this point in time.

Table 3. ECOG status at the time of progressed disease (PD), PALOMA-2[12]

ECOG PS at PD	Palbociclib + letrozole (n=444)		Letrozole + placebo (n=222)	
	n	%	n	%
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A11. Health-related quality of life data:

a. Please clarify whether the health-related quality of life data reported for the PALOMA-1 trial in the company submission are derived from pre-specified or post-hoc analyses.

The change-from-baseline analyses were pre-specified. The mixed model analyses were post-hoc.

b. Please clarify whether the health-related quality of life data reported for the PALOMA-2 trial in the company submission are derived from pre-specified or post-hoc analyses.

The analyses were pre-specified, however an evaluation of EQ-5D by neutropenia status was post-hoc.

c. Appendix 9 Table 15 to the company's submission provides EQ-5D scores for patients with and without neutropenia. Please provide the same data for patients in the placebo plus letrozole arm of the PALOMA-2 trial.

Due to the very small number of patients with neutropenia in the comparator arm making comparative conclusions difficult, it is considered that the below data serve for purposes of observation only, not analysis.

Table 4. PALOMA-2 plot of observed means for comparator arm, EQ-5D index in patients with and without neutropenia (PRO analysis set)[3]

Cycle	Letrozole + placebo (with neutropenia)			Letrozole + placebo (without neutropenia)			Difference
	n	Mean	(SD)	n	Mean	(SD)	P value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11				[redacted]	[redacted]	[redacted]	
Cycle 13				[redacted]	[redacted]	[redacted]	
Cycle 15				[redacted]	[redacted]	[redacted]	
Cycle 17	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Cycle 19				[redacted]	[redacted]	[redacted]	
Cycle 21				[redacted]	[redacted]	[redacted]	
Cycle 23				[redacted]	[redacted]	[redacted]	
Cycle 25				[redacted]	[redacted]	[redacted]	
Cycle 27	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Cycle 29				[redacted]	[redacted]	[redacted]	
Cycle 31				[redacted]	[redacted]	[redacted]	
Cycle 33				[redacted]	[redacted]	[redacted]	
Cycle 35				[redacted]	[redacted]	[redacted]	
Cycle 37				[redacted]	[redacted]	[redacted]	
EOT				[redacted]	[redacted]	[redacted]	

Section B: Clarification on decision model parameters and cost effectiveness data

B1. **Priority request: the PALOMA-2 trial population used in model.** Table 1 of the company submission states that subsequent to the scope issued by NICE a subgroup will be investigated for "those treated in the adjuvant setting compared with those who are presenting for the first time with metastatic disease (de novo)".The final paragraph in Section 1.4.1 states that the "…base case of the model uses the survival data from the PALOMA-2 trial for patients who were treated in the adjuvant setting only. For completeness, a scenario analysis is provided that uses the whole intention-to-treat population, which also includes patients with de novo disease." No further mention is made in the company submission of a subpopulation of patients from the PALOMA-2 trial being used to model the base case and no scenario analysis is given that specifically relates to the whole intention-to-treat population. Additionally, there does not appear to be any difference between the progression-free survival Kaplan-Meier curves from the intention-to-treat population given in Figure 12 and those used to fit the parametric models (Appendix 16). Please clarify and justify which population of the PALOMA-2 trial is used to model the base case and the scenarios.

All modelled input data are obtained from the ITT population, including those used in the scenario analyses. Subgroup data are only presented in Section 4 of the evidence submission, in the context of the efficacy results from the trials.

The quoted text in the question is incorrect and Pfizer acknowledges this has caused confusion. The sentences in question should read that only ITT data was used in all economic modelling, in both the base case and scenarios. No subgroup data were used in the economic modelling.

B2. **Priority request: the PALOMA-1 trial population used to model overall survival**. Given the issues raised in Question B1, please clarify which population from the PALOMA-1 trial was used to inform modelling of overall survival in the base case and scenarios.

The ITT population from PALOMA-1 was used to inform the OS of the comparator arm in the economic base case. The intervention arm had an assumption applied to estimate the relative OS in relation.

Scenarios analyses examining different assumptions for OS use the ITT data from PALOMA-1.

B3. **Priority request: Remodel using intention-to-treat populations.** If the intention-to-treat populations from the PALOMA-1 trial and the PALOMA-2 trial have not been used in the base case, please fit progression-free survival and overall survival models using the intention-to-treat populations.

To clarify, only the ITT population data was used in the evidence submission.

B4. **Priority request: Kaplan-Meier data.** Please provide the following Kaplan-Meier analyses (listed in a to h below) to the following specification:

Populations: Including all patients lost to follow-up or withdrawing from trial.

Censoring: Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be ***censored at the date of data cut-off****; i.e. not when last known to be alive (overall survival/post-progression survival), and not at the date of last tumour assessment.*

Format: Please present analysis outputs in Microsoft Excel using the format of the sample table shown at the end of this request.

Requested Kaplan-Meier analyses

ID	Trial data set	Population	Kaplan-Meier data requested
a	*The PALOMA-2 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
e	*The PALOMA-1 trial, latest data cut*	*intention-to-treat population*	Time to death from any cause stratified by treatment arm
f			Time to disease progression or death based on investigator assessment, stratified by treatment arm
g			Time from disease progression by investigator assessment to death from any cause (post-progression survival) stratified by treatment arm
h			Time to treatment discontinuation stratified by treatment arm

* The ERG is aware that the pre-specified level of significance for assessing overall survival had not been met at the time of the original progression-free survival analysis (data cut-off 01 May 2015) (company submission p.83). However, the ERG believes that any analysis of overall survival in PALOMA-2 that can be made available would be of central importance to this appraisal.

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
SKIP…		……	……	……	…	…
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

OS data for PALOMA-2 is not currently available (see response to question A2), and consequently the data for requested analyses (a) and (c) from the table above are not provided. In Excel files separate to this response document, new Kaplan-Meier data has been provided in the requested format for the other six datasets, encompassing PFS, OS, treatment discontinuation (TD) and post-progression survival (PPS):

(a) Data not provided, PALOMA-2 OS not available

(b) PALOMA-2, PFS, re-censored

(c) Data not provided, PALOMA-2 OS not available

(d) PALOMA-2, TD, re-censored

(e) PALOMA-1, OS, re-censored

(f) PALOMA-1, PFS, re-censored

(g) PALOMA-1, PPS, re-censored

(h) PALOMA-1, TD, re-censored

All the provided datasets are academic in confidence (AIC) as they are currently unpublished.

B5. **Priority request: EQ-5D.** Please clarify what is meant in Section 4.7.2.3 of the company submission by the statement "For all surveys, 95-100% of patients in the intention-to-treat population completed at least 1 question from baseline through cycle 37". Please explain what this means in terms of missing data included in the calculation of utility scores from the PALOMA-2 trial and how these missing data were dealt with. Specifically:

a. How many records included in the baseline utility calculation contained at least one missing value? And how many in the calculation of mean utilities per cycle?

In the baseline utility calculation, [redacted] of the patients in the trial completed at least 1 of the questions, and [redacted] completed all of the questions, in the EQ-5D questionnaire.[3]

Across the cycles (cycles 2 to 37), an average of [redacted] of patients completed at least 1 of the questions, and, on average, [redacted] of respondents completed all of the EQ-5D questionnaire per cycle.[3]

b. How many records included in the baseline utility calculation were complete (i.e. no missing responses in the five 3-level questions)? And how many in the calculation of mean utilities per cycle?

[redacted] had no missing responses ([redacted] in the palbociclib plus letrozole arm versus [redacted] in the letrozole plus placebo arm).[3]

c. Were records with missing values subject to imputation? If so, what proportion at each cycle, and how was this carried out?

No missing values were subject to imputation. Across all cycles (2 to 37), an average of only [redacted] of questionnaires were not *fully* completed at each cycle.[3] As such, due to very high completion rates, it is not anticipated that missing data impacts the results.

B6. **Priority request: EQ-5D.** Please provide results for EQ-5D utility scores (using the UK value set) in the PALOMA-2 trial (most recent data-cut) showing the number of valid patient responses, and the mean and standard deviation of the EQ-5D values at each observation cycle stratified by treatment for the intention-to-treat population and each of three subgroups defined by country of origin:

a. intention-to-treat population (319 sites)
b. USA and Canada (167 sites)
c. Europe, including Russia (109 sites)
d. Other (43 sites with patients from Asia and Australia).

Please present the results in Microsoft Excel using a format similar to the example table below:

Cycle	Number of valid responses	Mean utility estimate	Standard deviation of estimated utility

.	.	.	.
.	.	.	.

The data broken down by geographical regions have been presented in a separate Microsoft Excel document, as requested. However, the number of sites stated in the question ("319") is incorrect; data were collected from 186 sites in PALOMA-2, as presented in Table 14 of the company submission. To provide clarity, the sample sizes in each region are as follows:

a. intention-to-treat population (n=666)[1]
b. North America region (n=267)[12]
c. Europe (n=307)[12]
d. Asia Pacific region (n=92)[12]

B7. EQ-5D. Please provide the number of patients in the PALOMA-2 trial who completed the EQ-5D, stratified by treatment arm, for the following age ranges: 25–34; 35–44; 45–54; 55–64; 65–74; 75+.

Patients were not stratified by age. The number of patients that completed the EQ-5D differs per cycle. For example, this is due to patients coming off treatment because of progression. As such, it is difficult to make interpretations from a comparison of the number of respondents by treatment arm, either as an average or by specific cycle. Further, it is important to consider the 2:1 randomisation of patients.

A separate document has been sent that provides tables containing the number of respondents that completed the EQ-5D, by cycle, by treatment arm, by age group.[12]

B8. The PALOMA-2 trial clinical study report tables and figures. Please include the tables and figures from the PALOMA-2 trial clinical study report that are referred to but not included in the text (Section 14 of the clinical study report)

Section 14 of the clinical study report is only available table-by-table. As such, the entirety has not been sent, however the key tables have relate to the evidence presented across Tables 21, 24, 25 and 41 in the company's evidence submission are provided.

B9. **Dose reductions:** Table 36 of the PALOMA-2 clinical study report shows a total of [redacted] dose reductions of palbociclib. Please provide an analysis of these dose reduction events by treatment cycle, indicating how many during a treatment period (e.g. days 2-13 of cycle 1 or days 2-20 of subsequent cycles) and how many at other time (days 14 of cycle 1 to day 1 of cycle 2, or days 21 to day 1 for subsequent cycles).

Cycle	Dose reduction events in active treatment period *(i.e. days 1-21)*	Dose reduction events in 'rest' period *(i.e. days 22-28)*	Total dose reduction events

1	.	.	.
2, etc.	.	.	.

Table 5 details the breakdown of the [redacted] dose reduction events by treatment cycle for palboclicib treatment. These are summary statistics for the dose reductions as opposed to the start and end dates of every dose reduction, which would need to be done on an individual patient basis. This would neither be feasible within reasonable timescales, nor add any further information germane to the assessment of palbociclib's cost-effectiveness as a cohort Markov model is used, not a patient level simulation.

Table 5. Dose reductions by cycle in the palbociclib plus letrozole arm in PALOMA-2[3]

Cycle	N	N with dose reduction	% with dose reduction
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]

For the patients with one dose reduction, the median time to dose reduction from 125mg to 100mg was [redacted] days (mean [redacted] days), and the median number of days on

100mg was [redacted] (mean [redacted]). Supporting tables from the PALOMA-2 Clinical Study Report have been provided separately that contain further details on dose reductions and dose interruptions, and data for those with a second dose reduction.

The modelled PFS from PALOMA-2 reflects the fact that this cohort experienced [redacted] dose reduction events. As such, consideration of when these dose reduction events occurred and for how long dose was reduced for, does not impact the PFS of palbociclib plus letrozole in the economic model. Furthermore, palbociclib is priced the same across dose formulations; a dose reduction does therefore not affect the drug acquisition cost. Consequently, it is not expected that a more detailed examination of dose reduction events would impact either the numerator or the denominator in the ICER equation.

Section C: Textual clarifications and additional points

C1. Please clarify if median exposure to treatment data in the PALOMA-2 trial are academic in confidence data. The data are marked as such in the last paragraph in Section 5.3.4 and in Table 60 but not in the second paragraph of the same section.

The data in the second paragraph should be marked as AIC. Pfizer are now expecting the publication of PALOMA-2 before the end of November 2016. Marking of confidential data will be revised as needed, in line with NICE's requirements.

C2. Please confirm that publication of the PALOMA-2 data currently marked academic in confidence throughout the company submission is still expected to be published in December 2016.

The current expectation is that the PALOMA-2 manuscript will be now published before the end of November 2016. Pfizer suggest an appropriately timed revision of redacted data, as stated above in the response to question *C1*.

Pfizer have marked the date in the ERG's question AIC, as this information is not currently public.

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2. Pfizer. Clinical study report on trial A5481003: Phase 1/2, open-label, randomized study of the safety, efficacy and pharmacokinetics of letrozole plus PD 0332991 (oral CDK 4/6 inhibitor) and letrozole single agent for the first-line treatment of ER-positive, HER2-negative advanced breast cancer in postmenopausal women - data on file. 2015 28 July.
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4. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. The Lancet Oncology. 2015;16(1):25-35.
5. Pfizer. Protocol A5481008 - Statistical Analysis Plan (SAP). A Randomized, Multicenter, Double-Blind Phase 3 Study of PD-0332991 (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Postmenopausal Women With ER (+), HER2 (-) Breast Cancer Who Have Not Received Any Prior Systemic Anti-Cancer Treatment for Advanced Disease - data on file. March 2015.
6. Petrilli F, Barni S. Surrogate endpoints in metastatic breast cancer treated with
7. Hackshaw A, Knight A, Barrett-Lee P, Leonard R. Surrogate markers and survival in women receiving first-line combination anthracycline chemotherapy for advanced breast cancer. Br J Cancer. 2005;93(11):1215-21.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer [ID915]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: XXXXXXXXXXXXXXXX

Name of your organisation: Breast Cancer Now

Your position in the organisation: Senior Policy Officer

Brief description of the organisation: Breast Cancer Now is the UK's largest breast cancer charity, dedicated to funding ground-breaking research into the disease. Our ambition is that by 2050, everyone who develops breast cancer will live. We're bringing together all those affected by the disease to improve the way we prevent, detect, treat and stop breast cancer. And 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.

This submission reflects the views of Breast Cancer Now, based on our experience of working with people who are affected by breast cancer. We know that access to effective drugs is hugely important to our supporters and that quality of life is valued just as much as length of life.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Metastatic breast cancer is when cancer originating in the breast has spread to distant parts of the body, most commonly the lungs, brain, bones and liver. There is no cure for metastatic breast cancer, so most medicines aim to extend the length of life or to improve quality of life for patients. A patient can be diagnosed with metastatic (stage 4) cancer to begin with or they can develop the condition many years after treatment for their primary breast cancer has ended. Living with metastatic breast cancer is difficult to come to terms with for both the patient and their family. Patients' time is limited and the treatments usually have some side effects. Patients therefore tell us that

quality of life is just as important to take into account as length of life, as this means that they would be able to spend quality time with their loved ones.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Palbociclib is intended to be given to patients as a first line treatment for advanced or metastatic disease. A recent diagnosis of metastatic breast cancer will come as a shock to most patients and their families, as it is a terminal condition with a short life expectancy. People with younger children will be particularly keen to find treatments that will halt progression and extend life for as long as possible. The vast majority of recently-diagnosed patients would feel it is important to start treatment quickly to get their disease under control. The type and severity of side effects experienced will also play a role for patients, as these could impact negatively on their quality of life. Quality time with their loved ones will therefore also be a key objective in their treatment.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Patients, whose cancer is hormone receptor positive and HER2 negative, are usually offered aromatase inhibitors to control a new diagnosis of advanced disease. Aromatase inhibitors are generally tolerated well by patients but some patients will experience strong menopausal side effects, such as night sweats. Patients will continue on aromatase inhibitors until their disease progresses, indicating that their cancer has become resistant to the treatment. There are three aromatase inhibitors currently offered to this group of patients in England – anastrozole, letrozole and exemestane. Whether patients will be able to move from one aromatase inhibitor to another, once they progress will depend on their particular cancer and also on how well they tolerate the side effects of a particular drug. Once patients progress on an aromatase inhibitor, the next step after progression would be systemic (non-targeted) chemotherapies, which are associated with serious side effects.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

The PALOMA-1 and PALOMA-2 trials have recently shown that palbociclib plus letrozole, compared to letrozole alone, gives patients an extra 10 months of progression free survival on average. This is a significant step forward for the hormone positive, HER2-negative group of metastatic patients, for whom no new treatments have been approved by NICE since the introduction of aromatase inhibitors.

Delaying progression means more quality time with family and loved ones as well as a delay to starting on systemic (non-targeted) chemotherapies, which are traditionally associated with more severe side effects and a poorer quality of life for patients.

Delay to progression of disease can also have benefits for the mental health of patients, as lack of progression indicates that the medicine is working. A longer time to progression may mean that the patient is able to lead a more or less normal daily life throughout this time. Lack of progression of a metastatic cancer is also likely to bring some comfort to relatives and friends of the patient, as this is the best possible outcome for a terminal illness.

Both palbociclib and letrozole are taken orally, therefore minimising the length and frequency of hospital visits needed whilst on this medication. There is therefore no significant extra burden placed on family members, who would be accompanying the patient on trips to the hospital.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

As previously mentioned, delaying progression of advanced disease will delay the need for patients to move on to systemic non-targeted chemotherapies and the severe side effects associated with these. A delay in progression means there would be more quality time for patients and their families. Later progression may also help with some of the emotional impact of this illness, as it would mean the average patient would not progress for 24 months rather than 14 months on treatment (PALOMA-2 results). This is a significant difference, allowing the average patient to be stable on this medication for two years, from being diagnosed with a terminal illness. Patients would very much value this extra time.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

There are some increased side effects associated with palbociclib plus letrozole, compared with letrozole alone. Each patient's situation will be different and this will impact on their willingness and ability to take palbociclib. However, as long as all the side effects are clearly discussed with the patient, they will be able to make their own choice as to the level of risk they will be willing to take on.

There is some extra monitoring for the patients taking palbociclib, but this is mostly in the form of regular blood tests rather than lengthy trips to the hospital to administer their treatment, so is unlikely to be too burdensome for patients and their families.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

The current treatments available on the NHS are aromatase inhibitors. These are quite effective in controlling advanced hormone positive, HER2-negative disease. However, all patients will eventually progress on this treatment, after which point patients will only have the option of taking traditional chemotherapies to control their disease. Since traditional chemotherapies are generally associated with severe side effects and usually have a negative impact on quality of life for patients, patients generally prefer to delay this stage of treatment for as long as possible.

Please list any concerns patients or carers have about the treatment being appraised.

Palbociclib plus letrozole is associated with some increased side effects, compared to letrozole alone. These include low white blood cell count (neutropenia) and slightly higher levels of fatigue and nausea. These side effects will affect some patients more than others and the severity of side effects will determine whether patients will be able to continue on this treatment or whether they will need to switch to an aromatase inhibitor.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

We are not aware of any particular differences of opinion between patients for this treatment but we do know that patients will have different approaches and attitudes to the levels of risk they are happy to undertake. It is therefore important that the side effects of this drug are clearly discussed with the patient so that they can make an informed decision about whether this treatment is suitable for them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

This treatment has been tested in post-menopausal women with advanced hormone positive, HER2-negative breast cancer. Patients were excluded if they had any prior treatment for their advanced cancer. This treatment is likely to benefit a significant proportion of the metastatic breast cancer population. Hormone positive breast cancer is the most common type of breast cancer making up around 80% of all breast cancer patients, although a small proportion of these will also be HER2-positive and therefore not eligible for treatment with palbociclib.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Not that we are aware of.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in

the clinical trials.

Yes, as far as we are aware.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes, to the best of our knowledge.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not to the best of our knowledge.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Not that we are aware of.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Not that we are aware of.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

Palbociclib is a small molecule inhibitor of cyclin-dependent kinases uses CDK4 and CDK6. This is an innovative treatment which is first in class, in terms of both its mechanism and the progression free survival results, which show that this mechanism seems to be effective at controlling disease.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- This is an innovative, first-in-class drug that has strong progression free survival data. As it is given as a first line treatment for advanced breast cancer, it has an important role in extending the time that hormone treatments work at controlling patients' disease progression. This is an important delay before patients will eventually be offered generic chemotherapies which are known to have severe side effects.
- Palbociclib is potentially set to benefit a large proportion of the advanced breast cancer population, as the largest proportion of breast cancers are hormone positive, HER2 negative.
- This drug is given in oral form, which makes it simple for patients to take. Although there is some additional monitoring involved for palbociclib, patients are not required to spend long lengths of time at the hospital, so it

is unlikely that this will place a significant additional burden on patients and their families.

- There are some increased side effects from this drug plus letrozole, compared to letrozole alone, however not all patients will experience side effects. The benefits and risks of a treatment need to be clearly discussed with the patient to ensure they can make a decision that is right for them.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer [ID915]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Comments submitted by [redacted] behalf of:

Name of your organisation: NCRI/RCP/RCR/ACP

Comments coordinated by: [redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer [ID915]

What is the expected place of the technology in current practice?

This is a treatment for metastatic breast cancer which is hormone receptor positive and HER2 negative. It is a minimum standard that all breast cancer is defined in terms of hormone (oestrogen and progesterone) receptor status and HER-2 status. The specific subtype of hormone receptor positive HER-2 negative breast cancer makes up the majority (approximately 70%) of all breast cancers. When breast cancer has spread beyond the breast and regional lymph glands it is termed metastatic (stage 4) disease.
Treatment of this condition is likely to with a combination of systemic therapy (chemotherapy or endocrine therapy) but also supportive therapies including palliative radiotherapy, bisphosphonates and various other measures to help with symptoms. The principal decision to be made in the management of these patients is whether they should be treated with endocrine therapy alongside these supportive therapies or with chemotherapy alongside the same therapies. Those patients with a heavy burden of visceral disease or with short disease-free intervals since the time of their diagnosis with early breast cancer, or who are significantly unwell in themselves (sometimes termed 'in a visceral crisis') are usually treated with chemotherapy. However there is a large group of women with relatively low burden disease (quite often predominantly affecting the bones) whose breast cancer might be expected to have a somewhat indolent course and these patients would usually be treated with endocrine therapy. The endocrine therapy of choice at present is with an aromatase inhibitor drug. There are three available drugs (Anastrazole, Letrozole and the steroidal aromatase inhibitor Exemestane). It is important to recognise that these drugs are only suitable for women who are post-menopausal. (Pre-menopausal women may be given these drugs but would have to be rendered post-menopausal either by oophorectomy or the use of ovarian function suppression).
Whilst there will be debate between oncologists on which patients should be treated with chemotherapy and which with endocrine therapy on a case-by-case basis, by and large the broad groups who would benefit from these individual approaches are widely recognised and practice would be relatively uniform geographically across the UK. These patients tend to be treated in secondary care or tertiary referral centres. However secondary care centres treating breast cancer are widely distributed around the country (possibly up to a hundred breast units routinely treating metastatic breast cancer).

The relevant clinical guidelines are NICE Guidance on the Management of Advanced Breast Cancer. The technology under evaluation is with the drug Palbociclib. There are two key areas where the use of this drug has a firm evidence base: 1st line treatment and 2nd line treatment.

First line
This is the subject of this evaluation (in patients who are previously untreated for advanced breast cancer). The data for this indication come from the PALOMA1 study (Lancet Oncology 2015, volume 16, pages 25 – 35) and the PALOMA 2 study

(presented at the American Society of Clinical Oncology Meeting 2016, as yet unpublished in peer review).

The PALOMA 1 study will be available to the Committee. This is a study in 165 patients randomised to Palbociclib plus Letrozole or Letrozole alone. Patients had not received previous systemic therapy for advanced breast cancer and were required to have ER positive and HER-2 negative metastatic breast cancer. The addition of Palbociclib to Letrozole lead to an increase in median progression-free survival from 10.2 months to 20.2 months (P = 0.004). The PALOMA 2 trial had a similar design but with randomisation in a 2:1 manner to Palbociclib or Letrozole. In this study median progression-free survival increased from 14.5 months to 24.8 months (P < 0.0001). There was no specific subgroup of patients who appeared to benefit more than any other group (when the data were looked at in terms of age, race, sites of metastatic disease, prior hormonal therapy, disease-free interval, and prior chemotherapy). Furthermore biomarker analyses have so far not been shown to demonstrate any lab based biomarker (including Cyclin D1 or loss of P16) to be able to identify patients with a particular benefit from this drug.
The use of the palbociclib in this setting would be consistent with UK clinical practice where (in patients not selected for chemotherapy) endocrine therapy in the form of an aromatase inhibitor is widely used (in postmenopausal women).

Second line
It should also be noted that the PALOMA 3 trial (New England Journal of Medicine 2015, volume 373, pages 209 – 219) was a large phase three study which examined Palbociclib in combination with Fulvestrant in patients who had relapsed or progressed during prior endocrine therapy (patients were also allowed to have one prior line of chemotherapy in advanced disease). Therefore this study is best regarded as a second line study. In this study patients were randomised to Fulvestrant plus Palbociclib or Fulvestrant alone. Again an improvement in progression-free survival was demonstrated with the addition of Palbociclib (9.2 versus 3.8 months, P < 0.001). This use of Palbociclib would be consistent with UK based practice in some settings (where Fulvestrant is available). However not in all centres is Fulvestrant widely used.

The advantages and disadvantages of the technology
Palbociclib is orally administered and the toxicities are well documented in the relevant PALOMA 1 and PALOMA 2 papers. In both studies it is noted that Palbociclib causes neutropenia (grade 3 or grade 4 in 54% of patients in PALOMA 1 study). Whilst neutropenia can lead to delays and the need for dose reductions, it was not associated with increased rates of febrile neutropenia as is the case with neutropenia occuring in the context of chemotherapy. There are a variety of other day-to-day side effects listed in the published studies including low rates of nausea (2% grade 3) and fatigue but these are really relatively little different to those seen in the patients receiving Letrozole alone.

In patients on aromatase inhibitor alone, patients may be seen only every 8 – 12 weeks in clinic. However that being said many of these patients have bone

metastases so are quite often also seen monthly on a day unit for blood tests and to receive Denosumab or a bisphosphonate. With the addition of Palbociclib patients need to be seen monthly by a doctor or a nurse specialist (although in those patients on a bisphosphonate or Denosumab this would not be an extra visit). However in the first two cycles most protocols require the patients' return for a blood test two weeks after initiation of the cycle. There are therefore additional clinic visits and blood tests involved. In terms of the practicality of delivering this therapy for units used to handling chemotherapy drugs (as many are), this therapy is relatively straight forward to handle and on a day-to-day basis most patients anecdotally do seem to tolerate it well. It is a therapy that would be suitable for more widespread application in lower volume centres.

There is some access to the drug currently on a compassionate use programme (once patients have had four previous lines of therapy). Details on uptake of this programme will be available from the manufacturer. Experience of this drug is increasing with studies in the neoadjuvant setting (the PALLET study) and in the adjuvant setting (PALLAS study). Furthermore drugs with a similar mechanism of action (CDK4/6 inhibitors) made by different manufacturers are under investigation in a number of clinic trials (Ribociclib made by Novartis and Abemaciclib made by Lilly).

Any additional sources of evidence

As documented above.

Implementation issues

See above. Our experts do not think a significant amount of additional training would be required to implement this use of this drug.

Equality

Our experts do not think the proposal could exclude from full consideration people who might benefit. From the evidence base the one area of controversy would be in the use in pre-menopausal women. The PALOMA 2 trial involved post-menopausal women only although the PALOMA 3 trial allowed pre-menopausal women who had been treated with an ovarian function suppressor to enter. There is no other specific group with particular disabilities who our experts think will not have access to the drug for any of the reasons contained in this appraisal.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer [ID915]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:

Name of your organisation Royal Marsden NHS Foundation Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
None

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

Hormone receptor positive and HER negative breast cancer (hereafter referred to as HR positive) is the most common form of breast cancer, representing approximately 70% of all breast cancers. Patients with metastatic HR positive have incurable disease, but may live normal or near normal lives for many years with treatment (Turner et al Lancet 2016). The mainstay of treatment for HR positive breast cancer is endocrine therapy, therapies that target oestrogen receptor expression in the tumour. Many patients who present with metastatic HR positive breast cancer have either not had endocrine therapy before, or if they had endocrine therapy before they stopped it over a year prior to relapse. For these women endocrine therapy is the standard treatment, and for women with post-menopausal breast cancer an aromatase inhibitor such as letrozole or anastrazole (hereafter referred to as AI) is the current standard. For women with pre-menopausal metastatic HR positive breast cancer, standard treatment is to render the patient biochemically post-menopausal (with gonadotropin-releasing hormone analogue injections or by oophorectomy) and mange the patient as for post-menopausal women.

All metastatic HR positive tumours will eventually become resistant to AI and progress. Identifying therapies that enhance the effects of AI is of critical importance for the treatment of these women. Progression on therapy results in morbidity, worsening quality of life, and the need to change to more toxic treatments such as chemotherapy. Highly effective therapies are also likely to translate to improve overall survival.

There are no significant geographical variations in the first line management of metastatic HR positive breast cancer. This appraisal is not relevant to patients with visceral crisis, impending organ failure from metastatic cancer, who should be managed with chemotherapy first, before switching over to maintenance with an AI. In addition this appraisal is not relevant to patients who relapse on an AI, or within one year of stopping adjuvant AI, who are managed differently. There are no differences in opinion between professionals on the management of metastatic HR positive breast cancer, and all guidelines UK and international are consistent (with the exception of incorporation of palbocicilb into US guidance as detailed later). There are no standard clinical variables that can be used to predict benefit from AIs, with the exception of patients with visceral crisis who are considered for chemotherapy prior to maintenance AI.

Palbociclib in combination with letrozole substantially improves progression free survival in patients with metastatic HR positive breast cancer. The benefits are highly clinically meaningful, improving the median duration of tumour control from 14.5 months on placebo plus letrozole to 24.8 months on palbociclib plus letrozole (Finn et al NEJM 2016). Importantly palbociclib was well tolerated. Although there were frequent blood test abnormalities reflecting bone marrow suppression, with high rates of neutropenia being the most common adverse effect seen in 79.5% of patients, these blood test abnormalities rarely translated into clinical sequelae. Febrile

neutropenia was observed in only 1.8% of patients on palbociclib and letrozole. Symptomatic side effects were largely similar between palbociclib and placebo, with minor increases in fatigue, nausea, alopecia, diarrhoea, and stomatitis on palbociclib.

Palbociclib should be administered in secondary care by an oncologist who specialises in the management of breast cancer, who is experienced in the correct management of the drug, and managing effects of bone marrow suppression with dose delays, interruptions or reductions as required.

Palbociclib is not currently used in the NHS.

The management of HR positive breast cancer with AIs is supported by NICE guidance (CG81, Published date: February 2009 Last updated: July 2014). The guidance has not been updated since palbociclib obtained European marketing authorization. Palbociclib in combination with letrozole is recommended as first line therapy in the current American Society of Clinical Oncology Guideline (Rugo et al JCO 2016) and US National comprehensive cancer network (NCCN) Clinical Practice Guidelines in Oncology, Breast Cancer 2016 (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site)

The advantages and disadvantages of the technology

Aromatase inhibition for the management of metastatic HR positive breast cancer has been the standard therapy for over two decades. No drugs have been proven to improve over AIs during this time. Identification of a substantial benefit from the addition of palbociclib is therefore a highly important milestone in advancing the treatment of this form of breast cancer. Palbocicilib is strongly based on our understanding of the biology of HR positive breast cancer, with CDK4/6 identified as the key protein that allow HR positive breast cancer cells to grow. In many ways, CDK4/6 can be seen as being as critical to the biology of HR positive breast cancer as the oestrogen receptor itself. Multiple other phase III studies have demonstrated very substantial benefit from adding a CDK4/6 inhibitor to endocrine therapies, in the phase III PALOMA3 study (fulvestrant plus palbocicilb, Turner et al NEJM 2015) and in the phase III MONALEESA-2 study (letrozole plus ribociclib, Hortobagyi et al NEJM 2016, demonstrating class effect of CDK4/6 inhibitors). CDK4/6 inhibition is therefore the most important advance in the management of HR positive breast cancer in two decades. The PALOMA2 study of palbociclib and letrozole demonstrates the largest increase in progression free survival ever seen in an advanced breast cancer study.

The advantages and disadvantages of palbociclib and AI should be viewed with respect to therapy with AI alone.

The advantages of palbociclib and AI are substantially improved progression free survival, with the median duration of tumour control increasing from 14.5 months on placebo plus letrozole to 24.8 months on palbociclib plus letrozole (Finn et al NEJM 2016). Palbociclib causes relatively few symptomatic side effects, and is well tolerated by the majority of patients who take it. I have treated many patients with palbociclib in combination with endocrine therapy, in clinical studies and as part of a

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Single Technology Appraisal (STA)

now closed expanded access programme. Along with my colleagues at the Royal Marsden, we have treated 59 patients with palbociclib in combination with endocrine therapy in an expanded access programme. Many patients have no discernable increase in side effects compared to endocrine therapy alone. Quality of life was the same in patients on palbociclib and placebo (Rugo et al ESMO annual meeting 2016). Therefore, palbociclib offers substantial improvements in tumour control, with few side effects, giving highly clinically meaningful benefit. Treatment defers progression, with progression associated with increased morbidity, decreasing quality of life, and the need to treat with substantially more toxic therapies such as chemotherapy. The effect of palbociclib on overall survival is unknown at this time. Assessing the effects of a therapy on overall survival in HR positive breast cancer is highly challenging, as median overall survival extends to a median of 3-4 years, with multiple post-progression therapies available.

The disadvantages of therapy with palbociclib plus AI is the need for more close monitoring of the patient with blood tests than current standard practive on AI alone, and the small/modest increase in symptomatic adverse effects listed earlier. Although neutropenia is frequent on palbociclib, the sequela of febrile neutropenia is very rare at only 1.8% patients on therapy. Although neutropenia requires monitoring, and potential dose modification or delays to manage, the CDK4/6 induced neutropenia does not lead to frequent febrile neutropenia, in stark contrast to chemotherapy induced neutropenia. The development of neutropenia is an early adverse effect, and patients on long-term treatment require less frequent monitoring. Clear, simple guidelines on the management of bone marrow suppression on palbociclib were developed and implemented in the clinical trials. Patients on palbociclib will attend for more frequent blood tests in the first few months of therapy, and clinic attendances, compared to AI alone. The effect of these visits on quality of life has not been assessed in PALOMA2 as visits were matched on palbociclib and placebo arms. In my view it is highly unlikely that these visits would have an adverse impact on quality of life, as any detrimental effect would be outweighed by the knowledge of being able to access a new treatment combination that offers on average over two years in disease control.

The use of palbociclib and letrozole in the PALOMA2 study closely reflects how the drug would be used in standard clinical practice in the NHS, although in routine clinical practice clinic visits will be less frequent than in PALOMA2. In the ongoing palbociclib adjuvant trial PALLAS (NCT02513394), blood tests are conducted less frequently than in PALOMA2. In PALOMA2 blood tests and clinic visits were conducted every two weeks for the first 8 weeks and then every 4 weeks ongoing. In the PALLAS adjuvant trial, blood test and clinic visits are similarly conducted every two weeks for the first 8 weeks, but then only every 12 weeks (as opposed to 4 weeks). In current routine clinical practice, patients on letrozole alone are seen in the clinic initially 4-6 weeks after commencing letrozole, and then every 12 weeks for patients who are well on therapy, with blood tests on each visit. In routine clinical patients on letrozole and palbociclib will be seen in clinic less frequently after the initial 8 week period, likely approaching that with letrozole alone.

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Equality and Diversity

I do not believe that this appraisal has any impact on equality and diversity.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

There are no major implementation issues for palbociclib and letrozole. The therapies are oral, and monitoring of therapy is with standard blood tests.

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Single Technology Appraisal (STA)

Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone-receptor-positive, HER2-negative breast cancer [ID915]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by the Royal College of Physicians and consequently I will not be submitting a personal statement.

Name:

Signed: .....

Date: ..25th November 2016

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer [ID915]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Breast Cancer Now and consequently I will not be submitting a personal statement.

Name: .....

Signed:

Date: 03/01/17

STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer [ID915]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/194/07

Completed 30 November 2016

CONTAINS [redacted] AND [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2- breast cancer [ID915]

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Contributions of authors:

Fleeman N	Project lead, drafted clinical results section and supervised the final report
Stainthorpe A	Critique of the company economic model and proposal of alternative interpretations of the economic evidence
Bagust A	Checking and validation of the economic model and critique
Richardson M	Critical appraisal of the statistical evidence
Nolan S	Critical appraisal of the statistical evidence
Houten R	Summary and critical appraisal of economic evidence
Boland A	Critical appraisal of the clinical and economic evidence
Beale S	Critical appraisal of the clinical and economic evidence
Kotas E	Critical appraisal of the company's database searching
McEntee J	Critical appraisal of the submission
Malik Z	Clinical advice and critical appraisal of the clinical sections of the company's submission

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

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LIST OF ABBREVIATIONS

ABC	Advanced breast cancer
AE	Adverse event
ASCO	American Society of Clinical Oncology
BCS	Breast cancer specific
BICR	Blinded independent central review
BPI	Brief pain inventory
CBR	Clinical benefit rate
CDK	Cyclin-dependent kinase
CEAC	Cost effectiveness acceptability curve
CI	Confidence interval
CNS	Central nervous system
CS	Company submission
CSR	Clinical study report
DFI	Disease-free interval
DSU	Decision support unit
ECOG	Eastern cooperative oncology group
EMA	European medicines agency
EQ-5D	EuroQol-5D
ER	Oestrogen receptor
ER+	Oestrogen receptor-positive
ERG	Evidence review group
ESMO	European Society for Medical Oncology
FACT-B	Functional Assessment of Cancer Therapy-Breast
FACT-G	Functional Assessment of Cancer Therapy-General
HER2-	Human epidermal growth factor receptor 2 negative
H-H	Cumulative hazard
HR	Hazard ratio
HRQoL	Health-related quality of life
ITT	Intention-to-treat
K-M	Kaplan-meier
LET	Letrozole
MID	Minimally important difference
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PALOMA	Palbociclib: Ongoing trials in the Management of breast cancer 1 (trial acronymn for the PALOMA-1 and PALOMA-2 trials)
PAL+LET	Palbociclib in combination with letrozole (palbociclib arm of PALOMA-2 trial)
PFS	Progression-free survival

PH	Proportional hazard
PLACEBO+LET	Placebo plus letrozole (LET arm of PALOMA-2 trial)
PPS	Post-progression survival
PR+	Progesterone receptor positive
PS	Performance status
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
RCT	Randomised controlled trial
SAE	Serious adverse event
STA	Single technology appraisal
TOI	Trial outcome index
TD	Time to deterioration
TSAP	Trial statistical analysis plan
TTP	Time to progression

1 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 Pfizer in support of the use of palbociclib (Ibrance®) for the treatment of postmenopausal people with metastatic, hormone receptor-positive, human epidermal growth factor receptor 2-negative (HER2-) breast cancer previously untreated in the metastatic setting.

Palbociclib received a marketing authorisation, from the European Medicines Agency (EMA), on 9th November 2016, for the treatment of hormone receptor-positive, HER2- locally advanced or metastatic breast cancer (MBC) in combination with an aromatase inhibitor (which is the focus of this appraisal) or in combination with fulvestrant in women who have received prior endocrine therapy (which is expected to be the focus of a separate appraisal).

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

The population specified in the final scope issued by NICE is postmenopausal people with metastatic, hormone receptor-positive, HER2- breast cancer previously untreated in the metastatic setting. The ERG is satisfied that the evidence presented in the company submission (CS) is generalisable to the patient population in England and Wales that is described in the final scope issued by NICE. The intervention of interest in this appraisal is palbociclib (PAL) in combination with an aromatase inhibitor.

Evidence is appropriately presented for palbociclib in combination with letrozole (PAL+LET) versus letrozole (LET). Palbociclib is self-administered orally at a dose of 125mg each day for the first 21 days of a 28-day cycle. It is taken alongside letrozole. The latter is also self-administered orally, but at a dose of 2.5mg per day, every day of a 28-day cycle. LET is a commonly used aromatase inhibitor that is considered to be of equal efficacy to other aromatase inhibitors (anastrozole and exemestane) commonly used in NHS clinical practice in England and Wales.

The outcomes specified in the final scope issued by NICE include overall survival (OS), progression-free survival (PFS), response rates, adverse events (AEs) and health-related quality of life (HRQoL); these are standard outcomes used in oncology clinical trials and the company has presented data for all of these outcomes. The focus of this ERG report, however, is on the outcomes that the ERG considers are most relevant to understanding the clinical and cost effectiveness data submitted by the company for this appraisal, i.e. OS, PFS/time to progression (TTP), AEs and HRQoL. As specified in the final scope issued by NICE, the cost

effectiveness of treatments is expressed in terms of incremental cost per quality adjusted life year (QALY) gained. Outcomes are assessed over a 40-year time horizon (equivalent to a lifetime horizon) and costs are considered from an NHS perspective.

1.2 Summary of clinical effectiveness evidence submitted by the company

Clinical effectiveness data have been derived from two international multi-centre RCTs, the open-label PALOMA-1 trial (N=165; phase I/II) and the double-blind PALOMA-2 trial (N=666; phase III). Patients participating in the PALOMA-1 trial were sequentially enrolled into two cohorts. Recruitment into cohort 1 was based on patients having oestrogen receptor-positive (ER+) and HER2- tumours and recruitment into cohort 2 was based on the combination of ER+/HER2- status and amplification of cyclin D1 and/or loss of p16, or both. Across both cohorts, patients were randomised 1:1 to either the PAL+LET arm or the LET arm of the trial. Patients participating in the PALOMA-2 trial were randomised 2:1 to either the PAL+LET arm or the PLACEBO+LET arm of the trial.

The primary outcome for both trials was investigator assessed PFS; however, in both trials, assessments were also carried out by blinded independent central review (BICR). OS was a secondary outcome for both trials. All of the PALOMA-1 trial data presented by the company correspond to the data available on the cut-off date of 29 November 2013, and all of the PALOMA-2 trial data correspond to the data available on the cut-off date of 26 February 2016.

In both trials, patients randomised to receive PAL+LET spent more time in PFS and, therefore, more time on treatment than patients randomised to receive LET or PLACEBO+LET. In both trials, treatment with PAL+LET was shown to statistically significantly improve investigator assessed PFS compared to treatment with the comparator, by around 10 months (PALOMA-1 median PFS: 20.2 months versus 10.2 months; hazard ratio [HR]=0.488; 95% confidence interval [CI] 0.319 to 0.748, p=0004; PALOMA-2 median PFS: 24.8 months versus 14.5 months; HR=0.576; 95% CI 0.463 to 0.718, one-sided p<0.000001). Unlike results from the PALOMA-2 trial, results from the PALOMA-1 trial BICR assessed PFS analysis did not show a statistically significant median PFS benefit when treatment with PAL+LET was compared with LET (PALOMA-1 trial: HR=0.621; 95% CI 0.378 to 1.019, one-sided p=0.0286; PALOMA-2 trial: HR=0.653; 95% CI 0.505 to 0.844, one-side p=0.000532).

Results from subgroup analyses carried out using data from both trials, generally support the overall results. The analyses undertaken by the company include the subgroup of patients presenting with de novo metastases as well as those previously treated in the (neo)adjuvant setting. In the PALOMA-1 trial the PFS HR for patients with de novo disease was lower than the PFS HR in the ITT population (HR=0.341). In the PALOMA-2 trial, for patients with de

novo metastases, the PFS HR was slightly higher than the PFS HR for patients in the ITT population (HR=0.674). Therefore, for patients with de novo disease, the benefit was more pronounced in the PALOMA-1 trial and less pronounced in the PALOMA-2 trial. The HR estimates for patients previously treated in the (neo)adjuvant setting were similar in both trials (PALOMA-1 trial: HR=0.539; PALOMA-2 trial: HR=0.520).

Analyses of PALOMA-1 trial data suggest that treatment with PAL+LET leads to a large and statistically significant PFS benefit when compared with treatment with LET. However, this benefit is not mirrored in the OS results from this trial (median OS: 37.5 months versus 33.3 months; HR=0.813; 95% CI 0.492 to 1.345, stratified one-sided p=0.2105). The OS data from the PALOMA-1 trial are immature. The company claims that due to the variety of post-progression therapies given to patients, which were not accounted for in the analyses, the OS gain experienced by patients in the PAL+LET arm of the PALOMA-1 trial does not represent the true comparative OS benefit that occurs when the efficacy of treatment with PAL+LET is compared with treatment with LET. OS data were not available from the PALOMA-2 trial because, at the time of the planned analysis, an insufficient number of deaths had occurred to allow the final OS analysis to take place.

All patients in the PAL+LET arm of the PALOMA-1 trial reported an AE, and nearly all patients in the PALOMA-2 trial who were randomised to receive PAL+LET reported an AE (98.9%). AEs were also very common for patients in the trials who were randomised to receive either LET or PLACEBO+LET (84.4% and 95.5% respectively). Severe AEs (Grade 3 to 4 AEs) and serious AEs (SAEs) were more common in the cohort of patients treated with PAL+LET than in the cohort of patients treated with either LET or PLACEBO+LET. The two most common AEs reported for patients treated with PAL+LET in the PALOMA-1 and PALOMA-2 trials were neutropenia (74.7% and 79.5% respectively) and leukopenia (43.3% and 39.0% respectively). Neutropenia was also the most common Grade 3 to 4 AE reported by patients (54.2% and 66.4% of patients in the PAL+LET arm of the PALOMA-1 and PALOMA-2 trials, respectively). However, for the most part, neutropenia was asymptomatic and reversible. None of the cases of neutropenia that occurred in patients in either arm in the PALOMA-1 trial developed into febrile neutropenia. In the PALOMA-2 trial, only 8 of 444 patients (1.8%) in the PAL+LET arm developed febrile neutropenia, compared with no patients in the PLACEBO+LET arm. Febrile neutropenia was the most common SAE for patients treated with PAL+LET in the PALOMA-2 trial. The company argues that despite a high incidence of non-febrile neutropenia reported in the PALOMA-1 and PALOMA-2 trials, dose interruptions and dose reductions enabled patients to remain on PAL+LET.

HRQoL was captured through patient reported outcomes collected as part of both the PALOMA-1 and PALOMA-2 trials. As part of the PALOMA-1 trial, outcomes in relation to pain

(pain severity and pain interference with daily activities) were assessed using the modified Brief Pain Inventory (BPI). As part of the PALOMA-2 trial, HRQoL was captured by the Functional Assessment of Cancer Therapy-Breast (FACT-B) and EuroQol-5D (EQ-5D) questionnaires. Results from the PALOMA-1 trial demonstrate that the addition of PAL to LET does not significantly alter pain severity or pain interference with daily activities. Results from the PALOMA-2 trial show that there [redacted] between trial arms when change in baseline scores for FACT-B score, total Functional Assessment of Cancer Therapy-General (FACT-G) score, FACT-G subscale scores (for each of the four domains), Trial Outcome Index (TOI) score or Breast Cancer Specific (BCS) score are assessed. Results from [redacted]

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted.

Overall, the ERG is satisfied with the company's clinical effectiveness systematic review process and considers that the company's approach to evidence synthesis is appropriate. The ERG is confident that, despite excluding exemestane from the systematic review of RCT evidence, all relevant studies were included in the company's systematic review.

The ERG notes the possible PALOMA-1 trial biases identified by the EMA, as demonstrated by differences in investigator assessed and BICR assessed PFS estimates in the analysis of patients in cohort 1. As stated in the European Public Assessment Report, the EMA concluded that only findings from cohort 2 should be considered relevant to the efficacy assessment. Notwithstanding these possible biases, the ERG considers that the patient populations included in both the PALOMA-1 and PALOMA-2 trials are broadly similar and are relevant to the decision problem. The ERG considers that the PALOMA-2 trial was generally well designed and well conducted.

The ERG considers that the proportional hazards (PH) assumption is valid for the analyses of PFS data from the PALOMA-1 and PALOMA-2 trials. However, the ERG does not consider that the assumption of PH holds for the analysis of OS data from the PALOMA-1 trial. The OS hazard ratio should, therefore, be interpreted with caution.

The ERG observes that median PFS estimates, calculated using data from both trials, for patients treated with the comparator are within the range of median PFS estimates reported in previous trials of treatment with letrozole for patients with MBC treated in the first-line setting.

The ERG considers the results of the company's subgroup analyses should be treated with caution due to the small numbers of patients included in each analysis. This point is particularly important when results have been generated using data from the PALOMA-1 trial. Furthermore, the EMA's statement that only findings from cohort 2 of the PALOMA-1 trial should be considered relevant to the PFS efficacy assessment should be kept in mind when interpreting these results as the PALOMA-1 trial subgroup analyses include patients from both cohort 1 and cohort 2.

Across both trials, slight imbalances, in terms of the post-progression treatments received by patients in each treatment arm are noted, but given the small numbers of patients this finding is not unexpected. Therefore, although patients received a variety of different post-progression treatments, clinical advice to the ERG is that these treatments are reflective of treatments that are routinely offered to patients with MBC in clinical practice, and any benefit from treatment with PAL+LET in comparison to treatment with LET should, therefore, be reflected in the OS results.

The ERG agrees with the company's view that the main difference in safety profiles between patients treated with PAL+LET versus those treated with LET or PLACEBO+LET is largely a result of increased rates of non-febrile neutropenia in the cohort of patients treated with PAL+LET. The ERG also agrees with the company's view that the majority of cases of neutropenia are reversible and manageable and that the safety profile of PAL+LET is acceptable.

As patients participating in the PALOMA-1 and PALOMA-2 trials were only required to complete HRQoL questionnaires when they were progression-free and, therefore, the numbers of patients completing questionnaires decreased in each cycle. Thus, in later cycles, the numbers of patients responding are very small and the data are only reflective of the experience of relatively healthy patients. Nonetheless, the data from the earlier cycles that were collected during both trials appear to show [redacted] between treatment arms for patients in either the PALOMA-1 or PALOMA-2 trials.

1.4 Summary of submitted cost effectiveness evidence

To generate cost effectiveness results for this appraisal, the company developed a de novo partitioned survival model in Microsoft Excel. The model comprises three health states: pre-progression (stable) disease, progression (which is sub-divided into four different states: first, second and third subsequent lines of treatment and best supportive care [BSC]) and dead. All patients enter the model in the pre-progression health state and are treated with either PAL+LET or LET. Variants of this model structure have been used in previous NICE STAs. The model time horizon is 40 years. As recommended by NICE, a discount rate of 3.5% is

used for both costs and outcomes; outcomes are measured in quality adjusted life years (QALYs) and the model perspective is that of the UK NHS.

Pre-progression survival estimates for both treatment arms are based on Kaplan-Meier (K-M) data from the PALOMA-2 trial. Separate Weibull parametric functions, chosen on the basis of statistical fit and external validation, have been fitted to the PAL+LET and LET arms. Estimates of OS for both treatment arms are based on K-M data from the PALOMA-1 trial (K-M data are not available from the PALOMA-2 trial). The company observed that data from the PALOMA-2 trial show that median PFS for patients treated with PAL+LET is longer than that for patients treated with PLACEBO+LET. The company modelled OS in a way that preserved this survival benefit. A Weibull function was fitted to the K-M data from the PAL+LET arm of the PALOMA-1 trial. Then, to model OS for patients receiving LET, this Weibull function was scaled in such a way as to preserve the PALOMA-1 trial PFS benefit.

The health state utility values used to reflect patient quality of life in the pre-progression state were derived from EQ-5D scores collected, at baseline, from patients participating in the PALOMA-2 trial. This resulted in the pre-progression utility value used in the company model to represent quality of life for patients receiving PAL+LET being slightly higher than that for patients receiving LET. HRQoL in the post-progression state was estimated by adjusting the average baseline utility score for all patients participating in the PALOMA-2 trial using a published disease progression decrement. Resource use and costs were estimated using information from published sources and advice from clinical experts.

The company's base case incremental cost effectiveness ratio (ICER) for the comparison of the cost effectiveness of treatment with PAL+LET versus LET is £150,869 per QALY gained. Treatment with PAL+LET is more expensive (£94,101 versus £31.68) and more effective (+0.78 life years versus +0.63 QALYs) than treatment with LET. The company carried out a range of deterministic sensitivity analyses. The most influential adjustments were those made to the distributions used to model PFS and OS, and limiting the model time horizon to 5-years. The company's probabilistic sensitivity analysis (PSA) ICER (£151,058 per QALY gained) is very similar to the company's deterministic ICER. The PSA results also show that, when any threshold up to £100,000 per QALY gained is used, treatment with PAL+LET has zero probability of being cost effective compared with LET. The company performed scenario analyses using different approaches to modelling survival, health state utility values, resource use and costs.

1.5 Summary of the ERG's critique of cost effectiveness evidence

The two fundamental issues relating to the company's cost effectiveness model are: that there are no OS data available from the PALOMA-2 trial; and the issues regarding the reliability of

survival data from the PALOMA-1 trial. Other important issues relate to the estimation of time on treatment, and the calculation of pre- and post-progression utility values.

The company's attempts to overcome the lack of OS data from the PALOMA-2 trial are methodologically flawed, and result in inconsistencies both within the data and between the assumptions underpinning the company's methods and their implementation. The use of PFS and OS data from different trials, due to the lack of OS data in the PALOMA-2 trial, is methodologically flawed, as it assumes independence between the outcomes. PFS and OS are not independent measurements; they are taken from the same individuals at different times. The ERG considers the use of PFS and OS data from the same trial to be more methodologically robust, whilst noting the limitations of the data available from the PALOMA-1 trial.

The ERG considers that the evidence of a shorter post-progression survival (PPS) for treatment with PAL+LET than for LET in the PALOMA-1 trial does not justify the assumption of equal PPS in the base case, which in fact manifests as a small gain in PPS for PAL+LET in the model.

The company has assumed that all patients are treated until progression and has, therefore, used PFS to estimate the proportion of patients receiving treatment in each cycle. The true time to treatment discontinuation (TTD) can be overestimated if patients withdraw from treatment for reasons other than disease progression, or underestimated if patients are permitted to continue treatment after progression. The ERG re-estimated treated duration, and thus the cost of first-line treatment, based on TTD data provided by the company from the PALOMA-1 trial.

Since the difference between the average utility values from patients in the PALOMA-2 trial was not statistically significant, the ERG does not consider it appropriate to use different pre-progression utility values for treatment with PAL+LET and LET. The ERG advocate pooling the baseline EQ-5D values reported in the PALOMA-2 trial. In addition, the method of estimating post-progression utility from published disutility values has been implemented incorrectly and therefore the ERG has provided a new estimate of post-progression utility.

Other issues identified by the ERG include: the lack of half-cycle correction; the incorrect application of AE costs and calculation of AE incidence; the method of discounting; and the number of days per year. The ERG has also provided a scenario analysis to investigate the impact of using data from the PALOMA-2 trial to estimate PFS and TTD. Finally, the ERG has concerns about the approach taken by the company to estimate post-progression treatment costs and undertook a sensitivity analysis to investigate the impact of varying post-progression treatment costs.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Clinical evidence

- The comparator arm of the PALOMA-1 and PALOMA-2 trials was LET, an aromatase inhibitor used to treat patients with untreated MBC in NHS clinical practice, that is a valid comparator for this appraisal
- The EMA considers that it is reasonable to generalise the clinical effectiveness results associated with LET to other commonly used aromatase inhibitors in NHS clinical practice (i.e. exemestane and anastrozole)
- Results from the PALOMA-2 trial show that the median PFS for patients in the PAL+LET arm of the trial was higher than that for patients in the PLACEBO+LET arm.
- Despite an increased incidence of non-febrile neutropenia in the PAL+LET arms of both the PALOMA-1 and PALOMA-2 trials, there are no statistically significant differences in HRQoL between the arms

Cost effectiveness evidence

- The economic model was generally well constructed and easy to navigate
- The company has undertaken a large number of sensitivity and scenario analyses to explore uncertainty

1.6.2 Weaknesses and areas of uncertainty

Clinical evidence

- The discrepancy between PALOMA-1 trial investigator assessed and BICR assessed PFS may bias the findings from this trial, possibly in favour of treatment with PAL+LET rather than treatment with LET
- When comparing PFS HRs from the ITT populations with subgroup PFS HRs (de novo disease and patients previously treated in the adjuvant setting), the findings from the PALOMA-1 and PALOMA-2 trials are not consistent
- Analysis of data from the PALOMA-1 trial indicates a 10 month improvement in investigator assessed PFS for the cohort of patients treated with PAL+LET compared with those treated with LET; however, there is no corresponding statistically significant improvement in OS
- OS data from the PALOMA-1 trial are immature and are 3 years old (data cut-off date of 29 November 2013)
- PALOMA-2 trial OS data are not currently available due to there being too few events (deaths) to allow the final OS analysis to take place
- The PALOMA-1 trial is a relatively small trial compared to the PALOMA-2 trial and this may explain why there are some apparent imbalances in terms of baseline characteristics and treatments received on disease progression

Cost effectiveness evidence

- Modelling survival using data from two different trials is methodologically unsound

- There is no trial evidence to support the assumption that 100% of PFS gain for treatment with PAL+LET will translate into OS gain
- There is no trial evidence to support the assumption of equal PPS (zero PPS gain) for treatment with PAL+LET and treatment with LET
- The method used to adjust OS data from the PALOMA-1 trial to incorporate the assumptions of (i) PFS gain is equal to OS gain and (ii) zero PPS gain, results in neither of these assumptions holding in the model
- The Weibull model used to project PFS results in implausible hazard profiles in the long-term
- The company's use of PFS data rather than TTD data as the basis for calculating first-line drug acquisition costs leads to inaccurate cost estimates
- There is no valid basis for the company's assumption that, prior to disease progression, the HRQoL of patients prescribed PAL+LET is better than that of patients prescribed LET and, therefore, only one utility value should have been used to represent patient HRQoL in this health state
- An error in the company's calculation of the utility value used to represent the HRQoL of patients in the PPS state renders the company's estimate invalid
- The company model does not include a half-cycle correction
- The method employed by the company to discount costs and benefits was incorrect (per cycle rather than annually)
- The AE costs used in the company model are unreliable as they are based on annual rather than per cycle incidence rates and an average treatment cost (rather than AE-specific treatment costs)
- The algorithm used by the company to generate PSA results did not take into account any correlated uncertainty in the key model parameters (Weibull model scale and shape parameters)
- Within the company model a year comprises 364 rather than 365.25 days.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made 12 individual changes to the submitted model, namely: re-modelling OS; re-modelling PFS and TTD based on the PALOMA-1 trial data; re-modelling PFS and TTD based on the PALOMA-2 trial data; re-calculating pre- and post-progression utility values; adding a half-cycle correction; re-calculating AE costs and probabilities; changing discounting to annual rather than per cycle; and changing the number of days per year to 365.25.

The various changes implemented by the ERG for the comparison of treatment with PAL+LET versus treatment with LET yield a mixture of effects. When implemented individually, these revisions both increase and decrease the size of the ICERs per QALY gained. The combined effect of all of the ERG's revisions, when using PALOMA-1 trial data as the basis for modelling

PFS and TTD, is to decrease the company's base case ICER per QALY gained by £17,997 to £132,872. However, the combined effect of all of the ERG's revisions, when using the PALOMA-2 trial data as the basis for modelling PFS and TTD, increases the company's base case ICER per QALY gained by £62,337 to £213,206.

The ERG considers that it is unclear whether the company's base case cost effectiveness results overestimate or underestimate the size of the most probable ICER per QALY gained. The available data from the PALOMA-1 trial are flawed, but allow for the most methodologically robust approach to modelling survival; the available data from the PALOMA-2 trial are more robust, but require the application of methodologically unsound approaches to modelling survival to compensate for the absence of OS data from that trial.

The company's base case cost effectiveness results and the results generated following the application of either of the ERG's combined revision scenarios, are all considerably higher than the range normally considered acceptable by NICE.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

Key points from the description of the underlying health problem presented in the company submission (CS)[1] are reproduced (as bulleted items) in Box 1.

Box 1 Summary of company's description of underlying health problem

- Breast cancer is a heterogeneous disease composed of a growing number of biological subtypes that vary not only in aetiology and prognosis, but also in their responses to current anti-hormonal [endocrine therapy] and chemotherapy treatments
- Determination of hormone receptor and HER2 status of breast cancer tumours currently serves as the initial basis for most clinical decisions, and it has both prognostic and predictive importance in breast cancer
- Oestrogen and progesterone drive tumour growth, and tumours that express one or both receptors are typically referred to as hormone receptor-positive
- Most hormone receptor-positive tumours are both ER+ and PR+, while approximately 15% to 20% are only ER+
- Hormone receptor-positive breast cancers tend to grow more slowly than hormone receptor-negative tumours and are much more likely to respond to hormonal therapy [i.e. endocrine therapy] that lowers the amount of available oestrogen, or blocks existing oestrogen from binding its receptor
- The most common type of ABC is ER+/HER2-
- 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
- National-level data on ABC incidence in the UK are lacking; regional data suggest that 5% of women with breast cancer have metastatic disease at first diagnosis (de novo disease)
- Prognosis of patients with ABC is poor compared with that of patients with early-stage breast cancer, and survival rates fall as the disease advances: 5-year OS is 99% for women in the UK with stage I breast cancer, 90% for stage II, 60% for stage III, and 15% for stage IV (metastatic)
- Studies from European countries and the US consistently report average OS for patients with hormone receptor-positive/HER2- ABC as <5 years. Median OS of women receiving their first post-adjuvant systemic therapy can range from 32 to 48 months.

ABC=advanced breast cancer; ER+=oestrogen receptor positive; HER2=human epidermal growth factor receptor 2; HER2-=human epidermal growth factor receptor 2 negative; NICE=National Institute for Health and Care Excellence; OS=overall survival; PR+= progesterone receptor positive
Source: CS, Section 3.1 and Section 3.4

The Evidence Review Group (ERG) notes that for women with hormone receptor-positive breast cancer, the company presents information describing breast cancer in general, advanced breast cancer (ABC) and metastatic breast cancer (MBC). Hormone receptor-positive breast cancer is synonymous with oestrogen receptor-positive (ER+) breast cancer since most hormone receptor-positive tumours are ER+. MBC is a specific type of ABC; ABC incorporates stage III and stage IV disease, whilst MBC is defined as only stage IV breast cancer. Throughout the CS, the company uses the terms ABC and MBC interchangeably. Clinical opinion received by the ERG is that the health problems associated MBC are reflected by the tumour burden. However, the options available to treat patients with ABC and MBC, are effectively the same but may have differing effects in the metastatic population. The ERG,

therefore, considers that the company's description of the underlying health problem represents a reasonable summary of the issues facing patients with MBC.

2.1.1 Impact of metastatic breast cancer on quality of life

In Section 3.2 of the CS, the company highlights the effects of MBC on patients' health-related quality of life (HRQoL). In particular, the company argues that prolonging progression-free survival (PFS) also maintains a patient's HRQoL. Reasons for this include:

- Symptoms associated with disease progression are avoided while patients remain progression-free[2-4] and disease progression has been found to have a negative impact on HRQoL[5]
- Remaining progression-free delays the onset of chemotherapy which may be associated with many toxicities and reduced HRQoL[5-10]
- There exists among patients a perceived fear of chemotherapy[11,12] which can have a detrimental effect on HRQoL; in particular, high levels of anxiety have been reported[13,14]
- Patients who are progression-free are alive[15] and able to work[16] and maintain 'normality', e.g. fulfilling one's caring duties as partners, friends and mothers.[17]

In addition to the effect of MBC on a patient's HRQoL, diagnosis with MBC and subsequent treatment can negatively affect the caregivers of patients.[18] In particular, carers are at increased risk of depression and reduced quality of life compared to the general population.[19]

2.1.2 Correlation between progression-free survival and overall survival in patients with metastatic breast cancer

The company cites the results of seven studies that suggest that length of PFS correlates strongly with overall survival (OS).[20-25] However, the company acknowledges that it is uncertain whether OS can be directly predicted from PFS, noting biases in the modelling that was carried out in a review of 144 studies of treatment for MBC published in 2014.[20] Indeed, a review undertaken on behalf of NICE by the Decision Support Unit (DSU)[26] found that the level of evidence available to support a relationship between PFS and OS varies considerably by cancer type and is not always consistent even within one specific cancer type. The authors of a 2014 review of the literature on PFS and OS for various types of cancer concluded that only in metastatic colorectal and ovarian cancer treated with cytotoxic agents was there "…acceptable evidence of surrogacy" between PFS and OS.[27]

2.2 Critique of company's overview of current service provision

Key points from the overview of current service provision presented in the CS are reproduced (as bulleted items) in Box 2. Currently, the mainstay of treatment for patients presenting with early breast cancer is endocrine therapy, which, in the NHS, entails treatment with either tamoxifen, a nonsteroidal aromatase inhibitor (letrozole or anastrozole) or a steroidal aromatase inhibitor (exemestane). These endocrine therapies, which are all generic drugs, are also the mainstay of treatment for patients presenting with MBC who do not have imminently life-threatening disease (the focus of this appraisal). Overall, the ERG considers that the company's description of current service provision represents an accurate summary of the treatments available, their efficacy in terms of PFS and the importance of HRQoL as a treatment goal for the MBC patient population.

Box 2 Summary of company's overview of current service provision

Early breast cancer (postmenopausal women)

- The majority of early breast cancers are diagnosed within the UK National Breast Cancer Screening program
- Women diagnosed with early invasive breast cancer, regardless of age, are usually treated with surgery, and may be treated with chemotherapy-based regimens before surgery (neo-adjuvant) to downsize the tumour
- After surgery, most women with early invasive ER+ breast cancer, who are not at low risk of relapse typically receive adjuvant endocrine therapy for at least 5 years
- Several endocrine drugs are in clinical use for adjuvant therapy, including tamoxifen and aromatase inhibitors
- The aromatase inhibitors (anastrozole, exemestane and letrozole) are recommended by NICE for the adjuvant treatment of postmenopausal women with early invasive ER+ breast cancer
- Women at high risk of disease relapse are offered adjuvant chemotherapy before receiving adjuvant endocrine therapy.

Advanced breast cancer (ABC)

- ABC is a life-threatening disease that cannot be cured; the clinical goals are to delay disease progression while maintaining quality of life, alleviating symptoms and improving survival-related outcomes
- For ABC patients whose disease has progressed rapidly and/or has already spread to visceral organs, first-line chemotherapy is recommended
- Patients presenting with ABC who do not have imminently life-threatening disease should be treated with endocrine therapy [NICE guidance CG81 and ESMO and ASCO guidelines]
- Despite being standard of care in ER+ ABC, median PFS associated with treatment with currently approved endocrine therapies generally remains less than 1 year
- The ability to prolong PFS while maintaining HRQoL is, therefore, an important unmet medical need in the ER+/HER2- ABC setting.

ABC=advanced breast cancer; ASCO=American Society of Clinical Oncology; ER+=oestrogen receptor positive; ESMO=European Society for Medical Oncology; HER2-=human epidermal growth factor receptor 2 negative; HRQoL=health-related quality of life; NICE=National Institute for Health and Care Excellence; PFS=progression-free survival
Source: CS, Sections 2.5, 3.1, 3.3

2.3 Aromatase inhibitors for the treatment of metastatic breast cancer

In the ABC setting, letrozole is indicated as first-line treatment or following treatment with an anti-oestrogen, such as tamoxifen.[28] The indication for exemestane in the ABC setting is only following anti-oestrogen therapy (such as tamoxifen),[29] whereas anastrozole is indicated for the treatment of ABC in general,[30] with no restrictions to its place within the treatment pathway. Currently, aromatase inhibitors are only approved by NICE for use in the ABC setting where patients have had no prior treatment with endocrine therapy, or for those patients who have been previously treated with tamoxifen.[31] However, clinical advice to the ERG is that any aromatase inhibitor may be given as a first-line or subsequent line of treatment for post-menopausal patients, irrespective of whether patients have received treatment with tamoxifen or an aromatase inhibitor for early breast cancer.

In a retrospective study of medical record data of patients treated for ER+/HER2- MBC from four countries (United Kingdom [n=209], Belgium and the Netherlands [n=102] and Canada [n=127]) between 2008 and 2014 conducted by Mitra et al,[32] [redacted] were reported to be the two most commonly used treatments. The third most common treatment reported in this review was [redacted]. UK market research data[33] used by the company to estimate the potential number of patients eligible for treatment with palbociclib suggest that between [redacted] and the [redacted] as a first-line treatment for ER+/HER2- MBC [redacted]. By [redacted], the most common aromatase inhibitors (accounting for [redacted] of all treatments) were [redacted] followed by [redacted], and then [redacted]. The two most common chemotherapy regimens were [redacted] and [redacted].

Evidence reported in systematic reviews suggests that all aromatase inhibitors are of superior efficacy to tamoxifen for treating patients with MBC.[34-36] Evidence from an indirect treatment comparison showed that there were no differences in terms of OS, PFS or adverse events (AEs) between aromatase inhibitors that were used for the first-line treatment of patients with MBC.[36] Common AEs associated with treatment with aromatase inhibitors include arthralgia and bone pain.[36] Treatment with aromatase inhibitors may result in a loss of bone density, increasing the risk of osteoporosis and bone fractures.[37]

The ERG is aware of two trials[38,39] that compare exemestane versus anastrozole for the first-line treatment of MBC which were not included in the aforementioned systematic reviews.[34-36] The findings from one trial,[39] a randomised, open-label, phase II trial conducted in Spain, led the authors to conclude that no significant differences in clinical activity were observed in favour of exemestane over anastrozole, despite apparent numerical differences in median time to progression (TTP) between the arms (6.1 versus 12.1 months but not reported to be

statistically significant). The authors of the other trial,[38] a multi-centre, randomised, double-blind, phase III trial conducted in Japan reported almost identical TTP between arms (13.8 versus 13.7 months). The ERG is not aware of any trials that compare the use of letrozole with either anastrozole or exemestane as a first-line therapy for a MBC population.

As reported in Box 2 of this ERG report, the company reports that the median PFS with currently approved endocrine therapies for treating ER+ ABC is generally less than 1 year. Results of the five randomised controlled trials (RCTs) cited to support this statement[40-44] are summarised in a review published in 2013 by Cardosa et al.[45] The findings from the trials suggest a median PFS/TTP of between 5.6 and 8.3 months for patients treated with tamoxifen and between 8.2 months and 12.0 months for patients treated with aromatase inhibitors. As noted by the ERG, results from a recent Japanese trial show median PFS in excess of 12 months for patients treated with exemestane and anastrozole, whereas, more recently published results from trials that included patients receiving letrozole show PFS/TTP results of up to 15.6 months (in combination with placebo in CALGB 40503[46]). However, information presented in the retrospective study of medical record data by Mitra et al,[32] showed that, between 2008 and 2014, patients in UK clinical practice receiving first-line endocrine therapies had a median TTP of 12.17 months.

Patients previously treated with endocrine therapy may become resistant to treatment with aromatase inhibitors.[47] Primary resistance is typically defined as relapse occurring within 2 years of starting endocrine therapy.[47] Results from the BIG 1-98 trial[48] of adjuvant endocrine therapy, show that primary resistance occurred in 3.1% of patients treated with letrozole and 4.4% of patients treated with tamoxifen. Disease recurrence that takes place within a set period of time after completing treatment may also be considered as resistance; for example, the company considers that patients who had a disease-free interval (DFI) <12 months after completing treatment with an aromatase inhibitor in the adjuvant setting have resistant disease (CS, Section 4.8.1). Patients who have become resistant to a particular aromatase inhibitor in the adjuvant setting are, therefore, likely to be treated with a different aromatase inhibitor if they need treatment in the first-line MBC setting.[47]

Whilst in clinical practice patients may be treated more than once with aromatase inhibitors (i.e. for early breast cancer and for MBC), it is argued that there are no robust RCT data to support this approach.[47] The CALGB 40503 trial[46] is one of the first trials of patients with MBC to be published that includes patients who have been previously treated with aromatase inhibitors in the adjuvant setting. The PALOMA-1 trial[49] which compared palbociclib in combination with letrozole with letrozole alone also permitted patients to have had prior treatment with aromatase inhibitors (providing there was a DFI >12 months in the case of prior treatment with letrozole). The investigators of the BOLERO-2 trial[50] comparing everolimus in

combination with exemestane to exemestane (in combination with placebo) have also reported a subgroup analysis of patients treated in the first-line setting for MBC.[51] Patients in the BOLERO-2 trial had to be refractory to aromatase inhibitors (defined as recurrence during or within 12 months after the end of adjuvant treatment or progression during or within 1 month after the end of treatment for advanced disease).

The company highlights (CS, Section 3.3) that subsequent treatment following recurrence or progression in the first-line setting for MBC includes additional hormonal therapy (endocrine therapy) or chemotherapy. According to the recent study by Mitra et al,[32] the most common treatments for second-line treatment of MBC were [redacted]. The company highlights that other treatment options that are commonly received in the second-line setting include treatments that are not currently recommended by NICE, such as everolimus in combination with exemestane (which has been available via the Cancer Drugs Fund) and fulvestrant.

2.4 Palbociclib

This appraisal considers a new treatment option for patients with previously untreated metastatic, hormone receptor-positive, HER2- MBC: palbociclib in combination with an aromatase inhibitor. As highlighted in the CS, it is now recommended in the American Society of Clinical Oncology (ASCO) 2016 guideline[52] that a nonsteroidal aromatase inhibitor (i.e. letrozole or anastrozole) and palbociclib may be offered to postmenopausal women with treatment-naive hormone receptor-positive MBC.

Palbociclib is an oral anti-neoplastic agent. It is a selective small-molecule inhibitor of cyclin-dependent kinase 4 and 6 (CDKs 4 and 6)[53] as well as the redundant CDK 6/cyclin D1 kinase. Through its mechanism of action, palbociclib enhances the anti-proliferative efficacy of endocrine treatments through inhibition of the oestrogen receptor (ER) in breast cancer cells.[53] The company highlights results from the PALOMA-1,[49] PALOMA-2[15] and PALOMA-3[54] trials to demonstrate that this synergistic enhancement leads to improvements in PFS when treatment is compared with endocrine therapy alone. The company also argues that, by extending PFS, palbociclib should postpone the need for potentially burdensome chemotherapy. So, by prolonging PFS, patients experience a lower pain burden, stable HRQoL, and fewer severe AEs than would be expected when patients progress on endocrine therapy and start treatment with chemotherapy.

The company suggests that the mechanism by which palbociclib causes cell cycle arrest is important when considering palbociclib-induced neutropenia. Unlike chemotherapy-induced neutropenia, which is caused through irreversible human bone marrow cell death, results from the PALOMA-1, PALOMA-2 and PALOMA-3 trials show that, in most cases, cellular

proliferation resumed to near pre-treatment levels when the palbociclib dose was interrupted. Thus, the company considers that palbociclib represents an important change in terms of the treatment available to patients in the first-line ER+/HER2- MBC setting. The company suggests that this is the most important change, in terms of available treatments in this setting, since the introduction of aromatase inhibitors over 10 years ago.

The ERG notes that, alongside palbociclib, other oral CDK4/6 inhibitors are currently being investigated for their efficacy in clinical trials, including phase III trials. For patients with hormone receptor-positive, HER2- MBC previously untreated in the metastatic setting, the authors of the recently published MONALEESA-2 study[55] reported promising results for patients treated with ribociclib in combination with letrozole. Outside of clinical trials, CDK4/6 inhibitors are not, however, currently available to NHS patients treated in England and Wales. Therefore, palbociclib represents the first-in-class CDK4/6 inhibitor to be potentially available to these patients.

2.5 Number of patients potentially eligible for treatment with palbociclib

Company estimates, based on observed frequencies of different breast cancer subtypes and on the incidence of menopause, suggest that 48,867 women in England and Wales have breast cancer, of whom almost 7000 have ER+/HER2- ABC, of whom 5435 would be eligible to receive palbociclib (Table 1).

Table 1 Company's estimate of numbers of patients previously untreated in the metastatic setting

Population		Number	Assumption	Source
#	Decsription			
1	Women with breast cancer in England and Wales	England: 46,085 Wales: 2782	-	ONS data for 2014[56] Welsh Cancer and Surveillance Unit Intelligence data for 2001 to 2014[57]
2	Women with invasive breast cancer	44,061	90% of #1	NICE 2015 [58]
3	Women with early and locally advanced invasive breast cancer	41,858	95% of #2	NICE 2015[58]
4	Women presenting with advanced breast cancer at diagnosis (de novo disease)	2203	5% of #2	NICE 2015[58]
5	Women presenting with early breast cancer that die before disease progression	12,557	30% of #3	
6	Women with early and locally advanced breast cancer progressing into advanced stage	10,255	35% of (#3 - #5)	NICE 2015[58]
7	Total number of women developing advanced breast cancer per year	12,458	#4 + #6	NICE 2015[58]
8	Women with ER+/HER2- advanced breast cancer	6977	56% of #7	De Koven et al 2012[59]*
9	Postmenopausal women with ER+/HER2- advanced breast cancer†	5721	82% of #8	World Health Organization International Agency for Research on Cancer GLOBOCAN project[60]
10	Percentage women treated with first-line therapy (i.e. previously untreated in the metastatic setting)	6628	95% of #8	Pfizer, data on file
11	Percentage women treated with first-line therapy (i.e. previously untreated in the metastatic setting, ER+/HER2- advanced breast cancer)	5435	95% of #9	Pfizer, data on file

ER+=oestrogen receptor positive; HER2-=human epidermal growth factor receptor 2 negative; NICE=National Institute for Health and Care Excellence; ONS=Office for National Statistics
*The proportion in the published paper is of patients with MBC
†Women aged ≥50 years were considered to be postmenopausal
Source: CS, adapted from Table 8 and Table 87

In Section 6 of the CS it is stated that, based on market research data,[33] [redacted] of patients with ER+/HER2- ABC received an aromatase inhibitor in the last quarter of 2015. The company anticipates that [redacted].

The ERG calculates that [redacted] of 5435 equates to [redacted] patients. However, the company suggests (CS, Section 6) that the number of patients treated with palbociclib in 2017 would be [redacted] since a positive NICE recommendation can only have an effect part way through the calendar year i.e., that only [redacted] of all potentially eligible women, not just those receiving an aromatase inhibitor, would receive treatment with palbociclib.

If recommended by NICE, the company estimates that the number of patients treated with palbociclib would rise to [redacted] in 2018 and to [redacted] in 2019. These estimates constitute [redacted] and [redacted] of all potentially eligible women (not just those currently receiving an aromatase inhibitor) respectively, assuming a 0.6% increase in annual breast cancer incidence. The assumption of the rise in incidence is based on statistics obtained from the Cancer Research UK website[61] that indicate that there was a 6% rise in incidence in the UK between 2002-2004 and 2011-2013. However, the ERG observes that the Cancer Research UK website notes that "almost all of this entire rise" occurred "before the mid-2000s".

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2 summarises the decision problem, described by the company in the CS, in relation to the final scope issued by NICE.[62] Each parameter is discussed in more detail in the text following the table (Section 3.1 to Section 3.7).

Table 2 NICE scope and company's decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company's submission
Population	Postmenopausal people with metastatic, hormone receptor-positive, HER2- breast cancer previously untreated in the metastatic setting	As per final scope issued by NICE The ERG notes that patients in the trials who had previously received (neo)adjuvant treatment had a disease free interval of >12 months following (neo)adjuvant treatment with letrozole (PALOMA-1 and PALOMA-2 trials) and anastrozole (PALOMA-2 trial) before being treated for MBC
Intervention	Palbociclib in combination with an aromatase inhibitor	Palbociclib in combination with letrozole
Comparator (s)	Aromatase inhibitors (such as letrozole or anastrozole)	Letrozole
Outcomes	The outcome measures to be considered include: • overall survival (OS) • progression free survival (PFS) • response rate (RR) • adverse effects of treatment • health-related quality of life (HRQoL)	The outcome measures to be considered include: • overall survival (OS) • progression free survival (PFS) • response rate (RR) • clinical benefit rate (CBR) • adverse effects of treatment • health-related quality of life (HRQoL)
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	As per the final scope issued by NICE
Subgroups to be considered	None specified	Patients with MBC previously treated in the adjuvant setting compared with those who are presenting for the first time with MBC (de novo)
Other considerations	Guidance will only be issued in accordance with the marketing authorisation Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	No special considerations, including issues related to equity or equality, were identified Palbociclib in combination with an aromatase inhibitor is not considered by the company to meet NICE End of Life criteria The company has not submitted a Patient Access Scheme proposal

ERG=Evidence Review Group; NICE=National Institute for Health and Care Excellence; HER2=human epidermal growth factor receptor 2; HER2-=human epidermal growth factor receptor 2 negative; MBC=metastatic breast cancer
Source: NICE Final scope and CS, Table 1

3.1 Population

The population specified in the final scope issued by NICE is postmenopausal people with metastatic, hormone receptor-positive, HER2- breast cancer previously untreated in the metastatic setting. The evidence presented by the company is for postmenopausal women with ER+/HER2- MBC (as noted in Section 2.1 of this ERG report, most women with hormone receptor-positive disease have ER+ tumours). However, the anticipated European Medicines Agency (EMA) licence for palbociclib in combination with an aromatase inhibitor will not specify the menopausal status of patients (see Section 3.2 of this ERG report for a description of the anticipated licence). The vast majority (■) of patients referred to in the CS have untreated metastatic, hormone receptor-positive, HER2- breast cancer. The exceptions are:

1. Three patients (2%) in the PALOMA-1 trial had stage III disease (which is categorised as ABC, not MBC). Similarly, in the PALOMA-2 trial, ■ patients (■) had locoregional recurrence, local recurrence or regional recurrence (which is categorised as ABC, not MBC).
2. Patients were not permitted to have relapsed on neo(adjuvant) therapy with LET (PALOMA-1), or LET or anastrozole (PALOMA-2) within 12 months of receiving treatment with these aromatase inhibitors. However, as noted in Section 2.3 of this ERG report, results from the BIG 1-98 trial[48] show the proportion of patients treated with LET who relapsed within 2 years in the adjuvant setting is 3.1%, and that patients who have relapsed whilst being treated with LET are unlikely to be re-treated with LET again. Therefore, patients who have relapsed whilst being treated with LET are outside of the scope of this appraisal.
3. The proportions of patients in the PALOMA-1 and PALOMA-2 trials presenting with de novo disease (49.1% and 37.2% respectively) are higher than seen in clinical practice in England and Wales (5%,[58,63] see also Section 2, Box 1). This discrepancy is, however, is a common feature of trials conducted in the untreated MBC setting (with many trials of LET including approximately 30% to 50% of patients with de novo disease[42,46,64-66] or even more patients with de novo disease[67]). The ERG notes that the company has conducted subgroup analyses, using data from both the PALOMA-1 and PALOMA-2 trials, which allow findings for patients presenting with de novo disease to be compared with those from MBC patients who have previously been treated in the (neo)adjuvant disease setting.

Overall, the ERG is satisfied that the evidence presented in the CS is generalisable to the patient population in England and Wales that is described in the final scope issued by NICE.

3.2 Intervention

The intervention of interest in this appraisal is palbociclib in combination with an aromatase inhibitor. Palbociclib is self-administered orally at a dose of 125mg each day for the first 21 days of a 28-day cycle. It is taken alongside LET which is self-administered orally at a dose of 2.5mg per day, each and every day of the 28-day cycle. Treatment is stopped only on disease progression, or if patients can no longer tolerate the combination.

In accordance with the treatments administered in the PALOMA-1 and PALOMA-2 trials, the company has presented evidence for palbociclib in combination with letrozole (PAL+LET). As described in Section 2.3 of this ERG report, other aromatase inhibitors including anastrozole and exemestane are available to patients treated in the UK NHS, and all aromatase inhibitors are considered to be of equal efficacy and safety.[36] It is, therefore, expected that, in clinical practice, while palbociclib would most likely be given in combination with LET, it may possibly be given with other aromatase inhibitors. Indeed, the ERG observes that the EMA considers that it is reasonable to generalise the clinical effectiveness results associated with LET to other aromatase inhibitors.[68]

3.2.1 Licensing

Palbociclib received a positive opinion from the EMA on 16 September 2016 for the treatment of hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or MBC in combination with an aromatase inhibitor (which is the focus of this appraisal) or in combination with fulvestrant in women who have received prior endocrine therapy (which is expected to be the focus of a separate appraisal). In pre- or peri-menopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist. EMA marketing authorisation was granted on 9 November 2016.

3.2.2 Implications for practice

The company states that managing the administration of palbociclib is expected to be similar to that of managing the administration of other oral agents currently available in the NHS for patients with MBC (such as aromatase inhibitors). However, additional monitoring of complete blood count on days 1 and 14 of the first two cycles and day 1 of all subsequent cycles is required. Since palbociclib has myelosuppressive properties which may, therefore, predispose patients to infections, patients should also be monitored for signs and symptoms of infection (and treated as medically appropriate). In particular, while 3-monthly visits to see a consultant are typical for patients receiving endocrine therapy, more frequent visits may be required for patients treated with palbociclib if they have palbociclib-induced neutropenia and leukopenia. No concomitant therapies are administered with palbociclib for managing AEs. However, to ensure appropriate management of the AEs, the company states that health care

professionals will need to be taught how to use dose-modification guidelines and be informed about the fundamental differences between palbociclib-induced neutropenia and chemotherapy-induced neutropenia. Palbociclib-induced neutropenia is asymptomatic and reversible, whereas chemotherapy-induced neutropenia is not reversible and, therefore, requires recovery by re-population from the original haemopoietic stem cells. This often means that a patient with chemotherapy-induced neutropenia needs to receive growth factor stimulation (such as the use of granulocyte-colony stimulating factor 7) to support bone marrow recovery.[69]

Dose modification of palbociclib is recommended based on concerns with regard to a patient's safety and tolerability of the drug. For example, management of some AEs may require temporary dose interruptions and/or dose reductions, or permanent discontinuation. In total, two dose reductions are permitted: 125mg to 100mg each day and 100mg to 75mg each day. If further reductions are required then treatment with palbociclib should be discontinued. Tables 1 to 3 of the draft summary of product characteristics provided by the company in Appendix 1 to the CS) provide more detailed information on dose-modification guidelines.

3.3 Comparators

The comparators listed in the final scope issued by NICE are 'aromatase inhibitors (such as LET or anastrozole'; exemestane is not specifically mentioned. The evidence presented by the company focuses on the comparison of PAL+LET with LET. As all aromatase inhibitors are considered to be of equivalent efficacy and safety,[36] the relative efficacy and safety of PAL+LET compared with LET is expected to be the same as that of PAL in combination with any aromatase inhibitor compared with any aromatase inhibitor. Indeed, as noted in Section 3.2 of this ERG report, the ERG observes that the EMA considers that it is reasonable to generalise the clinical effectiveness results associated with LET to other aromatase inhibitors.[68]

The ERG notes that LET has been a treatment option for over 10 years and is now available as a generic drug. Other aromatase inhibitors used in clinical practice in England include anastrozole and exemestane. Both drugs are also available as generic agents. The ERG considers that the comparators specified in the final scope issued by NICE, and addressed by the company, represent the current standard of care for the patient population specified in the final scope issued by NICE.

3.4 Outcomes

The outcomes specified in the final scope issued by NICE are OS, PFS, response rates, AEs and HRQoL; these are standard outcomes used in oncology clinical trials and are the most important outcome measures for this appraisal. In addition to these endpoints, the company

has also reported data for clinical benefit rate (CBR). The company argues that CBR, which captures complete response (CR), partial response (PR) 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 measuring the benefit of breast cancer drugs.[70] The focus of this ERG report, however, is on the outcomes that the ERG considers 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/TTP, AEs and HRQoL. Nonetheless, for completeness, information relating to other outcomes are reported in the appendices to this ERG report.

3.5 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments is expressed in terms of incremental cost per quality adjusted life year (QALY) gained. Outcomes are assessed over a 40-year time horizon (equivalent to a lifetime horizon), and costs are considered from an NHS perspective.

3.6 Subgroups

The company has presented PFS findings for a number of pre-specified subgroups, including (but not limited to) comparisons of results for MBC patients in the PALOMA-1 trial with and without de novo disease and for patients in the PALOMA-2 trial with a DFI of ≤12 months, >12 months or patients with de novo disease. During the clarification process, the ERG asked the company to provide PFS findings from both the PALOMA-1 and PALOMA-2 trials, for MBC patients with de novo disease and for MBC patients who had previously undergone (neo)adjuvant therapy for early-stage disease.

3.7 Other considerations

The company has stated that there are no issues relating to equity and equality and no other considerations have been raised. The company does not consider that palbociclib in combination with an aromatase inhibitor meets NICE's End of Life criteria. Nor has the company submitted a Patient Access Scheme application.

4 CLINICAL EFFECTIVENESS

The company conducted two systematic reviews to identify clinical effectiveness evidence: one to find evidence from RCTs, and the other to find evidence from non-randomised and non-controlled studies.

4.1 Methods

Overall, the ERG is satisfied with the clinical effectiveness systematic review process as described in the CS for both reviews (see Sections 4.1.1 to 4.1.4 of this ERG report). The ERG considers that the company's approach to evidence synthesis (see Section 4.1.5 of this ERG report) is appropriate.

4.1.1 Literature search methods

Full details of the strategies used to locate clinical evidence are reported in Section 4.1, Section 4.11, Appendix 4 and Appendix 11 of the CS. The clinical effectiveness searches were originally designed to identify studies published between database inception and January 2015. They were then updated in January 2016 and again in April 2016. The ERG considers updating the searches to be good practice and the date range of the final searches to be appropriate. The company searched the following databases: MEDLINE, MEDLINE in Process, Embase and The Cochrane Library (all databases). Search terms used appeared to be relevant and included medical subject headings and free text terms as well as an RCT filter in the search for RCTs. Searches were limited to finding English language and human studies.

In addition to searches of electronic databases, the company reported results from hand searches of three conference sites: ASCO, European Society for Medical Oncology (ESMO) and American Association for Cancer Research (AACR). The company included details of the search terms used to search these additional resources in the CS (Appendix 4, table 5) and the ERG considers that these search terms were relevant. The company also reports having searched two clinical trial registries: clinicaltrials.gov and International Clinical Trial Registry Platform (ICTRP).

The ERG considers that the company's searches were reported and carried out to an adequate standard. The searches accurately reflect the population and the indication described in the final scope issued by NICE. The ERG is confident that no relevant references were missed.

4.1.2 Eligibility criteria

The company provides a detailed report of the inclusion/exclusion criteria applied to the selection of potentially relevant studies for the two systematic reviews (RCTs and non-

randomised and non-controlled studies) in the CS. These criteria are summarised in Table 3. Two independent reviewers applied eligibility criteria. Disputes relating to eligibility were resolved through discussion between reviewers until consensus, or through consultation with a third reviewer.

Table 3 Summary of eligibility criteria

Parameter	Review of RCT evidence	Review of non-randomised and non-controlled study evidence
Population	Postmenopausal women with ER+, HER2- ABC or MBC Studies had to include ≥50% patients with ER+ or hormone receptor-positive disease, and ≥50% postmenopausal women; or outcomes had to be reported separately for patients in these subgroups	
Intervention	Anastrozole, letrozole or palbociclib (as monotherapy or in combination) in a first-line setting	Palbociclib (as a monotherapy or in combination with any other drug)
Comparator	Anastrozole, letrozole or palbociclib (as a monotherapy or in combination) in a first-line setting	Any or none
Outcomes	A range of pre-specified efficacy (including, but not limited to, OS, PFS, ORR and CBR), AE and HRQoL outcomes*	A range of pre-specified efficacy, AE and HRQoL outcomes*
Study design	Phase II and phase III RCTs only†	Non-randomised, controlled, prospective clinical trials; long-term follow-up studies; prospective observational studies; phase I studies; retrospective studies†
Language	English only	English only
Date	No limit	No limit

*For full details of all efficacy, AE and HRQoL outcomes, see CS, Table 9 and Table 27
† Systematic reviews and meta-analyses were included at the title/abstract screening stage and used for identification of any additional primary studies not identified through the database searches, but were excluded during the full-text assessment
ABC=advanced breast cancer; AE=adverse event; CBR=clinical benefit rate; ER+=oestrogen receptor positive; HER2-=human epidermal growth factor receptor 2 negative; HRQoL=health-related quality of life; MBC=metastatic breast cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial
Source: CS, adapted from Table 9 and Table 27

The ERG notes that studies reporting the safety and efficacy of treatment with exemestane were not considered to be eligible for inclusion into either of the company's reviews. As noted in Section 3.3 of this ERG report, the comparators in the final scope issued by NICE were: 'aromatase inhibitors (such as LET or anastrozole)'. The final scope did not, therefore, explicitly include or exclude exemestane as a comparator. As noted in Section 2.3 of this ERG report, according to its indication [redacted] exemestane is more likely to be used in the second-, rather than first-line setting. However, [redacted], it is also used in the first-line setting [redacted]. The ERG is not aware of any studies that have investigated palbociclib in combination with exemestane, or which have included exemestane in the comparator arm of a relevant trial. Therefore the ERG is confident that, despite excluding exemestane from its systematic review of RCT evidence, all studies relevant to enable a

comparison of palbociclib to an aromatase inhibitor have been identified by, and included in, the company's systematic review.

The ERG notes that the eligibility criteria applied by the company enabled reviewers to exclude studies based on reported trial outcomes. This could, theoretically, introduce outcome selection bias by excluding any study that measured, but did not report, specific outcomes.[71] However, the ERG also notes that as a range of outcomes were specified and as there was no need for included studies to report *all* outcomes but just one of these outcomes, in this instance, including or excluding studies based on outcomes is unlikely to be an important issue with regard to bias.

4.1.3 Data extraction

It is stated in the CS that, for both systematic reviews, data from studies included in the systematic review were extracted into a pre-specified extraction grid developed in Microsoft Excel. It is unclear if data extraction was conducted by one, two, or more reviewers and if this was conducted independently or extracted by one reviewer and cross-checked by another. However, the ERG notes that for studies included in the company's cost effectiveness review, data were extracted by a single reviewer and verified by a second individual.

4.1.4 Quality assessment methods

A risk of bias assessment of the RCTs included in the systematic review of clinical effectiveness was undertaken by the company using the method recommended by NICE[72] (based on the Centre for Reviews and Dissemination's guidance[73]). The company also assessed the methodological quality of the non-randomised and non-controlled studies that they provided as supportive evidence using the Down and Black's checklist for non-randomised studies.[74] This checklist is cited as a checklist to consider using in Appendix H of the manual for developing NICE guidelines.[75,76] It is unclear whether the quality assessment of RCTs and/or non-randomised and non-controlled studies was completed by one reviewer, or independently by two reviewers.

4.1.5 Approach to evidence synthesis

The company's literature search for RCTs led to the identification of two trials that were considered to be directly relevant to the decision problem (the PALOMA-1 and PALOMA-2 trials). The company did not carry out a meta-analysis of efficacy outcomes or pool data for AEs from the two trials (although the company did present pooled data for some AEs occurring in patients treated with PAL+LET); instead the company described and reported findings from the studies narratively. As stated in the company response to the ERG during the clarification

process, its reason for this was that it considered that the PALOMA-2 trial (the larger, confirmatory, later phase trial) was the most robust data source.

Seven citations[77-83] reporting on four studies were considered relevant to the company's systematic review of non-randomised and non-controlled studies. Within the CS, the company has described the studies and reported findings narratively.

The ERG considers that the company's approach to evidence synthesis was appropriate for both systematic reviews. The ERG also considers that, for completeness, a meta-analysis of OS and PFS outcomes from the PALOMA-1 and PALOMA-2 trials, and pooling of the AE data from these two trials, may have been informative. However, the ERG also considers that the reporting of the PALOMA-1 and PALOMA-2 trial data narratively was also appropriate, and sufficient for the purposes of this appraisal.

4.2 Identified studies in the systematic reviews

4.2.1 Randomised controlled trial evidence

Two relevant trials were included in the systematic review of RCT evidence, the phase I/II, multi-centre, randomised, open-label PALOMA-1 trial (N=165) and the larger (N=666) phase III, multi-centre, randomised, double-blind, placebo-controlled PALOMA-2 trial. Both trials included postmenopausal women with ER+/HER2- ABC who had not received previous systemic treatment in the advanced or metastatic setting. The PALOMA-1 trial was designed to compare the efficacy and safety of treatment with PAL+LET with LET, whilst the PALOMA-2 trial was designed to compare the efficacy and safety of PAL+LET with placebo in combination with LET (PLACEBO+LET).

Patients were randomly allocated to treatment in a 1:1 ratio in the PALOMA-1 trial. Randomisation was performed using an interactive web-based randomisation system, stratified by disease site (visceral versus only bone versus other) and by DFI (>12 versus ≤12 months between completion of the last adjuvant treatment and disease recurrence) or de novo.

Patients were randomly assigned 2:1 to the PALOMA-2 trial via an interactive randomisation technology system. Patients were stratified by disease site (visceral versus non-visceral), DFI since completion of prior (neo)adjuvant therapy (de novo metastatic versus ≤12 months versus >12 months), and nature of prior (neo)adjuvant anti-cancer treatment (prior hormonal therapy versus no prior hormonal therapy).

The primary results from the PALOMA-1 trial have been published in a peer reviewed journal.[49] In addition, results relating to pain severity and pain interference,[84] and an expanded analysis

of subgroup data[85] have also been published. The company also cites conference presentations of subgroup analyses by age,[86] previous systemic treatment,[87] bone metastases,[88] long term safety[89] and pain severity and pain interference.[90] In addition to the published data, the company has also presented data from the Clinical Study Report (CSR).[91]

At the time of its systematic reviews, findings from the PALOMA-2 trial have been presented at the ASCO 2016 conference.[15] The company has also included data extracted from the CSR[92] within the CS. Subsequent to the company's submission to NICE, efficacy and safety findings from the PALOMA-2 trial have been published in a peer review journal[93] and HRQoL data presented at the ESMO conference in October 2016.[94]

The ERG considers that both the PALOMA-1 and PALOMA-2 trials are relevant to the NICE decision problem.

4.2.2 Non-randomised and non-controlled evidence

As noted in Section 4.1.5, seven citations[77-83] reporting on four studies were included in the systematic review of non-randomised and non-controlled evidence. The four non-randomised and non-controlled studies were all phase I or phase II studies investigating the use of palbociclib for the treatment of breast cancer, and are described using the following trial identifiers: NCT01320592,[77,78]NCT00141297,[79] NCT00721409 (phase 1)[80] and NCT01037790 (UPCC03909).[82,83] In total, the four studies only included 81 patients with ABC.

The ERG does not consider any of the identified studies to be relevant to the NICE decision problem since none of them included treatment with palbociclib in combination with an aromatase inhibitor. The ERG does, however, note that one of the studies,[80,81] investigated the use of palbociclib monotherapy during the first cycle followed by subsequent cycles of PAL+LET. This is the phase I part (n=12) of the phase I/II RCT, referred to as the PALOMA-1 trial. As noted above, the ERG considers the PALOMA-1 trial to be relevant to the decision problem.

In the remainder of this ERG report, the ERG only critiques the RCT evidence presented by the company.

4.3 Statistical approach used for the conduct and analysis of included studies

In this section, the ERG provides a description and critique of the statistical approaches used to analyse data collected during the PALOMA-1 and PALOMA-2 trials that relate to the outcomes stipulated in the final scope issued by NICE. Information relevant to the statistical approach taken by the company has been extracted from the clinical study reports (CSRs),[91,92] the trial statistical analysis plans (TSAPs),[95,96] the trial protocols [97,98] and the CS.

4.3.1 Analysis populations of the PALOMA-1 and PALOMA-2 trials

Outcome data were collected from different study populations as shown in Table 4.

Table 4 PALOMA-1 and PALOMA-2 trial outcome populations

Analysis	Study population
Efficacy	The ITT population was the primary population for evaluating all efficacy endpoints and patient characteristics. This population included all randomised patients The ITT population, with measurable disease at baseline, was also used for the analysis of ORR in the PALOMA-1 trial, and for the analysis of ORR, CBR and DOR in the PALOMA-2 trial
PROs	PALOMA-1: All analyses were performed on the PRO evaluable population, i.e. all randomised patients who completed the baseline PRO assessment received at least one dose of study treatment and completed at least one post-baseline PRO assessment PALOMA-2: Completion rates are reported for the ITT population, all other analyses were performed on the PRO evaluable population i.e. patients who completed a baseline assessment and at least one post-baseline assessment
Safety	The as-treated 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 therapy
Biomarker analyses	The subset of as-treated patients for which baseline assessment of at least one biomarker was available.

CBR=clinical benefit rate; DOR=duration of response; ITT=intention-to-treat; ORR=objective response rate; PRO=patient-reported outcome
Source: CS, adapted from Table 18

4.3.2 Outcomes analysed in the PALOMA-1 and PALOMA-2 trials

The PALOMA-1 trial

The PALOMA-1 trial is a phase I/II trial, meaning that initially, a single-arm phase I study was carried out to assess the safety of PAL+LET and to determine a recommended dose for the PAL+LET combination to be used in the phase II study. The primary outcome for the PALOMA-1 trial was investigator assessed PFS, although assessments were also carried out by blinded independent central review (BICR). TTP and OS were secondary outcomes. The definitions and methods of analysis for PFS, OS and TTP are provided in Table 5.

The following additional endpoints were also measured in this trial: CBR, ORR and duration of response (DOR). For completeness, these are described in appendices to this ERG report (Section 10.1).

Table 5 Description and method of analysis for key efficacy outcomes (PALOMA-1 trial)

Outcome	Description	Statistical analysis
Primary efficacy outcome		
PFS	Time from randomisation to radiological disease progression or death on study. Documentation of progression was by objective disease assessment calculated from the lesion measurements, as defined by RECIST 1.0	Hypothesis: [redacted]
Secondary efficacy outcomes		
OS	Time from the date of randomisation to the date of all-cause death. Patients last known to be alive were censored at date of last contact. Survival was assessed up until approximately 28 days from the last dose of study treatment	[redacted]
TTP	Time from the date of randomisation to the date of first documentation of objective progression	[redacted]

CI=confidence interval; DFI=disease-free interval; H0=null hypothesis; HA=alternative hypothesis; ITT=intention-to-treat; K-M=Kaplan-Meier; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; RECIST=response evaluation criteria in solid tumors; TTP=time to progression
Source: CS, adapted from Table 13, Table 19 and Table 20

The ERG is satisfied that the analysis method for each of these efficacy outcomes was pre-specified in the TSAP, and that all results were reported fully in the CSR. The ERG notes that one-sided hypothesis testing was used to assess PFS and TTP and, as part of the clarification process, asked the company to justify the use of this approach to hypothesis testing. The company states that one-sided hypothesis testing was deemed suitable due to there being "sufficient confidence" that treatment with PAL+LET was more effective than treatment with LET, and that it was more efficient (from a statistical perspective) in light of the expected small sample size and under the null hypothesis to use one-sided testing. The ERG is satisfied that the use of one-sided testing was appropriate, although it considers that more justification could have been provided regarding the basis for the company's confidence that PAL+LET is more effective than LET. Furthermore, the rationale for such an important statistical decision should have been provided in the protocol and/or in the TSAP.

The company states that the assumption of proportional hazards (PH) was verified for PFS, and that the results were satisfactory, referring to Figures 19 and 20 of the CS (CS, Section 4.4.1.2). However, these figures show data from the PALOMA-2 trial. The company does not mention whether any PH testing was conducted for OS. The ERG, therefore, requested clarification from the company on whether any PH testing had been conducted for the PFS or OS data from the PALOMA-1 trial. In the company's response to the ERG clarification letter, the company stated that figures demonstrating the assessment of PH (i.e. a log-cumulative hazard plot and a Schoenfeld residual plot) were not presented in the CS for the PFS data from the PALOMA-1 trial, because PFS data from the PALOMA-1 trial were not used in the economic evaluation. The company did not clarify whether any assessment of PH had been performed for either the PFS or OS data from the PALOMA-1 trial. Consequently, the ERG performed their own assessments of PH using PFS and OS data from the PALOMA-1 trial (see appendices to the ERG report, Section 10.2). The ERG considered that the PH assumption was valid for PFS data, but not for OS data. Therefore, the use of HRs to summarise treatment effect for OS is not appropriate.

The PALOMA-2 trial

The primary outcome of the PALOMA-2 trial was investigator assessed PFS, although assessments were also made by BICR. OS was a secondary outcome; TTP was not pre-specified as an endpoint. The definitions and methods of analysis for PFS and OS are listed in Table 6.

The following additional endpoints were also measured in this trial: ORR, CBR, DOR. For completeness, these are described in appendices to this ERG report (Section 10.1).

The ERG is satisfied that the analysis method for each of the reported efficacy outcomes was pre-specified in the TSAP, and that all results were reported fully in the CSR.

The company demonstrated that the assumption of PH was valid for PALOMA-2 trial PFS data by providing a log-cumulative hazard plot and a Schoenfeld residual plot (Figure 19 and Figure 20 of the CS, respectively). The ERG agrees that proportionality appears to hold for the PFS data and that the use of a HR to demonstrate PFS benefit is appropriate

Table 6 Description of efficacy outcomes reported (PALOMA-2 trial)

Outcome	Description	Statistical analysis
Primary efficacy outcome		
PFS	Time from randomisation to radiological disease progression or death on study. Documentation of progression was by objective disease assessment calculated from the lesion measurements, as defined by RECIST 1.1	[redacted]
Secondary efficacy outcomes		
OS	Time from the date of randomisation to the date of all-cause death. Patients last known to be alive were censored at date of last contact.	[redacted]

CI=confidence interval; H0=null hypothesis; HA=alternative hypothesis; ITT=intention-to-treat; K-M=Kaplan-Meier; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; RECIST=response evaluation criteria in solid tumors
Source: CS, adapted from Table 16, Table 19 and Table 20, and the company's response to the ERG clarification letter

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4.3.3 Interim analyses of progression-free survival

The PALOMA-1 trial

As stated in Section 4.2 of this ERG report, the PALOMA-1 trial was a phase I/II trial. The phase I element was described as the NCT00721409 (phase 1) study.[80,81] The phase II element was designed to assess the safety and efficacy of treatment with PAL+LET in comparison to treatment with LET alone.

During phase II patients were sequentially enrolled into two cohorts to determine whether selecting patients based on the ABC-associated biomarkers cyclin D1 (CCND1) or p16 might identify subpopulations that would be more likely to benefit from treatment with PAL+LET than the general population of patients eligible for inclusion in the trial. Patients were recruited to the first cohort (cohort 1) based solely on ER+/HER2- status. The second cohort (cohort 2) of patients was recruited based on the combination of ER+/HER2- status and amplification of cyclin D1 and/or loss of p16 or both. Across both cohorts, a total of 84 patients were randomised to receive PAL+LET, and 81 were randomised to receive LET.

An unplanned interim analysis of cohort 1 based on 32 PFS events was conducted after it was noted that almost twice as many patients in the control group were discontinuing treatment because of disease progression. The results of the interim analysis showed clinically meaningful activity of the PAL+LET combination compared with LET (hazard ratio [HR]=0.35, 95% confidence interval [CI] 0.17 to 0.72, p=0.006). The company states that these preliminary results from cohort 1 suggested that further patient selection based upon CCND1 amplification or p16 loss was unlikely to further improve patient outcomes in comparison to patient selection based on ER+/HER2- status alone. As a result, further enrolment into cohort 2 (i.e. based upon CCND1 amplification or p16 loss) was stopped, and the TSAP was amended so that all primary and secondary endpoints would be analysed in cohort 1 and 2 combined.

At the time recruitment was stopped, 165 patients had been randomised in total: 66 to cohort 1 and 99 to cohort 2. The sample size had been estimated to provide 80% power to detect a HR for PFS of 0.67 based on 114 PFS events, assuming that PFS would be increased from 9 months for LET patients to 13.5 months for PAL+LET patients. However, after 57 PFS events had occurred across both cohorts, the study protocol was amended to include a second interim analysis. This interim analysis, based on 61 PFS events, reported a HR for PFS of 0.37 (95% CI 0.21 to 0.63, one-sided p<0.0001). The investigators noted that events were being observed at a slower pace than anticipated, and consequently the protocol was amended to state that the final analysis would be performed after 95 PFS events had occurred. This

number of events would give >98% power to detect a HR for PFS of 0.50 at a one-sided α of 0.10, or 75% power to detect a HR for PFS of 0.67.

To take the results of the interim analyses into consideration, the significance level for the final analysis was adjusted using the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary. The adjusted level of significance for PFS was 0.0938.

The PALOMA-2 trial

The PALOMA-2 trial was designed to have one interim analysis, which was to be performed after 226 PFS events had occurred (approximately 65% of total PFS events expected). To account for this interim analysis in the overall significance level for the analysis of PFS, which was to be preserved at 0.025 (one-sided test), hierarchical group sequential testing was performed with an error spending function at a level of 0.025. Specifically, a p-value of 0.000013 was used as the efficacy boundary for the interim analysis. The interim analysis was conducted in October 2015 when 236 PFS events had occurred, corresponding to approximately 68% of the expected events for the study. At this time point, the Data Monitoring Committee (DMC) recommended that the study continue. The company was, and remains to be, blinded to the results of the interim analysis.

4.3.4 ERG critique of statistical approach of the PALOMA trials

A summary of the checks made by the ERG in relation to the statistical approach used by the company to analyse data from the PALOMA-1 and PALOMA-2 trials is provided in Table 7. Having carried out these checks, the ERG is satisfied with the statistical approach employed by the company, with the exception that, despite asking for clarification from the company, it remains unclear to the ERG whether the company performed any testing of the PH assumption for PALOMA-1 PFS and OS data. The ERG's own assessments of the assumption of PH demonstrate that the PH assumptions hold for PFS, but not for OS (see appendices to the ERG report, Section 10.2).

Table 7 ERG assessment of statistical approach used to analyse data from the PALOMA-1 and PALOMA-2 trials

Component	Statistical approach with ERG comments	
	PALOMA-1 trial	**PALOMA-2 trial**
Protocol amendments	Protocol amendments are provided in the CSR (pages 101-104) The protocol was amended several times to include interim analyses and to make changes based on the results of these interim analyses, as outlined in Section 4.3.3. The company states that these interim analyses were not performed with the intention of possibly stopping the trial; rather, they were performed to obtain information and to inform phase III study design (CS, page 63). The ERG believes it is preferable for phase II studies to make amendments to study design in order to inform phase III studies, rather than amendments being made at phase III level, and so is not concerned by the PALOMA-1 protocol amendments. Furthermore, all amendments were made before conduct of the final analysis	Protocol amendments are provided in the CSR (108-112) Protocol amendments are outlined in detail and rationale is provided for these changes. Amendments were made before conduct of the final analysis, and so were unlikely to have been driven by results of the trial
Sample size calculation	Provided in the CSR (page 100) The ERG is satisfied with the company's original sample size calculation. The ERG noted that the company recalculated the power the study would have at the final analysis when the number of events that the final analysis would be based on was amended due to information obtained from the second interim analysis	Provided in the CSR (page 90) The ERG is satisfied with the performed sample size calculation, and noted that the calculation accounted for the one planned interim analysis.
Analysis of AEs	Type, incidence, severity and seriousness of adverse events, their relationship to study medications and any laboratory abnormalities were investigated (CS, Table 13). Many different summaries of AEs are provided in the CSR; a complete list of the different summary tables is provided on pages 230-232 of the CSR The ERG is satisfied that the methodology used to analyse the AEs is appropriate	Type, incidence, severity and seriousness of adverse events, their relationship to study medications and any laboratory abnormalities were investigated (CS, Table 16). Many different summaries of AEs are provided in the CSR; a complete list of the different summaries is provided on pages 101-104 of the CSR The ERG is satisfied that the methodology used to analyse the AEs is appropriate
Sensitivity analyses for PFS	The CSR (page 93) lists 7 sensitivity analyses that were carried out for PFS. All sensitivity analyses were performed using both investigator assessed and BICR outcome data The ERG is satisfied that all sensitivity analyses were pre-specified in the TSAP (page 32) and the results of these analyses were fully reported in the CSR (page 148 and 151)	The CSR (pages 132-133) lists 14 sensitivity analyses that were carried out for PFS. All sensitivity analyses were performed using both investigator assessed and BICR outcome data The ERG is satisfied that sensitivity analyses were pre-specified in the TSAP (pages 36-38) and the results of these analyses were fully reported in the CSR (page 134).

Component	Statistical approach with ERG comments	
	PALOMA-1 trial	**PALOMA-2 trial**
Subgroup analyses for PFS	Subgroup analyses of PFS were performed for the following baseline and prognostic factors (CS, Table 26): Age (<65 years, ≥65 years) Baseline ECOG (0 or 1) Disease site (visceral, bone only, other) Previous chemotherapy (yes, no) Previous endocrine therapy (yes, no) Previous systemic therapy (yes, no) Previous chemotherapy only (yes, no) Previous chemotherapy and endocrine therapy (yes, no) DFI (≤12 months, ≤12 months + de novo, >12 months; ≤5 years, >5 years) Biomarker status (positive, negative, unknown) Region (North America, Europe) Histopathological grade (1/2, 3) Progesterone receptor (positive, negative) Number of disease sites involved (<2, ≥2) De novo advanced disease (yes, no) The ERG notes that a complete list of subgroup analyses was not pre-specified in the TSAP. It is stated that subgroup analyses of PFS may be performed for the baseline stratification factors, baseline patient characteristics, and selected biomarkers (TSAP, p 32)	Subgroup analyses of PFS were performed for the following baseline and prognostic factors (CS, Table 26): Age (<65 years, ≥65 years) Baseline ECOG (0 or 1/2) Disease site (visceral, non-visceral) Region (North America, Europe, Asia/Pacific) Ethnicity (White, Asian) Number of disease sites (1, 2, ≥3) DFI (≤12 months, >12 months, de novo) Previous chemotherapy (yes, no) Previous endocrine therapy (yes, no) Most recent therapy (aromatase inhibitor, anti-estrogen) Biomarker expression (yes/no or low/high) Bone-only disease at baseline (yes, no) Measurable disease (yes, no) The ERG notes that a complete list of subgroup analyses was not pre-specified in the TSAP. It is stated that the potential influences of the stratification factors and baseline patient characteristics such as age, ethnic origin, ECOG performance status, geographical region/country, and selected biomarkers on the primary PFS endpoint would be evaluated (TSAP, page 24)
Analysis of PROs	PROs of pain severity and pain interference with various activities of daily life were assessed in the phase II portion of the study using the mBPI-sf. The mBPI-sf pain severity and interference scales were summarized by cycle using observed values as well as changes from baseline, displaying univariate statistics such as mean, median, SD, and 95% CI of the mean (CSR, page 79 and page 99). No adjustments for multiple testing were performed despite the large number of statistical tests performed, therefore the issue of multiplicity ought to be considered when interpreting p-values from these analyses. The ERG is generally satisfied that the methodology used to analyse PROs data is appropriate	PROs were assessed using the breast cancer specific HRQoL questionnaire (FACT-B) and generic EQ-5D. Comparisons of change from baseline scores between treatment arms were based on a repeated-measures analysis using a mixed-effects model. The variables in the model were treatment, time, and treatment-by-time; baseline was a covariate (CS, section 4.7.3.2 and Table 20). Two-sided hypothesis testing was used for analyses (except for time to deterioration analyses). No adjustments for multiple testing were performed despite the large number of statistical tests performed, therefore the issue of multiplicity ought to be considered when analysis results. The ERG is generally satisfied that the methodology used to analyse PROs data is appropriate

AE=adverse event; BICR=blinded independent central review; CI=confidence interval; CS=company submission; CSR=clinical study report; DFI=disease-free interval; ECOG= Eastern Co-operative Oncology Group; EQ-5D=EuroQol-5 Dimensions; ERG=evidence review group; FACT-B=Functional Assessment of Cancer Therapy-Breast; HRQoL=health related quality of life; mBPI-sf=modified Brief Pain Inventory short form; PFS=progression-free survival; PRO=patient-reported outcome; SD=standard deviation; TSAP=trial statistical analysis plan
Source: CS, PALOMA-1 CSR, PALOMA-2 CSR, the company's response to the ERG clarification letter, and ERG comment

4.4 Quality assessment of included studies

Appendix 8 to the CS includes an assessment of the risk of bias for the PALOMA-1 and PALOMA-2 trials. The ERG has summarised this assessment in Table 8. The ERG's examination of the patient flow in both trials (CS, Figure 7 and Figure 8) shows that none of the patients in either trial were lost to follow-up. In both trials, the reasons for withdrawing treatment were generally similar across both arms, the most common reason being disease progression or relapse.

Table 8 Company's assessment of risk of bias for PALOMA-1 and PALOMA-2 trials

Study question	Company assessment		ERG Comment
	PALOMA-1	PALOMA-2	
Was randomisation carried out appropriately?	Yes	Yes	-
Was the concealment of treatment allocation adequate?	Yes	Yes	-
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Yes	PALOMA-1 trial: the company and the ERG noted some slight imbalances. As reported in Section 4.5 of this ERG report, overall, these imbalances are not considered likely to result in bias PALOMA-2 trial: it is unclear if differences in geographic region (See Section 4.5 of this ERG report) would introduce any bias
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	Yes	PALOMA 1 trial: bias may have been introduced due to the open-label design. To mitigate bias, retrospective assessments of tumour response and disease progression were made by independent radiologic review and were blinded to treatment group in 161 of 165 (97.6%) of randomised patients
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes / Yes	No / not applicable	PALOMA-1 trial: the company reports that twice as many patients in the control arm of cohort 1 discontinued the study compared with patients in cohort 2 because of disease progression, so an unplanned interim analysis was performed. The ERG notes that the findings from a final analysis of PFS reported by the EMA shows large differences between investigator assessed PFS and BICR assessed PFS for cohort 1 which the EMA state may indicate bias
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	The company highlights that at the time of PFS analysis, survival events had not reached the pre-specified number of events for a survival analysis to be conducted
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	Yes	-

EMA=European Medicines Agency; ERG=evidence review group; PFS=progression-free survival
Source: CS, adapted from Appendix 8 (Table 13)

As noted in Table 8, the ERG notes that the findings from a final analysis of cohort 1 shows large differences between investigator assessed PFS and BICR assessed PFS. These findings were reported by the EMA. According to the EMA, these results indicate that findings from cohort 1 may be significantly biased to the extent that the findings from the PALOMA-1 trial are not suitable for licensure. The EMA also conclude that only findings from cohort 2 should be considered relevant to the efficacy assessment.

Overall, the ERG considers that the PALOMA-2 trial was generally well designed and well conducted. In addition, the ERG agrees with the company's conclusion that this trial has a low risk of bias.

4.5 Characteristics of the patients in the included studies

Patients participating in the PALOMA-1 trial were recruited from 50 sites in Canada, France, Germany, Hungary, Ireland, Italy, Russia, South Africa, South Korea, Spain, Ukraine and USA. Patients participating in the PALOMA-2 trial were recruited from 186 sites in Australia, Belgium, Canada, France, Germany, Hungary, Ireland, Italy, Japan, Republic of Korea, Poland, Russian Federation, Spain, Taiwan, Ukraine, UK (seven sites) and USA. The vast majority of patients in both trials had MBC (98% in the PALOMA-1 trial and [redacted] in the PALOMA-2 trial).

In general, the trial eligibility criteria for the PALOMA-1 and PALOMA-2 trials were similar. In both trials, patients had to have ER+/HER2- ABC not amenable to resection or radiation therapy with curative intent. All patients in the PALOMA-1 and PALOMA-2 trials were required to have measurable disease according to response evaluation criteria in solid tumors criteria or bone-only disease. Prior treatment for ABC was not permitted. The presence of brain/central nervous system (CNS) metastases was also an exclusion criterion. Radiation covering <25% of bone marrow at least 2 weeks prior to initiation of study treatment was permitted in the PALOMA-1 trial; however, in the PALOMA-2 trial, patients who received prior radiotherapy to ≥25% of bone marrow were not eligible, regardless of when it had been administered.

While patients in both trials were not permitted to have brain/CNS metastases at trial entry, in the PALOMA-2 trial, patients with a history of CNS metastases or cord compression were eligible if they had been definitively treated with local therapy (e.g. radiotherapy, stereotactic surgery) and had remained clinically stable whilst not taking anticonvulsants and steroids for at least 4 weeks before randomisation. The recruitment criteria for the PALOMA-2 trial explicitly stated that patients with advanced, symptomatic, visceral spread, who were at risk of life-threatening complications in the short-term, including patients with massive uncontrolled effusions (pleural, pericardial, peritoneal), pulmonary lymphangitis, and >50% liver

involvement were to be excluded. It was also explicitly stated that, for patients entering the trial, chemotherapy was not clinically indicated.

Given the eligibility criteria for the PALOMA-1 trial, although not explicitly stated, it is likely that patients at risk of life-threatening complications, and for whom chemotherapy would be clinically indicated, would not have been included in the PALOMA-1 trial.

Other differences in eligibility criteria between the two trials relate to Eastern Cooperative Oncology Group (ECOG) performance status (PS) and prior treatment with an aromatase inhibitor in the adjuvant setting. The PALOMA-1 trial recruitment criteria excluded patients with ECOG PS 2, whereas the PALOMA-2 trial criteria included patents with ECOG PS 0 to 2; however, only 12 (1.8%) patients in the PALOMA-2 trial had ECOG PS 2. Patients included in the PALOMA-1 trial had to have a DFI >12 months following treatment with LET, whilst patients included in the PALOMA-2 trial had to have a DFI of >12 months following treatment with LET or anastrozole. This means that patients in both trials were unlikely to be resistant to LET (and those in the PALOMA-2 trial were also unlikely to be resistant to anastrozole). Advice received by the ERG is that, in clinical practice, most patients who receive aromatase inhibitors as first-line treatment for MBC have ECOG PS 0 to 2. However, in clinical practice, patients with ECOG PS>2 would be considered for treatment.

The company states that in both trials, baseline characteristics of patients were well balanced between the arms although it notes that there were slight imbalances in the proportions of patients with visceral disease, DFI, and previous treatment in the neo(adjuvant) setting in the PALOMA-1 trial. These differences all appear to favour the PAL+LET arm over the LET arm. However, the company states that these differences were not considered to be of clinical significance by the UK clinicians who were part of an advisory board. The ERG also notes additional apparent imbalances also identified by the EMA, namely time since diagnosis of breast cancer which may also favour the PAL+LET arm, proportion of patients with Grade 3 tumours which may favour the LET arm and differences in the proportion of patients with progesterone receptor-positive disease. The ERG notes that since the numbers of patients in the PALOMA-1 trial are relatively small, apparent imbalances in percentage terms may be exaggerated. The EMA also highlights possible differences by age and weight. It is stated that the differences in age may favour the LET arm.

The EMA highlights that apparent imbalances by treatment arm in the PALOMA-1 trial were due to the incorrect stratification factors being used at the time of randomisation which were discovered retrospectively during data review and source data verification. Sensitivity analyses using Case Report Form data were conducted to investigate the impact of the imbalances on the PFS results, using multivariate Cox PH models by investigator and BICR

assessments. These indicated that having additional patients with visceral disease in the LET arm may favour the PAL+LET arm in the comparison (BICR HR 0.4 for non-visceral versus visceral). However, the difference in mean and medians of age may favour the LET arm (BICR HR 0.5 for age ≥ 65 years versus < 65 years). These imbalances appear to add uncertainty to the results.

The ERG also notes imbalances in the PALOMA-2 trial [redacted]. It is unclear if differences by treatment arm according to geographic region would introduce any bias. In terms of PS, given that all patients had ECOG PS 0 to 1, these imbalances are not considered by the ERG to result in bias.

Patient baseline characteristics presented in the CS are summarised by the ERG in Table 9. The ERG notes the following minor differences between the two trials:

- The PALOMA-2 trial included proportionately [redacted] than the PALOMA-1 trial
- The PALOMA-2 trial included proportionately [redacted] patients with de novo ABC and proportionately [redacted] patients with DFI >12 months than the PALOMA-1 trial
- Compared with patients included in the PALOMA-1 trial, proportionately [redacted] patients included in the PALOMA-2 trial had received previous treatment with hormonal therapy (i.e. endocrine therapy)
- Compared with patients included in the PALOMA-1 trial, proportionately [redacted] patients in the PALOMA-2 trial had received hormonal therapy as their last therapy
- In patients whose last treatment was hormonal therapy, compared with patients in the PALOMA-1 trial, proportionally [redacted] patients included in the PALOMA-2 trial received an aromatase inhibitor.

In the CS (Section 4.14), the company argues that despite a high proportion of patients in the PALOMA-1 and PALOMA-2 trials presenting with de novo disease, clinical opinion, in the form of advisory boards, had supported the high external validity of the trial populations in terms of generalisability to clinical practice in England and Wales.[99,100] Despite slight differences in the patient populations of the two trials (as highlighted above), the ERG agrees with the company that the patient populations in both trials are representative of the patients who would be treated in clinical practice in the NHS in England and Wales. However it should be noted that the number of patients presenting with de novo MBC in England and Wales is likely to be considerably less than in the two trials.

Table 9 Baseline characteristics of the PALOMA-1 and PALOMA-2 trials

Characteristics	PALOMA-1		PALOMA-2	
	PAL+LET (n=84)	LET (n=81)	PAL+LET (n=444)	PLACEBO+LET (n=222)
Median age (range), years	63 (54 to 71)	64 (56 to 70)	62 (30 to 89)	61 28 to 88)
Ethnicity				
White	[redacted]	[redacted]	344 (77.5%)	172 (77.5%)
Black	[redacted]	[redacted]	8 (1.8%)	3 (1.4%)
Asian	[redacted]	[redacted]	65 (14.6%)	30 (13.5%)
Other	[redacted]	[redacted]	27 (6.1%)	17 (7.7%)
ECOG performance status				
0	46 (54.7%)	45 (55.6%)	257 (57.9%)	102 (45.9%)
1	38 (45.3%)	36 (44.4%)	178 (40.1%)	117 (52.7%)
2	0	0	9 (2.0%)	3 (1.4%)
Measurable disease at baseline	[redacted]	[redacted]	338 (76.1%)	171 (77.0%)
Disease site*				
Visceral	37 (44.0%)	43 (53.1%)	214 (48.2%)	110 (49.5%)
Non-visceral	47 (56.0%)	38 (46.9%)	230 (51.8%)	112 (50.5%)
Bone only	17 (20.2%)	12 (14.8%)	Not reported	Not reported
Other§	30 (35.7%)	26 (32.1%)	Not reported	Not reported
DFI*				
>12 months	25 (29.8%)	30 (37.0%)	178 (40.1%)	93 (41.9%)
≤12 months or de novo	59 (70.2%)	51 (63.0%)	266 (59.9%)	129 (58.1%)
Previous systemic treatment				
None (de novo)	44 (52.4%)	37 (45.7%)	167 (37.6%)	81 (36.5%)
Chemotherapy	34 (40.5%)	37 (45.7%)	213 (48.0%)	109 (49.1%)
Hormonal	27 (32.1%)	28 (34.6%)	249 (56.1%)	126 (56.8%)
Tamoxifen	24 (28.6%)	24 (29.6%)	Not reported	Not reported
Anastrozole	8 (9.5%)	11 (13.6%)	Not reported	Not reported
Letrozole	2 (2.4%)	1 (1.2%)	Not reported	Not reported
Exemestane	4 (4.8%)	2 (2.5%)	Not reported	Not reported
Most recent therapy				
Chemotherapy	[redacted]	[redacted]	Not reported	Not reported
Hormonal	[redacted]	[redacted]	249 (56.1%)	126 (56.8%)
Anti-oestrogen¥	[redacted]	[redacted]	154 (61.8%)	75 (59.5%)
Aromatase inhibitor	[redacted]	[redacted]	91 (36.5%)	44 (34.9%)
Other	[redacted]	[redacted]	4 (1.6%)	7 (5.6%)

DFI=disease-free interval; ECOG=Eastern Co-operative Oncology Group
*Data reported for disease site and DFI based on Case Report Form in the PALOMA-1 trial
§ [redacted]
¥ Reported as tamoxifen in the PALOMA-1 trial
Source: CS, Table 21 with additional data from CSR for PALOMA-1 trial (Tables 18, 19 and 22)

4.6 Results

All the data from the PALOMA-1 trial presented in this section correspond to the data cut-off date of 29 November 2013, which was the date of the final analysis of the primary outcome (i.e. PFS). All the data from the PALOMA-2 trial correspond to the data cut-off date of 26 February 2016, which was the date of the primary analysis of the primary outcome (i.e. PFS).

4.6.1 Time on treatment

In both trials, patients spent more time on treatment with PAL+LET than with LET or PLACEBO+LET (Table 10). The ERG notes that while median relative dose intensity (RDI) was similar between trials, time on treatment was longer in both arms of the PALOMA-2 trial than in the equivalent arms of the PALOMA-1 trial. There also appear to be differences in rates of cycle delay and dose interruptions in the PAL+LET arms of the two trials; rates of cycle delay and dose interruptions were also notably fewer in the PLACEBO+LET arm. However, rates of RDI for palbociclib/placebo and LET were similar in all arms of both trials.

Table 10 Time on treatment for patients in the PALOMA-1 and PALOMA-2 trials who received at least one dose of study treatment

Duration, delay and relative dose intensity	**PALOMA-1**			**PALOMA-2**			
	PAL+LET (n=83)		**LET (n=77)**	**PAL+LET (n=444)**		**PLACEBO+LET (n=222)**	
	PAL	**LET**	**LET**	**PAL**	**LET**	**PLACEBO**	**LET**
Median duration of treatment, days	420	428	231	603	617	413	420
Number (%) of patients with at least one							
Cycle delay	70 (84.3)	--	--	[redacted]	[redacted]	[redacted]	[redacted]
Dose reduction	33 (39.8)	--	--	[redacted]	[redacted]	[redacted]	[redacted]
Dose interruption	47 (56.6)	32 (38.6)	23 (29.9)	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity %*							
Mean (Standard deviation)	94.1 (26.2)	99.5 (1.1)	99.5 (2.2)	--	--	--	--
Median (Range)	95.4	100.0	100.0	93.0 (40.3 to 109.5)	99.9 (73.4 to 100.2)	99.6 (56.1 to 104.5)	100.0 (79.0 to 100.0)

* Defined as (actual dose / intended dose) x 100%
Source: CS, adapted from Tables 40 and 42

4.6.2 Progression-free survival / time to treatment progression

While the primary outcome of both trials was investigator assessed PFS, the company also provided BICR results for PFS in the intention-to-treat (ITT) population for both trials. Subgroup analyses for PFS were also conducted in both trials. As highlighted by the ERG in Section 4.3.2 of this report, TTP was a secondary outcome in the PALOMA-1 trial but not in the PALOMA-2 trial. The results of the analyses of PFS and TTP in the ITT populations of both trials are summarised in Table 11.

Table 11 Progression-free survival and time to treatment progression results in the PALOMA-1 and PALOMA-2 trials

Outcome	PALOMA-1		PALOMA-2	
	PAL+LET (n=84)	LET (n=81)	PAL+LET (n=444)	PLACEBO+LET (n=222)
PFS				
Median PFS, months (95% CI) – investigator assessment	20.2 (13.8 to 27.5)	10.2 (5.7 to 12.6)	24.8 (22.1 to NE)	14.5 (12.9 to 17.1)
Hazard ratio (95% CI) for progression or death – investigator assessment	0.488 (0.319 to 0.748, one-sided p=0.0004[a])		0.576 (0.463 to 0.718, one-sided p<0.000001[b])	
Median PFS, months (95% CI) – BICR[c]	25.7 (17.7 to NE)	14.8 (9.3 to 20.4)	30.5 (27.4 to NE)	19.3 (16.4 to 30.6)
Hazard ratio (95% CI) for progression or death – BICR[c]	0.621 (0.378 to 1.019, one-sided p=0.0286[a])		0.653 (0.505 to 0.844) one-sided p=0.000532[b])	
TTP				
Median TTP, months – investigator assessment	20.2	10.2	-	-
Hazard ratio (95% CI) for progression – investigator assessment	0.399 (0.265 to 0.601, p<0.0001)		-	-
Median TTP, months – BICR[c]	25.7	14.8	-	-
Hazard ratio (95% CI) for progression – BICR[c]	0.621 (0.378 to 1.019, stratified log rank p=0.0286)		-	

[a]P<0.0938 indicated a statistically significant result
[b]P<0.025 indicated a statistically significant result
[c]BICR was conducted on 97% of the ITT population for PALOMA-1, and the entire ITT population for PALOMA-2
'-'=not reported, BICR=blinded independent review; CI=confidence interval; ITT=intention-to-treat; NE=not evaluable; PFS=progression-free survival; TTP=time to progression
Source: CS, adapted from Tables 22 to 24, CSR, Table 36 and EMA[68] Table 29 and Table 34

Progression-free survival and time to progression results (ITT populations)

Compared to treatment with LET (PALOMA-1 trial) and PLACEBO+LET (PALOMA-2 trial), treatment with PAL+LET was shown to statistically significantly improve median PFS by around 10 months. The company also provided the Kaplan-Meier (K-M) data, from both trials, for the analysis of investigator assessed PFS (CS, Figure 9 and Figure 12). In both instances, the K-M data for the two treatment arms diverge early (from approximately 2 months in the PALOMA-1 trial, and approximately 3 months in the PALOMA-2 trial), and the treatment benefit for patients treated with PAL+LET is sustained over time.

The ERG notes that investigator assessed median PFS for patients in the PALOMA-2 trial treated with PLACEBO+LET is numerically higher than the investigator assessed median PFS reported for patients in the LET arm of the PALOMA-1 trial. The ERG notes that median PFS is considerably longer in both arms of the PALOMA-1 trial when assessed by BICR rather than by the investigator; the difference between arms is not however statistically different for BICR assessed PFS. Median PFS is also considerably longer in both arms of the PALOMA-2 trial when assessed by BICR rather than by the investigator. The investigator assessed median PFS is within the range of median PFS reported for LET or PLACEBO+LET in previous trials of first-line endocrine therapy for treating MBC[42,46,64-67,101,102] but only the BICR assessed PFS in the PALOMA-1 trial falls within this range. It should be noted that not all trials necessarily include patients with similar characteristics, however. For example, four trials[42,46,65,102] have permitted the use of chemotherapy for treating MBC prior to first-line hormonal treatment for MBC (although in two trials,[42,65] was received by <10% of patients).

Consistent with this PFS benefit, the median TTP calculated from PALOMA-1 trial data is 20.2 months in the PAL+LET arm and 10.2 months in the LET arm (HR=0.399; 95% CI 0.265 to 0.601, p<0.0001). The BICR results are broadly consistent with these results.

The univariate and multivariate analyses of PFS in the PALOMA-2 trial were in accordance with the results from the primary analysis, demonstrating a statistically significant improvement in PFS for PAL+LET in comparison to LET, for both investigator assessed and BICR data. These results are provided in appendices to this ERG report (Section 10.3, Table 37). Pre-specified progression-free survival subgroup analyses

PFS subgroup analyses were performed for various pre-specified demographic and prognostic factors (see Section 4.3.4 of this report [Table 7] and the company provided the results from these analyses in Figure 1 of the company response to the ERG clarification letter (PALOMA-1 trial) and in Figure 14 of the CS (PALOMA-2 trial).

The results of all subgroup analyses demonstrate a statistically significant treatment benefit for patients treated with PAL+LET in comparison to patients treated with LET, with the following exceptions:

- PALOMA-1 trial: DFI ≤12 months subgroup (excluding patients with de novo disease) - a trend was demonstrated favouring PAL+LET, although statistical significance was not achieved
- [redacted].

The company postulates that the treatment effect estimate for patients in the PALOMA-1 trial with a DFI ≤12 months may not have reached statistical significance due to the small number of patients in this subgroup (n=15 in the PAL+LET arm, n=14 in the LET arm). The ERG agrees that the small sample size may be the reason for the non-significant effect estimate, and notes that the p-value for the test for subgroup differences between this subgroup (patients with a DFI ≤12 months) and the subgroup of patients with a DFI >12 months is non-significant. Therefore, there is no evidence to suggest that there is a statistically significant difference between these groups (patients with DFI ≤12 months and patients with a DFI<12 months).

Regarding the subgroup of [redacted], the treatment effect estimate favoured treatment with PAL+LET over treatment with PLACEBO+LET ([redacted]) but the study was not powered to detect significant differences in this subgroup. The ERG, therefore, considers that the fact that the treatment effect estimate for this subgroup did not achieve statistical significance should not be a cause for concern.

The company highlights that results from the PALOMA-1 and PALOMA-2 trials indicate similar PFS benefit for the intervention arm compared with the comparator arm for the subgroups of women older than 65 and those younger than 65. The company states that these results are of particular importance as treatment advances for breast cancer have traditionally benefited younger women more than older women. The ERG notes that in the PALOMA-1 trial, the subgroup analysis results do suggest a greater treatment benefit for younger (age<65) women than older (age≥65) women, but that treatment with PAL+LET statistically significantly improves PFS in comparison to treatment with LET for both groups of women, and the p-value for the test for subgroup differences was non-significant. Data from the PALOMA-2 trial show the treatment effect estimates for these two subgroups are extremely similar, suggesting that older women gain as much benefit as younger women from treatment with PAL+LET in comparison to treatment with PLACEBO+LET.

The ERG notes the EMA's conclusion that only findings from cohort 2 should be considered relevant to the efficacy assessment in the PALOMA-1 trial (see Section 4.4 of this ERG report). Therefore, the results of all subgroup analyses should be treated with caution.

Progression-free survival subgroup analyses requested by the ERG

The company argues that because regional data suggest that only 5% of women in the UK with breast cancer have de novo metastases, the PFS HR for the PALOMA-2 ITT population may conservatively reflect the efficacy of PAL+LET in the context of the UK population. This is because in the PALOMA-2 trial, for patients with de novo metastases, the PFS HR was slightly higher than the PFS HR for patients in the ITT population, i.e. in patients with de novo disease, the benefit was less pronounced. As evident from data requested by the ERG (Table 12), this is in contrast to the results of the PALOMA-1 trial as the PFS HR for patients with de novo disease was lower than the PFS HR in the ITT population.

The findings must however be treated with caution due to the small numbers of patients included in the analyses, particularly in the PALOMA-1 trial. Furthermore, the ERG again notes the EMA's conclusion that only findings from cohort 2 should be considered relevant to the efficacy assessment in the PALOMA-1 trial (see Section 4.4). These subgroup analyses include patients from both cohort 1 and cohort 2 of the PALOMA-1 trial.

Table 12 Progression-free survival in the subgroup analyses requested by the ERG for the PALOMA-1 and PALOMA-2 trials

Outcome	PALOMA-1		PALOMA-2	
	PAL+LET (n=84)	LET (n=81)	PAL+LET (n=444)	PLACEBO+LET (n=222)
ITT population				
Median PFS, months (95% CI)	20.2 (13.8 to 27.5)	10.2 (5.7 to 12.6)	24.8 (22.1 to NE)	14.5 (12.9 to 17.1)
Hazard ratio (95% CI)	0.488 (0.319 to 0.748)		0.576 (0.463 to 0.718)	
Patients with de novo disease				
Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio (95% CI)	0.341 (0.194 to 0.599)		0.674 (0.457 to 0.993)	
Patients who have received prior neo(adjuvant) therapy				
Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio (95% CI)	0.539 (0.302 to 0.962)		0.520 (0.399 to 0.680)	

CI=confidence interval; ITT=intention-to-treat population; NE=not estimable; PFS=progression-free survival
Source: Company response to ERG clarification letter, A3

Biomarker analyses

The company also provided the results of the biomarker analyses for the PALOMA-1 and PALOMA-2 trials in appendix 10 of the CS. Analyses were performed on the subset of as-treated patients for which baseline assessment of at least one biomarker was available These exploratory analyses did not indicate that there were any particular biomarkers that should guide the use of PAL+LET in clinical practice.

Other analyses of progression-free survival in the PALOMA-1 trial

As noted in Section 4.4 of this ERG report, the EMA have stated that only findings from cohort 2 should be considered relevant to the efficacy assessment of the PALOMA-1 trial.[68] The investigator assessed and BICR assessed PFS findings for the two cohorts are summarised in Table 13. It can be clearly seen form the results that there is a large discordance between investigator assessed PFS and BICR assessed in cohort 1, which is less pronounced in cohort 2. In part, the large difference may again be attributable to small sample size in cohort 1 (n=66).

Table 13 Progression-free survival by cohort in the PALOMA-1 trial

Outcome	Cohort 1		Cohort 2	
	PAL+LET (n=34)	LET (n=32)	PAL+LET (n=50)	LET (n=49)
Investigator assessed PFS				
Median PFS, months (95% CI)	26.1 (11.2 to NE)	5.7 (2.6 to 10.5)	18.1 (13.1 to 27.5)	11.1 (7.1 to 16.4)
Hazard ratio (95% CI)	0.299 (0.156 to 0.572)		0.508 (0.303 to 0.853)	
One-sided p-value	p=0.0001		p=0.0046	
BICR assessed PFS				
Median PFS, months (95% CI)	31.6 (11.2 to NE)	38.6 (7.5 to 38.6)	20.3 (12.2 to NE)	14.6 (8.1 to 20.0)
Hazard ratio (95% CI)	0.731 (0.300 to 1.779)		0.576 (0.316 to 1.050)	
One-sided p-value	p=0.2442		p=0.0342	

BICR= blinded independent central review; CI=confidence interval; ITT=intention-to-treat population; NE=not estimable; PFS=progression-free survival
Source: EMA European Public Assessment Report, adapted from Figure 17

The ERG notes that if only the findings from cohort 2 are considered from the PALOMA-1 trial, then the gain in investigator assessed median PFS is reduced from approximately 10 months to 7 months. The difference based on BICR assessed median PFS is reduced from nearly 11 months to 5.7 months.

The company also refers to an analysis of treatments given to patients in the PALOMA-1 trial after their disease progressed[103] to demonstrate how the use of PAL+LET may delay the onset of subsequent therapies in comparison to LET. The company states that delaying chemotherapy is psychologically beneficial to patients in many ways (see Section 2.1 of this ERG report). This analysis showed that the median time from randomisation to first subsequent treatment was longer in the PAL+LET arm than in the LET arm when the subsequent treatment was endocrine therapy (428 days versus 369 days) and when it was chemotherapy (280 days versus 119 days). Additionally, the first subsequent chemotherapy was administered earlier to patients who had received PAL+LET (57 days) than to patients who received LET (136 days).

ERG comment on progression-free survival findings

The ERG considers the PFS data from the PALOMA-1 trial (whether from the ITT population or from subgroup analyses) to be less robust than the PFS findings from the PALOMA-2 trial. This is because the PALOMA-1 trial appears to be at greater risk of bias for reasons highlighted in Section 4.4 of this ERG report and because of the large differences reported by the EMA[68] in terms of investigator assessed PFS and BICR assessed PFS in cohort 1 of the PALOMA-1 trial. In the PALOMA-2 trial, median PFS in both arms of the trial appears to be substantially higher according to BICR when compared with investigator assessed PFS. However, the HR for BICR assessed PFS is not too dissimilar to the HR observed with investigator assessed PFS. Furthermore, differences between arms are statistically significant for both investigator assessed PFS and BICR assessed PFS in the PALOMA-2 trial. In the PALOMA-1 trial, statistically significant differences were only observed with investigator assessed PFS.

4.6.3 Overall survival

PALOMA-1 trial

The median follow-up was 29.6 months in the PAL+LET arm and 27.9 months in the LET arm. The median OS in the PAL+LET arm was 37.5 months (95% CI 28.4 to not reached [NR]) and in the LET arm was 33.3 months (95% CI 26.4 to NR). The probability of survival was higher for patients receiving PAL+LET than for those receiving LET at 1 year (89.0% versus 87.0%), at 2 years (77.1% versus 70.2%), and at 3 years (53.0% versus 44.0%). The company also provided the K-M curves for the analysis of OS (CS, Figure 11). The observed HR for the comparison of PAL+LET and LET for OS was 0.813 (95% CI 0.492 to 1.345, p=0.2105). However, the ERG notes that the K-M curves cross, and therefore the assumption of PH, which is used to generate the HR, does not hold. The OS hazard ratio should, therefore, be interpreted with caution.

It is important to note that the OS data reported in the PALOMA-1 trial are immature; the analysis was performed on OS data taken from a cut-off date of 29 November 2013, based on only 61 deaths among 165 patients and so, at the time, the trial was not powered to detect significant differences between the two treatments. The company states that a further OS analysis will become available on an event-driven basis, however the company did not report whether any analyses have been conducted in the subsequent three years to the OS analysis presented in the CS.

PALOMA-2 trial

OS data were not available from the PALOMA-2 trial. In accordance with the TSAP, OS was to be tested for significance when interim and final PFS analyses were performed, provided

PFS was statistically significant at this time. The interim PFS analysis was conducted on data available on 01 May 2015; however, PFS had not reached statistical significance at this time and, therefore, an OS analysis was not conducted.

At the time of the final PFS analysis (26 February 2016), data showed that an insufficient number of deaths had occurred and so the final OS analysis could not be carried out (only [redacted] deaths from 666 patients had occurred, which equates to only [redacted] of the required 390 total deaths pre-specified for the final OS analysis). The External Data Monitoring Committee reviewed the results and did not propose early closure of the trial for efficacy or express any safety concerns. Since the company remains blinded to the results of the interim OS analysis, the K-M OS curves and censoring information, part of the interim OS analysis, are unavailable at this time.

Treatment received on disease progression in the PALOMA-1 trial

The company claims that due to the variety and frequency of post-progression therapies received by patients, which were not accounted for in the analyses, OS data from the PALOMA-1 trial do not represent the true comparative survival gain by patients treated with PAL+LET when compared to patients treated with LET. While the ERG agrees with the company that the health of individual patients deteriorates at different rates post-progression, and so all patients may not be best suited to the same post-progression therapies, the ERG does not agree that the PALOMA-1 trial was unable to capture true OS benefit. By definition, an RCT such as the PALOMA-1 trial consists of balanced treatment groups, with a variety of patients with different baseline characteristics and prognostic factors in each treatment arm. Furthermore, the ERG considers that the population included in the PALOMA-1 trial is reflective of the population seen in clinical practice (see Section 4.5). Therefore, although patients receive a variety of different treatments post-progression, these post-progression treatments will be reflective of clinical practice, and any benefit from treatment with PAL+LET in comparison to treatment with LET alone should be, therefore, reflected in the OS results.

The ERG notes that data reported in a poster presented at the 38th San Antonio Breast Cancer Symposium in December 2015[103] (summarised in appendices to this ERG report, Section 10.4) appear to show some imbalances by treatment arm in terms of treatments received post-progression. A greater proportion of patients in the PAL+LET arm received subsequent chemotherapy than in the LET arm (51.5% versus 39.6% respectively) whereas a smaller proportion received subsequent endocrine therapy (45.4% versus 60.4% respectively) or other therapy (18.2% versus 24.5% respectively). These results may reflect slight differences in ECOG PS by treatment arm recorded at the time of progression. Data presented by the company during the clarification process show that at the time of disease progression, [redacted] of

patients had an ECOG PS ≥2 in the PAL+LET arm compared with [redacted] of patients in the LET arm. However, the numbers of patients in both arms who received subsequent treatment were very small (n=33 and n=53 respectively) as was the number of patients for whom ECOG PS was available for ([redacted] and [redacted] respectively). The ERG notes that small differences in actual numbers can result in large differences in proportions and therefore suggests that the data from the PALOMA-1 trial must be treated with caution.

Treatment received on disease progression in the PALOMA-2 trial

During the clarification process the company provided data showing that [redacted] in both arms of the PALOMA-2 trial. In this trial a large number of patients received subsequent treatments ([redacted] in the PAL+LET arm and [redacted] in the PLACEBO+LET arm). The most common post-progression hormonal treatments received by patients in the PAL+LET and PLACEBO+LET arms respectively were [redacted] and the most common chemotherapies were [redacted]. ECOG PS at time of progression by arm was [redacted] in this trial than in the PALOMA-1 trial: [redacted].

ERG comment on overall survival findings

The ERG considers that the post-progression treatments received by patients in both trials are treatments that are routinely offered to patients with MBC in clinical practice. However, clinical opinion received by the ERG is that patients in England and Wales are more likely to receive anthracycline based treatments on disease progression, especially when patients do not receive an anthracycline treatment as a component of adjuvant treatment. Baseline characteristics reported for the PALOMA-1 and PALOMA-1 trials include details of prior chemotherapy, not prior anthracycline based chemotherapy.

4.6.4 Other secondary efficacy outcome results

The company reported a number of other secondary outcomes, including ORR, CBR and DOR. These are described and critiqued in appendices to this ERG report.

4.6.5 Safety

Safety data for patients in the PALOMA-1 and PALOMA-2 trials treated with PAL+LET are reported in the CS.

Overview of treatment emergent adverse events (including death)

The company's overview of treatment emergent AEs reported in the CS are summarised by the ERG in Table 14. All patients in the PAL+LET arm of the PALOMA-1 trial reported an AE and in the PALOMA-2 trial, nearly all patients reported an AE. AEs were also common in the LET and PLACEBO+LET arms of the trials. The company reported the proportion of serious AEs (SAEs) and Grade 3 to 4 AEs in each arm for the PALOMA-1 and PALOMA-2 trials. Compared with LET and PLACEBO+LET arms, SAEs and Grade 3 to 4 AEs were more common with PAL+LET. Deaths from AEs were relatively uncommon in both trials. [redacted]

Table 14 Treatment emergent adverse events in the PALOMA-1 and PALOMA-2 trials

Adverse events	PALOMA-1		PALOMA-2	
	PAL+LET (n=83)	LET (n=77)	PAL+LET (n=444)	PLACEBO+LET (n=222)
	%	%	%	%
Patients with any AE	100.0	84.4	98.9	95.5
Patients with SAEs	21.7	6.3	19.6	12.6
Patients with Grade 3 or 4 AEs	75.9†	20.8	77.5	25.2
Patients with Grade 5 AEs (deaths)	1.2	0.0	2.3	1.8

AE=adverse event; SAE=serious adverse event
Source: CS, Sections 4.12.1 and 4.12.2 and EMA,[68] adapted from Table 49

Types of treatment-emergent adverse events and serious events

Treatment-emergent AEs that occurred in the PALOMA-1 and PALOMA-2 trials are presented in the CS (Table 39 and Table 41 respectively) and summarised in the appendices to this ERG report (Section 10.6, Table 41). The most commonly experienced AEs with PAL+LET were haematological toxicities, particularly neutropenia (74.7%) and leukopenia (43.4%). In the PALOMA-2 trial, the proportions were 79.5% and 6.3%. In the PAL+LET arm of the PALOMA-1 trial, neutropenia was the most common Grade 3 to 4 AE (54.2%). In the PALOMA-2 trial, the most common Grade 3 to 4 AE with PAL+LET was also neutropenia (66.4%).

In the PALOMA-1 trial, [redacted] were the only SAEs reported [redacted]. In the LET arm, [redacted]. In the PALOMA-2 trial, the most commonly reported all-causality SAE in the PAL+LET arm was [redacted] and in the PLACEBO+LET

arm it was [redacted]. All other all-causality SAEs were reported [redacted] of the patients in either arm of the PALOMA-2 trial.

Overall, therefore, the main difference between the treatment arms in terms of types of AEs reported appears to relate to incidence of neutropenia (to a large extent) and leukopenia (to a lesser extent).

Managing neutropenia

The company highlights that none of the cases of neutropenia in either arm in the PALOMA-1 trial developed into febrile neutropenia and that all cases of neutropenia in this trial were asymptomatic. In the PALOMA-2 trial, it is reported in the CS that only seven of 444 patients (1.6%) in the PAL+LET arm developed febrile neutropenia compared with none of the patients in the PLACEBO+LET arm; the recently published paper[93] reports that eight of 444 patients (1.8%) in the PAL+LET arm developed febrile neutropenia compared with none of the patients in the PLACEBO+LET arm. Additionally, it is stated by the company that the results of a subgroup analysis from the PALOMA-1 trial (data not presented or referenced in the CS) indicate that neutropenia, especially of more severe grades, tended to occur less frequently with increasing treatment cycles. Overall, the company considers that palbociclib-associated neutropenia is relatively uncomplicated. The ERG concurs that the data appear to support this assertion.

Treatment discontinuation due to adverse events

As shown in Table 15, [redacted]

The company highlights that treatment duration was longer with PAL+LET than with LET/PLACEBO+LET (see Section 4.6.1 of this ERG report). Therefore the company argues that despite a high incidence of neutropenia reported in the PALOMA-1 and PALOMA-2 trials, dose interruptions and dose reductions enabled patients to remain on PAL+LET, helping to prolong PFS as a result.

Table 15 Treatment discontinuation associated with adverse events the PALOMA-1 and PALOMA-2 trials

Discontinuation type due to adverse events	PALOMA-1		PALOMA-2	
	PAL+LET (n=83)	Letrozole (n=77)	PAL+LET (n=444)	PLACEBO+ LET (n=222)
	%	%	%	%
Permanent discontinuation from trial	[redacted]	[redacted]	2.5	1.8
Permanent discontinuation of palbociclib/placebo	[redacted]	[redacted]	9.2	5.4
Permanent discontinuation of letrozole	[redacted]	[redacted]	6.1	5.0
Temporary discontinuation of palbociclib/placebo	[redacted]	[redacted]¥	74.8	15.8
Temporary discontinuation of letrozole	[redacted]	[redacted]	17.3	9.9
Dose reduction of palbociclib/placebo	[redacted]	[redacted]	36.0	1.4

¥ [redacted]

Source: CSR for the PALOMA-1 trial, adapted from Table 68 and EMA,[68] adapted from Table 49

Subgroup analysis of adverse events

The company states that the results of subgroup analysis by age (younger or older than 65 years) in the PALOMA-1 trial suggest similar rates of Grade 3 to 4 AEs and rates of dose reductions and discontinuations regardless of age. The company argues that these results (which are not presented in the CS but have been presented in a journal publication[85]) further support the ability of palbociclib to benefit both younger and older patients. The ERG concurs with the company.

ERG comment on adverse events

The ERG concurs with the company that the main difference in the safety profiles of the treatments (PAL+LET compared with LET or PLACEBO+LET) is largely the result of increased rates of neutropenia in the palbociclib treated patients. The ERG also concurs with the company that the majority of cases of neutropenia experienced in the two trials are reversible and manageable, resulting in relatively few permanent treatment discontinuations and that the safety profile of PAL+LET is therefore acceptable.

4.6.6 Health-related quality of life

As part of the PALOMA-1 trial, outcomes in relation to pain (pain severity and pain interference with daily activities) were assessed using the modified Brief Pain Inventory (BPI). As has been recognised in a publication reporting results from the PALOMA-1 trial: "The BPI is not an instrument that can measure quality of life broadly; as such, this study was not designed to provide an analysis of patients' general well-being, emotional and physical functioning, global quality of life, or utility associated with study treatment."[84] However, a broader HRQoL analysis was conducted in the PALOMA-2 trial using the using the Functional Assessment of Cancer Therapy-Breast (FACT-B)[104] and EuroQol-5D (EQ-5D)[105] questionnaires.

The PALOMA-1 trial

As noted in Section 4.3.1 (Table 4) of this ERG report, all analyses were performed on the PRO evaluable population i.e. all randomised patients who completed the baseline PRO assessment, received at least one dose of study treatment and completed at least one post-baseline PRO assessment: 76 patients in the PAL+LET arm and 74 patients in the LET arm. Assessments were carried out on day 1 of each treatment cycle and at withdrawal or at the end of treatment. An examination of findings presented at the 2014 San Antonio Breast Cancer Symposium[90] and published this year in a peer reviewed journal[84] show that:

- Baseline observed mean pain severity and pain interference scores were similar between the two treatment arms
- Patients in the PAL+LET arm generally showed a consistently greater numeric reduction from baseline in pain severity and pain interference until "later" cycles; the ERG observes that the data appear to be less consistent after cycle 23, when 27.6% and 14.9% of all PRO patients in the PAL+LET and LET arms respectively completed the BPI
- The difference between treatment arms in the mean change of pain severity score from baseline was statistically significant at some of the earlier cycles (cycles 5, 6, 7, 8, 10, 12; $p<0.05$; no adjustments were made for multiplicity) representing a numerically greater decrease in the pain experienced by patients in the PAL+LET arm compared with those in the LET arm
- There were no statistically significant differences between treatment arms for mean change of pain severity score from baseline in the later cycles
- There were no statistically significant differences in change from baseline for mean change of pain interference score from baseline
- There were no statistically significant differences between treatment arms in pain severity score or pain interference score
- Whilst the change-from-baseline analyses were pre-specified, the between arm (mixed model) comparisons in the PALOMA-1 trial were post-hoc analyses
- A limitation of the study is that results were not adjusted for the concomitant use of opioids or other medications used to control pain.

The PALOMA-2 trial

All analyses were performed on the PRO evaluable population: [redacted] patients in the PAL+LET arm and [redacted] patents in the PLACEBO+LET arm. All possible outcomes that can be derived from the FACT-B and EQ-5D questionnaires were pre-specified outcomes in the PALOMA-2 trial. A large number of analyses were conducted. The key findings are as follows:

[redacted]

[redacted]

Health-related quality of life subgroup analyses

Results from a post-hoc subgroup analysis of patients, with and without bone disease baseline, participating in the PALOMA-1 trial are included in the CS. In addition, results from a post-hoc subgroup analysis of patients who were de novo or had disease recurrence >12 months from the end of adjuvant treatment in the PALOMA-1 trial have also been presented.[90] As with the HRQoL analyses for all trial patients, findings between arms in the PALOMA-1 trial were reported to be similar for all measures of pain reported.

The company also assessed the impact of neutropenia on HRQoL for patients in the PALOMA-2 trial in which patients in the PAL+LET arm were classified by neutropenia status. [redacted].

ERG comment on health-related quality of life

Common to trials that report HRQoL outcomes, patients in the PALOMA-1 and PALOMA-2 trials were only asked to complete questionnaires up until the time of disease progression. The number of patients eligible to complete questionnaires decreases with each cycle and the high HRQoL response rates reported by the company in the CS only apply to the number of eligible patients in any given cycle. For example, in the PALOMA-1 trial, it can be observed from the published data[84] that by cycle 16 and cycle 9 of the PAL+LET and LET arms respectively, only 50% of all originally eligible patients completed a questionnaire. The number of eligible patients had fallen to 25% by cycle 25 and cycle 18 in the PAL+LET and LET arms respectively. Thus, in later cycles, the numbers of patients responding are very small and the data are only reflective of the experience of relatively healthy patients. Nonetheless, the data from the earlier cycles in both trials do appear to show there is no difference in HRQoL between treatment arms for patients in either the PALOMA-1 trial or the PALOMA-2 trial.

4.7 Conclusions of the clinical effectiveness section

The primary sources of clinical evidence for this appraisal are the phase I/II PALOMA-1 trial and phase III PALOMA-2 trial. Evidence is presented for PAL+LET versus LET and PLACEBO+LET respectively. The EMA considers that it is reasonable to generalise the clinical effectiveness results associated with LET to other aromatase inhibitors; the ERG concurs with this viewpoint.

All patients in both trials had ABC (and [redacted] had MBC) that had been previously untreated in the metastatic setting. Patients in the trials did not have immediately life-threatening disease and so, if these patients were to be treated currently in clinical practice, they would most likely be given an aromatase inhibitor, as per the treatment of patients in the control arm of both trials. Despite a higher proportion of patients in the PALOMA-1 and PALOMA-2 trials presenting with de novo disease than would be seen in clinical practice (49.1% and 37.2% respectively compared with 5% seen in clinical practice in England and Wales[58,63]), the ERG is generally satisfied that the evidence derived from both trials is generalisable to the patient population in England and Wales described in the scope issued by NICE.

Both trials were international multi-centre RCTs. The PALOMA-2 trial was considered by the ERG to be of superior quality and lower risk of bias than the PALOMA-1 trial as this trial was designed as a double-blind trial (whereas the PALOMA-1 trial was designed as an open-label trial). The PALOMA-2 trial was also much larger than the PALOMA-1 trial and the findings from the PALOMA-2 trial therefore appear to be more robust than those from the PALOMA-1 trial.

Compared with LET or PLACEBO+LET, both trials demonstrated a large improvement in median PFS. The improvement in PFS was generally consistent across subgroups analysed by the company for the PALOMA-1 trial and was generally consistent across subgroups analysed for the PALOMA-2 trial. This included patients presenting with de novo disease and those who had received prior neo(adjuvant) therapy, although the magnitude of the effects differed by subgroups (albeit based on very few numbers of patients, particularly in the de novo subgroup of the PALOMA-1 trial). However, the improvements in PFS did not translate into a statistically significant improvement in median OS for patients in the PALOMA-1 trial and an estimate of median OS is not yet available for patients in the PALOMA-2 trial. It is not clear why there was no gain in OS in the PALOMA-1 trial given there was such a large gain in PFS although it should be noted, the OS data were are immature (37% of deaths) and are from a data cut-off date of 29 November 2013. A possible reason may be attributed to the quality of the PFS data in the PALOMA-1 trial. Investigator assessed PFS findings reported for cohort 1 of the PALOMA-1 trial differed markedly to BICR assessed PFS. This has led the EMA to conclude that only findings from cohort 2 should be considered relevant to the efficacy assessment.

Across the two trials, differences between the treatment arms in terms of safety were mostly attributable to a much higher rate of haematological toxicities, particularly neutropenia in patients treated with PAL+LET. While this included high rates of Grade 3 to 4 neutropenia, for the most part, neutropenia was asymptomatic and reversible with febrile neutropenia being reported by <2% of patients (all incidence occurring in the PALOMA-2 trial). The data suggest

neutropenia rarely results in permanent discontinuation of treatment with PAL+LET. Therefore the safety profile of PAL+LET is considered by the company and ERG to be acceptable. Importantly, compared with LET or PLACEBO+LET, patients remained progression-free for longer and were therefore treated with PAL+LET for longer; despite patients having an increased risk of neutropenia, there were no differences in patients' HRQoL estimates between the trial arms.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by the company in support of using PAL+LET to treat postmenopausal patients with locally advanced or metastatic, ER+/HER2- breast cancer that has been previously untreated in a metastatic setting. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has also provided an electronic version of their economic model, which was developed in Microsoft Excel.

5.2 ERG comment on the company's review of cost effectiveness evidence

5.2.1 Objective of cost effectiveness review

The objective of the company's literature search was to identify published estimates of the cost effectiveness of palbociclib to treat postmenopausal women with ER+/HER2- locally advanced or MBC who had received no prior systemic anti-cancer treatment for advanced disease.

Company searches

The company searched MEDLINE, MEDLINE In-Process, Embase, The Cochrane Library (The Health Technology Assessment [HTA] Database and the NHS Economic Evaluation Database only) and EconLit in January 2016. These searches were supplemented, in March 2016, by searches of conference proceedings from the 2014 and 2015 European Breast Cancer Conference, ESMO congress, International Health Economics Association (iHEA) conference and International Society for Pharmacoeconomics and Outcomes Research annual European and International meetings. In addition, in March 2016, the NICE and Scottish Medicines Consortium websites were searched for any relevant HTA submissions. The search strategies employed by the company are provided in Appendix 14 of the CS.

5.2.2 Eligibility criteria used in study selection

The inclusion/exclusion criteria used by the company to facilitate study selection are provided in the CS and reproduced in Table 16.

Table 16 Eligibility criteria for the cost effectiveness systematic review

Domain	Inclusion	Exclusion	Rationale
Population	First-line population: postmenopausal women with ER+, HER2- locally advanced or metastatic breast cancer who have not received any prior systemic anticancer treatment for advanced disease	Population not relevant, or outcomes not reported separately for the population of interest	This is the patient population relevant to the NICE decision problem for this submission
Intervention	Palbociclib	Studies not evaluating palbociclib	This is the intervention specified in the NICE decision problem for this submission
Comparator	Any pharmacological intervention	Non-pharmacological comparators	This encompasses all relevant comparators specified in the NICE decision problem for this submission
Outcomes	The outcomes of relevant study designs, including: costs life years QALYs incremental costs and QALYs ICERs	Studies presenting irrelevant outcomes only	These outcomes encompass the economic outcomes specified as relevant in the NICE decision problem for this submission
Study design	Economic evaluations, specifically one of the following analysis types: cost effectiveness cost utility cost benefit cost minimisation cost consequence	Any other study design	The study designs and publication types specified as eligible for inclusion were those considered most likely to report relevant data for this systematic review
Publication type	Economic evaluations and HTAs	Any other publication type, including non-systematic reviews, editorials and case reports	
	Systematic reviews of economic evaluations were included at the title/abstract screening stage and used for identification of any additional primary studies not identified through the database searches, but were excluded during the full-text review stage.		
Language	English	Any other language	The review team did not have the linguistic capability to review non-English language articles; however, studies were not limited to those conducted in specific geographical locations

ER=oestrogen receptor; HER2=human epidermal growth factor receptor 2; NICE=National Institute for Health and Care Excellence; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio; HTA=health technology assessment
Source: CS, Table 47

5.2.3 Included and excluded studies

Ten papers were identified from the company's literature searches; however, none of these met the review inclusion criteria. Nine of the studies were excluded at title and abstract stage; eight were ineligible due to the publication type or study design, and the remaining study was not conducted in the relevant population. The only paper[106] that was screened at full text level was excluded from the review, as the authors did not report economic outcomes.

5.2.4 Findings from cost effectiveness review

No cost effectiveness studies designed to support the use of palbociclib to treat postmenopausal women with ER+/HER2- locally advanced or MBC who had not received any prior systemic anti-cancer treatment for advanced disease were identified during the review process.

5.3 ERG critique of the company's literature review

Full details of the strategies used to locate cost effectiveness evidence were reported in Section 5.1 and Appendix 14 of the CS. The economic searches were conducted in January 2016. This search included population terms but did not include any indication terms; the ERG considers this approach to be appropriate. The search also included an economics filter. The ERG considers that the detail provided by the company, in relation to the literature reviews that were carried out to identify and assess published cost effectiveness evidence (including information on HRQoL, costs and resource use), was very useful.

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

The economic evaluation undertaken by the company is designed to compare the costs and benefits (in terms of QALYs) of treatment with PAL+LET versus LET in postmenopausal women with ER+/HER2- locally advanced or MBC. Data from the PALOMA-1 trial have been to estimate survival for patients receiving first-line treatment whilst data from the PALOMA-2 trial have been used to model post-progression survival. Data from the PALOMA-2 trial have also been used to estimate the incidence of AEs and, in conjunction with published figures, HRQoL. Published sources and expert advice have been used to estimate the value of model resource use and cost parameters.

In addition to base case results, the company has also presented results from one-way deterministic, probabilistic and scenario analyses.

5.4.1 Model structure

The company de novo model is a partitioned survival model that comprises three health states; pre-progressed (stable) disease, progression (which is sub-divided into four different states: first, second, and third subsequent lines of treatment and best supportive care [BSC]) and dead. All patients enter the model in the pre-progressed health state and are treated with either PAL+LET or LET. In each cycle patients can either remain in their current health state or, if their disease progresses, move to a worse health state (i.e. a further line of treatment or BSC) or to the death state (see Figure 1). Within the model it is assumed that each post-progression treatment sequence/line lasts for up to six cycles. After completing up to four lines of treatment, it is assumed that patients receive BSC up to the point of death.

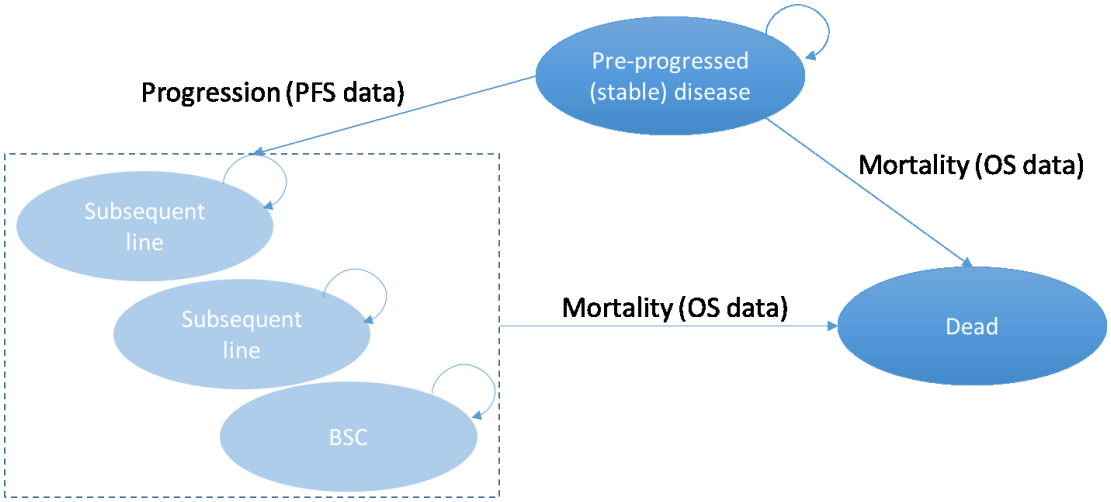

Figure 1 Model schematic

Source: CS, Figure 18

The model cycle length is 28 days (13 cycles per year, 364 days) and, due to the short length of the treatment cycle, a half-cycle correction was not implemented.

The company model structure is similar to that of other models that have been submitted to NICE as part of an STA process that have considered new treatments for advanced or metastatic cancers.[107]

5.4.2 Population

The population reflected in the company model is postmenopausal women with ER+/HER2- ABC who have never received systemic therapy in the LABC/MBC setting (i.e. those receiving first-line treatment).

5.4.3 Interventions and comparators

Intervention

PAL is supplied as a tablet and is used to treat patients in the model in line with its expected EMA marketing authorisation (i.e. 125 mg daily for 21 consecutive days with the subsequent 7 days off treatment until disease progression).

Comparators

It is stated within the final scope issued by NICE that the comparators for this appraisal are aromatase inhibitors; however, LET is the only aromatase inhibitor included as a comparator in the cost effectiveness analysis. The company suggests that, as LET is the most commonly used aromatase inhibitor in the NHS, and as the effectiveness of the other aromatase inhibitors are not significantly different from that of LET, modelling only one of the comparator options detailed in the final scope issued by NICE is justified.

LET is supplied as a tablet and is used to treat patients in the model in line with its EMA marketing authorisation, which reflects the dosage used in UK clinical practice (i.e. 2.5 mg daily, without a break until progression).

Subsequent lines of treatment

Doses of subsequent lines of treatment are not included in the company model. Only the monitoring costs of subsequent lines of therapy are included in the model.

5.4.4 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and PSS (Personal Social Services) and the model time horizon is 40 years. The company states both costs and benefits are discounted at a rate of 3.5% per annum.

5.4.5 Treatment effectiveness and extrapolation

Extrapolation method

To model effectiveness over a lifetime horizon, the company extrapolated survival data from the PALOMA-1 and PALOMA-2 trials. Regression modelling was used to fit parametric curves to K-M data. Six different models were considered: exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma. Model selection was based on standard statistical criteria (Akaike and Bayesian information criteria [AIC and BIC respectively]) and clinical plausibility (assessed through consultation with clinical experts and comparison with previously published curves).

Progression-free survival

Data from the PALOMA-2 trial were used as the basis for identifying a statistical model to represent pre-progression survival. In the base case, separate Weibull models were fitted to the PAL+LET and LET arms. Alternative models were explored in sensitivity analyses.

Overall survival

Overall survival data from the PALOMA-2 trial were unavailable and therefore the company based their survival estimates on data from a mix of data from the PALOMA-1 and PALOMA-2 trials. To estimate OS for patients treated with PAL+LET, the company fitted a Weibull distribution to the K-M OS data from the intervention arm of the PALOMA-1 trial.

Results from the PALOMA-2 trial demonstrate a median PFS difference of 10.3 months between the two arms of the trial. However, examination of the Weibull distributions used to model PFS (which were based on data from the PALOMA-2 trial) indicated that the difference in median PFS between PAL+LET and PLACEBO+LET was 9.2 months.

The company model representation of OS for patients receiving LET was then derived by scaling the Weibull distribution used to represent the OS of patients receiving PAL+LET (based on data from PALOMA-1) in such a way as to preserve the 9.2 month median PFS survival gain observed in the PALOMA-2 trial (Figure 2) from PAL+LET.

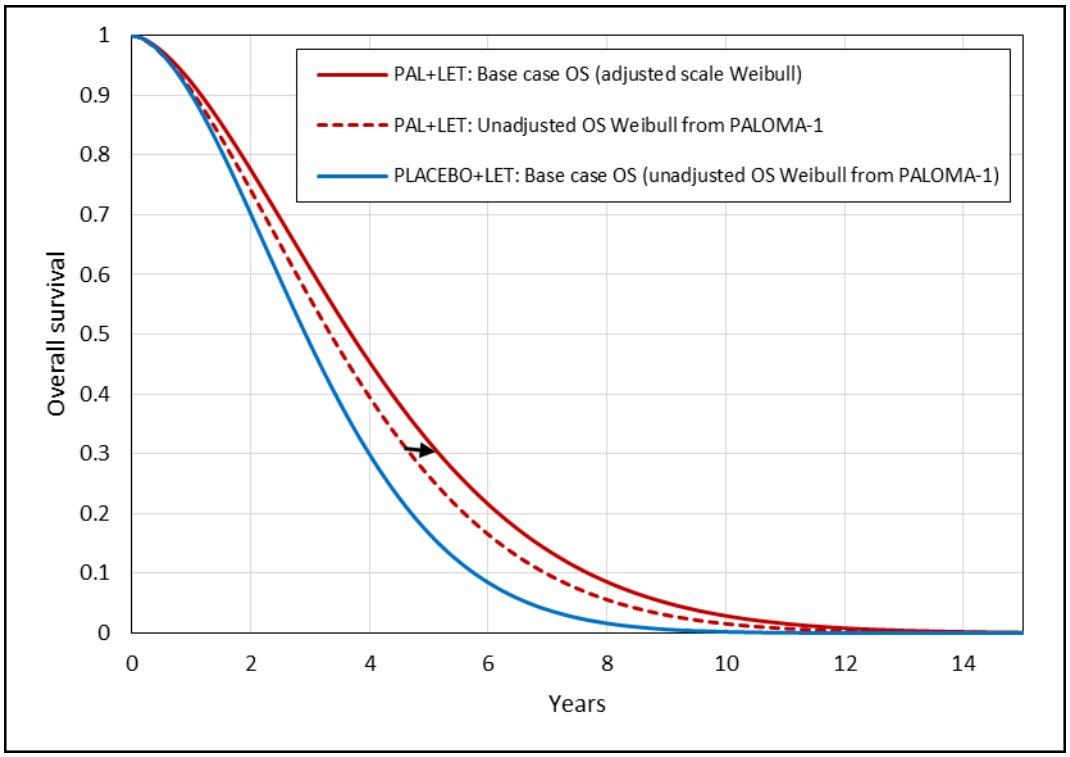

Figure 2 Company overall survival models using PALOMA-1 trial data: base case adjusted Weibull model (PAL+LET) and unadjusted Weibull model (PAL+LET and LET)

LET=letrozole; PAL+LET=palbociclib+letrozole; OS=overall survival
Source: Company model

Efficacy of subsequent treatments

The OS distributions implemented in the company model are based on K-M data from the PALOMA-2 trial. These data incorporate the influence of subsequent treatments and, therefore, no additional modelling was required to represent the effect of subsequent treatments on survival.

5.4.6 Adverse events

The company states that all Grade 3 and Grade 4 AEs observed during the course of the PALOMA-2 trial that have a measurable impact on costs and QALYs are included within their model. The probability of an AE occurring was calculated based on incidence and median exposure to first-line treatments. No account was taken of any AEs experienced as a result of receiving any subsequent therapy, as the inclusion of such AEs would have had a comparable impact on both treatment arms (as the length of time exposed to these treatments was the same for patients in both PALOMA-2 trial arms). Figures relating to the probability of a Grade 3 or a Grade 4 AE occurring in the model are presented in Table 17.

Table 17 Adverse event probabilities used in the company model

	PAL+LET	LET
Probabilities used in the model		
Any Grade 3 AE	44.38%	19.44%
Any Grade 4 AE	8.39%	1.95%

AE=adverse event; LET=letrozole; PAL=palbociclib
Source: CS, Table 60

5.4.7 Health-related quality of life

During the PALOMA-2 trial, HRQoL data were collected using the EuroQol five-dimensions (EQ-5D), three-levels questionnaire. A summary of the utility values used in the company model is presented in Table 18.

Pre-progression utility values

No statistically significant differences in baseline or on treatment EQ-5D index scores were estimated when the company compared results from the PAL+LET and the PLACEBO+LET arms of the PALOMA-2 trial. However, the company used the individual treatment baseline utility values to represent HRQoL for the duration of the pre-progression state ([redacted] for patients receiving PAL+LET and [redacted] for patients receiving LET). The company considers that treatment with palbociclib delivers benefits to HRQoL that may not be captured by the EQ-5D questionnaire (see CS Section 3.2.1 and Appendix 11.8 of this report).

The utility values derived from the data collected during the PALOMA-2 trial include decrements to HRQoL that may be caused by AEs; therefore, in the company base case, no

disutilty adjustments have been applied (as to do so would be considered double counting). However, disutility adjustments (based on data reported in the Lloyd et al (2006)[5] paper) are applied in a scenario analysis.

The company undertook a systematic literature review to identify alternative estimates of utility values that might be used to represent the HRQoL of patients in the pre-progression and post-progression health states. No appropriate alternative utility values were identified.

Post-progression utility value

In the base case, the company assumed that utility values for all subsequent post-progression states (three lines of treatment and BSC) are assumed to be equal. The company considers this assumption to be conservative as, in the PALOMA-2 trial, patients treated with PAL+LET had a utility at baseline that was higher than that of patients treated with LET. The utility value applied throughout all post-progression health states has been calculated using the Lloyd (2006)[5] disease progression decrement. This decrement has been applied to the average baseline utility value which was calculated from data that were collected from patients in both arms of the PALOMA-2 trial.

Table 18 Summary of utility values for cost effectiveness analysis

Health state	PAL+LET		LET		Source
	Mean	95% CI	Mean	95% CI	
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]	PALOMA-2 EQ-5D data on file
Post-progression (all lines)	0.4492	-	0.4492	-	PALOMA-2 EQ-5D data on file adjusted using Lloyd 2006[5] disease progression multiplier

CI=confidence interval, EQ-5D=EuroQol-five dimensions questionnaire; LET=letrozole; PAL=palbociclib
Source: CS, Table 62

5.4.8 Resources and costs

The company carried out literature searches to identify published papers that reported UK NHS costs, PSS costs and resource use of relevance to a model designed to explore the cost effectiveness of PAL+LET. Only one relevant study[108] was identified. This study[108] was carried out at a single centre in Wales.[108] Details relating to this study are provided in the CS (Table 64).

Drug acquisition costs

The drug acquisition costs (for first-line treatments) used in the company model are detailed in Table 19. Costs associated with subsequent lines of therapy were not included in the model.

Table 19 Drug acquisition costs

Technology	Licensed dose	Package information	Cost per package	Source
PAL	125 mg daily used in model (100 mg and 75mg also available)	125 mg tablets, 21 tablets in pack	Proposed list price: £2,950	Unpublished. Note, the same price for all mg
LET	2.5 mg daily	2.5 mg tablets, 28 tablets in pack	£1.52 (SD: £1.47)	eMIT 2016[109]

LET=letrozole; mg=milligram; PAL=palbociclib; SD=standard deviation
Source = CS Table 65

Drug wastage

Both PAL and LET are available in cycle packs (21 days and 28 days respectively). Once a pack has been opened, another patient cannot use the same pack. Drugs are costed on the basis that each patient in the pre-progressed health state is issued with a pack of PAL and/or LET on the first day of each cycle and, therefore, if the patient ceases treatment at any point before the end of that cycle any unused treatment is wasted.

Monitoring and administration costs

As both PAL and LET are provided in tablet form, the company assumed that there are no costs associated with drug administration.

The company assumed that patients who are treated with PAL require a monthly blood test; the company assumes that monthly monitoring of patients treated with LET is not required. The resource use and monitoring cost associated with monthly blood tests are detailed in Table 20.

Table 20 Resource use and costs for patients receiving LET

Resource use		Source
Assumption	1 full blood count every month	Draft SPC (CS, Appendix 1)
Cost	£3.01	DAPS05 (Haematology outpatient appointment) NHS Reference Costs 2014/15[110]

SPC=summary of product characteristics
Source: CS, Table 66 and Table 67

Health state resource use and unit costs

In the model, the company has assumed that the level of resource depends on the patient's health state and their treatment. The estimates of resource use are based on levels reported in the NICE Clinical Guideline for Advanced Breast Cancer (2009),[31] with adjustments made on the advice of Clinical Nurse Specialists (CNSs) to reflect current NHS practice, and any differences to resource use associated with receipt of different lines of treatment.

In the base case 75% of patients are assumed to receive subsequent treatment on disease progression and that, after each line of subsequent treatment, 75% of patients go on to receive another line of subsequent treatment. The remaining patients move directly to BSC, where they remain until death. To estimate resource use for patients receiving subsequent lines of

treatment, the duration of time spent in each subsequent line of treatment was assumed to be six cycles. This assumption is based on clinical expert opinion that, either by choice or for health reasons, not all surviving patients continue to receive active treatment. Background health state costs are provided in Table 21.

Table 21 Background health state unit costs

Resource use	Unit cost	Source
Community nurse visit	£55.50	PSSRU 2015[111]
Community nurse travel time	£27.75	Assumption
Consultant visit (oncologist) – first visit	£177.83	NHS Reference Costs 2014/15[110]
Consultant visit (oncologist) – follow-up visit	£131.97	NHS Reference Costs 2014/15[110]
GP contact (surgery visit)	£38.50	PSSRU 2015[111]
GP contact (home visit)	£198.00	PSSRU 2015[111]
Clinical nurse specialist	£86.00	PSSRU 2015[111]
Social worker visit	£67.00	PSSRU 2015[111]
Social worker travel time	£33.50	Assumption
Palliative care	£55.50	Assumption
CT scan	£121.68	NHS Reference Costs 2014/15[110]
Therapist (community occupational therapist and hospital occupational therapist)	£39.00	PSSRU 2015[111]
Physiotherapist (hospital occupational therapist)	£36.00	PSSRU 2015[111]
Lymphoedema nurse	£55.50	Assumption

CT= computerised tomography scan; GP=general practitioner; PSSRU=personal social services research unit
Source: CS, Table 69

The company assumed that resource use during the final 2 weeks of life (terminal care) is the same for all patients but differs depending on whether this period is spent in hospital, in a hospice or at home. The proportion of patients assumed to reside in hospital, hospice and at home, along with the unit costs associated with spending 2 weeks in any of these settings, are shown in Table 22.

Table 22 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 CG 81 Package 3[31]	£5,521.73	NICE CG 81 Package 3[31] unit costs, inflated from 2006/07 to 2014/15 values
Hospice	10%		£6,883.98	
Home	50%		£2,848.87	

CG=clinical guideline; NICE=National Institute for Health and Care Excellence
Source: CS, Table 70

Adverse events

Within the company model, patients who have multiple AEs occurring simultaneously within a single cycle only incur one cost (and one disutility value.

Neutropenia was the most common Grade 3 and Grade 4 event experienced by patients in the PALOMA-2 trial and the estimated resource use required to treat this AE is used within the company model to represent the resource use required to treat all Grade 3 and Grade 4 AEs. The cost is implemented at the start of each cycle and is assumed to last no more than than one cycle. The resource use assumptions and unit costs used in the company model are detailed in Table 23.

Table 23 Resource use assumptions and unit costs for grade 3 or 4 adverse events

Neutropenia	Resource use assumption	Unit cost	Note about unit cost	Source
Grade 3	1 oncologist visit per event (20 min visit) for patient management and dose modification	£43.99	WF01A service code 800 Clinical Oncology (Previously Radiotherapy) Non-Admitted Face to Face Attendance, Follow-up	NHS Reference Costs 2014/15[110]
Grade 4	1 oncologist visit per event (30 min visit) for patient management and dose modification	£65.99		

Source: CS, Table 71

5.4.9 Cost effectiveness results

Estimates, generated by the company model, for total costs, life years gained (LYG), QALYs and incremental cost effectiveness ratios (ICERs) per QALY gained for the comparison of the cost effectiveness of treatment with PAL+LET versus LET are shown in Table 24. In the base case, treatment with PAL+LET generates more benefits than treatment with LET (+0.78) and +0.63 QALYs) but at an increased cost of £94,853. The company base case ICER for the comparison of treatment with PAL+LET versus LET is £150,869 per QALY gained.

Table 24 Base case deterministic results for PAL+LET vs LET

Technologies	Total costs	Total LYG	Total QALYs	Incremental			ICER per QALY gained
				Costs	LYG	QALYs	
LET	£21,843	3.02	1.77				
PAL+LET	£116,696	3.79	2.40	£94,853	0.78	0.63	£150,869

LET=letrozole; LYG=life years gained; PAL=palbociclib; QALYs=quality adjusted life years
Source: CS, Table 74

A summary of the predicted resource use for each of the cost categories is presented in Table 25. Over 97% of the difference in costs between the intervention and comparator technologies is due to the difference in the costs of the first-line therapies.

Table 25 Summary of predicted resource use by category of cost

Item	Cost		Increment	Absolute increment	% absolute increment
	PAL+LET	PAL			
Drug acquisition costs	£92,101.27	£31.68	£92,069.59	£92,069.59	97.07%
Within cycle wastage costs	£0.00	£0.00	£0.00	£0.00	0.00%
Drug administration costs	£0.00	£0.00	£0.00	£0.00	0.00%
Drug monitoring costs	£93.79	£0.00	£93.79	£93.79	0.10%
AE costs	£782.02	£205.10	£576.92	£576.92	0.61%
Pre-progression health state costs	£5,290.91	£3,533.90	£1,757.01	£1,757.01	1.85%
Second-line treatment background health state costs	£495.84	£626.26	-£130.42	£130.42	0.14%
Third-line treatment background health state costs	£791.83	£982.17	-£190.35	£190.35	0.20%
Fourth-line treatment background health state costs	£1,016.85	£1,223.99	-£207.14	£207.14	0.22%
BSC	£12,365.25	£11,366.38	£998.86	£998.86	1.05%
Terminal care	£3,758.38	£3,873.67	-£115.29	£115.29	0.12%
Total	£116,696.13	£21,843.16	£94,852.97	£94,852.97	**100.00%**

AE=adverse events; BSC=best supportive care; LET=letrozole; PAL=palbociclib
Source: CS, Table 79

5.4.10 Sensitivity analyses

Deterministic sensitivity analysis

The company carried out one-way sensitivity analyses to explore the sensitivity of model results to variations in the magnitude of 12 model inputs. Results are presented in the CS as a tornado diagram, which is reproduced in Figure 3. The results show that varying the OS and PFS parametric model coefficients has the biggest effect on the company's cost effectiveness results.

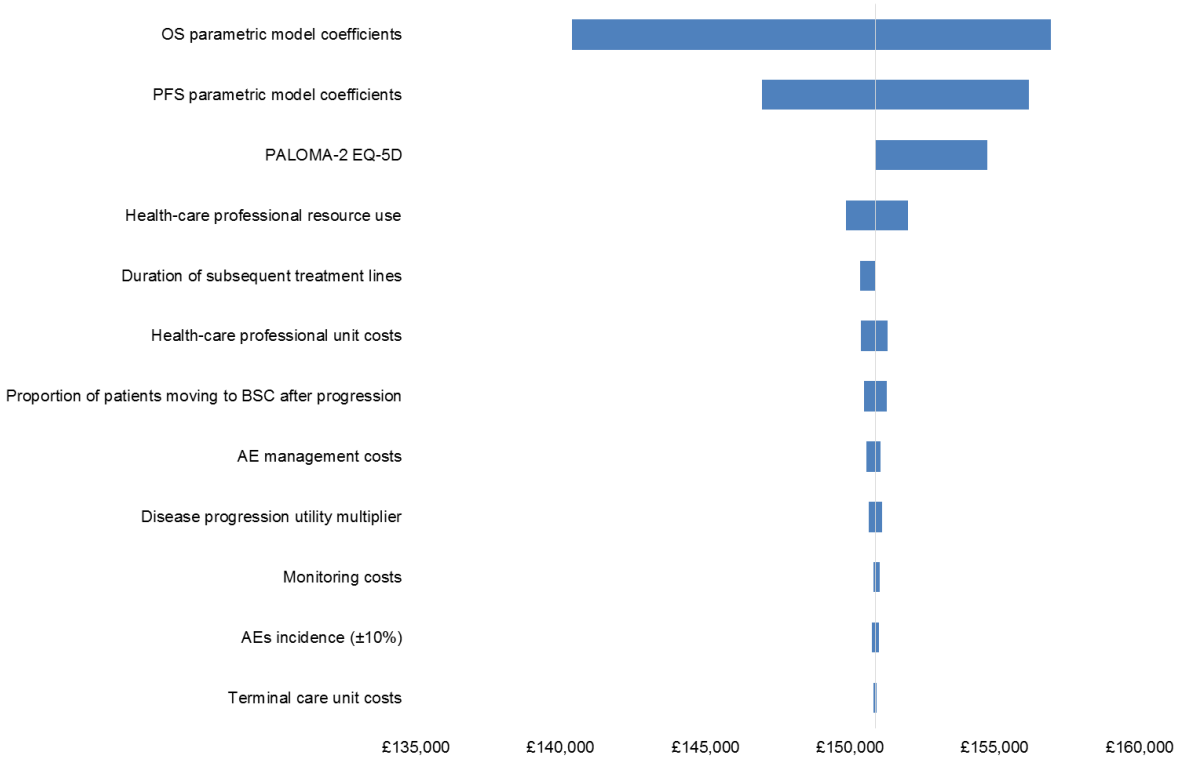

Figure 3 Tornado diagram of one-way sensitivity analyses (PAL at list price)
AE=adverse event; BSC=best supportive care; OS=overall survival; PAL=palbociclib; PFS=progression-free survival
Source: CS, Figure 28

In addition, the company carried out a further 10 one-way sensitivity analyses to explore the effect on model results of varying model assumptions. Results displayed in Table 26 show that, apart from the scenario in which a 5-year time horizon was implemented (which the company states is too short to fully capture all of the relevant costs and benefits in this patient population) amendments to OS and PFS assumptions have the largest influence on the resultant ICERs per QALY gained.

Table 26 List of sensitivity analyses varying model assumptions (PAL at list price)

Scenario	Parameter varied	Incremental costs	Incremental QALYs	Deterministic ICER
13	Use the Beauchemin linear regression method	£100,711	0.86	£116,806
14	Use unadjusted OS from PALOMA-1-Weibull for both arms	£91,384	0.49	£187,881
15	Use unadjusted OS from PALOMA-1 - Log-logistic for both arms	£95,112	0.63	£150,273
16	PFS parametric models - Gompertz for both arms	£84,696	0.44	£193,312
17	AEs: include AE disutility values	£94,853	0.57	£166,954
18	Model horizon: 5 years	£84,718	0.42	£199,943
19	Model horizon: 10 years	£94,201	0.61	£153,485
20	Model horizon: 15 years	£94,834	0.63	£150,934
21	Exclude discounting costs and benefits	£102,608	0.73	£140,954
22	Baseline utility (pre-progressed state): assume same value	£94,853	0.57	£166,802
23	Disease progression multiplier: use Nafees[112] value	£94,853	0.63	£150,334
24	Assume gradual utility decrease with every line of progression	£94,853	0.62	£152,781
25	Assume no post-progression sequential modelling: direct move to BSC	£94,121	0.63	£149,704
26	Use the health state costs from the NICE TA295 submission[113]	£94,522	0.63	£150,342

AE=adverse event; BSC=best supportive care; CI=confidence interval; ICER=incremental cost effectiveness ratio; OS=overall survival; PAL=palbociclib; PFS=progression-free survival; QALY=quality adjusted life year
Source: CS, Table 84

Probabilistic sensitivity analysis

The company undertook a probabilistic sensitivity analysis (PSA) to derive the mean ICER per QALY gained for the comparison of PAL+LET versus LET. The PSA was run for 1000 iterations. Results from the deterministic analysis and the PSA are shown in Table 27. The probabilistic ICER per QALY gained for PAL+LET versus LET is £151,058, which is very similar to the deterministic ICER per QALY gained (£150,869).

Table 27 PSA results for PAL+LET versus LET (PAL at list price)

	Incremental costs	Incremental QALYs	ICER per QALY gained
Deterministic result	£94,853	0.63	£150,869
Average value from PSA	£94,951	0.63	£151,058

ICER=incremental cost effectiveness ratio; LET=letrozole; PAL=palbociclib; QALY=quality adjusted life year; PSA=probabilistic sensitivity analysis
Source: CS, Table 80

The results from the PSA are presented as a scatter plot (cost effectiveness plane) in Figure 4. An examination of this figure shows that, at a cost effectiveness threshold of £30,000 per QALY gained, PAL+LET has a 0% probability of being cost effective compared with LET. The

cost effectiveness acceptability curve (CEAC) is shown in Figure 5. It is not until beyond a threshold of £100k per QALY that PAL+LET has any probability of being cost effective compared to LET.

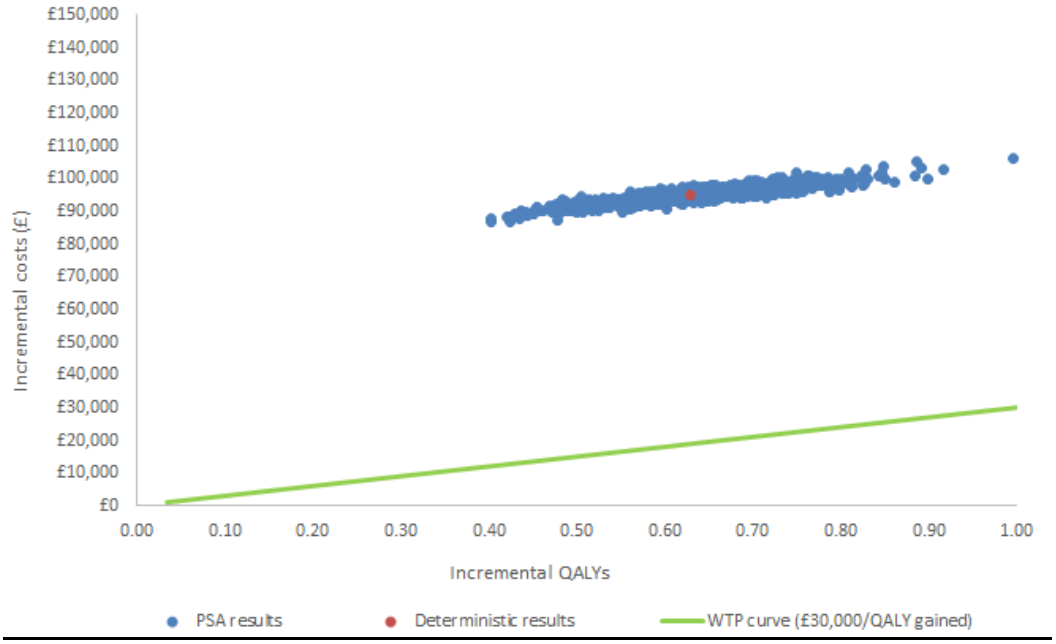

Figure 4 Cost effectiveness plane for the comparison of PAL+LET vs LET (PAL at list price)

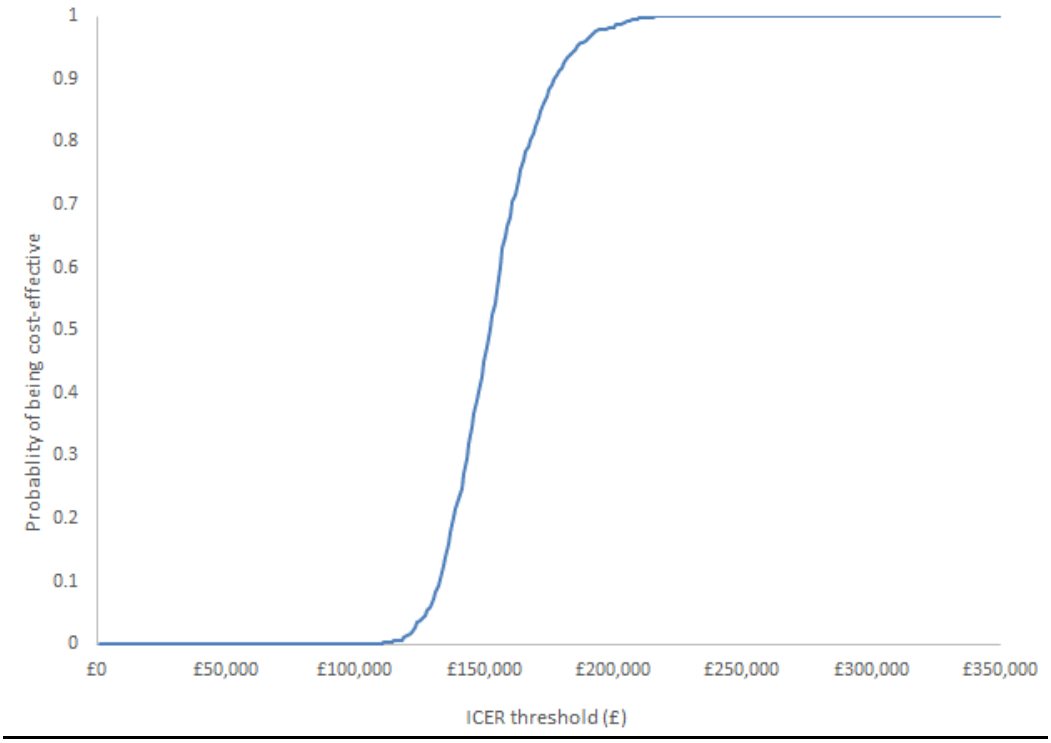

Figure 5 Cost effectiveness acceptability curve for PAL+LET vs LET (PAL at list price)

5.4.11 Scenario analyses

The company presented scenario analyses in two parts; the first five scenarios explored assumptions that drive the base case ICER beyond a £30,000 per QALY threshold and the second five scenarios demonstrate the impact to model results of combinations of amendments to parameter values or assumptions.

Results in Table 28 show the changes in ICERs per QALY that result from varying assumptions. The removal of the OS gain for PAL+LET increases the ICER per QALY gained by approximately £162,000.

Table 28 Exploratory scenario analyses varying model assumptions (PAL at list price)

#	Assumptions varied	Change in ICER from base case
Base case deterministic ICER		£150,869 per QALY
27	Only PFS gain for PAL (10.3 months) No OS gain for PAL (0 months)	+ £161,766
28a	Increased OS improvements with PAL: a 5-year incremental gain	- £89,047
28b	Increased OS improvements with PAL: a 5-year incremental gain, *but removing post-progression costs*	- £108,075
29	Increase in utility of +0.1 for patients in the PFS state	- £16,735
30	A comparator with the same monthly acquisition costs *(i.e. fixed cost of £2,951.52 per month, but only for respective treatment durations)*	- £97,795
31	Reduced treatment duration by 12 months in each arm *(PFS reduced from 15.7 to 3.7 months for LET, and from 24.9 to 12.9 months for PALb)*	- £64,450

ICER=incremental cost effectiveness ratio; LET=letrozole; OS=overall survival; PAL=palbociclib; PFS=progression-free survival; QALY=quality adjusted life year
Source: CS, Table 85

The ICERs per QALY gained displayed in Table 29 result from implementing combinations of changes to baseline assumptions. Scenario 36 is the only scenario that generates an ICER below a threshold of £30,000 per QALY. In this scenario, the cost of LET is assumed to be the same as that for PAL, there are no costs associated with post-progression, there is an OS gain of 24 months for patients receiving PAL+LET compared with LET and the utility value associated with being in the pre-progression state is increased by 0.1.

Table 29 Combining scenarios to evaluate exploratory ICERs per QALY gained (PAL at list price)

#	Assumptions changed	Incremental costs	Incremental QALYs	ICER per QALY gained
32	Comparative monthly acquisition costs Value of PFS utility increase (+0.1) *No change to base case OS assumption*	£33,013	0.82	£47,187
33	Comparative monthly acquisition costs (#30) Value of PFS utility increase (+0.1) Incremental OS gain of 12 months	£35,734	0.82	£43,819
34	Comparative monthly acquisition costs Value of PFS utility increase (+0.1) Incremental OS gain of 12 months Removal of post-progression costs	£33,013	0.82	£40,482
35	Comparative monthly acquisition costs (#30) Value of PFS utility increase (+0.1) Incremental OS gain of 24 months	£45,963	1.27	£36,194
36	Comparative monthly acquisition costs Value of PFS utility increase (+0.1) Incremental OS gain of 24 months Removal of post-progression costs	£33,013	1.27	£26,996

PFS=progression-free survival; OS=overall survival; PAL=palbociclib; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: CS, Table 86

5.4.12 Model validation and face validity check

The company took a number of steps to try and ensure the validity of the extrapolations and parameter values employed in their model:

- Utility values were sourced directly from the phase III trial (PALOMA-2) and from a source[5] established in previous STA submissions for people with ABC[113,114]
- Clinical opinion was sought to validate the estimates of resource use, and national databases (NHS Reference Costs,[110] PSSRU[111] and eMIT[109]) were used to source costs
- Detailed modelling of subsequent treatment lines allowed the complexity of subsequent therapies to be explored
- Validation of the model and its findings were undertaken internally by the model developers on behalf of the company and by an external independent health economist.

5.5 Detailed critique of the company's economic model

5.5.1 NICE Reference Case checklist

Table 30 NICE Reference Case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by the Institute	Yes
Comparator(s)	Alternative therapies routinely used in the NHS	Letrozole is the only aromatase inhibitor compared to palbociclib although there are others available for the indication described in the scope
Perspective costs	NHS and PSS	PSS costs were not fully considered in the CS
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes
Synthesis of evidence on outcomes	Systematic review	The company uses data from PALOMA-1 and PALMOA-2 trials to estimate survival and HRQoL estimates for initial therapy. A systematic review was conducted to estimate the outcomes of subsequent therapy
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standard and validated instrument	Yes
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	The company used an annual discount rate of 3.5% per annum for costs and benefits. Discounting is implemented per cycle, rather than on an annual basis, within the model
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

HRQoL=health-related quality of life; PSS=Personal Social Services

5.5.2 Drummond checklist

Table 31 Drummond critical appraisal checklist completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partly	In the model, PFS and OS were estimated using survival data from different trials. Projecting OS from PFS data from a different trial adds uncertainty to the effectiveness evidence used in the model (and therefore adds uncertainty to the size of the ICER per QALY gained)
Were all the important and relevant costs and consequences for each alternative identified?	Partly	Costs of subsequent therapy and AEs whilst on subsequent lines of treatment are not included in the model
Were costs and consequences measured accurately in appropriate physical units?	Partly	The days of the year modelled equated to 364 rather than the ERGs preferred 365.25. The HRQoL multiplier for progressed disease was implemented incorrectly. The annual incidence rate of AEs was implemented each cycle in the model.
Were the cost and consequences valued credibly?	Partly	An oncologists consultation was used as the cost to treat neutropenia taken from NHS reference costs and was assumed to last 60 minutes. This cost was weighted according to the Grade of neutropenia with Grade 3 incurring a 20 minute appointment and Grade 4 a 30 minute appointment thus cutting the reference cost by two-thirds and half respectively.
Were costs and consequences adjusted for differential timing?	Yes	Costs and benefits were not discounted on an annual basis
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

PFS=progression free survival, OS=overall survival, AE=adverse events

5.6 Detailed critique and exploratory analyses undertaken by the ERG

The company's Microsoft Excel spreadsheet model is constructed according to conventional practice and is generally implemented correctly.

5.6.1 Key issues in the company model

The two fundamental issues relating to the company's cost effectiveness model are: the absence of OS data from the PALOMA-2 trial; and issues regarding the reliability of survival data from the PALOMA-1 trial (Section 4.4). The company's attempts to overcome the lack of OS data from the PALOMA-2 trial are methodologically flawed, and result in inconsistencies (i) within the survival data used in the company model and (ii) between the assumptions underpinning the company's survival projection methods and their implementation.

Specific issues in the model connected to the lack of reliable survival data are:

- use of data from two different trials (PFS from PALOMA-2 and OS from PALOMA-1) introduces inconsistencies in the model estimates of survival
- no evidence to support the assumption that 100% of PFS gain for treatment with PAL+LET versus LET translates into OS gain
- assumption that there is no difference in PPS between treatment with PAL+LET and treatment with LET when evidence suggests that PPS is shorter for patients treated with PAL+LET than for those treated with LET
- method used to adjust OS data from the PALOMA-1 trial to incorporate the assumptions of (i) PFS gain is equal to OS gain and (ii) zero PPS gain, results in neither of these assumptions holding in the model.

Other issues identified by the ERG include:

- using PFS as a proxy for time on treatment, when TTD data provide a more accurate basis for estimating treatment acquisition costs
- calculating pre-progression health state utility values using data from the PALOMA-2 trial ITT population when using values collected from just the European population would have been more relevant to the NHS
- using different pre-progression health state utility values to reflect the quality of life of patients in the intervention and comparator arms when evidence from the PALOMA-2 trial indicated that there was no statistically significant difference between the two values
- absence of half-cycle correction
- incorrect use of a published method for calculating a post-progression health state utility value
- unjustified proportionate use of a NHS Reference Cost for costing the treatment of AEs
- incorrect calculation of the incidence of AEs
- discounting on a per cycle rather than on an annual basis.

The ERG has also included a sensitivity analysis which allows investigation of the impact of including the drug acquisition and administration costs associated with subsequent lines of treatment within the model. These costs are not included in the company's base case model.

There are no OS data available from the phase III PALOMA-2 trial. The company has modelled patient survival using PFS data from the PALOMA-2 trial and (adjusted) OS data from the smaller, phase I/II PALOMA-1 trial. However, using PFS from one trial and OS from another is methodologically flawed as it assumes independence between the outcomes. PFS and OS are not independent measurements; they are taken from the same individuals at different times. There is a relationship between PFS and OS are within trials because the data points come from the same set of individuals, however, the nature of their relationship is not necessarily generalisable between trials or across indications.[26]

The company's implementation of the assumptions that PFS gain for treatment with PAL+LET translates into equal OS gain and that PPS is equal for patients treated with either PAL+LET or LET is flawed. Neither of these assumptions hold in the model, as the company's method of adjusting OS to ensure median OS gain equals median PFS gain results in a mean PPS gain for treatment with PAL+LET (and thus a greater OS gain than PFS gain for treatment with PAL+LET).

The assumptions that OS gain for treatment with PAL+LET is equal to PFS gain and that there is no difference in PPS between treatment with PAL+LET and treatment with LET also ignore a pertinent feature of the data from the PALOMA-1 trial: that patients treated with PAL+LET seem to have a shorter life expectancy after progression than those treated with LET.

The ERG has investigated alternative methods of modelling of time-to-event data using PFS and OS from the PALOMA-1 trial only, in order to maintain consistency between PFS and OS. This method is also subject to uncertainties, as the data from the PALOMA-1 trial used for modelling has limitations and the results based on data from the PALOMA-1 trial should be treated with caution (Section 4.4); despite these limitations, the ERG considers using PFS data and OS data from the same trial to be a more methodologically sound approach than the one taken by the company. The ERG notes that the EMA has identified discrepancies between the investigator assessed and BICR-assessed PFS data from the PALOMA-1 trial (Table 8) and has declared only part of the data from that trial to be relevant for efficacy assessment. In light of the EMA's view, the ERG has also provided a scenario analysis in Section 5.6.13 to investigate the use of PFS data from the PALOMA-2 trial.

The company also includes with arguments alongside its base case cost effectiveness analysis to suggest that the current NICE methodology[115] for estimating cost effectiveness underestimates the benefit of the intervention. The ERG does not agree that the NICE

methodology is especially punitive to the intervention in this submission nor that the scenarios provided by the company to address its concerns are meaningful. The assumptions and scenarios put forward by the company are examined in detail in the appendices to this ERG report, Section 10.9.

5.6.2 Re-censoring Kaplan-Meier data

During the clarification process, the ERG requested that the company provide K-M data re-censored using the following rules:

- Patients without a documented event (TTD, PFS, OS) at the point of data cut-off should be re-censored at data cut-off
- Patients who have withdrawn from the trial for any reason and are no longer considered to be part of the trial should be re-censored at the time of withdrawal.

The conventional censoring rule applied to survival data is to censor on the date of last known contact any patients who have not experienced a given event (treatment discontinuation, disease progression, death) at the time of data cut-off. However, this rule can distort results when the data are immature. The ERG requested during the clarification process that K-M data be re-censored to limit potential bias from the application of the conventional censoring rule.

When trials are stopped early or are subject to early analysis, the conventional censoring rule (censor when last contacted/reviewed) always understates the time patients are exposed to risk but is much less likely to understate events, especially deaths. That is, at the time of an interim or early data cut-off, there are many patients still at risk in the trial who are still being followed up beyond data cut-off and will feature in later analyses, but who are censored weeks or months before data cut-off in an interim analysis because that is the last time that they were contacted. But, if a patient dies between the time of their last contact and the time of data cut-off, that death would likely still be recorded as an event. Thus, in the period between last tumour assessment and data cut-off, there may be fewer people recorded at risk than there are in reality, whereas the number of events such as deaths will still likely reflect the true frequency.

The result is that the inter-event period hazard rates calculated by the K-M algorithm are exaggerated when multiple patients are censored in any period. The resulting K-M estimated time-to-event trends may therefore be distorted by ‘informative censoring’ (patients are more likely to be censored early if they are still alive at data cut-off) and poorly reflect the true profile of time-to-event hazards.

All of the ERG's analyses of PFS, PPS, OS and TTD are based on re-censored K-M data. The company's analyses of PFS, PPS, OS and TTD are based on K-M data censored according to the conventional rule.

5.6.3 Time-to-event evidence: overall survival and post-progression survival

The company's modelling of OS in the base case is informed by the assumption that 100% of PFS gain translates into OS gain and that there is no difference in PPS between treatment with PAL+LET and treatment with LET. This is an important assumption because patients continue to accrue QALYs and costs beyond progression that can have a substantial effect on the overall ICER per QALY gained. If there is no difference in PPS between the two treatments, the costs and benefits of the drug are limited to those that accrue in PFS. The ERG does not agree that the company's assumption is justified.

The company provides no evidence for the assumption of zero PPS gain. The assumption of zero PPS gain is not even a conservative one, as evidence from the PALOMA-1 trial indicates that PPS is shorter for treatment with PAL+LET than for treatment with LET (a PPS loss). Re-censored K-M data provided by the company during the clarification process indicate that mean PFS gain in the PALOMA-1 trial, until the data cut on 29 November 2013, was [redacted] months and mean OS gain was [redacted] months. Mean PPS *loss* for treatment with PAL+LET was [redacted] months. Although data are sparse (18 deaths in the post-progression state in the PAL+LET arm and 26 in the LET arm),

Figure 6 shows that patients treated with LET in the PALOMA-1 trial tend to live longer after progression than patients treated with PAL+LET.

[redacted]

Figure 6 PPS K-M data for PAL+LET and LET (PALOMA-1)

Source: Clarification response B4

To implement the assumption of zero PPS gain, the company has attempted to reconcile OS data from the PALOMA-1 trial and PFS data from the PALOMA-2 trial. This approach is methodologically flawed, as PFS and OS data are measurements from the same set of individuals in a trial and so are not independent of one another. The company fitted separate Weibull models to data from both arms of the PALOMA-1 trial, but adjusted only the curve for the treatment with PAL+LET in order to increase the modelled median OS gain so that it matched median PFS gain from the PALOMA-2 trial. The company justifies leaving the OS curve unadjusted for treatment with LET by comparing it to the results of other trials in the published literature.[40,42,116] However, the company does not compare the relationship of PFS to OS for treatment with LET in these trials.

Figure 7 shows that there is a pronounced difference between PFS for the LET arm of the PALOMA-1 and PALOMA-2 trials, but that the PAL+LET arms in the two trials are similar. Given that the difference between investigator assessed PFS in the LET arms of the PALOMA-1 and PALOMA-2 trials is substantial, the ERG does not consider that the company is justified in leaving OS for treatment with LET unadjusted in order to create an OS curve to fit alongside PFS modelled from the PALOMA-2 trial.

Figure 7 Comparison of PFS K-M data from the PALOMA-1 and PALOMA-2 trials

Source: Clarification response B4

The company's assumption of zero PPS gain is flawed when implemented in the model. The company has adjusted the OS curve fitted to data from the PALOMA-1 trial for treatment with PAL+LET so that median OS gain in the model equals median (modelled) PFS gain from the

PALOMA-2 trial. This method does not, however, result in equality between *mean* OS gain and *mean* PFS gain. Because of the way the shape and scale parameters interact in the Weibull model, increasing the median of a curve to a predefined level has a proportionately larger effect on the mean value of that same curve. This means that, by adjusting projected OS for treatment with PAL+LET, the company model actually includes a small (0.49 months) gain in PPS for treatment with PAL+LET. The appendices to this ERG report, Section 10.8, include a more detailed discussion of the effect of adjusting a Weibull model.

The company has attempted to justify its extension of OS for treatment with PAL+LET beyond what is seen in the PALOMA-1 trial with reference to, first, issues of potential confounding in the PALOMA-1 trial and, second, literature identifying a correlation between PFS and OS in advanced breast cancer. The company notes that OS was a secondary outcome measure in the PALOMA-1 trial and that data are immature, and states that the study was substantially underpowered to detect statistically significant differences in OS. The ERG understands by this that the company is arguing that OS data from the PALOMA-1 trial are too flawed to be used for modelling purposes.

The ERG agrees with the company that the PALOMA-1 data have limitations for modelling. However, the company's approach, first, does little to mitigate the problems inherent in the OS data from the PALOMA-1 trial and, second, adds further uncertainties by adjusting the model for treatment with PAL+LET. The company still uses data from the LET arm to model OS for treatment with LET without adjustment and uses the shape of the OS data from the PAL+LET arm to model OS for treatment with PAL+LET. The only amendment the company makes to the OS data from the PALOMA-1 trial is an adjustment of the scale parameter in the Weibull model for treatment with PAL+LET.

ERG exploratory analyses

The ERG considers it unnecessary to introduce further uncertainties into the model by adjusting the OS data from the PALOMA-1 trial, especially when there are already concerns about the robustness of OS K-M data (few recorded events, old data cut) from the PALOMA-1 trial. The ERG's preferred approach to projecting time-to-event data is based on using the re-censored K-M data directly from the PALOMA-1 trial and appending a parametric projection beyond the limits of the trial data to project OS across the model time horizon.

The ERG analysed the re-censored OS K-M data provided by the company during the clarification process (

Figure 8) and did not observe a statistically significant difference between the two arms of the trial (log rank test p=0.488, Mann-Whitney U p=0.734). The ERG notes that the PALOMA-1 trial had not been powered to detect differences in OS, and so considered it appropriate to

produce separate projections for the intervention and the comparator. However, the difference in the ERG's revised estimates of mean OS for the two treatments should be treated with caution, as they are based on data that are not statistically significantly different.

Since OS hazards are proportional after the curves cross at approximately 8 months (Section 10.2), the ERG concluded it was justified to pool the data to produce a more robust estimate of the overall OS trend than could have been found by modelling the arms separately, before applying HRs from a Cox PH regression analysis (of data after the crossing of the curves at 8 months) to the pooled trend to fit separate projections.

Figure 8 OS K-M data for patients treated with PAL+LET and LET (PALOMA-1 trial)

LET=letrozole; PAL+LET=palbociclib+letrozole; OS=overall survival
Source: Clarification response B4

The pooled OS data from the PALOMA-1 trial exhibit apparently increasing hazards over time, which can in fact be modelled as two sections of constant, but different, hazards that change at around 20 months. These constant hazards are represented by straight lines in the cumulative hazard plot in Figure 9 and translate into piecewise exponential OS estimates.

Figure 9 Cumulative hazard plot of pooled OS with two-part exponential trend

OS=overall survival
Source: Clarification response B4, ERG calculations

The ERG used HRs from the Cox PH regression analysis to adjust the exponential model from the second half of the pooled analysis to forecast OS for treatment with PAL+LET and treatment with LET. The ERG then fitted these adjusted exponential tails to the relevant OS K-M data for the intervention and comparator (Figure 10).

Figure 10 ERG OS projections and company model base case OS

LET=letrozole; PAL+LET=palbociclib+letrozole; OS=overall survival
Source: Company model; Clarification response B4; ERG calculations

The ERG's revised OS model for treatment with PAL+LET yields lower estimates than the company's model until around 8 years, after which the ERG's model estimates higher OS than the company base case for patients treated with PAL+LET. The ERG's revised model also yields lower estimates of OS than the company base case in the early part of the model for patients treated with LET, but yields higher estimates than the company base case after approximately 4 years.

Mean OS in the ERG's revised model is 47.7 months for PAL+LET and 41.2 months for LET, which gives a projected mean OS gain of 6.6 months for treatment with PAL+LET. This is in comparison to a mean gain of 11.2 months in the company base case. The ERG notes that this projected OS gain is based on data whose means are not statistically significantly different, therefore there is considerable uncertainty in the estimate. Applying the ERG's revised OS estimates in the model increases the ICER per QALY gained by £38,441 to £189,310.

5.6.4 Time-to-event evidence: progression-free survival

The two key problems with the company's estimates of PFS are: first, that it uses data (from the PALOMA-2 trial) to inform its modelling of PFS that are inconsistent with the data (from the PALOMA-1 trial) used to model OS; and second, that the Weibull model used in the base case produces implausible results.

The ERG considers it methodologically sound to use data from the same trial to estimate PFS and OS, as this approach maintains consistency between PFS, PPS and OS within the model.

The Weibull models used by the company to model PFS for treatment with PAL+LET and treatment with LET each have monotonically increasing hazards. This means that, the longer a patient remains progression free, the more likely they are to progress or die than they were previously (

Figure 11). The logic here is that patients who have done well following treatment, either because of the treatment itself or because of some underlying characteristic, and who have lived for many years after beginning treatment are actually at greater risk of progression (or death) than patients who were sicker or less responsive and died earlier – that is, the further a patient is from randomisation, the more likely they are to progress or die. The impact of increasing general mortality due to age only accounts for a small proportion of these increasing hazards, so the model effectively forecasts that patients will be at greater risk from the disease several years after randomisation than they were when first diagnosed with advanced or MBC. The ERG considers the phenomenon of monotonically increasing hazards, continued over the 40 years of the model time horizon, to be implausible.

Figure 11 Hazard profiles for company base case PFS

LET=letrozole; PLACEBO+LET=placebo+letrozole; PFS=progression free survival
Source: Company model; ERG calculations

ERG exploratory analyses

The ERG considers it preferable to use data from the PALOMA-1 trial as the basis for modelling PFS to maintain consistency with the OS data from the PALOMA-1 trial used for modelling survival. The ERG acknowledges that the data from the PALOMA-1 trial have some limitations (Section 4.4). The ERG urges caution in the interpretation of its revised PFS estimates due to the unreliability of the PFS data from the PALOMA-1 trial.

The ERG prefers to use direct trial K-M data, when available, to model early events and only use later data to model a projection once a long-term trend has been established. This means that early features of the data that can be awkward to model parametrically, such as deaths due to AEs or administrative issues such as time to first assessment, are captured by the trial data. It also means that the most accurate data available are used and no assumptions are required that add to the uncertainty in the model.

The company provided the ERG with re-censored investigator assessed PFS data from the PALOMA-1 trial during the clarification process. Mean PFS gain for patients treated with PAL+LET versus LET in the PALOMA-1 trial was [redacted] months.

Examination of the re-censored K-M data reveals clear exponential trends in both the PAL+LET and LET arms of the PALOMA-1 trial (Figure 12 and

Figure 13). The steep drop in PFS at around 3 months (Figure 12) indicates that treatment with PAL+LET appears to offer protection against early progression in around 20% of patients versus treatment with LET.

Figure 13 shows that patients treated with PAL+LET have a lower hazard of progression in the long-term versus those treated with LET (the gradient of the exponential trend applied to the cumulative hazard is steeper for treatment with LET than for PAL+LET).

Figure 12 PFS K-M data and exponential trend (PALOMA-1 trial)

LET=letrozole; PAL+LET=palbociclib+letrozole; PFS=progression free survival
Source: Clarification question B4; ERG calculations

Figure 13 PFS cumulative hazard plot of K-M data and exponential trend (PALOMA-1 trial)

LET=letrozole; PAL+LET=palbociclib+letrozole; PFS=progression free survival
Source: Clarification question B4; ERG calculations

The well-established exponential trend in the PAL+LET treatment arm of the PALOMA-1 trial allows projection of PFS beyond the limits of the available K-M data for treatment with PAL+LET. The ERG extrapolated PFS for treatment with PAL+LET by appending the exponential trend established early in the K-M data to a data point close to the end of the K-M data. The data point chosen as the first point of extrapolation (16.6 months) was identified using the smallest of the weighted squared residuals calculated from the K-M data and fitted exponential curve. Extrapolation was not necessary for treatment with LET, as the final patient at risk died at [redacted] (Figure 12).

The ERG's projected PFS yielded estimates below those in the company model throughout the model time horizon for both treatments, except for a brief period in the first year for treatment with PAL+LET (

Figure 14).

Figure 14 ERG PFS projections using PALOMA-1 trial data vs company model PFS

ERG=Evidence Review Group; K-M=Kaplan-Meier; LET=letrozole; PAL+LET=palbociclib+letrozole; PFS=progression free survival
Source: Company model; Clarification response B4; ERG calculations

Mean PFS gain increased for PAL+LET in the ERG's model versus mean PFS gain in the company base case (13.3 months in the ERG's revised model versus 10.7 months in the base case). Applying the ERG's PFS projections based on the re-censored PALOMA-1 K-M data decreases the ICER per QALY gained by £29,461 to £121,408.

5.6.5 Time-to-event evidence: time to treatment discontinuation

The company has assumed that all patients in the model are treated to progression and has, accordingly, used PFS to estimate the proportion of patients receiving treatment in each cycle.

Figure 15, however, shows that some patients in the PALOMA-1 trial stopped treatment for reasons other than progression or death, which indicates that the time spent on treatment in this trial was less than the time spent in the progression-free state. It is unclear whether the TTD data for the PAL+LET arm of the PALOMA-1 trial represent PAL alone (that is, patients may have continued treatment with LET monotherapy) or whether it represents the discontinuation of all first-line treatments.

It is important to model time on treatment using trial TTD data where possible, as using PFS as a proxy can lead to an overestimation of the costs of treatment acquisition and administration (or an underestimation, if patients are permitted to continue treatment after progression).

Figure 15 shows how, at around 3 months, some patients treated with LET actually received treatment for a brief period after their progression was confirmed. Treatment beyond progression was not specified in the trial protocol.[97]

The company provided the ERG with TTD data from the PALOMA-1 trial during the clarification process. The difference between PFS and TTD was greater for patients treated with PAL+LET than for patients treated with LET (

Figure 15). The difference between PFS and TTD can be explained in the most part by the proportion of patients discontinuing treatment due to AEs: [redacted] of patients who discontinued treatment with PAL+LET in the PALOMA-1 trial did so due to AEs,[91] in comparison to [redacted] of patients who discontinued treatment with LET due to AEs.

Figure 15 PFS and TTD K-M data (PALOMA-1 trial data re-censored)
LET=letrozole; PAL+LET=palbociclib+letrozole; PFS=progression free survival; TTD=time to treatment discontinuation
Source: Clarification response B4

ERG exploratory analyses

To amend the model to calculate treatment costs using TTD rather than PFS, the ERG investigated methods of projecting the TTD K-M data provided by the company during the clarification process. The ERG found exponential trends established in the TTD data from the PALOMA-1 trial from around 9 months in the PAL+LET arm and around 5 months in the LET arm (

Figure 17).

The ERG used the trend in the PAL+LET arm to append exponential extrapolations to points near the end of the K-M data for treatment with PAL+LET. The extrapolation point was identified by choosing the K-M data point with the smallest weighted squared residual of the difference between the K-M data and the fitted exponential curve. The final K-M data point in the LET arm of the re-censored PALOMA-1 data set was censored, but, rather than extrapolating an estimate for this point, the ERG used the final PFS K-M point from the PALOMA-1 trial as a proxy in order that patients in the model did not receive treatment with

LET beyond progression when the ERG's PFS revisions were also applied.

Figure 16 Cumulative hazard plot of TTD K-M data and exponential trends (PALOMA-1 trial)

LET=letrozole; PAL+LET=palbociclib+letrozole; TTD=time to treatment discontinuation
Source: Clarification response B4

Figure 17 TTD K-M data and exponential trends PALOMA-1 trial data (re-censored)

LET=letrozole; PAL+LET=palbociclib+letrozole; TTD=time to treatment discontinuation

Source: Clarification response B4

Figure 18 shows the ERG's TTD projections using PALOMA-1 trial data alongside the ERG's PFS projections. The ERG's revisions using TTD K-M data from the PALOMA-1 trial reduce mean time on treatment by 10.2 months to 20.7 months for treatment with PAL+LET and by 7.3 months to 12.9 months for treatment with LET.

Figure 18 ERG TTD and PFS projections (PALOMA-1 trial data)

ERG=Evidence Review Group; K-M=Kaplan_Meier; LET=letrozole; PAL+LET=palbociclib+letrozole; PFS=progression free survival; TTD=time to treatment discontinuation
Source: Company model; ERG calculations

Applying the ERG's TTD projections based on the re-censored PALOMA-1 K-M data in the model alongside the company's base case PFS projections decreases the ICER per QALY gained by £47,941 to £102,928.

5.6.6 Health state utility values: pre-progression

The ERG does not consider the company to be justified in using a [redacted] for treatment with PAL+LET versus LET ([redacted]), as [redacted] found between the utility values calculated from the responses to the EQ-5D questionnaire in the two arms PALOMA-2 trial.[92]

The EQ-5D questionnaire was completed by patients on [redacted], and at the end of randomised treatment. [redacted] in each cycle in the ITT population completed the EQ-5D from baseline to cycle 21 in the PAL+LET arm ([redacted]) and from [redacted] in the PLACEBO+LET arm, after which [redacted] (

Figure 19). A [redacted] proportion of patients in the PLACEBO+LET arm [redacted] the EQ-5D questionnaire at each time point than did patients in the PAL+LET arm.

Figure 19 EQ-5D utility values and completion rates over time (PALOMA-2 trial)

Source: Company clarification responses B4 and B6; ERG calculations

Since [redacted] from patients in the PALOMA-2 trial was [redacted], the ERG considers that utility values should have been pooled and an overall average should have been used for both treatments. The company investigates in Scenario 22 the impact on the ICER per QALY gained of using an average of the two pre-progression utilities by applying a utility value of [redacted]. Using a pre-progression utility value of [redacted] for both treatments, the company's Scenario 22 increases the company's base case ICER per QALY gained by £14,991 to £165,860.

ERG exploratory analyses

The ERG has attempted to replicate the calculation of the pre-progression utility values used in the model using the data provided by the company during the clarification process, but was not able to identify the method used to yield the values [redacted]. The ERG has instead calculated alternative pre-progression utility values using the mean utility values from European patients in the PALOMA-2 trial. The ERG considers that using responses from European patients alone is likely to be a better approximation of responses of UK patients than using responses from the full ITT population, whilst still retaining a large enough data set to give a reliable average.

The ERG is also satisfied that it is valid to use utility values calculated from EQ-5D responses from the PALOMA-2 trial alongside time-to-event data from the PALOMA-1 trial in the absence

of EQ-5D data from the PALOMA-1 trial. This is because utility data are less prone to serious differences than time-to-event data provided the disease area and stage of disease are broadly similar.

The ERG calculated a weighted average utility value using the mean values per cycle and the the number of respondents per cycle from both arms of the PALOMA-2 trial for the first 21 cycles of treatment (since [redacted] of each arm in [

Figure 19], so can be considered reliable).

The average pooled cycle utility for European patients in the first 21 cycles in the PALOMA-2 trial was [redacted]. Applying the recalculated pre-progression utility values for PAL+LET and LET in the model increases the ICER per QALY gained by £16,858 to £167,727.

5.6.7 Health state utility values: post-progression

The company has made an error in the calculation of post-progression utility values using the published results of a study by Lloyd et al.[5] The company used the utility decrement associated with disease progression in the Lloyd[5] paper to derive a multiplier, which it then applied to the (average) pre-progression utility value from the PALOMA-2 trial. The company's resulting post-progression utility value used for both treatments in the base case is 0.4492.

This method assumes that the utility decrement associated with progressed disease can be applied linearly. However, a logistic transformation was applied to the data used in the Lloyd[5] study before analysis in order that it approximated the normal distribution necessary to allow use of a standard regression analysis. This means that the resulting utility gains and decrements reported in the paper cannot be directly applied or linearly adjusted and must be re-calculated to take into account the logistic transformation.

The ERG has recalculated the post-progression utilities using the results of the mixed model analysis given in the Lloyd[5] paper, including the logistic transformation of the data, and calibrated the result to the UK average age (48.52 years[117]) in the UK value set. The ERG's recalculated post-progression utility value is 0.5052. Applying this recalculated post-progression utility value in the model increase the ICER per QALY gained by £277 to £151,146.

5.6.8 Half-cycle correction

The company did not include a half-cycle correction to improve the accuracy of the cost and outcomes estimates. All patients progression-free and/or alive at the beginning of a cycle are assumed by the company to accrue costs and benefits throughout the entire cycle. However, some patients progress or die during a cycle and do not accrue the full costs and benefits for

that cycle. It is more accurate to assume costs and benefits apply to the average number of patients progression-free and/or alive in a cycle, which can be achieved by averaging the number of patients at the beginning and end of a cycle (mid-cycle correction).

Applying a mid-cycle correction to PFS and OS in the model reduces both incremental costs and incremental QALYs, and reduces the base case ICER per QALY gained by £2,182 to £148,687.

5.6.9 AE costs

The company is not justified in using a proportion of the relevant NHS Reference Cost[110] to represent a meeting of 20 minutes (Grade 3) or 30 minutes (Grade 4) with a consultant oncologist. This is because NHS Reference Costs[110] provide a currency for payment for the average patient[118] and do not represent an hourly cost (unless that is how much of the resource the average patient uses).

The ERG has amended the model to apply the full NHS Reference Cost[110] of £132 (Healthcare resource group currency code WF01A service code 800) to both Grade 3 and Grade 4 AEs. This increases the ICER per QALY gained by £1,603 to £152,472.

5.6.10 AE incidence calculation

The company has made two errors when calculating the incidence of AEs: first, the company used the median rather than mean time on treatment to calculate the probability of an AE; second, the company has applied annual rather than cycle AE probabilities to each cycle in the model. The ERG has amended these errors, which increases the time on treatment used in the probability calculations for both treatments, and substantially reduces the probability of AEs in each cycle.

Applying both of the ERGs corrections to the AE incidence calculation decreases the ICER per QALY gained by £854 to £150,015.

5.6.11 Discounting

In the company model, discounting of costs and outcomes is applied on a per cycle basis, rather than annually in line with NHS budgeting and accounting years. This has the effect of increasing the incremental QALYs more than the incremental costs.

The ERG has amended discounting to be applied on an annual basis. Application of this amendment decreases both incremental costs and incremental QALYs, and decreases the ICER per QALY gained by £159 to £150,710.

5.6.12 Days per year

The company has assumed 364 days per year in the model as a basis for several calculations, as there are 364 days in 13 28-day cycles. The ERG does not agree with using 364 days to approximate the number of days per year and has amended the value to 365.25 days.

Amending the number of days per year to 365.25 increases the ICER by £2 to £150,871.

5.6.13 ERG scenario analysis: using PALOMA-2 trial data

The ERG notes that the findings from a final analysis of cohort 1 from the PALOMA-1 trial shows large differences between investigator assessed PFS and BICR assessed PFS (Table 8). These findings were reported by the EMA. According to the EMA, these results indicate that findings from cohort 1 may be significantly biased to the extent that the findings from the PALOMA-1 trial are not suitable for licensure. The EMA also conclude that only findings from cohort 2 should be considered relevant to the efficacy assessment.

The ERG did not request K-M data from the PALOMA-1 trial to be split by cohort, so was unable to model PFS for cohort 2 from the PALOMA-1 trial. The ERG has instead provided a scenario analysis using re-censored, investigator assessed PFS data from the PALOMA-2 trial, along with TTD data from the same trial, as an alternative to using investigator assessed PFS data from the PALOMA-1 trial. This scenario analysis is subject to some of the same methodological flaws present in the company's base case, as it introduces inconsistencies into the relationship between PFS and OS.

The ERG has used re-censored K-M data from the PALOMA-2 trial directly for the first 19.2 months for treatment with PAL+LET and 18.1 months for treatment with LET, after which it appended exponential projections that had been calibrated using respective K-M data from 5 months onwards. The ERG's revised PFS projections based on data from the PALOMA-2 trial yield higher estimates of PFS for treatment with both PAL+LET and LET versus the company base case (

Figure 20). Mean PFS gain for treatment with PAL+LET in the ERG scenario analysis is 11.5 months versus 13.3 months in the ERG's revised model using PFS data from the PALOMA-1 trial and versus 10.7 months in the company base case.

Figure 20 ERG revised PFS model (scenario analysis: PALOMA-2 trial data) and company base case PFS projections

Source: Company model; Clarification response B4; ERG calculations

The ERG has also remodelled TTD using data from the PALOMA-2 trial to maintain consistency (

Figure 21). The ERG used the same approach to modelling TTD from the PALOMA-2 trial as it used to model PFS (K-M data plus exponential extrapolation). The ERG's remodelling of TTD from the PALOMA-2 trial reduces time on treatment versus PFS by 3.4 months for treatment with PAL+LET and 2.7 months for treatment with LET.

Figure 21 ERG revised PFS and TTD models (scenario analysis: PALOMA-2 trial data)

Source: Clarification response B4; ERG calculations

In the ERG scenario, applying the ERG's revised PFS using data from the PALOMA-2 trial increases the ICER per QALY gained versus the company base case by £6,155 to £156,984. Applying the ERG's revised TTD using data from the PALOMA-2 trial decreases the ICER per QALY gained versus the base case by £4,631 to £146,238.

5.6.14 ERG sensitivity analysis: subsequent treatments costs

The ERG does not agree with the company that it is reasonable to omit drug acquisition costs for subsequent treatments post-progression and considers that the company should have carried out a more thorough costing of post-progression treatments in this appraisal. The ERG's revised PFS and OS estimates increase time spent in PPS, and thus the cost of PPS, substantially more for patients treated with LET than they do for patients treated with PAL+LET (Table 32), which indicates that the model is sensitive to the cost of subsequent treatments when PPS is not assumed to be equal for the intervention and comparator. The ERG was not able to perform a full costing of post-progression treatments, so carried out a simple sensitivity analysis to investigate the magnitude of the impact of adding drug costs to the subsequent therapy calculations.

Mean PPS gain for treatment with PAL+LET in the company's base case model is 0.49 months, which decreases to a 6.7 month mean PPS loss when the ERG's revised PFS and OS estimates are applied. The incremental cost of subsequent treatment more than doubles versus the base case when the ERG's PFS and OS estimates are applied; subsequent treatment costs are £528 lower for treatment with PAL+LET than for LET in the base case, but are £1,487 lower for treatment with PAL+LET when the ERG's PFS and OS estimates are applied.

Table 32 Cost of subsequent treatment for PAL+LET and LET (excluding BSC)

	Total subsequent treatment costs (excluding BSC)		
	PAL+LET	LET	Difference
Company base case	[redacted]	[redacted]	[redacted]
Using ERG preferred PFS and OS estimates	[redacted]	[redacted]	[redacted]

BSC=best supportive care; ERG=Evidence Review Group; LET=letrozole; PAL+LET=palbocicliob+letrozole; OS=overall survival; PFS=progression free survival
Source: Company model, ERG calculations

The ERG used its revised PFS and OS estimates based on PALOMA-1 trial data in order to introduce a reduced time spent in PPS for patients treated with PAL+LET versus those treated with LET (-6.7 months). The difference in subsequent treatment costs for patients treated with PAL+LET versus LET ranged from -£1,841 if drugs cost £100 per cycle to -£36,840 if drugs cost £10,000 per cycle (

Table 33). The impact on the ICER per QALY gained ranged from -£3,606 for drugs costing £100 per cycle to -£70,047 for drugs costing £10,000 per cycle.

The ICER per QALY gained decreases with an increase in subsequent treatment costs because the analysis uses ERG estimates of PFS and OS in order that the model includes a mean PPS loss for treatment with PAL+LET. This reduces the time spent both on first-line and subsequent treatment for patients receiving PAL+LET in particular, which substantially reduces the total cost of treatment for these patients. However, the key conclusion of the sensitivity analysis is that the ICER per QALY gained changes substantially depending on the cost of subsequent treatment. The ERG thus considers that the company should have included a more through costing of post-progression treatments in its model.

Table 33 Subsequent treatment cost sensitivity analysis

Drug acquisition and administration cost per cycle	Total subsequent treatment costs (excluding BSC)			ICER per QALY gained	ICER difference from base case
	PAL+LET	LET	Difference		
£100	[redacted]	[redacted]	[redacted]	£147,262	-£3,606
£1,000	[redacted]	[redacted]	[redacted]	£141,222	-£9,646
£10,000	[redacted]	[redacted]	[redacted]	£80,822	-£70,047

BSC=best supportive care; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; LET=letrozole; PAL+LET=palbocicliob+letrozole; QALY=quality adjusted life year
Source: Company model, ERG calculations

5.6.15 Company probability sensitivity analysis

Figure 4 shows the CEAC for the company's base case. The scatterplot is essentially one-dimensional along the QALY axis, with very little variability in the cost axis. Tthis result is due to the way in which the company has formulated the PSA. The PSA macro is set up to exclude any correlated uncertainty in the key model parameters (Weibull model scale and shape parameters). This leads to apparently minimal uncertainty in the estimate of the probabilistic ICER and therefore virtually no spread in the CEAC. The ERG therefore places no confidence in the PSA results which are inconsistent with the use of multiple Weibull models in projecting future costs and outcomes.

5.7 Conclusions of the cost effectiveness section

The various changes implemented by the ERG for the comparison of treatment with PAL+LET versus treatment with LET yield a mixture of effects. When implemented individually, these revisions both increase and decrease the size of the ICERs per QALY gained. The combined effect of all of the ERG's revisions, when using PALOMA-1 data as the basis for modelling PFS and TTD, decreases the ICER per QALY gained by £17,997 to £132,872. However, the

combined effect of all of the ERG's revisions, when using PALOMA-2 data as the basis for modelling PFS and TTD, increases the ICER per QALY gained by £62,337 to £213,206.

The ERG considers that there is considerable uncertainty as to whether the company's base case results overestimate or underestimate the size of the most probable ICER per QALY gained. The available data from the PALOMA-1 trial is flawed, but allows for the most methodologically robust approach to modelling survival; the available data from the PALOMA-2 trial is more robust, but requires the application of methodologically unsound approaches to modelling survival to compensate for the absence of OS data from that trial.

The cost effectiveness results that are generated in the company's base case and following the application of either of the ERG's combined revision scenarios are all considerably higher than the range normally considered acceptable by NICE.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG has made ten changes to the submitted model to address the points raised in Section 5.6. The combined impact on the ICER per QALY gained as a result of the following changes are given in Scenario B in Table 34:

R1) OS estimates based on data from the PALOMA-1 trial

R2) PFS estimates based on data from the PALOMA-1 trial

R3) TTD estimates based on data from the PALOMA-1 trial

R4) re-calculate pre-progression utility values from the PALOMA-2 trial data

R5) re-calculate post-progression utility values using information in the Lloyd study[5]

R6) use mid-cycle correction

R7) re-calculate cost of treating AEs using full NHS Reference Costs

R8) correct AE incidence calculation

R9) change discounting to annual

R10) use 365.25 days per year instead of 364

The ERG has made a further two changes to the submitted model to provide alternatives to using PALOMA-1 trial data to model PFS and TTD. The combined impact on the ICER per QALY gained as a result of the substituting the following changes for R2) and R3) in Scenario B are given in Scenario C in Table 34:

R11) PFS estimates based on data from the PALOMA-2 trial

R12) TTD estimates based on data from the PALOMA-2 trial

Details of all Microsoft Excel revisions made by the ERG to the company's model are presented in the appendices to this report (Section 10.10).

6.1 Summary of ERG revisions to company model

The cost effectiveness results obtained by applying each of the ERG's model revisions are shown in Table 34.

The ERG's revised base case scenario encompassing all of the ERG's revisions to the company's model, using the ERG's revised PFS and TTD estimates based on data from the PALOMA-1 trial (Scenario B in Table 34) yields an ICER per QALY gained of £132,872, which is £17,997 lower than in the company's base case. The ERG's revised base case for the comparison of treatment with PAL+LET versus treatment with LET using PALOMA-1 trial data

generates both incremental costs (£59,934) and benefits (0.451 QALYs) that are lower than those generated by the company. The ERG's revised base case using PALOMA-1 trial data to model PFS and TTD also reduces incremental life years gained (0.454 years) compared to the company's base case.

The reduction in the ICER per QALY gained in Scenario B, when all the ERG's revisions are applied simultaneously and using PALOMA-1 trial data, is principally a result of the reduction in treatment costs due to using TTD rather than PFS to estimate the proportion of patients receiving treatment in each cycle. The reduction in treatment costs is proportionately much larger for patients receiving PAL+LET than patients receiving LET, which decreases the ICER per QALY gained. The substantial decrease in the ICER per QALY gained due to lower treatment costs is mitigated, however, by decreases in the incremental QALYs accrued for treatment with PAL+LET due to less time spent in PPS for these patients and to equal pre-progression utility values assumed to apply to both the intervention and comparator.

The ERG's revised base case scenario encompassing all of the ERG's revisions to the company's model, using the ERG's revised PFS and TTD estimates based on data from the PALOMA-2 trial (Scenario C in Table 34), yields an ICER per QALY gained of £213,206, which is £62,337 higher than in the company's base case. The ERG's revised base case for the comparison of treatment with PAL+LET versus treatment with LET using PALOMA-2 trial data generates both incremental costs (£88,452) and benefits (0.415 QALYs) that are lower than those generated by the company. The ERG's revised base case using PALOMA-2 trial data to model PFS and TTD reduces incremental life years gained (0.454 years) compared to the company's base case.

Table 34 Cost effectiveness results: ERG revisions to company base case

Model scenario ERG revision	PAL+LET			LET			Incremental			ICER	ICER
	Cost £	QALYs	Life years	Cost £	QALYs	Life years	Cost £	QALYs	Life years	£/QALY[+]	Change
A. Company original base case	***£116,696***	***2.402***	***3.793***	***£21,843***	***1.773***	***3.016***	***£94,853***	***0.629***	***0.777***	***£150,869***	
R1) ERG OS estimates based on data from PALOMA-1	£114,359	2.314	3.598	£23,381	1.834	3.152	£90,977	0.481	0.447	£189,310	+£38,441
R2) ERG PFS estimates based on data from PALOMA-1	£107,386	2.314	3.793	£25,458	1.639	3.016	£81,928	0.675	0.777	£121,408	-£29,461
R3) ERG TTD estimates based on data from PALOMA-1	£86,544	2.402	3.793	£21,831	1.773	3.016	£64,712	0.629	0.777	£102,928	-£47,941
R4) ERG recalculated pre-progression utility values from PALOMA-2 trial	£116,696	2.353	3.793	£21,843	1.787	3.016	£94,853	0.566	0.777	£167,727	+£16,858
R5) ERG recalculated post-progression utility values using Lloyd 2006[5]	£116,696	2.480	3.793	£21,843	1.852	3.016	£94,853	0.628	0.777	£151,146	+£277
R6) Use mid-cycle correction	£115,308	2.376	3.759	£21,875	1.748	2.982	£93,433	0.628	0.778	£148,687	-£2,182
R7) Use full reference costs for AEs	£118,088	2.402	3.793	£22,227	1.773	3.016	£95,861	0.629	0.777	£152,472	+£1,603
R8) Correct AE incidence calculation	£115,962	2.402	3.793	£21,646	1.773	3.016	£94,317	0.629	0.777	£150,015	-£854
R9) Change discounting to annual	£118,449	2.438	3.851	£22,187	1.800	3.062	£96,262	0.639	0.789	£150,710	-£159
R10) Use 365.25 days per year	£116,698	2.402	3.793	£21,844	1.773	3.016	£94,854	0.629	0.777	£150,871	+£2
B. ERG revised base case using PALOMA-1 PFS, OS and TTD (R1:R9)	***£87,478***	***2.280***	***3.619***	***£27,544***	***1.829***	***3.164***	***£59,934***	***0.451***	***0.454***	***£132,872***	***-£17,997***
R11) ERG PFS estimates based on data from PALOMA-2	£121,946	2.452	3.793	£20,708	1.808	3.016	£101,238	0.645	0.777	£156,984	+£6,115
R12) ERG TTD estimates based on data from PALOMA-2	£113,783	2.402	3.793	£21,842	1.773	3.016	£91,942	0.629	0.777	£146,238	-£4,631
C. ERG revised base case using PALOMA-2 PFS and TTD (R1 & R4:R9)	***£110,970***	***2.386***	***3.619***	***£22,518***	***1.971***	***3.164***	***£88,452***	***0.415***	***0.454***	***£213,206***	***+£62,337***

Costs, QALYs and life years discounted

N.B. incremental undiscounted life years are 0.931 in the company base case and 0.549 in the ERG's revised base case estimates

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; LET=letrozole; OS=overall survival; PAL+LET=palbociclib+letrozole; PFS=progression-free survival; QALYs=quality adjusted life years; TTD=time to treatment discontinuation

[+] Rounding errors account for difference between ICERs calculated using the incremental cost and QALY values given in the table and ICERs in this column

7 END OF LIFE

The company has not made a case for PAL+LET to be considered under NICE's End of Life criteria.

8 OVERALL CONCLUSIONS

8.1 NHS clinical practice

Despite a higher proportion of patients in the PALOMA-1 and PALOMA-2 trials presenting with de novo disease than would be seen in NHS clinical practice, the ERG is generally satisfied that the evidence derived from both trials is generalisable to the patient population in England and Wales described in the final scope issued by NICE. The EMA considers that it is reasonable to generalise the clinical effectiveness results associated with LET to other aromatase inhibitors; the ERG concurs with this viewpoint.

8.2 Clinical effectiveness

Efficacy evidence is derived from two trials. The phase III PALOMA-2 trial was considered by the ERG to be of superior quality and lower risk of bias than the phase I/II PALOMA-1 trial as the former trial was larger and designed as a double-blind trial, whereas the PALOMA-1 trial was designed as an open-label trial. Furthermore, investigator assessed PFS findings reported for cohort 1 of the PALOMA-1 trial differed markedly to BICR assessed PFS. This has led the EMA to conclude that only findings from cohort 2 should be considered relevant to the efficacy assessment. OS data from the PALOMA-1 trial are also immature and are from a data cut-off date of 29 November 2013. There are no OS data currently available from the PALOMA-2 trial. Despite a large gain in investigator assessed median PFS (of approximately 10 months) for patients treated with PAL+LET versus LET or PLACEBO+LET in both the PALOMA-1 and PALOMA-2 trials, no statistically significant improvement in median OS for patients in the PALOMA-1 trial or the PALOMA-2 trial was observed.

Differences between the treatment arms in terms of safety were mostly attributable to a much higher rate of haematological toxicities, particularly neutropenia in patients treated with PAL+LET. While this included high rates of Grade 3 to 4 neutropenia, for the most part, neutropenia was asymptomatic and reversible, with febrile neutropenia being reported by <2% of patients (all incidence occurring in the PALOMA-2 trial). These data suggest neutropenia rarely results in permanent discontinuation of treatment with PAL+LET. Therefore, the safety profile of PAL+LET is considered by the company and the ERG to be acceptable.

There were no statistically significant differences between trial arms in terms of HRQoL measures reported in either of the PALOMA-1 trial or the PALOMA-2 trial. Thus, while the trials did not demonstrate that prolonging PFS improved HRQoL over time, the trials did suggest an increase in incidence of AEs for patients treated with PAL+LET compared with LET or PLACEBO+LET; however, this increase in incindence of AEs did not appear to affect HRQoL.

8.3 Cost effectiveness

There is considerable uncertainty as to whether the company's base case cost effectiveness results overestimate or underestimate the size of the most probable ICER per QALY gained. When implemented individually, the ERG's revisions both decrease and increase the estimated ICER per QALY gained versus the company base case. However, the company's base case cost effectiveness results, as well as those generated following the application of all the ERG's revisions, are considerably higher than the range normally considered acceptable by NICE.

The available data from the PALOMA-1 trial are flawed, but allow for the most methodologically robust approach to modelling survival and yields an ICER estimate of £132,872 per QALY gained (£17,997 lower than in the company's base case); the available data from the PALOMA-2 trial are more robust, but require the application of methodologically unsound approaches to modelling survival to compensate for the absence of OS data from that trial, and yield an ICER estimate of £213,306 per QALY gained (£62,337 higher than in the company's base case).

8.4 Implications for research

While LET, anastrozole and exemestane, the aromatase inhibitors currently used in NHS clinical practice can be considered to be of equal efficacy, studies comparing palbociclib in combination with, and versus, other aromatase inhibitors would add to the evidence base. The ERG notes that the EMA highlight that ongoing clinical studies examining palbociclib in combination with anastrozole and exemestane are underway.

More evidence for the impact of palbociclib in combination with an aromatase inhibitor on OS is required. While OS data from the PALOMA-2 trial will add to the evidence base when the data become available, more mature data from the PALOMA-1 trial would also be informative.

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10 APPENDICES

10.1 Additional secondary efficacy endpoints reported in the PALOMA-1 and PALOMA-2 trials

The PALOMA-1 trial

The company focuses on the investigator assessed results for the secondary outcomes, ORR, CBR, DOR and TTP, although BICR results were also provided in the CS for comparison. The definitions and methods of analysis for these secondary efficacy outcomes are provided in Table 5.

Table 35 Description and method of analysis for secondary efficacy outcomes (other than time to progression and overall survival) reported in the PALOMA-1 trial

Outcome	Description	Statistical analysis
ORR	Defined according to RECIST 1.0 from the lesion measurements	[redacted]
CBR	Defined as per RECIST 1.0 as complete response, partial response or stable disease lasting at least 24 weeks	[redacted]
DOR	Time from first documentation of complete or partial response to date of first documentation of objective progression or death	[redacted]

CBR=clinical benefit rate; CI=confidence interval; DOR=duration of response; ITT=intention-to-treat; K-M=Kaplan-Meier; OR=odds ratio; ORR=objective response rate; RECIST=response evaluation criteria in solid tumors
Source: CS, adapted from Table 13, Table 19 and Table 20

The ERG is satisfied that the analysis method for each of these efficacy outcomes was pre-specified in the TSAP, and that all results were reported fully in the CSR. The ERG notes that one sided hypothesis testing was used for the outcomes of ORR and CBR, and asked the company to provide to justify the use of this approach to hypothesis testing. As part of their response to the ERG clarification letter, the company confirmed that one-sided hypothesis testing was deemed suitable due to there being sufficient confidence that PAL+LET was more effective than LET alone, and additionally, that it was more efficient statistically, considering an expected small sample size, under the null hypothesis to use one-sided testing. The ERG is satisfied with the company's justification, although the ERG considers that rationale for such an important statistical decision ought to have been provided in the protocol and/or TSAP.

The PALOMA-2 trial

Although the company focuses on the investigator assessed results for the secondary outcomes, ORR, CBR, and DOR, BICR results were also provided in the CS for comparison. The definitions and methods of analysis for these efficacy outcomes are listed in Table 6.

Table 36 Description of efficacy outcomes reported in the PALOMA-2 trial

Outcome	Description	Statistical analysis
ORR	Defined according to RECIST 1.1 from the lesion measurements	[redacted]
CBR	Defined as per RECIST 1.1 as complete response, partial response or stable disease lasting at least 24 weeks	[redacted]
DOR	Time from first documentation of complete or partial response to date of first documentation of objective progression or death	[redacted]

CBR=clinical benefit rate; CI=confidence interval; CR=complete response; DOR=duration of response; ITT=intention-to-treat; K-M=Kaplan-Meier; OR=odds ratio; ORR=objective response rate; PR=partial response; RECIST=response evaluation criteria in solid tumors; SD=stable disease
Source: CS, adapted from Table 16, Table 19 and Table 20, and the company's response to the ERG clarification letter

The ERG is satisfied that the analysis method for each of these efficacy outcomes was pre-specified in the TSAP, and that all results were reported fully in the CSR.

10.2 ERG assessment of proportional hazards in the PALOMA-1 trial

The ERG requested clarification from the company on whether any PH testing had been conducted for the PFS or OS data from the PALOMA-1 trial. In the company's response to the ERG clarification letter, it was not clear whether the company had performed an assessment of PH for either the PFS or OS data. Consequently, the ERG performed their own assessments of PH using PFS and OS data from the PALOMA-1 trial. The ERG produced cumulative hazard versus cumulative hazard (H-H) plots and log-log plots for PFS (Figure 22 and Figure 23) and OS data (Figure 24 and Figure 25). To demonstrate proportionality of hazards, the H-H plot should demonstrate a straight line trend, with individual data points distributed close to and on either side of the trend line, which should pass through the graph origin (zero value on both axes). The log-log plots should show that the curves for both treatments are approximately parallel if the PH assumption is valid.

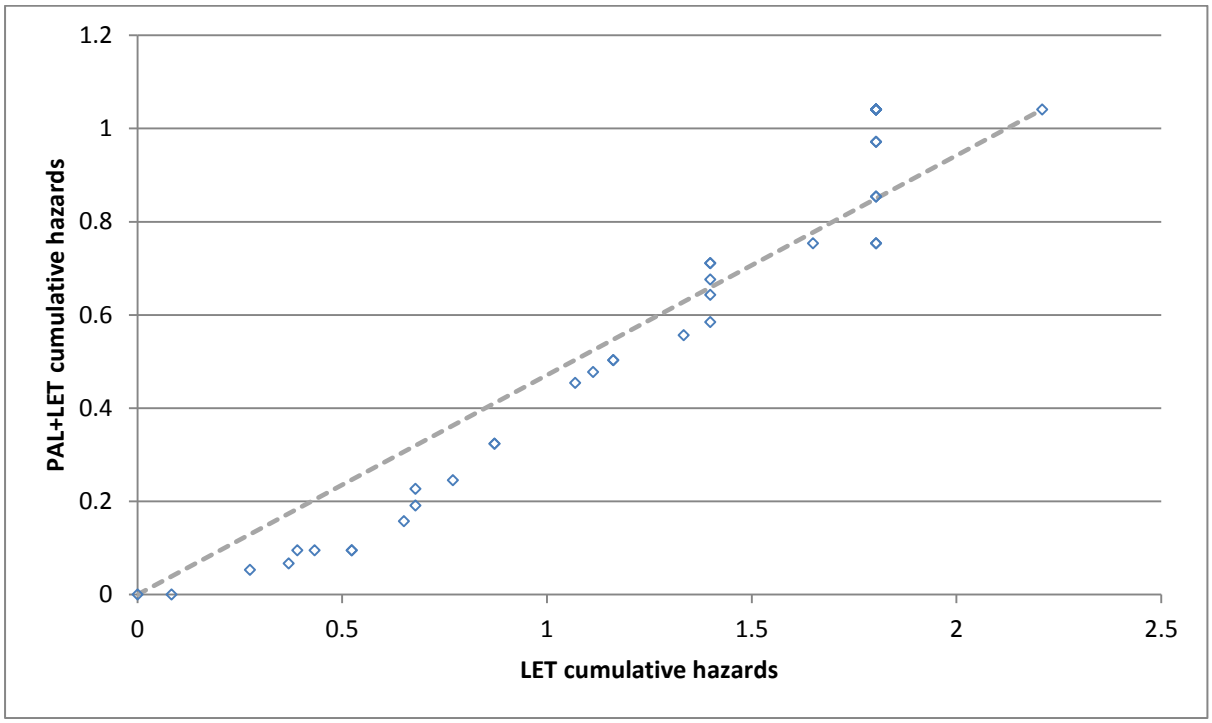

Figure 22 PALOMA-1 PFS H-H plot

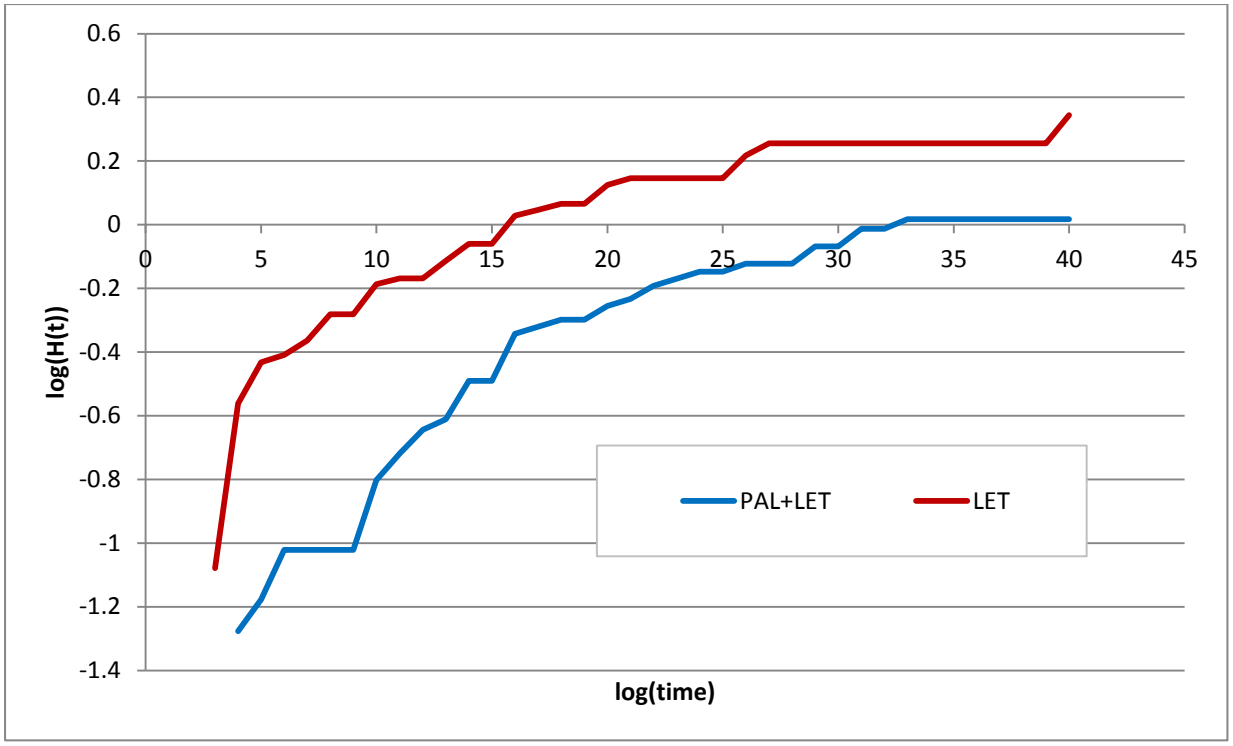

Figure 23 PALOMA-1 PFS log-log plot

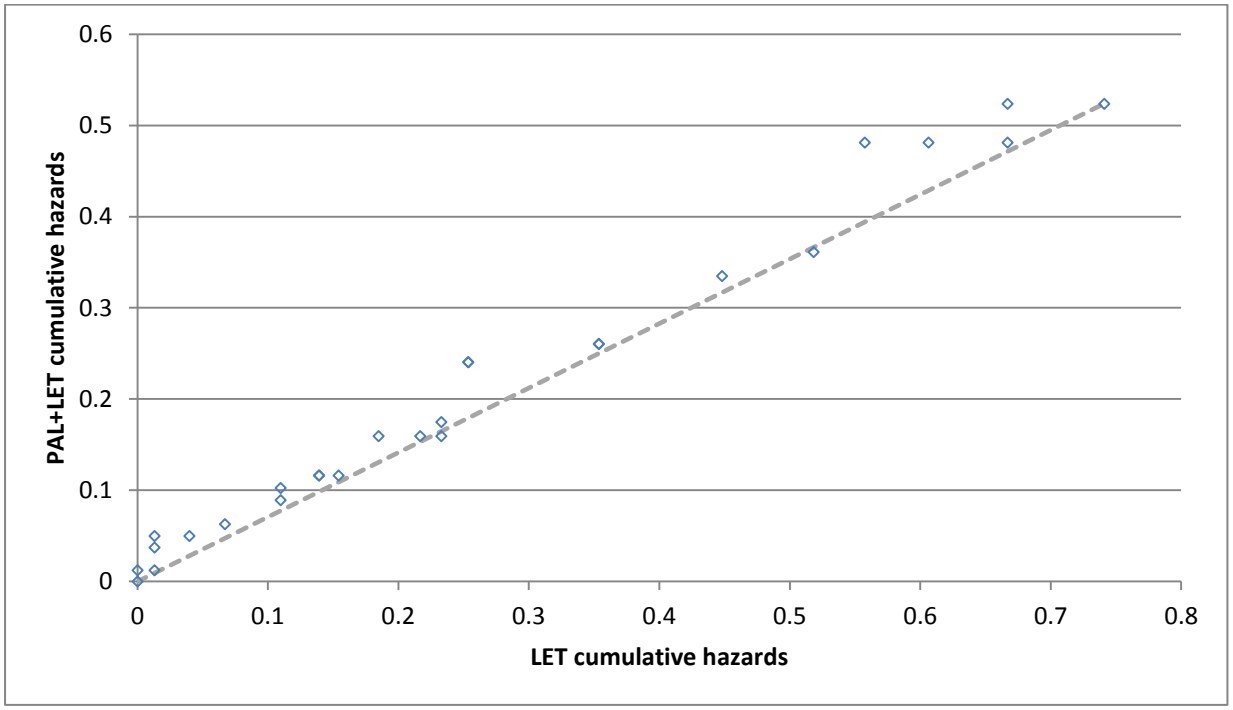

Figure 24 PALOMA-1 OS H-H plot

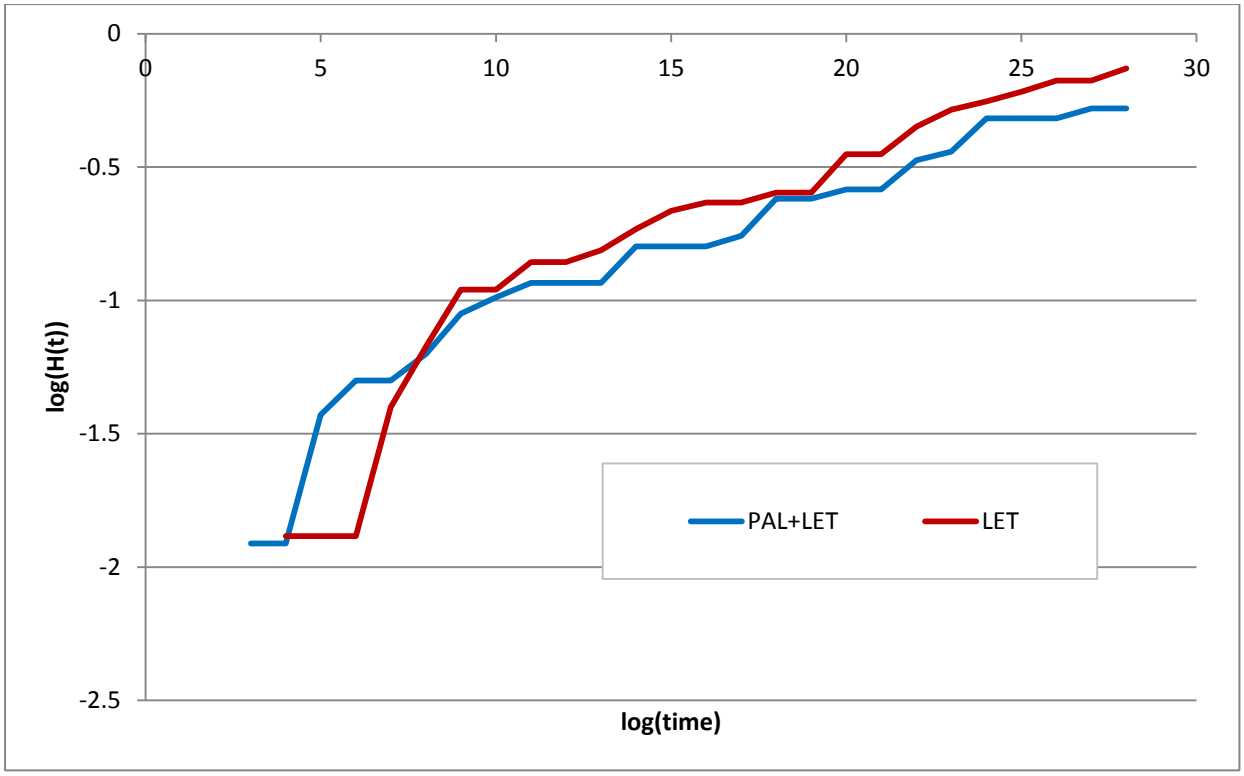

Figure 25 PALOMA-1 OS log-log plot

The ERG considered that it is reasonable to assume that the PH assumption is valid for PFS data, as the log-log plot (Figure 23) demonstrates that the curves are approximately parallel for PAL+LET and LET. Although, individual data points aren't quite randomly scattered about the trend line in the H-H plot (Figure 22), further investigation revealed that when considering data from 100 days onwards, the H-H plot is satisfactory (data not shown). In the first 100 days, the PH assumption does not hold due to the drop off in PFS in the LET arm at the time of the first tumour assessment. The ERG considers that PH is valid for the remainder of the trial period.

For OS, the log-log plot clearly demonstrates that the curves for PAL+LET and LET cross at approximately 8 months, indicating that the assumption of PH is not valid. Therefore, the use of HRs to summarise treatment effect for OS is not appropriate.

10.3 Results from univariate and multivariate analyses of progression-free survival in the PALOMA-2 trial

The results of the univariate and multivariate analyses of PFS are provided in Table 37.

Table 37 Results of the univariate and multivariate analyses of PFS

PFS analysis		**PAL+LET versus PLACEBO+LET, hazard ratio (95% CI)**
Univariate	Investigator assessed	[redacted]
	BICR	[redacted]
Multivariate	Investigator assessed	[redacted]
	BICR	[redacted]

BICR=blinded independent central review; CI=confidence interval; PFS=progression-free survival

10.4 Subsequent treatment received on disease progression in the PALOMA-1 trial

Data on second-line treatment received following disease progression in the PALOMA-1 trial presented at the 38th San Antonio Breast Cancer Symposium in December 2015[103] are summarised in Table 38.

Table 38 First subsequent treatment after progression on study treatment in the PALOMA-1 trial*

Type of treatment received	PAL+LET n=33	LET n=53
Endocrine therapy, n (%)†	15 (45.4)	32 (60.4)
• Exemestane	1 (3.0)	7 (13.2)
• Fulvestrant	9 (27.3)	12 (22.6)
• Letrozole	1 (3.0)	5 (9.4)
• Medroxyprogesterone	4 (12.1)	1 (1.9)
• Tamoxifen	0 (0.0)	7 (13.2)
Chemotherapy, n (%)†	17 (51.5)	21 (39.6)
• Capecitabine	1 (3.0)	4 (7.5)
• Cyclophosphamide	1 (3.0)	3 (5.7)
• Cyclophosphamide/epirubicin/fluorouracil	2 (6.1)	1 (1.9)
• Docetaxel	1 (3.0)	2 (3.8)
• Doxorubicin	1 (3.0)	4 (7.5)
• Epirubicin	2 (6.1)	1 (1.9)
• Fluorouracil	1 (3.0)	2 (3.8)
• Gemcitabine	3 (9.1)	1 (1.9)
• Mitoxantrone	1 (3.0)	1 (1.9)
• Paclitaxel	10 (30.3)	8 (15.1)
• Vinorelbine	1 (3.0)	0 (0.0)
Other therapy, n (%)†	6 (18.2)	13 (24.5)
• Bevacizumab	3 (9.1)	4 (7.5)
• Blinded therapy	3 (9.1)	3 (5.7)
• Everolimus	0 (0.0)	3 (5.7)
• Other	0 (0.0)	5 (9.4)

*These are patients for whom post-progression treatment data were available at data cut-off; note: disease progression on study treatment had occurred in 40 of the 84 patients (47.6%) in the PAL+LET arm and 59 of the 81 patients (72.8%) in the LET-alone arm

† Patients with >1 therapy as the first subsequent therapy after disease progression starting on the same day are reported under each therapy

Source: Finn et al 2015,[103] Table 3

10.5 Other secondary efficacy outcome results from the PALOMA-1 and PALOMA-2 trials

The PALOMA-1 trial

The results of the analyses for the secondary outcomes of PALOMA-1 not reported in the main body of this ERG report are provided in Table 39. ORR was analysed for both the ITT population, and in the subpopulation of patients with measurable disease. All other outcomes were analysed using the ITT population. The company presented both investigator assessed and BICR results where applicable.

Table 39 Additional secondary efficacy outcome results from the PALOMA-1 trial[a]

Outcome	PAL+LET (n=84)	LET (n=81)	p-value between arms[b]
ITT population (n)	84	81	-
Patients with measurable disease (n)	65	66	-
ORR, % (95% CI)			
Investigator assessed	43 (32 to 54)	33 (23 to 45)	p=0.13
BICR[c]	30 (20 to 41)	21 (13 to 32)	p=0.1314
ORR in patients with measurable disease, % (95% CI)			
Investigator assessed	55 (43 to 68)	39 (28 to 52)	p=0.047
BICR[c]	49 (35 to 63)	32.7 (20 to 47)	p=0.0728
CBR, % (95% CI)			
Investigator assessed	81 (71 to 89)	58 (47 to 69)	p=0.0009
BICR[c]	71 (61 to 81)	51 (39 to 62)	p=0.0046
Stable disease lasting at least 24 weeks, %			
Investigator assessed	38.1	24.7	-
BICR[c]	41.7	29.6	-

[a]Results are presented for the ITT population unless otherwise noted
[b]All p-values are one-sided p-values, although no formal testing was performed for secondary endpoints; nominal p-values were reported but no multiplicity adjustments were made for the secondary analyses
[c]BICR was conducted on 97% of the ITT population
BICR=blinded independent central review; CI=confidence interval; CBR=clinical benefit rate; ITT=intention-to-treat; NE=not estimable; ORR=objective response rate; OS=overall survival; TTP=time to progression
Source: CS, adapted from Table 22 and Table 23, and CSR, Table 36

In the ITT population, ORR was higher among patients who received PAL+LET than among those who received LET alone, although this difference was not found to be statistically significant (investigator assessed ORR: 43% versus 33%, p=0.13). The ITT population included patients with both measurable and non-measurable disease. The company states that non-measurable disease was comprised principally by bone-only disease, and that it was important to include these patients in the trial owing to their significant representation of the advanced breast cancer (ABC) population. However, the company states that there are inherent inaccuracies associated with assessing ORR for non-measurable/bone-only disease and that the inclusion of these patients in the ITT population for the analysis of ORR may have contributed to the failure of the ITT population to report significant ORR differences between

the two trial arms. In the measurable disease population, a statistically significant difference was identified for ORR between PAL+LET and LET alone (55% versus 39%, p=0.047).

Results for BICR also suggested a trend in favour of PAL+LET in terms of ORR for both the ITT and measurable disease populations, although the ERG notes that ORR was considerably lower for both treatment groups when assessed by BICR, in comparison to ORR obtained by investigator-assessment.

CBR was found to be statistically significantly higher for PAL+LET patients than LET patients (81% versus 58%, p=0.0009). The company argues that CBR may be a better measure of treatment benefit than ORR for a treatment which has a disease stabilisation component, as CBR incorporates both stable disease for at least 24 weeks, and ORR. Within CBR, the proportion of patients showing stable disease for at least 24 weeks was higher for PAL+LET patients than for those receiving LET alone (38.1% versus 24.7%). BICR results for both CBR and stable disease were broadly comparable to those obtained by investigator-assessment. Clinical advice to the ERG was that CBR is indeed a better tool for assessing efficacy than ORR, as bone only disease is incredibly difficult to assess response rates with existing imaging modalities. The ERG therefore agrees with the company that is appropriate to consider ORR in patients with measurable disease as well as in the ITT population, and also to consider the results of the analyses of CBR.

The PALOMA-2 trial

The results of the analyses for the secondary outcomes of PALOMA-2 not reported in the main body of this ERG report are provided Table 40. ORR and DOR were analysed for both the ITT population, and in the subpopulation of patients with measurable disease. All other outcomes were analysed using the ITT population. The company presented both investigator assessed and BICR results where applicable.

In the ITT population, ORR was higher among patients who received PAL+LET than those who received PLACEBO+LET (42.1% versus 34.7%), although this difference was not found to be statistically significant (odds ratio [OR]=1.40; 95% CI 0.98 to 2.01). The BICR result for this population achieved statistical significance. In the population of patients with measurable disease, a statistically significant difference was identified for ORR between PAL+LET and PLACEBO+LET (55.3% versus 44.4%), corresponding to an OR of 1.55 (95% CI 1.05 to 2.28). For the measurable disease population, the BICR result was in accordance with investigator assessed ORR.

CBR was found to be statistically significantly higher for PAL+LET patients than PLACEBO+LET patients (84.9% versus 70.3%), corresponding to an OR of 2.39 (95% CI 1.58 to 3.59). BICR results for CBR were broadly comparable to those obtained by investigator-

assessment. Within CBR, the proportion of patients showing stable disease for at least 24 weeks was [redacted] for PAL+LET patients than for those receiving PLACEBO+LET [redacted].

Table 40 Additional secondary efficacy outcome results from the PALOMA-2 trial[a]

	PAL+LET (n=84)	LET (n=81)	p-value between arms[b]
ITT population (n)	444	222	-
Patients with measurable disease (n)	338	171	-
ORR, % (95% CI)			
Investigator assessed	42.1 (37.5 to 46.9)	34.7 (28.4 to 41.3)	0.0310
BICR[c]	[redacted]	[redacted]	[redacted]
ORR in patients with measurable disease, % (95% CI)			
Investigator assessed	55.3 (49.9 to 60.7)	44.4 (36.9 to 52.2)	0.0132
BICR[c]	[redacted]	[redacted]	[redacted]
CBR, % (95% CI)			
Investigator assessed	84.9 (81.2 to 88.1)	70.3 (63.8 to 76.2)	<0.0001
BICR[c]	[redacted]	[redacted]	[redacted]
DOR, median (months), (95% CI)			
Investigator assessed	22.5 (19.8-28.0)	16.8 (14.2-28.5)	NA
BICR[c]	[redacted]	[redacted]	[redacted]
DOR in patients with measurable disease, median (months) (95% CI)			
Investigator assessed	22.5 (19.8-28.0)	16.8 (15.4-28.5)	NA
BICR[c]	[redacted]	[redacted]	[redacted]
Stable disease ≥24 weeks in confirmed cases of the ITT population, %			
Investigator assessed	[redacted]	[redacted]	-

[a]Results refer to the ITT population unless otherwise noted
[b]All p-values are one-sided p-values
[c]BICR was conducted on the entire ITT population
BICR=blinded independent central review; CBR=clinical benefit response; CI=confidence interval; DOR=duration of response; ITT=intention-to-treat; NA=not applicable; NE=not estimable; ORR=objective response rate
Source: CS, adapted from Table 24 and 25, and the CSR, Table 27

10.6 Most common adverse events in the PALOMA trials

Table 41 Most common (>20% in any treatment arm) treatment emergent adverse events in the PALOMA-1 and PALOMA-2 trials

Adverse events, n (%)	PALOMA-1						PALOMA-2					
	PAL+LET (n=83)			LET (n=77)			PAL+LET (n=444)			LET (n=222)		
	All-Grade	Grade 3	Grade 4	All-Grade	Grade 3	Grade 4	All-Grade	Grade 3	Grade 4	All-Grade	Grade 3	Grade 4
Neutropenia*	62 (74.7)	40 (48.2)	5 (6.0)	4 (5.2)	1 (1.3)	0	353 (79.5)	249 (56.1)	46 (10.4)	14 (6.3)	2 (0.9)	1 (0.5)
[redacted]												
Leukopenia*	36 (43.4)	16 (19.3)	0	2 (2.6)	0	0	173 (39.0)	107 (24.1)	3 (0.7)	5 (2.3)	0	0
Fatigue	34 (41.0)	2 (2.4)	2 (2.4)	18 (23.4)	1 (1.3)	0	166 (37.4)	8 (1.8)	0	61 (27.5)	1 (0.5)	0
Nausea	21 (25.3)	2 (2.4)	0	10 (13.0)	1 (1.3)	0	156 (35.1)	1 (0.2)	0	58 (26.1)	4 (1.8)	0
Arthralgia	19 (22.9)	1 (1.2)	0	12 (15.6)	2 (2.6)	0	148 (33.3)	3 (0.7)	0	75 (33.8)	1 (0.5)	0
Alopecia	18 (21.7)	0	0	2 (2.6)	0	0	146 (32.9)	0	0	35 (15.8)	0	0
Diarrhoea	17 (20.5)	3 (3.6)	0	8 (10.4)	0	0	116 (26.1)	6 (1.4)	0	43 (19.4)	3 (1.4)	0
Cough	10 (12.0)	0	0	8 (10.4)	0	0	111 (25.0)	0	0	42 (18.9)	0	0
Anaemia	29 (34.9)	4 (4.8)	1 (1.2)	5 (6.5)	1 (1.3)	0	103 (23.2)	23 (5.2)	1 (0.2)	20 (9.0)	4 (1.8)	0
Back pain	12 (14.5)	0	1 (1.2)	12 (15.6)	1 (1.3)	0	96 (21.6)	6 (1.4)	0	48 (21.6)	0	0
Headache	12 (14.5)	0	0	8 (10.4)	0	0	95 (21.4)	1 (0.2)	0	58 (26.1)	4 (1.8)	0
Hot flush	17 (20.5)	0	0	9 (11.7)	0	0	93 (20.9)	0	0	68 (30.6)	0	0

Source: CS, Tables 39 and 41 and published paper for the PALOMA-2 trial[93]

*In the PALOMA-2 trial, neutropenia was categorised according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms neutropenia and neutrophil count decreased and leukopenia was categorised according to the MEDRA preferred terms leukopenia and white blood cell count decreased

10.7 Calculation of post-progression utility values

Utility values were transformed using the formula from Lloyd et al:[5]

$$Transformed\ utility = ln\left(\frac{1 - utility}{utility}\right)$$

And back transformed using the following formula:

$$Utility = \frac{1}{1 + \exp(transformed\ utility)}$$

10.8 Adjusting a parametric curve using medians

The primary assumption underlying the company's modelling of OS in the base case is that post-progression survival is equal for patients treated with PAL+LET and PLACEBO+LET; that is, all survival gain is accrued in the progression-free state. However, this assumption is not borne out in the model, as using *medians* to recalibrate the OS curve for PAL+LET has resulted in a *mean* PPS gain for patients treated with PAL+LET. By subtracting PFS from OS on a cycle-by-cycle basis, the ERG has calculated a mean PPS gain for PAL+LET of 0.49 months in the base case.

The reason that mean OS gain increases when a Weibull model is adjusted based on its median is because the ratio of median to mean is based on the interaction of the shape and scale parameters used to specify the curves. The Weibull distribution fitted to the OS K-M data from the PAL+LET arm of the PALOMA-1 trial and the adjusted version of this model used in the base case are both right skew, which means that the mean is greater than the median in both cases. The ratio of median to mean is also different in both of these Weibull models. The combination of the right skew and the dynamic ratio of median to mean means that adjusting the scale parameter, as the company has, in order to achieve a larger median OS gain has a proportionately greater effect on mean OS for PAL+LET and, thus, on mean OS gain.

Table 42 shows how the ratio of median to mean OS gain when using the adjusted base case model for PAL+LET is proportionately greater than when using the unadjusted Weibull model (0.830 versus 0.773).

Table 42 Comparison of median and mean OS between the base case and the unadjusted PALOMA-1 model

	Median in model (months)		Mean in model (months)		Median:Mean	
	OS	OS Gain	OS	OS Gain	OS	OS Gain
PAL+LET (base case adjusted Weibull)	44.3	9.3	49.9	11.2	0.888	0.830
PAL+LET (PALOMA-1 IPD Weibull)	40.1	5.1	45.3	6.6	0.885	0.773
PLACEBO+LET (PALOMA-1 IPD Weibull)	35.0	-	38.7	-	0.904	-

Source: Company model, ERG calculations
*Note: Some values given in the CS differ from those in the model. Model values have been used where discrepancies exist.

10.9 Company scenario analyses 27 to 36

The company argues that limitations it has identified in the ICER per QALY gained calculation, might be mitigated by the adoption of certain assumptions regarding the cost of the comparator, the pre-progression utility value, the modelling of OS, and the cost of care in the post-progression state. The company has put together several assumptions in different combinations that yield ICERs per QALY gained of under £50,000 (company Scenarios 32 to 36). Since each of these assumptions in isolation has flaws and/or breaches standard NICE methods, the ERG considers the uncertainty inherent in the combined scenarios to render them uninformative.

The company presents a variety of exploratory scenarios in which it investigates the effects on the ICER per QALY gained of varying the assumptions in the model beyond the parameters of the standard sensitivity analyses. The ICERs per QALY gained in the company's exploratory scenarios range from £26,996 to £312,635 (Table 43).

Table 43 Company exploratory scenario analyses varying model assumptions (palbociclib at list price)

Scenario # in CS	Assumptions varied	ICER/QALY gained	ICER change
Base case deterministic ICER		**£150,869**	**-**
27	Only PFS gain for PAL+LET (10.3 months) No OS gain for PAL+LET (0 months)	£312,635	+ £161,766
28a	Increase median OS gain for PAL+LET to 5 years	£61,822	- £89,047
28b	Increase median OS gain for PAL+LET to 5 years, *but removing post-progression costs*	£42,794	- £108,075
29	Increase in utility of +0.1 for patients in the PFS state	£134,134	- £16,735
30	A comparator with the same monthly acquisition costs *(i.e. fixed cost of £2,951.52 per month, but only for respective treatment durations)*	£53,074	- £97,795
31	Reduced treatment duration by 12 months in each arm *(PFS reduced from 15.7 to 3.7 months for LET, and from 24.9 to 12.9 months for PAL+LET)*	£86,419	- £64,450
32	• Comparative monthly acquisition costs • Value of PFS utility increase (+0.1) *No change to base case OS assumption*	£47,187	-£103,682
33	• Comparative monthly acquisition costs (#30) • Value of PFS utility increase (+0.1) • Incremental median OS gain of 12 months	£43,819	-£107,050
34	• Comparative monthly acquisition costs • Value of PFS utility increase (+0.1) • Incremental median OS gain of 12 months • Removal of post-progression costs	£40,482	-£110,387
35	• Comparative monthly acquisition costs (#30) • Value of PFS utility increase (+0.1) • Incremental median OS gain of 24 months	£36,194	-£114,675

Scenario # in CS	Assumptions varied	ICER/QALY gained	ICER change
36	• Comparative monthly acquisition costs • Value of PFS utility increase (+0.1) • Incremental median OS gain of 24 months • Removal of post-progression costs	£26,996	-£123,873
From scenarios 33 and 34	Incremental OS gain of 12 months	£134,294	-£16,575
From scenarios 35 and 36	Incremental OS gain of 24 months	£95,656	-£55,213
From scenarios 28b, 34, 35 & 36	Remove all post-progression costs	£150,303	-£566

ICER=incremental cost effectiveness ratio; PFS=progression free survival; QALY=quality adjusted life year; OS=overall survival
Source: CS Table 85; CS Table 86; ERG calculations

The company's exploratory scenarios fall into to one (or a combination) of four categories: OS gain for PAL+LET; acquisition costs of letrozole; PFS utility values; and post-progression costs.

Company exploratory scenarios: OS gain for PAL+LET

The ERG considers it justifiable to explore alternative OS scenarios given the problems inherent in the PALOMA-1 data, however the ERG considers the magnitude of the gains modelled to be implausible given the preliminary data available from the PALOMA-1 and PALOMA-2 trials, and is not aware of any other data that would support such gains.

The company presents these scenarios to demonstrate the importance of OS on the ICER per QALY gained. The company states that that treatment with PAL+LET would need to extend life by approximately 9 years to yield an ICER per QALY gained of around £50,000 (with palbociclib at list price and all other base case assumptions remaining the same), which it notes is not clinically plausible. However, the price of the drug also influences the impact of extended time spent in PFS. If the cost of palbociclib were to increase or decrease, and all other elements of the model were to stay the same, the size of the OS gain required to bring the ICER down towards the NICE threshold would also increase or decrease

The company supports its modelling of improved OS gains for treatment with PAL+LET versus treatment with LET by suggesting that people with stable disease are less likely to die (and thus time in PFS will be reflected in time in OS). Supported by additional evidence, amendments to the model structure could be made to apply differential death rates to the pre-progression and post-progression health states within the model and produce further scenario analyses. However, the lack of maturity of the OS data means any such estimates at present, if calculated, would carry substantial uncertainty.

Company exploratory scenarios: acquisition costs of letrozole

The company argues that the introduction of a new treatment, such as palobociclib, as an add-on therapy or into a therapy area with no new treatment or breakthrough, inherently values that new treatment less than if the therapy area had already benefitted from recent innovation. The company attempts to show that this is the case by running a scenario where the price of LET monotherapy is equal to the price of PAL+LET. Whilst the ERG agrees that a comparison with a generic drug makes it relatively more difficult to demonstrate cost-effectiveness in the mathematical sense, NICE methods do not allow for deviation on this basis as the true opportunity cost for the NHS must be considered in potentially reallocating resources from a generic to a proprietary drug.

The ERG also considers the implementation of this scenario to be methodologically flawed as, rather than changing the price of letrozole to equal that of palbociclib and thus double the cost of the combined therapy, only the price of letrozole when used as monotherapy is amended. The ERG does not therefore consider the comparative acquisition costs scenario as plausible in practice as if letrozole had a higher list price, this would also be the price for use in combination with palbociclib.

Company exploratory scenarios: PFS utility values

The company argues that PFS is undervalued for a number of reasons in Section 3.2.1 of the CS and presents a sensitivity analysis in which the utility of the PFS health state is increased by 0.1 which results in an ICER of £134,134. The ERG considers that many of the arguments put forward by the company are in fact adequately reflected in the utility values used to represent the health states within the model. The benefit of having stable disease (being in the pre-progressed health state) in the model is an improvement in health-related quality of life of more than 0.2 (on the 0-1 utility scale) over the progressed health state, in both the company estimated and the ERG re-calculated utility values. This incremental benefit exists for the duration of any PFS extension offered by PAL + LET treatment in comparison to LET alone. The value used to estimate progressed utility is taken from a study of patients receiving chemotherapy and therefore any difference in AE profiles or psychological impacts between the treatments received pre- and post-progression is represented within the difference between the health-related quality of life values.

The ability to continue to work is captured within the activities of daily living question which forms part of the EQ-5D questionnaire in which patients would indicate a lower score if their normal working pattern was disrupted. The costs to the patients of being unable to undertake paid employment cannot be considered as part of the NICE appraisal process without discriminating in favour of individuals of working-age.

The company argues that the burden on carers of patients with this disease is so substantial that its exclusion contributes to undervaluing the benefit of PFS. The company does not however present any evidence to quantify the health-related quality of life impact of caring for a patient with progressed disease may have, nor explore this as an individual hypothetical scenario within the modelling.

The data used to value PFS in this model are the best available and consistent with the NICE reference case, which is used to benchmark all appraisals. Any departure from EQ-5D values directly obtained from patients would only be supported given significant evidence of the insufficiency of the EQ-5D to capture all elements relevant to patients in this disease area. Given that the arguments put forward by the company do not appear specific to postmenopausal women with ER+/HER2- ABC who have never received systemic therapy in the LABC/MBC setting but could in fact be relevant to all patients with ABC, or the population of people with breast cancer as a whole, any methodological change to the valuation of utility would have implications for all appraisals of breast cancer interventions.

Company exploratory scenarios: post-progression costs

The company includes the removal of post-progression costs as part of their scenarios with combinations of amendments (Scenarios 28b, 34 & 36). As the only post-progression costs that are included within the company model are the costs of monitoring patients undergoing further therapy, the impact of removing these costs is minimal. As shown in Table 43, the ICER decreases by £566.

In addition, the DSU discussion paper regarding cost-effectiveness at zero price[119] considers scenarios in which non-treatment related costs could be excluded however concludes that a narrow perspective does not enable full consideration of the opportunity cost to the NHS of the introduction of a new technology and therefore the ERG does not consider this element of the scenario analyses plausible.

10.10 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 - L.

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	Description
R1)	Mod_A	ERG OS estimates based on data from PALOMA-1
R2)	Mod_B	ERG PFS estimates based on data from PALOMA-1
R3)	Mod_C	ERG TTD estimates based on data from PALOMA-1
R4)	Mod_D	ERG recalculated pre-progression utility values from PALOMA-2 trial
R5)	Mod_E	ERG recalculated post-progression utility values using Lloyd 2006[5]
R6)	Mod_F	Use mid-cycle correction
R7)	Mod_G	Use full reference costs for AEs
R8)	Mod_H	Correct AE incidence calculation
R9)	Mod_I	Change discounting to annual
R10)	Mod_J	Use 365.25 days per year
R11)	Mod_K	ERG PFS estimates based on data from PALOMA-2
R12)	Mod_L	ERG TTD estimates based on data from PALOMA-2

Instructions for modifying the company model

1. Move all sheets from *palbo 915_ERG additional model data.xlsx* into company model

2. 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) ERG OS	Mod_A	OS_L1	X58 copy down to X578	Amend PAL+LET OS =IF(Mod_A=0,CHOOSE(OS_model_scenario,W58,U58,V58),'ERG time to event_P1'!N11) N.B. amend formatting to multiple decimal places after pasting
R1) ERG OS	Mod_A	OS_L1	M58 copy down to M578	Amend LET OS =IF(Mod_A=0,K58, 'ERG time to event_P1'!O11)
R2) ERG PFS estimates based on data from PALOMA-1 AND R11) ERG PFS estimates based on data from PALOMA-2	Mod_B Mod_K	PFS_L1	W57 copy down to W577	Amend PAL+LET PFS =IF(AND(Mod_B=0,Mod_K=0),U57,IF(AND(Mod_B=1, Mod_K=0), 'ERG time to event_P1'!F11, IF(AND(Mod_B=0, Mod_K=1), 'ERG time to event_P2'!F11)))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R2) ERG PFS estimates based on data from PALOMA-1 AND R11) ERG PFS estimates based on data from PALOMA-2	Mod_B Mod_K	PFS_L1	M57 copy down to M577	Amend LET PFS =IF(AND(Mod_B=0,Mod_K=0),K57, IF(AND(Mod_B=1, Mod_K=0), 'ERG time to event_P1'!G11, IF(AND(Mod_B=0, Mod_K=1), 'ERG time to event_P2'!G11))) N.B. amend formatting to multiple decimal places after pasting
R3) ERG TTD estimates based on data from PALOMA-1 AND R12) ERG TTD estimates based on data from PALOMA-2	Mod_C Mod_L	EnginePAL_LET	AP11 copy down to AP531	Amend PAL+LET TTD =IF(AND(Mod_C=0,Mod_L=0),$F11*AP$9, IF(AND(Mod_C=1,Mod_L=0),'ERG time to event_P1'!V11*$AP$9, IF(AND(Mod_C=0,Mod_L=1), 'ERG time to event_P2'!V11*$AP$9)))
R3) ERG TTD estimates based on data from PALOMA-1 AND R12) ERG TTD estimates based on data from PALOMA-2	Mod_C Mod_L	EngineLET_PBO	AP11 copy down to AP531	Amend LET TTD =IF(AND(Mod_C=0,Mod_L=0),$F11*AP$9, IF(AND(Mod_C=1,Mod_L=0),'ERG time to event_P1'!W11*$AP$9, IF(AND(Mod_C=0,Mod_L=1), 'ERG time to event_P2'!W11*$AP$9)))
R4) ERG recalculated pre-progression utility values from PALOMA-2 trial	Mod_D	Utility	C18	Amend PAL+LET pre-progression utility =IF(mod_D=0,IF(D18="",CHOOSE(I18,E18,F18,G18,H18),D18), [redacted])
R4) ERG recalculated pre-progression utility values from PALOMA-2 trial	Mod_D	Utility	C12	Amend LET pre-progression utility =IF(Mod_D=0,IF(D12="",CHOOSE(I12,E12,F12,G12,H12),D12), [redacted])

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R5) ERG recalculated post-progression utility values using Lloyd 2006	Mod_E	Utility	C19 copy down to C21	Amend PAL+LET post-progression utility =IF(D19="",IF(Mod_E=0,E19,0.5052),D19)
R5) ERG recalculated post-progression utility values using Lloyd 2006	Mod_E	Utility	C13 copy down to C15	Amend LET post-progression utility =IF(D13="",IF(Mod_E=0,E13,0.5052),D13)
R6) Use mid-cycle correction	Mod_F	ERG_mid cycle correction	B11 copy down to B532	Create mid-cycle PFS for PAL+LET =PFS_L1!W57
R6) Use mid-cycle correction	Mod_F	ERG_mid cycle correction	E11 copy down to E532	Create mid-cycle PFS for LET =PFS_L1!M57
R6) Use mid-cycle correction	Mod_F	ERG_mid cycle correction	J11 copy down to J532	Create mid-cycle OS for PAL+LET =OS_L1!X58
R6) Use mid-cycle correction	Mod_F	ERG_mid cycle correction	M11 copy down to M532	Create mid-cycle OS for LET =OS_L1!M58
R6) Use mid-cycle correction	Mod_F	EnginePAL_LET	D11 copy down to D531	Amend PAL+LET OS for mid-cycle correction =IF(Mod_F=0,MAX(1E-50,OS_L1!X58), MAX(1E-50,'ERG_mid cycle correction'!L11))
R6) Use mid-cycle correction	Mod_F	EnginePAL_LET	E11 copy down to E531	Amend PAL+LET PFS for mid-cycle correction =IF(Mod_F=0,PFS_L1!W57,'ERG_mid cycle correction'!D11)
R6) Use mid-cycle correction	Mod_F	EngineLET_PBO	D11 copy down to D531	Amend LET OS for mid-cycle correction =IF(Mod_F=0,MAX(1E-50,OS_L1!M58), MAX(1E-50,'ERG_mid cycle correction'!O11))
R6) Use mid-cycle correction	Mod_F	EngineLET_PBO	E11 copy down to E531	Amend LET PFS for mid-cycle correction =IF(Mod_F=0,PFS_L1!M57,'ERG_mid cycle correction'!G11)
R7) Use full reference costs for AEs	Mod_G	Cost_AE	C46 copy down to C47	Amend AE costs for Grade 3 and Grade 4 neutropenia =IF(Mod_G=0,IF(D46="",CHOOSE(I46,E46,F46,G46,H46),D46), 132)

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R8) Correct AE incidence calculation	N/A	AE_P_2	F96 copy across and down to G97	Calculate AE rates =(-LN(1-C80)/$C$73)
R8) Correct AE incidence calculation	N/A	AE_P_2	H96 copy across and down to I97	Calculate AE cycle probabilities =1-EXP(-F96*28)
R8) Correct AE incidence calculation	Mod_H	AE_P_2	C96 copy across and down to D97	Change annualised AE probability to cycle probability =IF(Mod_H=0,1-((1-CHOOSE($C$91,C80,B89*C80,B90*C80,C85))^(GenSettings!$C$62/C$73)),H96)
R8) Correct AE incidence calculation	Mod_H	AE_P_2	C73	Change duration on treatment for PAL+LET from median to mean and make dynamic =IF(Mod_H=0,603, IF(AND(Mod_H=1,Mod_C=0, Mod_L=0), Results_Deterministic!F41*DaysInMonth, IF(AND(Mod_H=1, Mod_C=1,Mod_L=0), 'ERG time to event_P1'!V8, IF(AND(Mod_H=1, Mod_C=0,Mod_L=1), 'ERG time to event_P2'!V8))))
R8) Correct AE incidence calculation	Mod_H	AE_P_2	D73	Change duration on treatment for LET from median to mean and make dynamic =IF(Mod_H=0,420, IF(AND(Mod_H=1,Mod_C=0,Mod_L=0), Results_Deterministic!E41*DaysInMonth, IF(AND(Mod_H=1, Mod_C=1,Mod_L=0), 'ERG time to event_P1'!W8, IF(AND(Mod_H=1, Mod_C=0,Mod_L=1), 'ERG time to event_P2'!W8))))
R9) Change discounting to annual	Mod_I	Discounting	B6 copy down to B526	Change discounting to annual =IF(Mod_I=0,A6/13,ROUNDDOWN(A6/13,0))
R10) Use 365.25 days per year	Mod_J	GenSettings	C62	Change to 365.25 days per year =IF(Mod_J=0,364,365.25)

ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer [ID915]

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The company identified 8 overall issues in relation to factual inaccuracies in the original Evidence Review Group (ERG) report. All were considered by the ERG to require minor changes to the text. The pages of the report affected are presented here. Please note:

- New text added by the ERG is in *italics*.
- Text deleted completely (as opposed to being re-worded) is struck out.
- Unaltered text which is considered to be of relevant context to that added, amended or deleted (such as headings or sentences preceding or following the added, amended or deleted text) is presented in its original font.
- All other unaltered text is greyed out.

- The PALOMA-1 trial is a relatively small trial compared to the PALOMA-2 trial and this may explain why there are some apparent imbalances in terms of baseline characteristics and treatments received on disease progression

Cost effectiveness evidence

- Modelling survival using data from two different trials is methodologically unsound
- There is no trial evidence to support the assumption that 100% of PFS gain for treatment with PAL+LET will translate into OS gain
- There is no trial evidence to support the assumption of equal PPS (zero PPS gain) for treatment with PAL+LET and treatment with LET
- The method used to adjust OS data from the PALOMA-1 trial to incorporate the assumptions of (i) PFS gain is equal to OS gain and (ii) zero PPS gain, results in neither of these assumptions holding in the model
- The Weibull model used to project PFS results in implausible hazard profiles in the long-term
- The company's use of PFS data rather than TTD data as the basis for calculating first-line drug acquisition costs leads to inaccurate cost estimates
- There is no valid basis for the company's assumption that, prior to disease progression, the HRQoL of patients prescribed PAL+LET is better than that of patients prescribed LET and, therefore, only one utility value should have been used to represent patient HRQoL in this health state
- *Incorrect* calculation of the utility value used to represent the HRQoL of patients in the PPS state renders the company's estimate invalid
- The company model does not include a half-cycle correction
- *The company employed a per-cycle rather than annual method of discounting*
- The AE costs used in the company model are unreliable as they are based on annual rather than per cycle incidence rates and an average treatment cost (rather than AE-specific treatment costs)
- The algorithm used by the company to generate PSA results did not take into account any correlated uncertainty in the key model parameters (Weibull model scale and shape parameters)
- Within the company model a year comprises 364 rather than 365.25 days.

1.4 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made 12 individual changes to the submitted model, namely: re-modelling OS; re-modelling PFS and TTD based on the PALOMA-1 trial data; re-modelling PFS and TTD based on the PALOMA-2 trial data; re-calculating pre- and post-progression utility values; adding a half-cycle correction; re-calculating AE costs and probabilities; changing discounting to annual rather than per cycle; and changing the number of days per year to 365.25

comparison of palbociclib to an aromatase inhibitor have been identified by, and included in, the company's systematic review.

The ERG notes that the eligibility criteria applied by the company enabled reviewers to exclude studies based on reported trial outcomes. This could, theoretically, introduce outcome selection bias by excluding any study that measured, but did not report, specific outcomes.[71] However, the ERG also notes that as a range of outcomes were specified and as there was no need for included studies to report *all* outcomes but just one of these outcomes, in this instance, including or excluding studies based on outcomes is unlikely to be an important issue with regard to bias.

4.1.3 Data extraction

It is stated in the CS that, for both systematic reviews, data from studies included in the systematic review were extracted into a pre-specified extraction grid developed in Microsoft Excel. It is unclear if data extraction was conducted by one, two, or more reviewers and if this was conducted independently or extracted by one reviewer and cross-checked by another. However, the ERG notes that for studies included in the company's cost effectiveness review, data were extracted by a single reviewer and verified by a second individual.

4.1.4 Quality assessment methods

A risk of bias assessment of the RCTs included in the systematic review of clinical effectiveness was undertaken by the company using the method recommended by NICE[72] (based on the Centre for Reviews and Dissemination's guidance[73]). The company also assessed the methodological quality of the non-randomised and non-controlled studies that they provided as supportive evidence using the Down and Black's checklist for non-randomised studies.[74] This checklist is cited as a checklist to consider using in Appendix H of the manual for developing NICE guidelines.[75,76] It is unclear whether the quality assessment of RCTs and/or non-randomised and non-controlled studies was completed by one reviewer, or independently by two reviewers.

4.1.5 Approach to evidence synthesis

The company's literature search for RCTs led to the identification of two trials that were considered to be directly relevant to the decision problem (the PALOMA-1 and PALOMA-2 trials). The company did not carry out a meta-analysis of efficacy outcomes or pool data for AEs from the two trials (although the company did present pooled data for some AEs occurring in patients treated with *palbociclib from the PALOMA-1, PALOMA-2 and PALOMA-3 trials*); instead the company described and reported findings from the *PALOMA-1 and PALOMA-2 trials* narratively. As stated in the company response to the ERG during the clarification

process, its reason for this was that it considered that the PALOMA-2 trial (the larger, confirmatory, later phase trial) was the most robust data source.

Seven citations[77-83] reporting on four studies were considered relevant to the company's systematic review of non-randomised and non-controlled studies. Within the CS, the company has described the studies and reported findings narratively.

The ERG considers that the company's approach to evidence synthesis was appropriate for both systematic reviews. The ERG also considers that, for completeness, a meta-analysis of OS and PFS outcomes from the PALOMA-1 and PALOMA-2 trials, and pooling of the AE data from *only* these two trials, may have been informative (*since the PALOMA-3 trial investigated palbociclib in combination with fulvestrant and included patients previously treated for MBC*). However, the ERG also considers that the reporting of the PALOMA-1 and PALOMA-2 trial data narratively was also appropriate, and sufficient for the purposes of this appraisal.

4.2 Identified studies in the systematic reviews

4.2.1 Randomised controlled trial evidence

Two relevant trials were included in the systematic review of RCT evidence, the phase I/II, multi-centre, randomised, open-label PALOMA-1 trial (N=165) and the larger (N=666) phase III, multi-centre, randomised, double-blind, placebo-controlled PALOMA-2 trial. Both trials included postmenopausal women with ER+/HER2- ABC who had not received previous systemic treatment in the advanced or metastatic setting. The PALOMA-1 trial was designed to compare the efficacy and safety of treatment with PAL+LET with LET, whilst the PALOMA-2 trial was designed to compare the efficacy and safety of PAL+LET with placebo in combination with LET (PLACEBO+LET).

Patients were randomly allocated to treatment in a 1:1 ratio in the PALOMA-1 trial. Randomisation was performed using an interactive web-based randomisation system, stratified by disease site (visceral versus only bone versus other) and by DFI (>12 versus ≤12 months between completion of the last adjuvant treatment and disease recurrence) or de novo.

Patients were randomly assigned 2:1 to the PALOMA-2 trial via an interactive randomisation technology system. Patients were stratified by disease site (visceral versus non-visceral), DFI since completion of prior (neo)adjuvant therapy (de novo metastatic versus ≤12 months versus >12 months), and nature of prior (neo)adjuvant anti-cancer treatment (prior hormonal therapy versus no prior hormonal therapy).

The primary results from the PALOMA-1 trial have been published in a peer reviewed journal.[49] In addition, results relating to pain severity and pain interference,[84] and an expanded analysis

of patients had an ECOG PS ≥2 in the PAL+LET arm compared with **** of patients in the LET arm. However, the numbers of patients in both arms who received subsequent treatment were very small (n=33 and n=53 respectively) as was the number of patients for whom ECOG PS was available for (**** and **** respectively). The ERG notes that small differences in actual numbers can result in large differences in proportions and therefore suggests that the data from the PALOMA-1 trial must be treated with caution.

Treatment received on disease progression in the PALOMA-2 trial

During the clarification process the company provided data showing that ********** in both arms of the PALOMA-2 trial. In this trial a large number of patients received subsequent treatments (***** in the PAL+LET arm and ***** in the PLACEBO+LET arm). The most common post-progression hormonal treatments received by patients in the PAL+LET and PLACEBO+LET arms respectively were ********** and the most common chemotherapies were **********. ECOG PS at time of progression by arm was ********** in this trial than in the PALOMA-1 trial: **********.

ERG comment on overall survival findings

The ERG considers that the post-progression treatments received by patients in both trials are treatments that are routinely offered to patients with MBC in clinical practice. However, clinical opinion received by the ERG is that patients in England and Wales are more likely to receive anthracycline based treatments on disease progression, especially when patients do not receive an anthracycline treatment as a component of adjuvant treatment. Baseline characteristics reported for the PALOMA-1 and *PALOMA-2* trials include details of prior chemotherapy, not prior anthracycline based chemotherapy.

4.6.4 Other secondary efficacy outcome results

The company reported a number of other secondary outcomes, including ORR, CBR and DOR. These are described and critiqued in appendices to this ERG report.

4.6.5 Safety

Safety data for patients in the PALOMA-1 and PALOMA-2 trials treated with PAL+LET are reported in the CS. *Pooled data for palbociclib in combination with LET or fulvestrant are presented in the CS (Table 43) and used to inform the information presented in the draft summary of product characteristics. In this section of the ERG report, the ERG has confined its critique of AEs to PAL+LET versus LET or PLACEBO+LET from the PALOMA-1 and PALOMA-2 trials. In both trials, data are presented for the as-treated population. In the PALOMA-1 trial, this included five fewer patients than in the ITT population, in the PALOMA-2 trial this population is identical to the ITT population.*

Overview of treatment emergent adverse events (including death)

The company's overview of treatment emergent AEs reported in the CS are summarised by the ERG in Table 14. All patients in the PAL+LET arm of the PALOMA-1 trial reported an AE and in the PALOMA-2 trial, nearly all patients reported an AE. AEs were also common in the LET and PLACEBO+LET arms of the trials. The company reported the proportion of serious AEs (SAEs) and Grade 3 to 4 AEs in each arm for the PALOMA-1 and PALOMA-2 trials. Compared with LET and PLACEBO+LET arms, SAEs and Grade 3 to 4 AEs were more common with PAL+LET. Deaths from AEs were relatively uncommon in both trials. **********

Table 14 Treatment emergent adverse events in the PALOMA-1 and PALOMA-2 trials

Adverse events	PALOMA-1		PALOMA-2	
	PAL+LET (n=83)	LET (n=77)	PAL+LET (n=444)	PLACEBO+LET (n=222)
	%	%	%	%
Patients with any AE	100.0	84.4	98.9	95.5
Patients with SAEs	21.7	6.3	19.6	12.6
Patients with Grade 3 or 4 AEs	75.9†	20.8	77.5	25.2
Patients with Grade 5 AEs (deaths)	1.2	0.0	2.3	1.8

AE=adverse event; SAE=serious adverse event
Source: CS, Sections 4.12.1 and 4.12.2 and EMA,[68] adapted from Table 49

Types of treatment-emergent adverse events and serious events

Treatment-emergent AEs that occurred in the PALOMA-1 and PALOMA-2 trials are presented in the CS (Table 39 and Table 41 respectively) and summarised in the appendices to this ERG report (Section 10.6, Table 41). The most commonly experienced AEs with PAL+LET were haematological toxicities, particularly neutropenia (74.7%) and leukopenia (43.4%). In the PALOMA-2 trial, the proportions were 79.5% and 6.3%. In the PAL+LET arm of the PALOMA-1 trial, neutropenia was the most common Grade 3 to 4 AE (54.2%). In the PALOMA-2 trial, the most common Grade 3 to 4 AE with PAL+LET was also neutropenia (66.4%).

In the PALOMA-1 trial, ********** were the only SAEs reported **********. In the LET arm, **********. In the PALOMA-2 trial, the most commonly reported all-causality SAE in the PAL+LET arm was ********** and

5.4.3 Interventions and comparators

Intervention

PAL is supplied as a *capsule* and is used to treat patients in the model in line with its expected EMA marketing authorisation (i.e. 125 mg daily for 21 consecutive days with the subsequent 7 days off treatment until disease progression).

Comparators

It is stated within the final scope issued by NICE that the comparators for this appraisal are aromatase inhibitors; however, LET is the only aromatase inhibitor included as a comparator in the cost effectiveness analysis. The company suggests that, as LET is the most commonly used aromatase inhibitor in the NHS, and as the effectiveness of the other aromatase inhibitors are not significantly different from that of LET, modelling only one of the comparator options detailed in the final scope issued by NICE is justified.

LET is supplied as a tablet and is used to treat patients in the model in line with its EMA marketing authorisation, which reflects the dosage used in UK clinical practice (i.e. 2.5 mg daily, without a break until progression).

Subsequent lines of treatment

Doses of subsequent lines of treatment are not included in the company model. Only the monitoring costs of subsequent lines of therapy are included in the model.

5.4.4 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and PSS (Personal Social Services) and the model time horizon is 40 years. The company states both costs and benefits are discounted at a rate of 3.5% per annum.

5.4.5 Treatment effectiveness and extrapolation

Extrapolation method

To model effectiveness over a lifetime horizon, the company extrapolated survival data from the PALOMA-1 and PALOMA-2 trials. Regression modelling was used to fit parametric curves to K-M data. Six different models were considered: exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma. Model selection was based on standard statistical criteria (Akaike and Bayesian information criteria [AIC and BIC respectively]) and clinical plausibility (assessed through consultation with clinical experts and comparison with previously published curves).

Table 19 Drug acquisition costs

Technology	Licensed dose	Package information	Cost per package	Source
PAL	125 mg daily used in model (100 mg and 75mg also available)	125 mg *capsule*, 21 *capsule*s in pack	Proposed list price: £2,950	Unpublished. Note, the same price for all mg
LET	2.5 mg daily	2.5 mg tablets, 28 tablets in pack	£1.52 (SD: £1.47)	eMIT 2016[109]

LET=letrozole; mg=milligram; PAL=palbociclib; SD=standard deviation
Source: CS, Table 65

Drug wastage

Both PAL and LET are available in cycle packs (21 days and 28 days respectively). Once a pack has been opened, another patient cannot use the same pack. Drugs are costed on the basis that each patient in the pre-progressed health state is issued with a pack of PAL and/or LET on the first day of each cycle and, therefore, if the patient ceases treatment at any point before the end of that cycle any unused treatment is wasted.

Monitoring and administration costs

As PAL and LET are provided in *capsule and* tablet form *respectively*, the company assumed that there are no costs associated with drug administration.

The company assumed that patients who are treated with PAL require a monthly blood test; the company assumes that monthly monitoring of patients treated with LET is not required. The resource use and monitoring cost associated with monthly blood tests are detailed in Table 20.

Table 20 Resource use and costs for patients receiving LET

Resource use		Source
Assumption	1 full blood count every month	Draft SPC (CS, Appendix 1)
Cost	£3.01	DAPS05 (Haematology outpatient appointment) NHS Reference Costs 2014/15[110]

SPC=summary of product characteristics
Source: CS, Table 66 and Table 67

Health state resource use and unit costs

In the model, the company has assumed that the level of resource depends on the patient's health state and their treatment. The estimates of resource use are based on levels reported in the NICE Clinical Guideline for Advanced Breast Cancer (2009),[31] with adjustments made on the advice of Clinical Nurse Specialists (CNSs) to reflect current NHS practice, and any differences to resource use associated with receipt of different lines of treatment.

In the base case 75% of patients are assumed to receive subsequent treatment on disease progression and that, after each line of subsequent treatment, 75% of patients go on to receive another line of subsequent treatment. The remaining patients move directly to BSC, where they remain until death. To estimate resource use for patients receiving subsequent lines of

All of the ERG's analyses of PFS, PPS, OS and TTD are based on re-censored K-M data. The company's analyses of PFS, PPS, OS and TTD are based on K-M data censored according to the conventional rule.

5.6.3 Time-to-event evidence: overall survival and post-progression survival

The company's modelling of OS in the base case is informed by the assumption that 100% of PFS gain translates into OS gain and that there is no difference in PPS between treatment with PAL+LET and treatment with LET. This is an important assumption because patients continue to accrue QALYs and costs beyond progression that can have a substantial effect on the overall ICER per QALY gained. If there is no difference in PPS between the two treatments, the costs and benefits of the drug are limited to those that accrue in PFS. The ERG does not agree that the company's assumption is justified.

The company provides no evidence for the assumption of zero PPS gain. The assumption of zero PPS gain is not even a conservative one, as evidence from the PALOMA-1 trial indicates that PPS is shorter for treatment with PAL+LET than for treatment with LET (a PPS loss). Re-censored K-M data provided by the company during the clarification process indicate that *restricted* mean PFS gain in the PALOMA-1 trial, until the data cut on 29 November 2013, was [redacted] months and *restricted* mean OS gain was [redacted] months. *Restricted* mean PPS *loss* for treatment with PAL+LET was [redacted] months. Although data are sparse (18 deaths in the post-progression state in the PAL+LET arm and 26 in the LET arm), Figure 6 shows that patients treated with LET in the PALOMA-1 trial tend to live longer after progression than patients treated with PAL+LET.

Figure 6 PPS K-M data for PAL+LET and LET (PALOMA-1)

Source: Clarification response B4

Figure 11 Hazard profiles for company base case PFS

LET=letrozole; PLACEBO+LET=placebo+letrozole; PFS=progression free survival
Source: Company model; ERG calculations

ERG exploratory analyses

The ERG considers it preferable to use data from the PALOMA-1 trial as the basis for modelling PFS to maintain consistency with the OS data from the PALOMA-1 trial used for modelling survival. The ERG acknowledges that the data from the PALOMA-1 trial have some limitations (Section 4.4). The ERG urges caution in the interpretation of its revised PFS estimates due to the unreliability of the PFS data from the PALOMA-1 trial.

The ERG prefers to use direct trial K-M data, when available, to model early events and only use later data to model a projection once a long-term trend has been established. This means that early features of the data that can be awkward to model parametrically, such as deaths due to AEs or administrative issues such as time to first assessment, are captured by the trial data. It also means that the most accurate data available are used and no assumptions are required that add to the uncertainty in the model.

The company provided the ERG with re-censored investigator assessed PFS data from the PALOMA-1 trial during the clarification process. *Restricted* mean PFS gain for patients treated with PAL+LET versus LET in the PALOMA-1 trial was [redacted] months.

Examination of the re-censored K-M data reveals clear exponential trends in both the PAL+LET and LET arms of the PALOMA-1 trial (Figure 12 and Figure 13). The steep drop in PFS at around 3 months (Figure 12) indicates that treatment with PAL+LET appears to offer protection against early progression in around 20% of patients versus treatment with LET. Figure 13 shows that patients treated with PAL+LET have a lower hazard of progression in

Figure 15, however, shows that some patients in the PALOMA-1 trial stopped treatment for reasons other than progression or death, which indicates that the time spent on treatment in this trial was less than the time spent in the progression-free state. It is unclear whether the TTD data for the PAL+LET arm of the PALOMA-1 trial represent PAL alone (that is, patients may have continued treatment with LET monotherapy) or whether it represents the discontinuation of all first-line treatments.

It is important to model time on treatment using trial TTD data where possible, as using PFS as a proxy can lead to an overestimation of the costs of treatment acquisition and administration (or an underestimation, if patients are permitted to continue treatment after progression). Figure 15 shows how, at around 3 months, some patients treated with LET actually received treatment for a brief period after their progression was confirmed. Treatment beyond progression was not specified in the trial protocol.[97]

The company provided the ERG with TTD data from the PALOMA-1 trial during the clarification process. The difference between PFS and TTD was greater for patients treated with PAL+LET than for patients treated with LET (Figure 15). The difference between PFS and TTD can be explained in the most part by the proportion of patients discontinuing treatment due to AEs: *out of those patients in the PALOMA-1 trial who had discontinued their randomised treatment by the time of data cut-off ([redacted] in the PAL+LET arm and [redacted] in the LET arm), [redacted] of patients who had received treatment with PAL+LET discontinued due to AEs in comparison to [redacted] of patients who had received treatment with LET.* [91]

*Figure 15 PFS and TTD K-M data (PALOMA-1 trial data re-censored)

LET=letrozole; PAL+LET=palbociclib+letrozole; PFS=progression free survival; TTD=time to treatment discontinuation
Source: Clarification response B4

progression utility value of ***** for both treatments, the company's Scenario 22 increases the company's base case ICER per QALY gained by £14,991 to £165,860.

ERG exploratory analyses

The ERG has attempted to replicate the calculation of the pre-progression utility values used in the model using the data provided by the company during the clarification process, but was not able to identify the method used to yield the values of **********. The ERG has instead calculated alternative pre-progression utility values using the mean utility values from European patients in the PALOMA-2 trial. The ERG considers that using responses from European patients alone is likely to be a better approximation of responses of UK patients than using responses from the full ITT population, whilst still retaining a large enough data set to give a reliable average.

The ERG is also satisfied that it is valid to use utility values calculated from EQ-5D responses from the PALOMA-2 trial alongside time-to-event data from the PALOMA-1 trial in the absence of EQ-5D data from the PALOMA-1 trial. This is because utility data are less prone to serious differences than time-to-event data provided the disease area and stage of disease are broadly similar.

The ERG calculated a weighted average utility value using the mean values per cycle and the number of respondents per cycle from both arms of the PALOMA-2 trial for the first 21 cycles of treatment ********** of each arm in [Figure 19], so can be considered reliable).

The average pooled cycle utility for European patients in the first 21 cycles in the PALOMA-2 trial was *****. Applying the recalculated pre-progression utility values for PAL+LET and LET in the model increases the ICER per QALY gained by £16,858 to £167,727.

5.6.7 Health state utility values: post-progression

The company has *incorrectly calculated* post-progression utility values using the published results of a study by Lloyd et al.[5] The company used the utility decrement associated with disease progression in the Lloyd[5] paper to derive a multiplier, which it then applied to the (average) pre-progression utility value from the PALOMA-2 trial. The company's resulting post-progression utility value used for both treatments in the base case is 0.4492.

This method assumes that the utility decrement associated with progressed disease can be applied linearly. However, a logistic transformation was applied to the data used in the Lloyd[5] study before analysis in order that it approximated the normal distribution necessary to allow use of a standard regression analysis. This means that the resulting utility gains and

decrements reported in the paper cannot be directly applied or linearly adjusted and must be re-calculated to take into account the logistic transformation.

The ERG has recalculated the post-progression utilities using the results of the mixed model analysis given in the Lloyd[5] paper, including the logistic transformation of the data, and calibrated the result to the UK average age (48.52 years[117]) in the UK value set. The ERG's recalculated post-progression utility value is 0.5052. Applying this recalculated post-progression utility value in the model increase the ICER per QALY gained by £277 to £151,146.

5.6.8 Half-cycle correction

The company did not include a half-cycle correction to improve the accuracy of the cost and outcomes estimates. All patients progression-free and/or alive at the beginning of a cycle are assumed by the company to accrue costs and benefits throughout the entire cycle. However, some patients progress or die during a cycle and do not accrue the full costs and benefits for that cycle. It is more accurate to assume costs and benefits apply to the average number of patients progression-free and/or alive in a cycle, which can be achieved by averaging the number of patients at the beginning and end of a cycle (mid-cycle correction). *The company notes in the CS that it did not include a half-cycle correction due to the short (28 day) cycle length used in the model. It is not clear whether a 28-day cycle can generally be expected to be short enough to have minimal impact on the resulting ICER per QALY gained,[118] so the ERG considers it necessary to investigate the impact of a mid-cycle correction.*

Applying a mid-cycle correction to PFS and OS in the model reduces both incremental costs and incremental QALYs, and reduces the base case ICER per QALY gained by £2,182 to £148,687.

5.6.9 AE costs

The company is not justified in using a proportion of the relevant NHS Reference Cost[110] to represent a meeting of 20 minutes (Grade 3) or 30 minutes (Grade 4) with a consultant oncologist. This is because NHS Reference Costs[110] provide a currency for payment for the average patient[119] and do not represent an hourly cost (unless that is how much of the resource the average patient uses).

The ERG has amended the model to apply the full NHS Reference Cost[110] of £132 (Healthcare resource group currency code WF01A service code 800) to both Grade 3 and Grade 4 AEs. This increases the ICER per QALY gained by £1,603 to £152,472.

5.6.10 AE incidence calculation

The company has made two errors when calculating the incidence of AEs: first, the company used the median rather than mean time on treatment to calculate the probability of an AE; second, the company has applied annual rather than cycle AE probabilities to each cycle in the model. The ERG has amended these errors, which increases the time on treatment used

first line in combination with letrozole (Structured abstract),. Health Technology Assessment Database: NIHR Horizon Scanning Centre (NIHR HSC),. 2014,.

107. National Institute for Health and Care Excellence (NICE). Dabrafenib for treating unresectable, advanced or metastatic BRAFv600 mutation-positive melanoma (TA 321). 2014.

108. Holt S, Bertelli G, Humphreys I, Valentine W, Durrani S, Pudney D, *et al.* A decision impact, decision conflict and economic assessment of routine Oncotype DX testing of 146 women with node-negative or pNImi, ER-positive breast cancer in the U.K (Provisional abstract). Br J Cancer. 2013; 108(11): Available from: http://onlinelibrary.wiley.com/o/cochrane/cleed/articles/NHSEED-22013043900/frame.html.

109. Department of Health. Drugs and pharmaceutical market information (eMIT). [updated Updated 4 May 2016May 2016]; Available from: www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit.

110. National Health Service. Reference costs 2014-20152015 November.

111. Curtis L, Burns A. Unit Costs of Health and Social Care. 2015.

112. Nafees B, Patel C, Ray D, Gray L, Lau H, Lloyd A. An Assessment of Health-State Utilities in Metastatic Breast Cancer in the United Kingdom. ISPOR 21st Annual International Meeting, Washington, DC, USA, May 21 - May 25, 2016. 2016.

113. National Institute for Health and Care Excellence. Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy (Technology appraisal guidance 295, 28 August 2013)2013.

114. National Institute for Health and Care Excellence (NICE). Fulvestrant for the treatment of locally advanced or metastatic breast cancer (TA 236). 2011.

115. Excellence NIfHaC. Guide to the methods of technology appraisal 2013. 2013; Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword (Accessed 24 November 2016).

116. Bergh J, Jonsson P-E, Lidbrink EK, Trudeau M, Eiermann W, Brattstrom D, *et al.* FACT: An open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. J Clin Oncol. 2012; 30:1919-25.

117. Kind PH, Geoffrey; Macran, Susan. UK population norms for EQ-5D: Centre for Health Economics, University of York 1999.

118. Drzal R, Szmurlo D, Plisko R. PRM81 - Can we determine the optimal cycle length for which half-cycle correction should always be applied? Value Health. 2013; 16:A27.

119. Department of Health. A simple guide to payment by results. 2012; Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213150/PbR-Simple-Guide-FINAL.pdf (Accessed 24 November 2016).

120. Davis S. Assessing technologies that are not cost-effective at a zero price: report by the Decision Support Unit. 2014; Available from: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0088909/pdf/PubMedHealth_PMH0088909.pdf (Accessed 30 November 2016).

The company argues that the burden on carers of patients with this disease is so substantial that its exclusion contributes to undervaluing the benefit of PFS. The company does not however present any evidence to quantify the health-related quality of life impact of caring for a patient with progressed disease may have, nor explore this as an individual hypothetical scenario within the modelling.

The data used to value PFS in this model are the best available and consistent with the NICE reference case, which is used to benchmark all appraisals. Any departure from EQ-5D values directly obtained from patients would only be supported given significant evidence of the insufficiency of the EQ-5D to capture all elements relevant to patients in this disease area. Given that the arguments put forward by the company do not appear specific to postmenopausal women with ER+/HER2- ABC who have never received systemic therapy in the LABC/MBC setting but could in fact be relevant to all patients with ABC, or the population of people with breast cancer as a whole, any methodological change to the valuation of utility would have implications for all appraisals of breast cancer interventions.

Company exploratory scenarios: post-progression costs

The company includes the removal of post-progression costs as part of their scenarios with combinations of amendments (Scenarios 28b, 34 & 36). As the only post-progression costs that are included within the company model are the costs of monitoring patients undergoing further therapy, the impact of removing these costs is minimal. As shown in Table 43, the ICER decreases by £566.

In addition, the DSU discussion paper regarding cost-effectiveness at zero price[120] considers scenarios in which non-treatment related costs could be excluded however concludes that a narrow perspective does not enable full consideration of the opportunity cost to the NHS of the introduction of a new technology and therefore the ERG does not consider this element of the scenario analyses plausible.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2- negative breast cancer [ID915]

You are asked to check the ERG report from Liverpool reviews and implantation group Lr*i*G to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 9 December 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Classification of company's discounting as "incorrect"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 – the company's method of discounting is stated as incorrect, and then subsequently on page 104. The company acknowledges the ERG's rationale for discounting annually rather than per cycle, however the company disputes that discounting per cycle is "incorrect" by definition.	It is suggested that the text stating this is "incorrect" (i.e. classifying it as an error) is removed, as applying discounting per cycle as opposed to per annum is a difference in modelling assumption.	The NICE Methods Guide states that an annual discount rate of 3.5% should be applied, but the Guide does not specify whether this should be applied once per year (i.e. on an annual basis) or on a more granular level (i.e. per month) when constructing the economic model. This issue was discussed at the recent appraisal for crizotinib (TA406) in which the Committee conceded that there is indeed no clear guide to how discounting should be methodologically applied to the model, and per cycle vs. per year is a matter of differences in modelling technique.	Text amended on page 17

Issue 2 Exclusion of half-cycle correction

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 – discussion of company's exclusion of half-cycle correction, and then further discussion of the issue on page 103. The company acknowledges the ERG's rationale for including half-cycle correction; however the company put forward rationale for not including the correction but this does not feature in the ERG's discussion.	It is suggested that the ERG reflect on the company's rationale for not including half-cycle correction when debating its inclusion. The CS states: "Due to the short length of the treatment cycle, the half-cycle correction was not implemented; the inclusion of a half-cycle correction with such a short cycle length would be expected to have minimal impact on the results."	The company believe that the cycle length was already sufficiently short (under one month) to not require such a correction, or that this correction would not have a meaningful impact. The company suggest, for balance, this rationale for exclusion is reflected in the ERG's critique.	Additional text added on page 103 as follows: "The company notes in the CS that it did not include a half-cycle correction due to the short (28 day) cycle length used in the model. It is not clear whether a 28-day cycle can generally be expected to be short enough to have minimal impact on the resulting ICER per QALY gained,[118] so the ERG considers it necessary to investigate the impact of a mid-cycle correction."

Issue 3 Classification of company's post-progression survival utility as an "error"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 – classification of utility post- progression as an error, and then subsequently on page 102. The company acknowledges the ERG's position that for a more accurate post- progression utility score the calculation should use a logistic-transformation, however the company's estimate was explained with workings in the CS and there is no "error" in the company's calculations as such.	It is suggested that the text stating this was "error" is removed as the workings for the calculation are set out and the estimate is calculated in line with these. Instead, it is suggested text is included to reflect the fact the company calculated the figure in an alternative way to the ERG.	The company acknowledges the ERG's method for calculations, but disputes the erroneous classification of its estimate.	Text amended on page 17 to read: "Incorrect calculation of the utility value used to represent the HRQoL of patients in the PPS state renders the company's estimate invalid" Text amended on page 102 to read: "The company has incorrectly calculated post-progression utility values using the published results of a study by Lloyd et al."

Issue 4 Pooling of AEs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 35 – statement that the company did not pool AEs from the trials. Although the surrounding text is discussing specifically the PALOMA-1 and PALOMA-2 trials, it should be noted that the CS does pool AEs from the PALOMA-1, PALOMA-2 and PALOMA-3 trials.	It is suggested that either the statement that the CS did not pool AEs is removed and Table 43 from the CS is reflected here, or that it is acknowledged that AEs were pooled by the company, but from all three PALOMA trials.	Current text suggests to the reader that presentation of pooled AEs was not considered, when the CS does indeed present such data.	Text amended slightly on pages 35 and 36 to highlight that the pooling of AE data included that from the PALOMA-3 trial and to qualify that the ERG considered pooling of AE data from *only* the PALOMA-1 and PALOMA-2 trials may also have been informative. The following text has also been added for clarity on page 60: Pooled data for palbociclib in combination with LET or fulvestrant are presented in the CS (Table 43) and used to inform the information presented in the draft summary of product characteristics. In this section of the ERG report, the ERG has confined its critique of AEs to PAL+LET versus LET or PLACEBO+LET from the PALOMA-1 and PALOMA-2 trials. In both trials, data are presented for the as-treated population. In the PALOMA-1 trial, this included five fewer patients than in the ITT population, in the PALOMA-2 trial this population is identical to the ITT population.

Issue 5 Typo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59 – "the PALOMA-1 and PALOMA-1 trials"	Should read "PALOMA-1 and PALOMA-2 trials"	Typo	Text amended

Issue 6 Palbociclib as a capsule

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 71 and 73 Palbociclib specified as coming as a tablet, when it is a capsule.	Change tablet to capsule.	Palbociclib comes in a capsule. This may have been taken from a related typo in the CS.	Text amended on pages 71 and 75, and in Table 19 (on page 75)

Issue 7 Use of restricted mean

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 89 (repeated on page 95) – Presentation of mean PFS and OS gain are presented up to the datacut from PALOMA- 1. As these are not the true means (i.e. some patients were still on treatment at the time of calculation), it should be stated these are restricted means and an underestimate of the actual mean OS.	State that in the text the true mean is expected to be longer due to patients still on treatment.	The means being presented are "restricted" means.	Text amended on pages 89 and 95

Issue 8 Incorrect data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 98 - Discontinuations due to AEs stated as [redacted] These are incorrect.	Change discontinuations due to AEs to 13.1% vs. 2.5% (sourced from page 311 from PALOMA-1 CSR)	Incorrect data.	Text has been amended for clarity on page 98. The calculated percentage of patients who discontinued treatment with PAL+LET in the PALOMA-1 trial due to AEs has not been changed. The calculated percentage of patients who discontinued treatment with LET in the PALOMA-1 trial due to AEs has been corrected from [redacted] to [redacted] The proportions given in the ERG report are the conditional probabilities of discontinuing due to AEs, given that a patient has discontinued. Because TTD is calculated from patients who have discontinued treatment, it is more informative to use data from this subgroup rather than the ITT population in this instance. Table 14.1.1.2.2.b in the PALOMA-1 CSR states that, at the time of the 29 November 2013 data cut, [redacted] subjects had discontinued, out of which [redacted] did so due to AEs. This means that [redacted] of subjects that had discontinued treatment with PAL+LET did so due to AEs. A similar calculation shows that [redacted] of subjects that had discontinued treatment with LET did so due to AEs.

Pre-meeting briefing
Palbociclib for the treatment of postmenopausal people with metastatic, hormone receptor-positive, human epidermal growth factor receptor 2-negative (HER2-) breast cancer previously untreated in the metastatic setting

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

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

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

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

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

List of abbreviations	
ABC	Advanced breast cancer
AE	Adverse event
CI	Confidence Interval
ER	Oestrogen receptor
ERG	Evidence Review Group
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health Related Quality of Life
ICER	Incremental cost-effectieness ratio
ITT	Intention to treat
K-M	Kaplan-Meier
MA	Marketing Authorisation
MBC	Metastatic breast cancer
ORR	Overal response rate
OS	Overall survival
PFS	Progression-free survival
PPS	Post-progression survival
QALY	Quality-adjusted life year
SMPC	Summary of Product Characteristics
TTD	Time to discontinuation

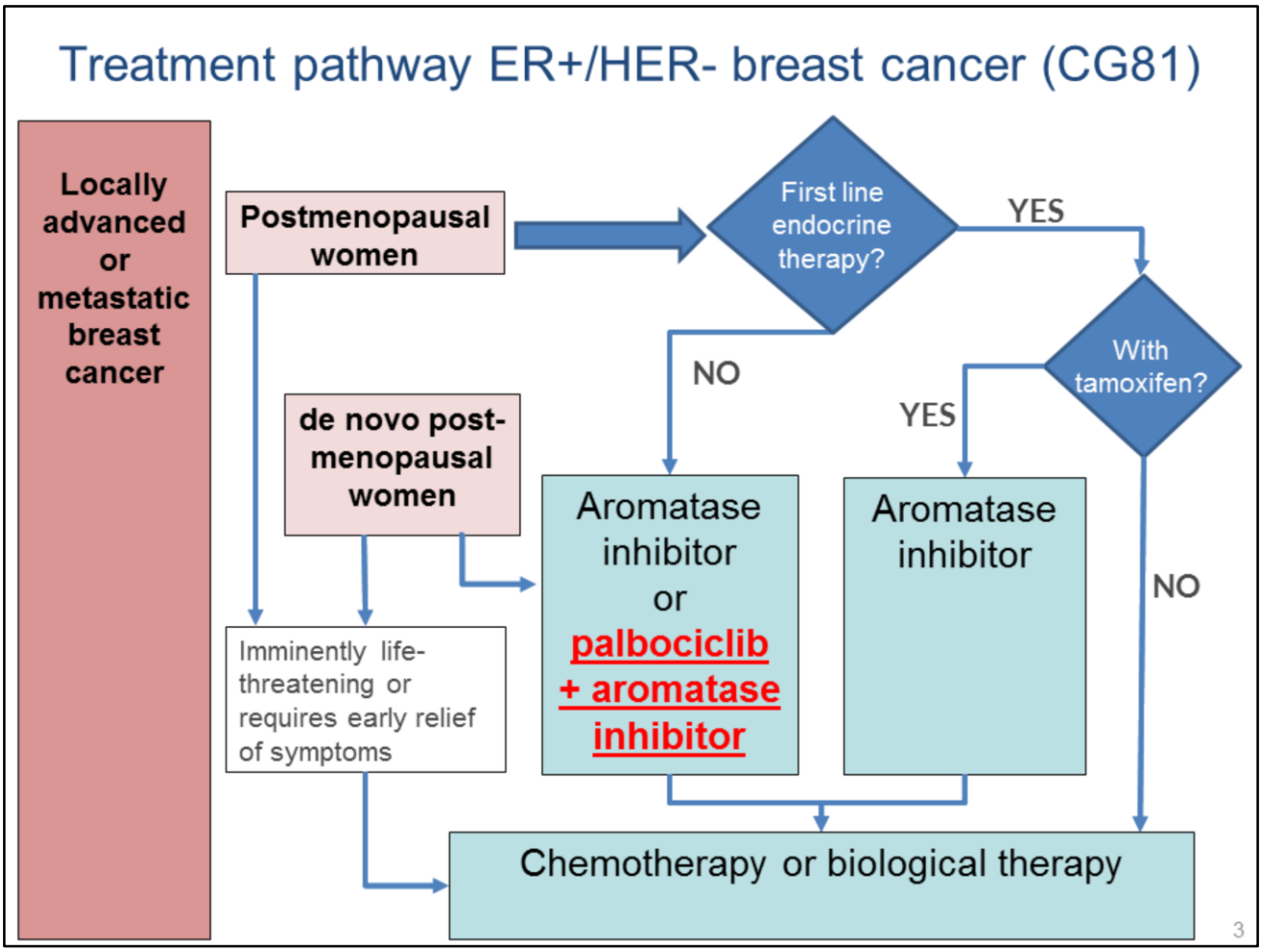
ER+/HER2- advanced breast cancer

- Breast cancer arises from the tissues of the ducts or lobules of the breast. Advanced breast cancer has been defined as "Women and men with invasive adenocarcinoma of the breast of clinical stage 4 (that is, with known metastatic disease)" (CG81)
- Locally advanced breast cancer (stage 3) is where the cancer has spread to lymph nodes and/or other tissue in the breast. Metastatic breast cancer (stage 4) is where the cancer has spread to other sites in the body.
- Over 46,417 people were diagnosed with breast cancer in England in 2014, and there were approximately 9,554 deaths from breast cancer in 2014.
- Approximately 5% of people with invasive breast cancers have locally advanced or metastatic disease when they are diagnosed, and around 35% of people with early or locally advanced disease will progress to metastatic breast cancer
- Oestrogen receptor (ER) positive and human epidermal growth factor receptor (HER) negative is the most common type of UK metastatic breast cancer, accounting for 56.3% of cases.
- The estimated number of people who are post-menopausal with metastatic ER+/HER2- breast cancer previously untreated in the metastatic setting is estimated to be 5,435 (see table 8 of company submission)

2

Also see section 3 of the company submission.

- The company use advanced breast cancer (ABC) and metastatic breast cancer (MBC) interchangeably within the company submission



- CG81 - 1.3.1: Offer endocrine therapy as first-line treatment for the majority of patients with ER-positive advanced breast cancer.

- CG81 - 1.3.3: For patients with ER-positive advanced breast cancer who have been treated with chemotherapy as their first-line treatment, offer endocrine therapy following the completion of chemotherapy. **[2009]**

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

- CG81 - 1.3.4: Offer an aromatase inhibitor (either non-steroidal or steroidal) to:
    - postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy
    - postmenopausal women with ER-positive breast cancer previously treated with tamoxifen. [2009]

- CG81 - 1.3.4: Offer tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen.

Palbociclib (Ibrance, Pfizer)

- Marketing authorisation (granted November 2016**)**
  - 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.

- Administration:
  - Oral treatment in combination with an aromatase inhibitor; 125mg once daily for 21 consecutive days, followed by 7 days off treatment
  - Requires full blood count prior to the start of therapy, at the beginning of each cycle, on Day 14 of the first 2 cycles, and as clinically indicated
- Cost:
  - List price: £2,950 per pack of 21 capsules

- Palbociclib in combination with fulvestrant is subject of a separate appraisal.
- In combination with an aromatase inhibitor, such as letrozole. The expected recommended dosage for women with metastatic HR-positive, HER2-negative ABC is expected to be (license pending) 125mg once daily for 21 consecutive days, followed by 7 days off treatment, repeated in cycles, until disease progression. Letrozole is administered continuously i.e. without the 7 days treatment break.
- A first dose reduction to 100mg daily is allowed as required for the management of AEs. As a second dose reduction, the recommended dose is 75mg daily
- Letrozole: average £1.40 (SD: £1.86) per pack of 28 tablet
- Full blood count is required due to the risk of haematological toxicities adverse events, commonly neutropenia.

Decision Problem

	Final scope issued by NICE	Decision problem
Intervention	Palbociclib in combination with an aromatase inhibitor	
Population	Post-menopausal people with metastatic, hormone receptor-positive, HER2-negative breast cancer previously untreated in the metastatic setting.	Evidence submitted is in post-menopausal women
Comparator(s)	Aromatase inhibitors (such as letrozole or anastrazole)	
Outcomes	• overall survival (OS) • progression free survival (PFS) • response rate (RR) • adverse effects of treatment • health-related quality of life (HRQL)	In addition to the outcomes listed in the final scope issued by NICE the decision problem addressed also includes clinical benefit rate (CBR)
Subgroups	None	Those treated in the adjuvant setting compared with those who are presenting for the first time with metastatic disease

Source: table 1, page 8-9 of the company submission

Rationale if different:

- Population: Palbociclib's expected license does not specify menopausal status when combined with an aromatase inhibitor
- Outcomes: CBR captures CR, PR and absence of progression (stable disease) for at least 24 weeks. It is regarded as a well-established robust measure of anti-tumour activity
    - 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.8 In this submission, CBR outcomes are presented alongside ORR outcomes in order to demonstrate the superior anti-tumour activity of palbociclib over standard of care.
- Subgroups: The majority of patients who are treated for ABC in the UK have previously undergone adjuvant therapy. However, a small proportion of patients receive their first diagnosis of breast cancer at the metastatic stage and data suggests the comparative efficacy of these patients may differ (reference to PALOMA-2 CSR)

- The company have not provided a cost-effectiveness analysis for those treated in the adjuvant setting compared with those who are presenting for the first time with metastatic disease
    - Rationale from the company is that the forest plot for PALOMA-2 showed statistically significant improvements in PFS across all subgroups. Therefore no subgroups have been analysed as part of the cost-effectiveness evaluation
- The ERG noted heterogeneity for those treated in the adjuvant setting compared with those who are presenting for the first time with metastatic disease between the PALOMA-1 and PALOMA-2 trials
    - For further details of the ERG's critique see Table 12, page 55 of the ERG report

Patient and professional feedback

- In patients on aromatase inhibitor alone, patients may be seen only every 8 – 12 weeks in clinic, and with the addition of palbociclib patients need to be seen monthly. However many patients have bone metastases so are quite often already seen monthly
- Experience of this drug is increasing with studies in the neoadjuvant setting (the PALLET study) and in the adjuvant setting (PALLAS study)
- Drugs with a similar mechanism of action (CDK4/6 inhibitors) are under investigation
- Patients say that quality of life is just as important as length of life
- No new treatments have been approved by NICE for this group of patients since the introduction of aromatase inhibitors
- Both palbociclib and letrozole are taken orally, therefore minimising the length and frequency of hospital visits needed whilst on this medication
- Palbociclib has increased risk of side-effects, but for individual patients a longer progression-free survival will be more important, as delaying progression will delay the need for patients to move on to non-targeted chemotherapies, which are associated with severe side effects and poorer quality of life

  - PALLET study: A Phase II Randomized Study Evaluating the Biological and Clinical Effects of the Combination of Palbociclib With Letrozole as Neoadjuvant Therapy in Post-Menopausal Women With Estrogen-Receptor Positive Primary Breast Cancer

  - PALLAS study: A Randomized Phase III Trial of Palbociclib With Standard Adjuvant Endocrine Therapy Versus Standard Adjuvant Endocrine Therapy Alone for Hormone Receptor Positive (HR+) / Human Epidermal Growth Factor Receptor 2 (HER2)-Negative Early Breast Cancer

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Clinical-effectiveness evidence

Company submission section 4

Overview of the clinical evidence

Key clinical evidence:

- PALOMA-1
  - Randomised open–label controlled phase I/II trial.
  - Overall survival incorporated into the company's base-case model
- PALOMA-2
  - Randomised placebo-controlled phase III trial
  - Progression-free survival, utilities, and safety data incorporated into the company's base-case model

- Other clinical evidence:
- PALOMA-3
  - Randomised placebo-controlled phase III trial
  - population of post-menopausal and pre/peri-menopausal women who have received prior endocrine therapy
  - Results have been summarised and adverse event data pooled with other trials
  - Summary of PALOMA-3 can be found in table 5, page 21 of the company submission
  - Pooled adverse event data from PALOMA-1/2/3 can be found in table 43, page 106 of the company submission

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- 5x non-randomised identified by systematic review
  - All studies were all Phase 1 or 2 trials investigating palbociclib for the treatment of breast cancer
  - Studies have not been incorporated into the model
  - Overall, the ERG is satisfied with the clinical effectiveness systematic review process as described in the CS for both reviews (see Sections 4.1.1 to 4.1.4 of this ERG report). The ERG considers that the company's approach to evidence synthesis (see Section 4.1.5 of the ERG report) is appropriate.

PALOMA – Definition of outcomes

Primary efficacy outcome	
PFS	Time from randomisation to radiological disease progression or death on study.
Secondary efficacy outcomes	
OR	Defined according from the lesion measurements
CBR	Defined as complete response, partial response or stable disease lasting at least 24 weeks
OS	Time from the date of randomisation to the date of all-cause death. Patients last known to be alive were censored at date of last contact. Kaplan-Meier analysis was used to estimate OS probability
DOR	Time from first documentation of complete or partial response to date of first documentation of objective progression or death. Outcome calculated for patients with complete or partial response
TTP	***PALOMA-1 only***. Time from the date of randomisation to the date of first documentation of objective progression
Patient reported outcomes (PROs)	
mBPI-sf scores	***PALOMA-1*** only. Validated self-report questionnaire. 13 questions that assess severity and impact of pain on daily function
EQ-5D	***PALOMA-2 only***. Generic HRQL and general health status was assessed using EQ-5D
FACT-B	***PALOMA-2 only***. Breast cancer specific health-related quality of life was assessed using FACT-B
Safety	
Safety	Type, incidence, severity, seriousness of adverse events, their relationship to study medications and any laboratory abnormalities

PFS - Progression-free survival; OR - objective response; CBR - clinical benefit rate; OS - overall survival; DOR - duration of response; TTP - Time to progression; mBPI-sf - modified brief pain inventory-short form; FACT - Functional Assessment of Cancer Therapy-Breast

Source: table 12, page 44-45 and table 13, page 46-47 of the company submission

Source: Section 4 (table 12, page 44-45) of company submission

- PALOMA-1
  - OS and Safety was assessed until approximately 28 days after the last dose of study treatment.
- RECIST
  - Documentation of OR, CBR, or progression was by objective disease assessment calculated using RECIST 1.0 (PALOMA-1) or RECIST 1.1 (PALOMA-2)
- mBPI-SF:
  - 4-item Pain Severity Scale (worst pain, least pain, average pain, and pain right now)
  - 7-item Pain Interference Scale (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life)
  - Patients were to complete the self-administered questionnaire at baseline (Day 1, Cycle 1), on Day 1 of each subsequent cycle, and at the end of treatment or study withdrawal
  - They were to complete the mBPI-sf prior to having any tests, receiving any therapy, and before any discussion of the patient's progress with their physician or other healthcare personnel
- EQ-5D and FACT-B
  - Patients were to complete each instrument pre-dose on [redacted]
- Adverse events
  - Classified using the MedDRA classification system 16.1 (PALOMA-1) or 18.1 (PALOMA-2). Severity of events was graded according to the CTCAE 3.0 (PALOMA-1) or CTCAE 4.0 (PALOMA-2) whenever possible

Clinical trial evidence – PALOMA-1

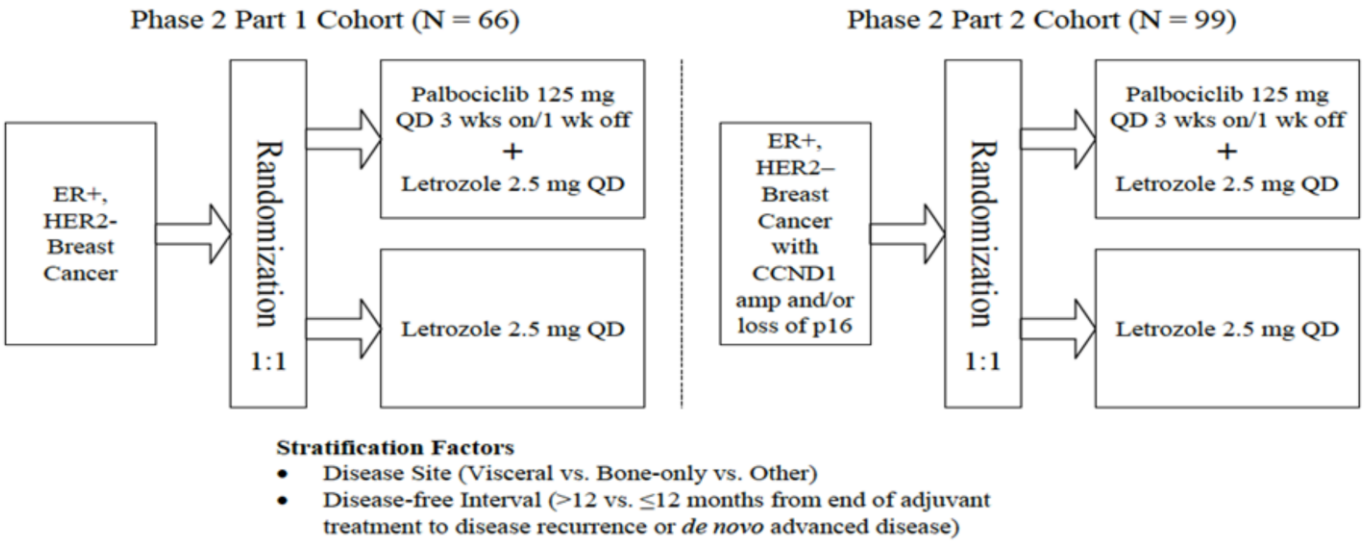
Design	Phase I/II, open label, multicentre (50 sites), RCT
Population	N=165, postmenopausal women with ER+/HER- locally advanced or metastatic breast cancer
Intervention	n=84; palbociclib plus letrozole. 125mg, oral, 28-day cycle is once-daily for 21 days then 7 days off; letrozole 2.5mg, oral, once-daily continuous daily dosing.
Comparator	n=81; letrozole monotherapy 2.5mg, oral, once-daily continuous daily dosing
Outcomes	Primary outcome: Investigator-assessed PFS, as defined by RECIST 1.0
	Secondary outcomes: OR, CBR, OS, pain (mBPI-sf), DOR, TTP, Safety
Subgroups	Disease free interval (DFI) (≤12 months, ≤12 months + de novo, >12 months; ≤5 years, >5 years)
Other	All PALOMA-1 data correspond to the data cut-off date of 29 November 2013. [redacted]

PFS - progression-free survival; OR - objective response; CBR - clinical benefit rate; OS - overall survival; mBPI-SF - Modified Brief Pain Inventory-short form; DOR - duration of response; TTP - time to progression

Source: table 11, page 40-42 of company submission

- Patients continued on the assigned study treatment until disease progression, unacceptable toxicity, consent withdrawal, or death. Dose interruptions and reductions were allowed for the management of toxic effects
- Patients were randomly allocated in a 1:1 ratio. Randomisation was performed using an interactive web-based randomisation system, stratified by disease site (visceral *vs* only bone *vs* other) and by DFI (>12 *vs* ≤12 months between completion of the last adjuvant treatment and disease recurrence) or *de novo*.
- Inclusion criteria:
  - Patients were women aged 18 years or older.
  - Patients were classified as postmenopausal and diagnosed with adenocarcinoma of the breast with evidence of (a) locally recurrent disease not amenable to resection or radiation therapy with curative intent, or (b) metastatic disease.
  - Patients had ER+/HER2- tumours.
  - Patients had measurable disease according to RECIST version 1.0 or bone-only disease (Phase 2 only).
  - Patients had an ECOG performance status 0 or 1.
  - All acute toxic effects in patients due to prior therapy or surgical procedures had resolved to CTCAE Grade ≤1, except alopecia or other toxicities not considered a safety risk.
- Disease was assessed by CT or MRI of chest, abdomen, and pelvis; X-ray scans of bone lesions; and clinical evaluation of superficial disease within 28 days of initiation of study treatments, at the end of cycle 2 and on day 1 of every other cycle starting from cycle 4. Disease assessment was repeated at withdrawal or the end of treatment. It was also assessed whenever progression was suspected and to confirm partial or complete response at least 4 weeks after initial documentation of response.
- Brain CT or MRI was required only when signs and symptoms suggested presence of metastatic brain disease. Post-screening repeat brain scans were required only if metastases were suspected. Bone scans were required within 28 days of initiation of study treatments, and baseline bone lesions were followed every 12 weeks using the most appropriate imaging technique, as well as at withdrawal or end of treatment. A bone scan was required at the time of confirmation of complete response for patients who had bone metastases.

Clinical trial evidence – PALOMA-1



Stratification Factors

- Disease Site (Visceral vs. Bone-only vs. Other)
- Disease-free Interval (>12 vs. ≤12 months from end of adjuvant treatment to disease recurrence or *de novo* advanced disease)

- PALOMA-1 contained separate part 1 cohort (ER+/HER2- status only) and part 2 cohort (ER+/HER2- status + biomarker positive patients)
- After an unplanned interim analysis of cohort 1 further enrolment into cohort 2 was stopped and the company amended the statistical analysis plan (SAP) to combine the two cohorts for analysis

Source: figure 5, page 43 of company submission

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- An unplanned interim analysis of cohort 1 based on 32 PFS events was conducted after it was noted that almost twice as many patients in the control group were discontinuing treatment because of disease progression. The results of the interim analysis showed clinically meaningful activity of the PAL+LET combination compared with LET (hazard ratio [HR]=0.35, 95% confidence interval [CI] 0.17 to 0.72, p=0.006). The company states that these preliminary results from cohort 1 suggested that further patient selection based upon CCND1 amplification or p16 loss was unlikely to further improve patient outcomes in comparison to patient selection based on ER+/HER2- status alone. As a result, further enrolment into cohort 2 (i.e. based upon CCND1 amplification or p16 loss) was stopped, and the TSAP was amended so that all primary and secondary endpoints would be analysed in cohort 1 and 2 combined.

- ERG says: "The ERG believes it is preferable for phase II studies to make amendments to study design in order to inform phase III studies, rather than amendments being made at phase III level, and so is not concerned by the PALOMA-1 protocol amendments. Furthermore, all amendments were made before conduct of the final analysis"

Clinical trial evidence – PALOMA-2

Design	Phase III, double-blind, multicentre (186 sites [7 UK]), RCT
Population	N=666, postmenopausal women with ER+/HER- locally advanced or metastatic breast cancer
Intervention	n=444; palbociclib plus letrozole. Palbociclib - 125mg, oral, 28-day cycle is once-daily for 21 days then 7 days off; letrozole - 2.5mg, oral, once-daily continuous daily dosing.
Comparator	n=222; placebo plus letrozole Placebo - oral, 28-day cycle is once-daily for 21 days then 7 days off; letrozole - 2.5mg, oral, once-daily continuous daily dosing
Outcomes	Primary outcome: Investigator-assessed PFS, as defined by RECIST 1.1 Secondary outcomes: OR, CBR, OS, HRQL (EQ-5D and FACT-B), DOR, Safety, biomarker expression vs PFS
Subgroups	Disease free interval (DFI) (≤12 months, >12 months, de novo)
Other	All PALOMA-2 data presented in this submission correspond to the data cut-off date of 26 February 2016

PFS - progression-free survival; OR - objective response; CBR - clinical benefit rate; OS - overall survival; HRQL - Health related quality of life; FACT - Functional Assessment of Cancer Therapy-Breast; DOR - duration of response; TTP - time to progression

Source: table 14, page 47-51 of company submission

- Patients were to continue receiving assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. Dose interruptions and reductions were allowed for the management of toxic effects.
- [redacted]
- Inclusion criteria:
  - Women 18 years or older who had a proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease not amenable to resection or radiation therapy with curative intent, and for whom chemotherapy was not clinically indicated.
  - Patients had histologically or cytologically confirmed diagnosis of ER+/HER2- breast cancer documented in local laboratory results.
  - Patients had not received previous treatment with any systemic anti-cancer therapy for their locoregionally recurrent or metastatic ER-positive disease;
  - Patients were postmenopausal based on prior bilateral surgical oophorectomy, spontaneous cessation of regular menses for at least 12 consecutive months or levels of follicle-stimulating hormone and estradiol in the blood levels within postmenopausal ranges in the absence of alternative pathological or physiological causes.
  - Patients had measurable disease as defined per RECIST 1.1 or bone-only disease, with bone lesions confirmed by CT, MRI or bone X-ray.
  - Patients had ECOG performance status of 0-2.
- Disease was assessed by CT or MRI of chest, abdomen, pelvis, bone lesions, and other clinically indicated sites; as well as clinical evaluation of superficial disease. This assessment was performed within 28 days prior to randomisation and every 12 weeks (±7 days) from the date of randomisation. Disease assessment was repeated at withdrawal or the end of treatment. Radiographic tumor assessments could be performed at any time, if deemed necessary by the investigator because of clinical suspicion of disease progression

PALOMA – Patient Characteristics (I)

Characteristics	PALOMA-1		PALOMA-2	
	PAL+LET (n=84)	LET (n=81)	PAL+LET (n=444)	PLACEBO+LET (n=222)
Median age (range), years	63 (54 to 71)	64 (56 to 70)	62 (30 to 89)	61 (28 to 88)
Ethnicity				
White	[redacted]	[redacted]	**344 (77.5%)**	**172 (77.5%)**
Black	[redacted]	[redacted]	8 (1.8%)	3 (1.4%)
Asian	[redacted]	[redacted]	**65 (14.6%)**	**30 (13.5%)**
Other	[redacted]	[redacted]	27 (6.1%)	17 (7.7%)
ECOG performance status				
0	46 (54.7%)	45 (55.6%)	257 (57.9%)	102 (45.9%)
1	38 (45.3%)	36 (44.4%)	178 (40.1%)	117 (52.7%)
2	Excluded	Excluded	9 (2.0%)	3 (1.4%)
Measurable disease				
yes	[redacted]	[redacted]	338 (76.1%)	171 (77.0%)
Disease site*				
Visceral	37 (44.0%)	43 (53.1%)	214 (48.2%)	110 (49.5%)
Non-visceral	47 (56.0%)	38 (46.9%)	230 (51.8%)	112 (50.5%)
Bone only	17 (20.2%)	12 (14.8%)	NR	NR
Other§	30 (35.7%)	26 (32.1%)	NR	NR

*Data reported for disease site and DFI based on Case Report Form in the PALOMA-1 trial

§ [redacted]

Source: Table 9; page 50 of the ERG report.

Original source: Company submission (table 21) and CSR for PALOMA-1 trial (Tables 18, 19 and 22)

The ERG notes the following minor differences between the two trials (marked in bold):

- The PALOMA-2 trial included proportionately [redacted] than the PALOMA-1 trial

For further details of the patient characteristics of the PALOMA-1 and PALOMA-2 trials see section 4.5 (page 47 to 50) of the ERG report

PALOMA – Patient Characteristics (II)

Characteristics	PALOMA-1		PALOMA-2	
	PAL+LET (n=84)	LET (n=81)	PAL+LET (n=444)	PLACEBO+LET (n=222)
Disease-free interval (DFI)				
>12 months	**25 (29.8%)**	**30 (37.0%)**	**178 (40.1%)**	**93 (41.9%)**
≤12 months / de novo	**59 (70.2%)**	**51 (63.0%)**	**266 (59.9%)**	**129 (58.1%)**
Previous systemic treatment				
None	44 (52.4%)	37 (45.7%)	167 (37.6%)	81 (36.5%)
Chemotherapy	34 (40.5%)	37 (45.7%)	213 (48.0%)	109 (49.1%)
Any hormonal	**27 (32.1%)**	**28 (34.6%)**	**249 (56.1%)**	**126 (56.8%)**
Tamoxifen	24 (28.6%)	24 (29.6%)	NR	NR
Anastrozole	8 (9.5%)	11 (13.6%)	NR	NR
Letrozole	2 (2.4%)	1 (1.2%)	NR	NR
Exemestane	4 (4.8%)	2 (2.5%)	NR	NR
Most recent therapy				
Chemotherapy	[redacted]	[redacted]	NR	NR
Any hormonal	[redacted]	[redacted]	**249 (56.1%)**	**126 (56.8%)**
Anti-oestrogen	[redacted]	[redacted]	154 (61.8%)	75 (59.5%)
Aromatase inhibitor	[redacted]	[redacted]	**91 (36.5%)**	**44 (34.9%)**
Other	[redacted]	[redacted]	4 (1.6%)	7 (5.6%)

Source: Table 9; page 50 of the ERG report.
Original source: Company submission (table 21) and CSR for PALOMA-1 trial (Tables 18, 19 and 22)

The ERG notes the following minor differences between the two trials (marked in bold):

- The PALOMA-2 trial included proportionately fewer patients with de novo ABC and proportionately more patients with DFI >12 months than the PALOMA-1 trial
- Compared with patients included in the PALOMA-1 trial, proportionately more patients included in the PALOMA-2 trial had received previous treatment with hormonal therapy (i.e. endocrine therapy)
- Compared with patients included in the PALOMA-1 trial, proportionately more patients in the PALOMA-2 trial had received hormonal therapy as their last therapy
- In patients whose last treatment was hormonal therapy, compared with patients in the PALOMA-1 trial, proportionally [redacted] patients included in the PALOMA-2 trial received an aromatase inhibitor.

For further details of the patient characteristics of the PALOMA-1 and PALOMA-2 trials see section 4.5 (page 47 to 50) of the ERG report

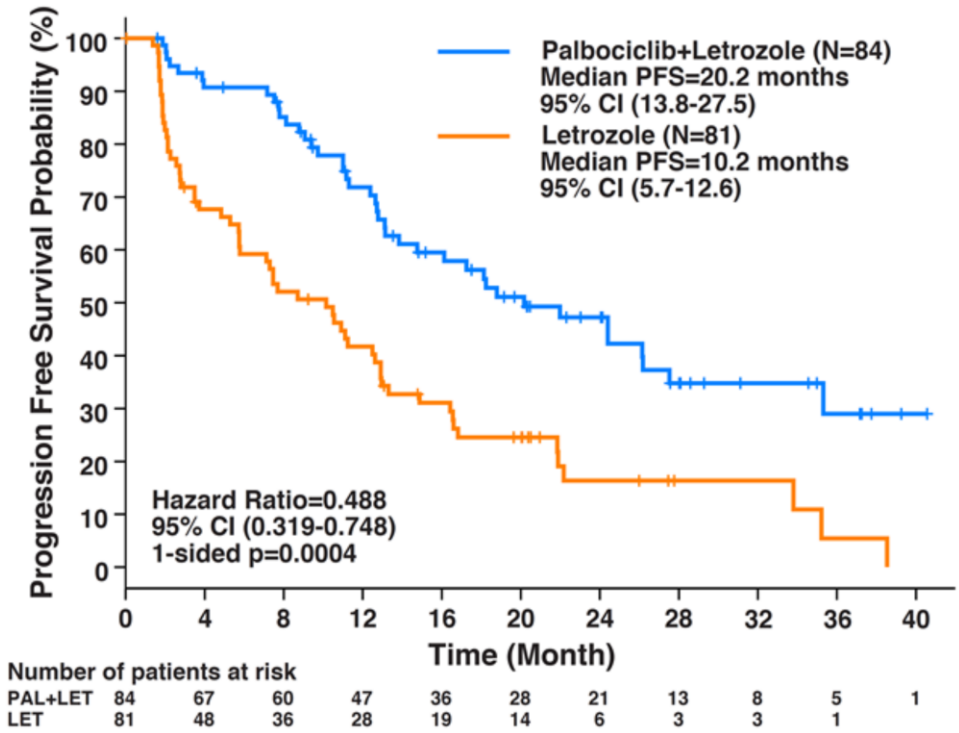
Clinical results – PALOMA-1 OS and PFS

Outcome	Palbociclib-letrozole (n = 84)	Letrozole (n = 81)
Progression-free survival (95%CI) - Investigator-assessed		
Median months	20.2 (13.8 to 27.5)	10.2 (5.7 to 12.6)
HR progression / death	0.488 (0.319 to 0.748, one-sided p = 0.0004)	
Progression-free survival (95%CI) – BICR**		
Median months	25.7 (17.7 to NE)	14.8 (9.3 to 20.4)
HR progression / death	0.621 (0.378 to 1.019, one-sided p = 0.0286)	
Overall survival (95%CI) - Investigator-assessed		
Median OS, months	37.5 (28.4-not reached)	33.3 (26.4-not reached)
HR (95%CI) death	0.813 (0.492 to 1.345, stratified 1-sided p = 0.2105)	
BICR - blinded independent central review; HR - hazard ratio; NE - not estimable; **BICR was conducted on 97% of the intention-to-treat population.		
Source: table 22, page 70 of the company submission		

- Progression-free survival was generally consistent across subgroups analysed by the company for the PALOMA-1 trial. For further details see figure 13, page 82 of the company submission

PALOMA-1 Kaplan-Meier – Progression-free survival

- PFS data from PALOMA-1 was not used to inform the company's economic model, as data from PALOMA-2 was available



Source: figure 9, page 71 of the company submission

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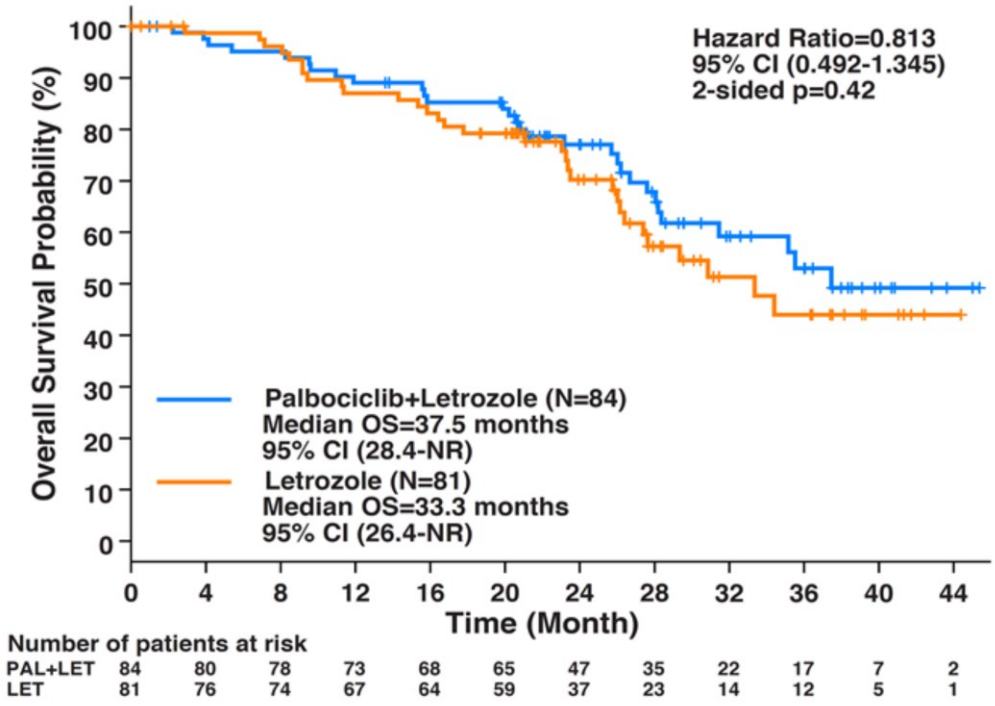
PALOMA-1 Kaplan-Meier – Overall Survival

- OS data from PALOMA-1 (2013 data cut) are used to inform the company's economic model, as data from PALOMA-2 are not currently available.



Source: figure 11, page 74 of the company submission

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- This analysis was based on only 61 deaths among 165 patients, so the study was substantially underpowered to detect significant differences in OS between the two treatments. Further OS analysis will become available on an event-driven basis and [redacted]
- The ERG say: It is not clear why there was no gain in OS in the PALOMA-1 trial given there was such a large gain in PFS although it should be noted, the OS data were immature. The OS data are however from a data cut-off of 29 November 2013. It is surprising that OS data from a more recent data-cut have not been made available.

PALOMA-1 – Secondary outcomes

Outcome	Palbociclib-letrozole (n = 83)			Letrozole (n = 77)		
Adverse events						
Grade	All	Grade 3	Grade 4	**All**	Grade 3	Grade 4
Patients (%)	83 (100)	49 (59.0)	14 (16.9)	65 (84.4)	16 (20.8)	0 (0)

Source: table 39, page 101 of the company submission

Drug	Palbociclib-letrozole (n = 83)		Letrozole (n = 77)
	Palbociclib	Letrozole	Letrozole
Duration of treatment			
Median, days	420.0	428.0	231.0
Number (%) of patients with at least one:			
Cycle delay	70 (84.3)	--	--
Dose reduction	33 (39.8)	--	--
Dose interruption	47 (56.6)	32 (38.6)	23 (29.9)
Relative dose intensity*, %			
Mean (SD)	94.1 (26.2)	99.5 (1.1)	99.5 (2.2)
Median	95.4	100.0	100.0

Source: table 40, page 102 company submission

- For results of further secondary outcome see table 22, page 70 and table 39, page 101 of the company submission
- Included patients which underwent blinded independent central review, which was only conducted on 97% of the intention-to-treat population
- Most common adverse events (all grades) for Palbociclib-letrozole (n = 84)
  - Neutropenia - 62
  - Leukopenia - 36
  - Fatigue - 34
  - Anaemia - 29
  - Nausea - 21
- Most common adverse events (all grades) for Letrozole (n = 81)
  - Fatigue – 18
  - Back pain – 12
  - Arthralgia -12
  - Nausea -10
  - Hot flush - 9

Company says: "Around 60% of these were severity grade 3 or 4, but were generally manageable with dose modifications as per the protocol guidance . Indeed, the management of AEs is reflected in the number of dose interruptions, reductions and cycle delays compared to letrozole alone. As such, there were very few episodes of febrile neutropenia and no deaths attributed to this adverse event."

Rationale: palbociclib causes cell arrest which permits recovery in neutrophil numbers following dose modification, which contrasts with the apoptosis-dominated mechanism associated with chemotherapy-induced neutropenia

Clinical results – PALOMA-2 OS and PFS

Outcome	Palbociclib-letrozole (n = 84)	Placebo-letrozole (n = 81)
Progression-free survival (95%CI) - Investigator-assessed		
Median PFS, months	24.8 (22.1 to NE)	14.5 (12.9 to 17.1)
HR progression / death	0.576 (0.463 to 0.718, one-sided p < 0.000001)	
Progression-free survival (95%CI) – BICR		
Median PFS, months	30.5 (27.4-NE)	19.3 (16.4 to 30.6)
HR progression / death	0.653 (0.505 to 0.844, stratified log-rank one-sided p = 0.000532)	
Overall survival (OS)		
Not yet analysed. Investigators, patients, and Pfizer remain blinded to the OS data. As of 26 February 2016 there have been only [redacted] of the required 390 total deaths needed for the final OS analysis+		

BICR - blinded independent central review; HR - hazard ratio; NE - not estimable

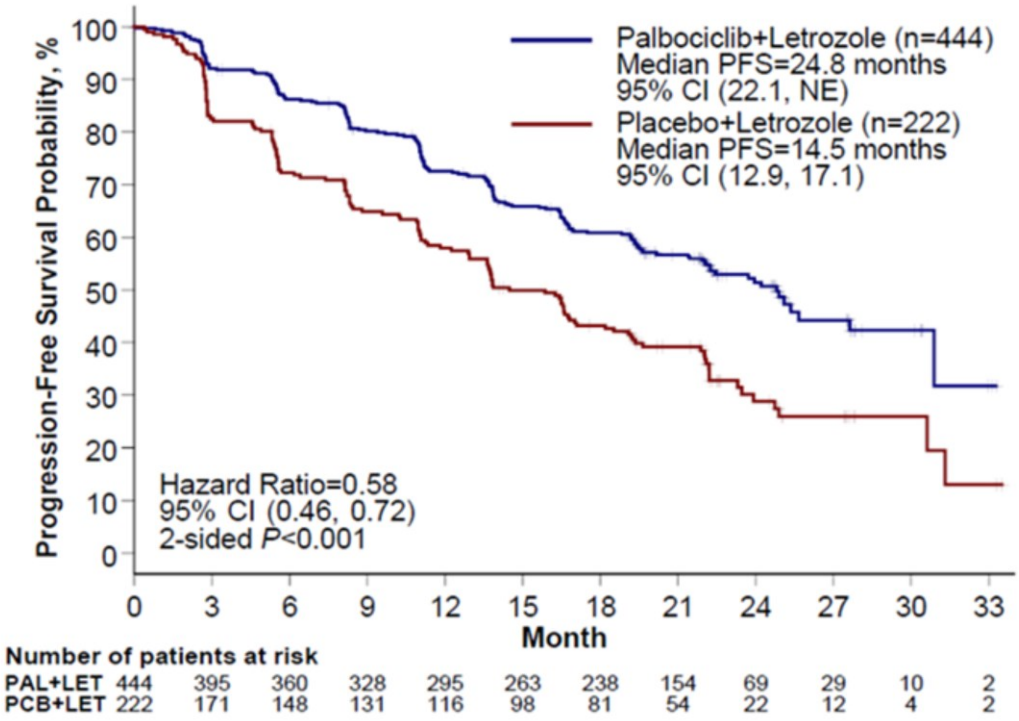
Source: table 24, page 75 of the company submission;
+page 2 of the company clarification response

- Multivariate analyses (using Cox proportional hazard model) of palbociclib plus letrozole versus letrozole plus placebo:
  - BICR: HR [redacted] (95% CI: [redacted])[3]
  - Investigator assessed: HR [redacted] (95% CI: [redacted])
  - Source: Page 6 of the company clarification response

- Progression-free survival was [redacted]. For further details see figure 14, page 83 of the company submission
- The company says:
  - Among women with de novo metastases the hazard ratio was slightly higher than the ITT, and amongst those who have had adjuvant therapy the hazard ratio is lower than the ITT.
  - Considering that regional data suggest that only 5% of women in the UK with breast cancer have metastatic disease at first diagnosis ('de novo' disease), this suggests the ITT hazard ratio may conservatively reflect palbociclib's efficacy in the context of the UK population.

Kaplan-Meier – Progression-free survival

- Kaplan-Meier analysis of progression-free survival in the intention-to-treat population of PALOMA-2



Source: figure 12, page 77 of the company submission

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- The PFS data of the ITT population from PALOMA-2 are used for inputs in the economic model to inform the rate of progression.

PALOMA-2 – Secondary outcomes

	Palbociclib-letrozole (n=444)			Placebo-letrozole (n=222)		
Adverse events						
Grade	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Patients (%)	439 (98.9)	276 (62.2)	60 (13.5)	212 (95.5)	49 (22.1)	5 (2.3)
Pre-progression health-related quality of life, final score (95% CI)						
FACT-B		[redacted]			[redacted]	
EQ-5D		[redacted]			[redacted]	

Source: section 4.7.2.3, page 78-80, and table 41, page 104 of the company submission

	Palbociclib-letrozole (n=444)		Placebo-letrozole (n=222)	
	Palbociclib	Letrozole	Placebo	Letrozole
Duration of treatment				
Median, days	603	617	413	420
Number (%) of patients with at least one:				
Cycle delay	[redacted]	[redacted]	[redacted]	[redacted]
Dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
Dose interruption	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity*, %				
Median	93.0 (40.3-109.5)	99.9 (73.4-100.2)	99.6 (56.1-104.5)	100.0 (79.0-100.0)

Source: table 42, page 104 of the company submission

- For results of further secondary outcome see table 22, page 70 and table 39, page 101 of the company submission

- There was no significant change in quality of life.
  - FACT-B: [redacted]
  - EQ-5D: [redacted]

- Most common adverse events (all grades) for Palbociclib-letrozole (n = 84)
  - Neutropenia - 62
  - Leukopenia - 36
  - Fatigue - 34
  - Anaemia - 29
  - Nausea - 21

- Most common adverse events (all grades) for Letrozole (n = 81)
  - Fatigue – 18
  - Back pain – 12
  - Arthralgia -12
  - Nausea -10
  - Hot flush - 9

Company says: "Around 60% of these were severity grade 3 or 4, but were generally manageable with dose modifications as per the protocol guidance . Indeed, the management of AEs is reflected in the number of dose interruptions, reductions and cycle delays compared to letrozole alone. As such, there were very few episodes of febrile neutropenia and no deaths attributed to this adverse event."

Rationale: palbociclib causes cell arrest which permits recovery in neutrophil numbers following dose modification, which contrasts with the apoptosis-dominated mechanism associated with chemotherapy-induced neutropenia

ERG Critique – PALOMA-1

- It is not clear why there was no gain in OS in the PALOMA-1 trial given there was such a large gain in PFS although it should be noted, the OS data were immature
- The ERG notes that the findings from a final analysis of PFS reported by the EMA shows large differences between investigator and BICR assessed PFS for cohort 1

	Cohort 1		Cohort 2	
	PAL+LET (n=34)	LET (n=32)	PAL+LET (n=50)	LET (n=49)
Progression-free survival (95%CI) - Investigator-assessed				
Median months	26.1 (11.2 to NE)	5.7 (2.6 to 10.5)	18.1 (13.1 to 27.5)	11.1 (7.1 to 16.4)
Hazard ratio	0.299 (0.156 to 0.572)		0.508 (0.303 to 0.853)	
p-value	p=0.0001		p=0.0046	
Progression-free survival (95%CI) - BICR				
Median months	31.6 (11.2 to NE)	38.6 (7.5 to 38.6)	20.3 (12.2 to NE)	14.6 (8.1 to 20.0)
Hazard ratio	0.731 (0.300 to 1.779)		0.576 (0.316 to 1.050)	
p-value	p=0.2442		p=0.0342	

Source: table 13, page 56 of the ERG report[1]

[1]Adapted from European Public Assessment Report, Figure 17

- According to the EMA, this indicates that findings from cohort 1 may be significantly biased to the extent that the findings from the PALOMA-1 trial are not suitable for licensure.
- The EMA also conclude that only findings from cohort 2 should be considered relevant to the efficacy assessment.

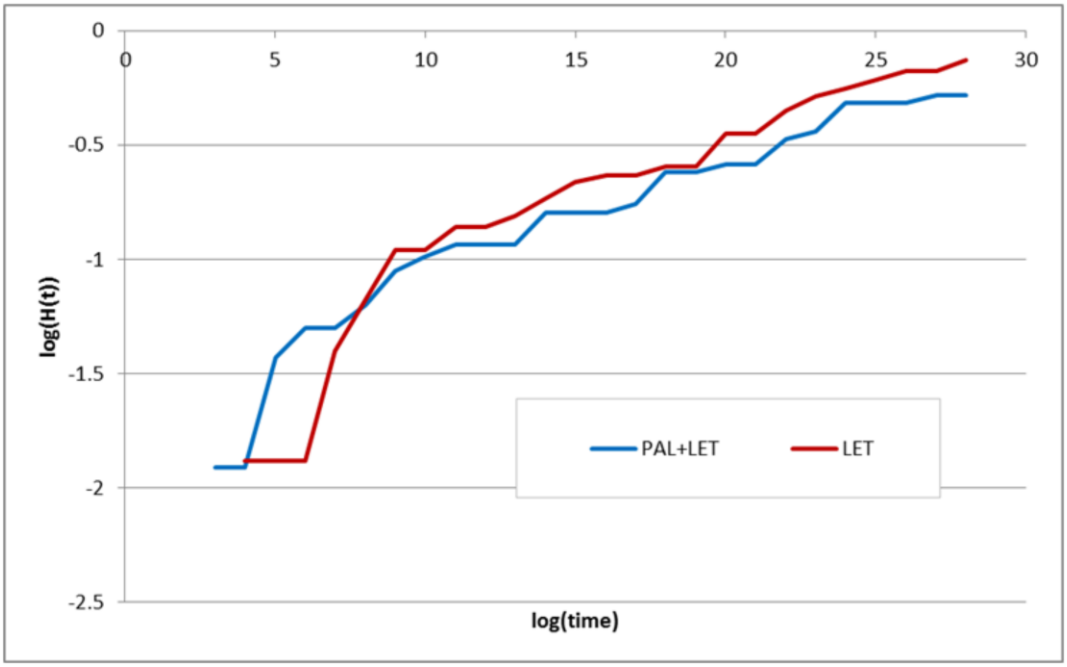
- The ERG notes that one-sided hypothesis testing was used to assess PFS and TTP and, as part of the clarification process, asked the company to justify the use of this approach to hypothesis testing. The company states that one-sided hypothesis testing was deemed suitable due to there being "sufficient confidence" that treatment with PAL+LET was more effective than treatment with LET, and that it was more efficient (from a statistical perspective) in light of the expected small sample size and under the null hypothesis to use one-sided testing. The ERG is satisfied that the use of one-sided testing was appropriate, although it considers that more justification could have been provided regarding the basis for the company's confidence that PAL+LET is more effective than LET. Furthermore, the rationale for such an important statistical decision should have been provided in the protocol and/or in the TSAP.

- The EMA highlights that apparent imbalances by treatment arm in the PALOMA-1 trial were due to the incorrect stratification factors being used at the time of randomisation which were discovered retrospectively during data review and source data verification. Sensitivity analyses using Case Report Form data were conducted to investigate the impact of the imbalances on the PFS results, using multivariate Cox PH models by investigator and BICR assessments. These indicated that having additional patients with visceral disease in the LET arm may favour the PAL+LET arm in the comparison (BICR HR 0.4 for non-visceral versus visceral). However, the difference in mean and medians of age may favour the LET arm (BICR HR 0.5 for age ≥ 65 years versus < 65 years). These imbalances appear to add uncertainty to the results.

- The ERG notes that data reported in a poster presented at the 38th San Antonio Breast Cancer Symposium in December 2015 (summarised in appendices to this ERG report, Section 10.4) appear to show some imbalances by treatment arm in terms of treatments received post-progression. A greater proportion of patients in the PAL+LET arm received subsequent chemotherapy than in the LET arm (51.5% versus 39.6% respectively) whereas a smaller proportion received subsequent endocrine therapy (45.4% versus 60.4% respectively) or other therapy (18.2% versus 24.5% respectively). These results may reflect slight differences in ECOG PS by treatment arm recorded at the time of progression. Data presented by the company during the clarification process show that at the time of disease progression, [redacted] of patients had an ECOG PS ≥2 in the PAL+LET arm compared with [redacted] of patients in the LET arm. However, the numbers of patients in both arms who received subsequent treatment were very small (n=33 and n=53 respectively) as was the number of patients for whom ECOG PS was available for ([redacted] and [redacted] respectively). The ERG notes that small differences in actual numbers can result in large differences in proportions and therefore suggests that the data from the PALOMA-1 trial must be treated with caution.

ERG Critique – PALOMA-1 proportional hazards

- The ERG considered that the proportional hazards (PH) assumption was valid for PFS data, but not for OS data. Therefore, the use of HRs for OS is not appropriate.



Source: Figure 25 (OS log-log plot), page 128 of the ERG report

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ERG Critique – Overview

- The ERG is satisfied that the analysis method for each of the outcomes was pre-specified, and that all results were reported fully
- Both trials were international multi-centre RCTs
  - PALOMA-1 shows large differences between investigator assessed PFS and BICR assessed PFS for cohort 1 (data submitted to EMA)
  - PALOMA-2 trial was much larger, and double-blinded. The findings of the therefore appear to be more robust than those from the PALOMA-1 trial
- PAL+LET treatment led to higher rates of neutropenia
  - The company noted that managing palbociclib-associated neutropenia is relatively uncomplicated and reversible
  - The ERG concurs that the data appear to support this assertion
- While the PALOMA trials have a high proportion of patients presenting with de novo disease the ERG agrees the patient populations in both trials are representative of the patients who would be treated in clinical practice
- All OS data are from a data cut-off of 29 November 2013 of PALOMA-1. It is surprising a more recent data-cut have not been made available

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- Neutropenia
  - The company highlights that none of the cases of neutropenia in either arm in the PALOMA-1 trial developed into febrile neutropenia and that all cases of neutropenia in this trial were asymptomatic.
  - The company suggests that the mechanism by which palbociclib causes cell cycle arrest is important when considering palbociclib-induced neutropenia. Unlike chemotherapy-induced neutropenia, which is caused through irreversible human bone marrow cell death, results from the PALOMA-1, PALOMA-2 and PALOMA-3 trials show that, in most cases, cellular proliferation resumed to near pre-treatment levels when the palbociclib dose was interrupted.

Cost-effectiveness evidence

Company submission section 5

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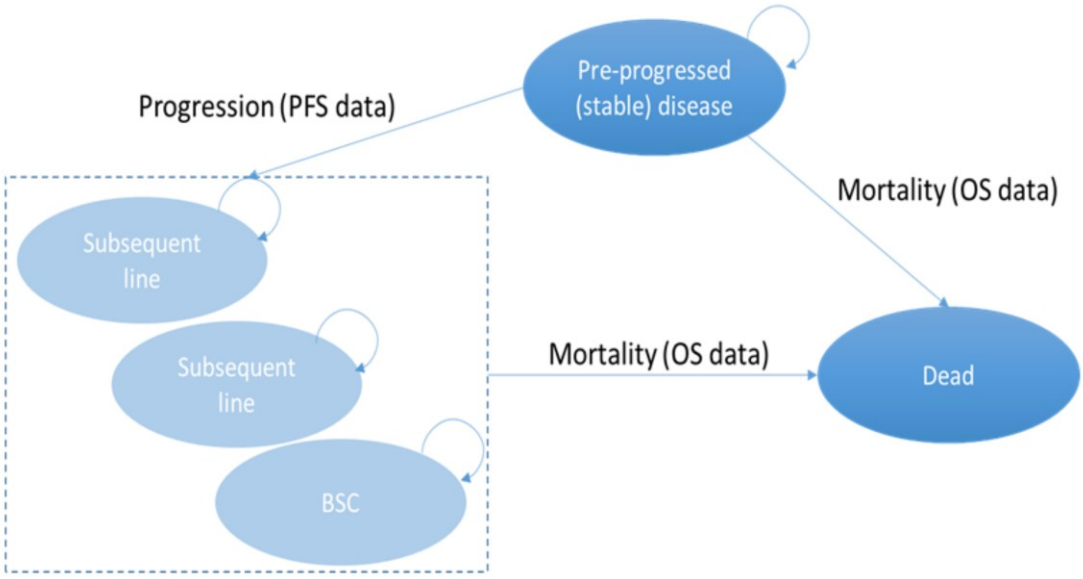
Model structure

- Partitioned survival model, with all patients entering in the pre-progressed health state
- It is assumed that 25% of post-progression patients would not switch to a subsequent line, and would instead receive BSC until death



Source: Figure 18; page 120 of the company submission

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- The model cycle length was 28 days (13 cycles per year) and, due to the short length of the treatment cycle, a half-cycle correction was not implemented
- Lifetime time horizon (40 years)
- ERG say: "The company model structure is similar to that of other models that have been submitted to NICE as part of an STA process that have considered new treatments for advanced or metastatic cancers"
- Duration of time spent in subsequent lines in the model was assumed as 6 cycles per line for both treatment arms; it was found that varying this number had minimal impact on the ICER

Company key inputs and assumptions

	Source / assumption	Company rationale
PFS	PALOMA-2 + Weibull extrapolation	PALOMA-2 is the larger more recent trial, whilst Weibull was both conservative and the best fit
OS	PALOMA-1 + Weibull and adjusted OS to reflect median PFS gain in PALOMA 2	PALOMA-1 trial only OS available. Adjustment as literature identifies a correlation between PFS and OS in advanced breast cancer
Treatment duration	Until progression (PALOMA-2)	No restriction to a pre-defined number of cycles
Safety	Grade 3 and 4 of >5% incidence only (PALOMA-2)	Other appraisals do not consider grade 1, 2 As low incidence grade 5 events not considered
Safety costs	Equal to those of neutropenia grade 3 or grade 4	neutropenia was the most prevalent adverse event
Utilities	PALOMA-2* then Lloyd 2006 multiplier for post-progression	Only PALOMA-2 contained EQ-5D data, and only up to disease progression
Administration cost	None	Both regimens are orally self-administered by patients at home
Sequence	25% patients progress to BSC at each transition	clinical expert opinion that (either choice or health reasons) people would not want treatment
*The ERG were unable to replicate the results presented by the company		
Source: adapted from table 72 and 73; page 149-156 of the company submission		

- For full details see the tables

- Rationale for adverse events severity is that there are differences between palbociclib-induced neutropenia and chemotherapy-induced neutropenia. Palbociclib-induced neutropenia is asymptomatic and reversible, whereas chemotherapy-induced neutropenia is not reversible and, therefore, requires recovery by re-population from the original haemopoietic stem cells. This often means that a patient with chemotherapy-induced neutropenia needs to receive growth factor stimulation (such as the use of granulocyte-colony stimulating factor 7) to support bone marrow recovery.

- The question of whether PFS can be considered an acceptable surrogate end-point for overall survival depends not only on the formal validation studies used to reach that conclusion but also on there being a standardised definition and unbiased ascertainment of disease progression in those clinical trials. A recent publication by Petrilli and Barni (2014) focused on the specific molecular subtypes within metastatic breast cancer while previously analyses focused on general breast cancer without evaluating the subtypes. Randomised phase 3 trials for metastatic breast cancer were identified and correlations between endpoints were evaluated. The Spearman's rank correlation coefficient between hazard ratios in PFS/TTP and hazard ratios in OS was 0.73 (95% CI, 0.719-0.738; $P<0.00001$); the slope of the regression line was 0.56 ± 0.0034, indicating that an agent producing a 10% risk reduction for PFS will provide a 5.6% risk reduction for OS (source: page 25 of the company submission)

Company base-case ICERs (deterministic)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental			ICER (£ per QALY)
				Costs (£)	LYGs	QALYs	
Company base case							
Letrozole	£21,843	3.02	1.77				
Palbociclib + letrozole	£116,696	3.79	2.40	£94,853	0.78	0.63	**£150,869**

LY - Life year; QALY - Quality Adjusted Life Year; LYG - Life year gain; ICER - Incremental Cost Effectiveness Ratio

source: table 74, page 157 of the company submission

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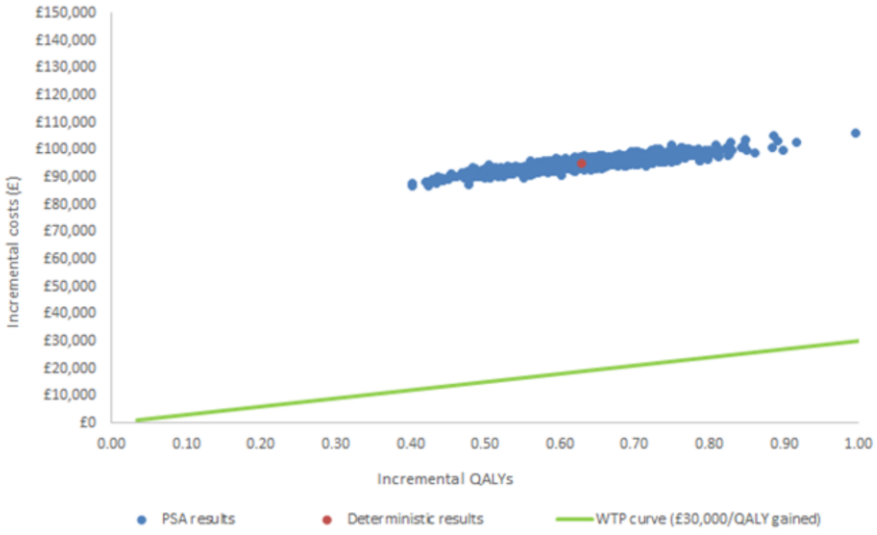
Company probabilistic sensitivity analysis

	Incremental costs (£)	Incremental QALYs	ICER (per QALY)
Deterministic result	£94,853	0.63	£150,869
Average value from PSA	£94,951	0.63	£151,058

- ERG places no confidence in the PSA results as the macro is set up to exclude any correlated uncertainty in the key model parameters.



Source: Table 80 and Figure 26, page 161 of the company submission

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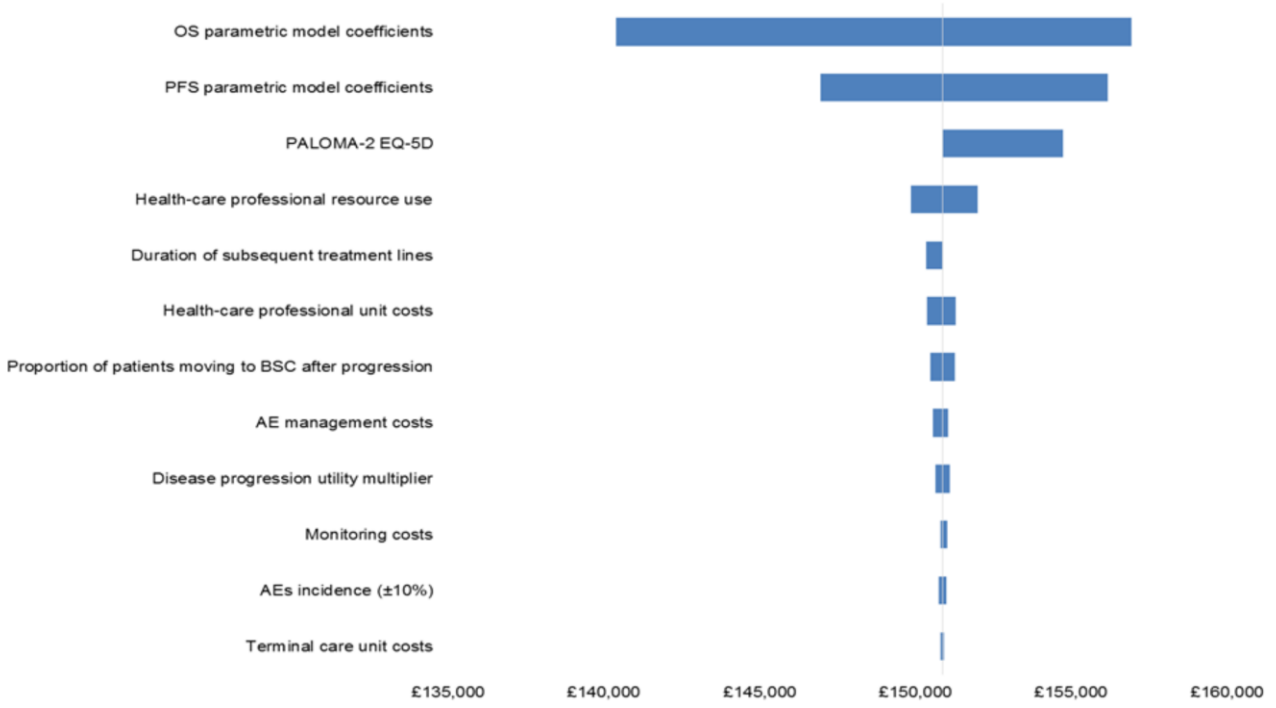
ERG says: The scatterplot is essentially one-dimensional along the QALY axis, with very little variability in the cost axis. This result is due to the way in which the company has formulated the PSA. The PSA macro is set up to exclude any correlated uncertainty in the key model parameters (Weibull model scale and shape parameters). This leads to apparently minimal uncertainty in the estimate of the probabilistic ICER and therefore virtually no spread in the CEAC. The ERG therefore places no confidence in the PSA results which are inconsistent with the use of multiple Weibull models in projecting future costs and outcomes.

Company deterministic sensitivity analysis

- Company performed sensitivity analysis on model inputs between the limits of their 95% confidence interval



Source: Figure 28, page 163 of the company submission

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Company Scenario analyses (I)

Scenario # in CS	Assumptions varied	ICER/QALY gained	ICER change
Base case deterministic ICER		£150,869	
27	Only PFS gain for PAL+LET (10.3 months) No OS gain for PAL+LET (0 months)	£312,635	+ £161,766
28a	Increase median OS gain for PAL+LET to 5 years	£61,822	- £89,047
28b	Increase median OS gain for PAL+LET to 5 years, but removing post-progression costs	£42,794	- £108,075
29	Increase in utility of +0.1 for patients in the PFS state	£134,134	- £16,735
30	A comparator with the same monthly acquisition costs (i.e. fixed cost of £2,951.52 per month, but only for respective treatment durations)	£53,074	- £97,795
31	Reduced treatment duration by 12 months in each arm (PFS reduced from 15.7 to 3.7 months for LET, and from 24.9 to 12.9 months for PAL+LET)	£86,419	- £64,450
32	• Comparative monthly acquisition costs • Value of PFS utility increase (+0.1) No change to base case OS assumption	£47,187	-£103,682
33	• Comparative monthly acquisition costs (#30) • Value of PFS utility increase (+0.1) • Incremental median OS gain of 12 months	£43,819	-£107,050

- The company's exploratory scenarios that lead to a cost-effective ICER fall into to a combination of four categories: OS gain for PAL+LET; acquisition costs of the comparator; PFS utility values; and post-progression costs.

- The company has given the following rationales for the scenarios:

OS gain

- The current cost per QALY approach does not reflect the full value of PFS, and in doing so, a disproportionate expectation is placed on overall survival and the resultant ICERs severely underestimate the benefit of palbociclib. This scenario adjusts OS to reflect a 5-year gain with palbociclib, with modelled median OS for letrozole of months and for palbociclib. This is implemented in the model using the same functionality as was used in the base case (see Section 5.3.2).

Acquisition costs of letrozole

- Palbociclib is an add-on therapy, resulting in 100% of the drug acquisition costs contributing towards the incremental costs. Even if it were not an add-on therapy, the comparator arm acquisition costs are minimal accounting for only £1.52 per cycle due to letrozole being generic, bringing a similar situation where almost all of the intervention's acquisition costs are incremental. This scenario examines the impact on the ICER should the comparator arm monthly acquisition costs be the same as the intervention and consistent with other newer oncology medical innovations which are approved by NICE.

Increased PFS utility value

- Lloyd (2006) presents pre-progression utility of [redacted] (PALOMA-2 is [redacted] for the two arms) and post-progression utility of 0.49. The value of keeping a patient progression free is thus a utility benefit of [redacted].
- We believe the value of PFS to society and to patients is greater than this, and this does not reflect the benefits of remaining progression-free to women with ABC as detailed in section 3.2.1. As such, a scenario has been conducted that examines the impact on the ICER should a utility benefit of remaining progression-free be greater than just controlling the disease. More specifically these include delaying the onset of chemotherapy, the psychological benefits from being on a successful treatment, being able to stay in work and continue with normal life, and the ability to continue a family life at home and care for a family as before. In this scenario, the utility estimate for both treatment arms is increased by 0.1 in the progression-free state, as a proxy reflection of a more comprehensive valuation of the benefits of PFS.

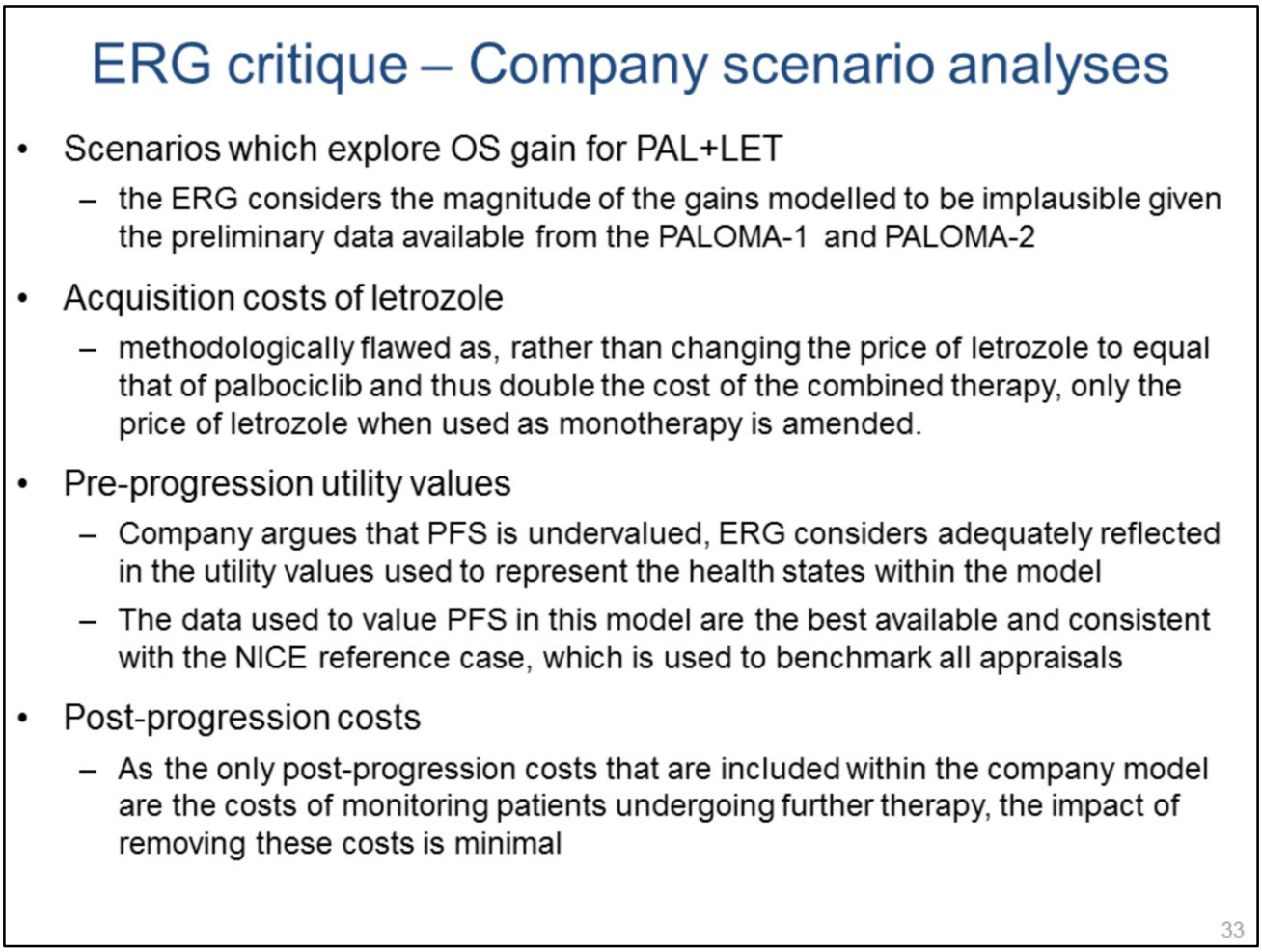
Post-progression costs

- (No rationale given)

Company Scenario analyses (II)

Scenario # in CS	Assumptions varied	ICER/QALY gained	ICER change
Base case deterministic ICER		£150,869	-
34	• Comparative monthly acquisition costs • Value of PFS utility increase (+0.1) • Incremental median OS gain of 12 months • Removal of post-progression costs	£40,482	**-£110,387**
35	• Comparative monthly acquisition costs • Value of PFS utility increase (+0.1) • Incremental median OS gain of 24 months	£36,194	**-£114,675**
36	• Comparative monthly acquisition costs • Value of PFS utility increase (+0.1) • Incremental median OS gain of 24 months • Removal of post-progression costs	£26,996	**-£123,873**
From scenarios 33 and 34	Incremental OS gain of 12 months	£134,294	**-£16,575**
From scenarios 35 and 36	Incremental OS gain of 24 months	£95,656	**-£55,213**
From scenarios 28b, 34, 35 & 36	Remove all post-progression costs	£150,303	**-£566**

Source: table 43, page 137 of the ERG report and section 5.8.3, page 169-172 of the company submission



- The company's exploratory scenarios that lead to a cost-effective ICER fall into to a combination of four categories: OS gain for PAL+LET; acquisition costs of the comparator; PFS utility values; and post-progression costs.

- OS gain
    - The company presents these scenarios to demonstrate the importance of OS on the ICER per QALY gained. The company states that that treatment with PAL+LET would need to extend life by approximately 9 years to yield an ICER per QALY gained of around £50,000 (with palbociclib at list price and all other base case assumptions remaining the same), which it notes is not clinically plausible. However, the price of the drug also influences the impact of extended time spent in PFS. If the cost of palbociclib were to increase or decrease, and all other elements of the model were to stay the same, the size of the OS gain required to bring the ICER down towards the NICE threshold would also increase or decrease

- Acquisition costs of letrozole
    - The ERG also considers the implementation of this scenario to be methodologically flawed as, rather than changing the price of letrozole to equal that of palbociclib and thus double the cost of the combined therapy, only the price of letrozole when used as monotherapy is amended. The ERG does not therefore consider the comparative acquisition costs scenario as plausible in practice as if letrozole had a higher list price, this would also be the price for use in combination with palbociclib.

- PFS utility values
    - The benefit of having stable disease (being in the pre-progressed health state) in the model is an improvement in health-related quality of life of more than 0.2 (on the 0-1 utility scale) over the progressed health state, in both the company estimated and the ERG re-calculated utility values. This incremental benefit exists for the duration of any PFS extension offered by PAL + LET treatment in comparison to LET alone. The value used to estimate progressed utility is taken from a study of patients receiving chemotherapy and therefore any difference in AE profiles or psychological impacts between the treatments received pre- and post-progression is represented within the difference between the health-related quality of life values.
    - ability to continue to work is captured within the activities of daily living question which forms part of the EQ-5D questionnaire
    - costs to the patients of being unable to undertake paid employment cannot be considered as part of the NICE appraisal process without discriminating in favour of individuals of working-age.
    - burden on carers of patients with this disease is so substantial that its exclusion contributes to undervaluing the benefit of PFS. The company does not however present any evidence to quantify the health-related quality of life impact

- Post-progression costs
    - In addition, the DSU discussion paper regarding cost-effectiveness at zero price considers scenarios in which non-treatment related costs could be excluded however concludes that a narrow perspective does not enable full consideration of the opportunity cost to the NHS of the introduction of a new technology and therefore the ERG does not consider this element of the scenario analyses plausible.

ERG critique – Alternative censoring

- The ERG requested data using an alternative censoring method
  - Conventional censoring is on the date of last known contact any patients
  - ERG preferred method with immature data is to censor at the point of data cut-off or at the time of withdrawal from the study
- This is because using the conventional method:
  - People still alive would be cut off early (at last tumour assessment)
  - People who die between assessment and data cut-off would likely still be recorded as an event
- Therefore the conventional method will underestimate the people still at risk, whilst accurately reflecting the number of events – leading to a distorted time-to-event trend
- All the company's time-to-event analyses use conventional censoring
- All the ERG's time-to-event analyses use the alternative censoring method
- The alternative censoring had little impact on the K-M data in this instance, but the ERG would require access to the IPD in order to explore fully.

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ERG critique – Overall and post-progression survival (I)

- Modelling of OS in the base case is informed by the assumption that 100% of PFS gain will translate into OS gain. The ERG does not agree that this assumption is justified
- Company has attempted to reconcile OS data from the PALOMA-1 trial and PFS data from the PALOMA-2 trial – which is not methodologically sound
- Company has adjusted the fitted OS curve from the PALOMA-1 trial for treatment with PAL+LET so that median OS gain in the model equals median (modelled) PFS gain from the PALOMA-2 trial.
  - This does not result in equality between *mean* OS gain and *mean* PFS gain
  - Adjusting the scale parameter has a proportionately greater effect on mean OS and therefore on mean OS gain
- The ERG does not agree that OS data from the PALOMA-1 trial are insufficiently reliable to provide a basis for modelling, and considers using the OS data from the PALOMA-1 trial, alongside other time-to-event data from the same trial, to be preferable to the method used by the company

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- 100% of PFS gain will translate into OS gain – this is an important assumption, because patients continue to accrue QALYs and costs beyond progression that can have a substantial effect on the overall ICER per QALY gained. If there is no difference in post-progression survival (PPS) between the two treatments, the costs and benefits of the drug are limited to those that accrue in PFS. The ERG does not agree that this assumption is justified.

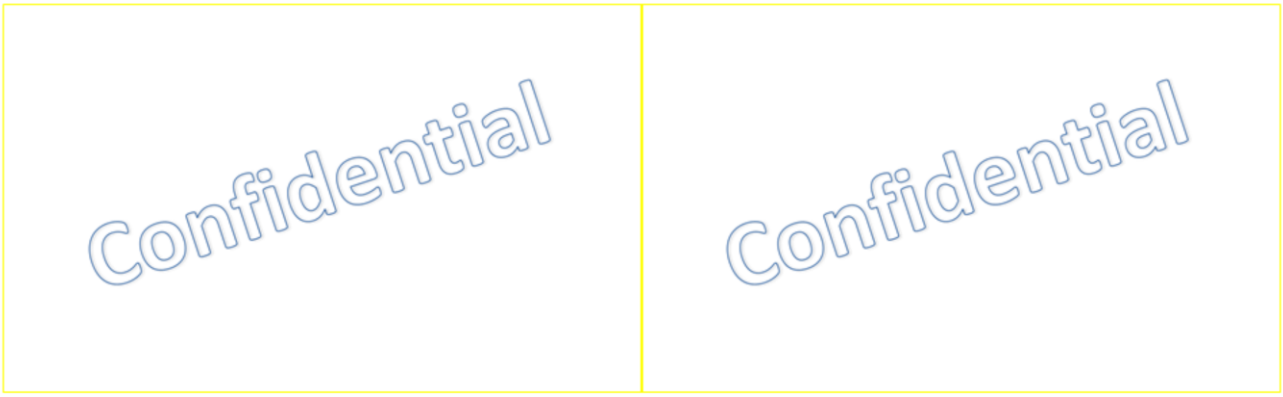
- Combining PALOMA-1 OS data with PALOMA-2 PFS data – Usually, the results of different trials will be combined via meta-analysis and will use relative effects to compare treatment arms from different studies. Randomisation allows investigators to be reasonably certain that the baseline hazards for patients in the trial are balanced between arms, which means that relative effects can be compared (where appropriate) with other trials. However, direct, rather than relative, results from different trials might differ markedly because of explicit or hidden differences in the patient populations in different trials. The explicit baseline characteristics differ between the patient populations (Section 4.5) of the PALOMA-1 and PALOMA-2 trials, which may affect the baseline hazards of each trial population and so make direct comparison impossible.

- Adjustment of the fitted OS curve – Because of the way the shape and scale parameters interact in the Weibull model, increasing the median of a curve to a predefined level has a proportionately larger effect on the mean value of that same curve. This means that, by adjusting projected OS for treatment with PAL+LET, the company model actually includes a small (0.49 months) gain in PPS for treatment with PAL+LET.

- Adjustment of the fitted OS curve – The ratio of median to mean is also different in both of these Weibull models. The combination of the right skew and the dynamic ratio of median to mean means that adjusting the scale parameter, as the company has, in order to achieve a larger median OS gain has a proportionately greater effect on mean OS for PAL+LET and, thus, on mean OS gain. The ratio of median to mean OS gain when using the adjusted base case model for PAL+LET is proportionately greater than when using the unadjusted Weibull model (0.830 versus 0.773).

ERG critique – Overall and post-progression survival (II)

- No evidence for the assumption of zero post-progression survival (PPS) gain:
  - Evidence from the PALOMA-1 trial indicates a restricted mean PPS loss for treatment with PAL+LET of [redacted] months (left-hand figure)
- ERG fit a two-part exponential curve to re-censored OS K-M data (right-hand figure)
  - Restricted mean OS gain of 6.6 months for ERG analysis versus 11.2 months for the company base case for treatment with PAL+LET
  - ERG notes that this projected OS gain is based on data whose restricted means are not statistically different, therefore there is considerable uncertainty in the estimate



Source: Figure 6 (PPS), page 89 and Figure 10 (OS projections), page 93 of the ERG report

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- The ERG analysed the re-censored OS K-M data provided by the company during the clarification process (left hand figure) and found no statistically significant difference between the two arms of the trial (log rank test p=0.488, Mann-Whitney U p=0.734)

- Two-part exponential curve – The pooled OS data from the PALOMA-1 trial exhibits apparently increasing hazards over time, which can in fact be modelled as two sections of constant, but different, hazards that change at around 20 months. These constant hazards are represented by straight lines in the cumulative hazard plot and translate into piecewise exponential overall survival estimates.

- Although there is no statistically significant difference in OS in the available data, the ERG has assumed that the apparent separation of the curves toward the end of the K-M data will continue. The ERG found that proportional hazards held adequately after the crossing of the arms at 8 months, so considered it appropriate to use Cox PH regression to estimate the HRs of the separate PAL+LET and LET arms versus the pooled OS data. It used these HRs to adjust the exponential model from the second half of the pooled analysis in order to forecast OS for treatment with PAL+LET and treatment with LET. The ERG then fitted these adjusted exponential tails to the relevant OS K-M data for the intervention and comparator (Left hand figure).

- Restricted means: these are not the true means (i.e. some patients were still on treatment at the time of calculation), and could be considered to be an underestimate of the actual mean OS.

ERG critique – Progression-free survival (I)

- ERG identified two key issues with the company's estimates of PFS
  - Data from the PALOMA-2 trial are inconsistent with the data from the PALOMA-1 trial used to model OS
  - Weibull model used in the base case produces implausible results
- ERG prefers that the PFS data from the PALOMA-1 trial are used
- The Weibull models used by the company to model PFS in both arms of the PALOMA-1 trial have monotonically increasing hazards
  - This means that, the longer a patient remains progression free, the more likely they are to progress or die than they were previously
  - ERG considers this to be implausible over the 40 year time horizon used in the model
  - Re-censored K-M data reveals clear exponential trends

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- PALOMA-1/2 PFS data – The ERG considers that the PFS data from the PALOMA-2 trial are, in themselves, more reliable than those from the PALOMA-1 trial. However, because no OS data are available from the PALOMA-2 trial, the ERG considers that introducing inconsistencies by mixing direct PFS data from one trial with direct OS data from another is less justifiable than using a full set of time-to-event data from a single Phase II trial.

- monotonically increasing hazards – This means that, the longer a patient remains progression free, the more likely they are to progress or die than they were previously. The logic here is that patients who have done well following treatment, either because of the treatment itself or because of some underlying characteristic, and who have lived for many years after beginning treatment are actually at greater risk of progression (or death) than patients who were sicker or less responsive and died earlier.

ERG critique – Progression-free survival (II)

- The ERG used the full K-M data for the LET arm
- The ERG used K-M data until 16.6 months, then an exponential extrapolation
  - Switching point identified using the smallest of the weighted squared residuals
- Mean modelled PFS gain was 13.3 months (ERG) versus 10.7 months (Company)

Source: Figure 14 (ERG PALOMA-1 PFS projections), page 97 of the ERG report

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ERG critique – Time to treatment discontinuation

- The company assumes all patients in the model are treated to progression
- ERG use K-M data, and extrapolate using exponential for PAL+LET
- Mean time to treatment discontinuation in the model was
  - For PAL+LET: 20.7 months (ERG) versus 30.9 months (Company)
  - For LET: 12.9 months (ERG) versus 20.2 months (Company)

Source: Figure 18 (TTD and PFS projections for PALOMA-1), page 100 of the ERG report

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- The difference between PFS and TTD can be explained in the most part by the proportion of patients discontinuing treatment due to AEs: [redacted] of patients who discontinued treatment with PAL+LET in the PALOMA-1 trial did so due to AEs, in comparison to [redacted] of patients who discontinued treatment with LET due to AEs. Source: Clinical Study Report

- The ERG used the trend in the PAL+LET arm to append exponential extrapolations to points near the end of the K-M data for treatment with PAL+LET. The extrapolation point was identified by choosing the K-M data point with the smallest weighted squared residual of the difference between the K-M data and the fitted exponential curve. The final K-M data point in the LET arm of the re-censored PALOMA-1 data set was censored, but, rather than extrapolating an estimate for this point, the ERG used the final PFS K-M point from the PALOMA-1 trial as a proxy in order that patients in the model did not receive treatment with LET beyond progression when the ERG's PFS revisions were also applied.

ERG critique – Utility values

- The Company used higher pre-progression utility values for PAL+LET versus LET ([redacted] versus [redacted])
  - The ERG does not consider the company to be justified in using a higher pre-progression utility value for PAL+LET, as there was no significant difference found in the EQ-5D in the two arms PALOMA-2 trial.
  - ERG was not able to identify the method used to yield the values
  - ERG calculated alternative pre-progression utility values using the mean utility values from European patients in the PALOMA-2 trial
  - ERG calculated an average pooled cycle utility for European patients of [redacted]
- Company uses post-progression utility values using the published results of a study by Lloyd et al (0.4492 for both treatments)
  - Company did not take into account the logistic transformation of the data
  - The ERG recalculated using the results of the mixed model analysis given in the Lloyd et al paper, including the logistic transformation of the data, and calibrated the result to the UK average age (48.52 years) in the UK value set
  - The ERG's recalculated post-progression utility value is 0.5052

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- The ERG is also satisfied that it is valid to use utility values calculated from EQ-5D responses from the PALOMA-2 trial alongside time-to-event data from the PALOMA-1 trial in the absence of EQ-5D data from the PALOMA-1 trial. This is because utility data are less prone to serious differences than time-to-event data provided the disease area and stage of disease are broadly similar.

- The ERG noted that because the EQ-5D questionnaire was only completed until disease progression, although [redacted] of [eligible] respondents completed all of the EQ-5D questionnaire per cycle (source: page 15 of the company clarification response), the proportion of the ITT population who completed the questionnaire dropped significantly.
  - The ERG therefore calculated a weighted average utility value using the mean values per cycle and the number of respondents per cycle from both arms of the PALOMA-2 trial for the first 21 cycles of treatment (since mean utility values were stable and completion rates were above 80% for the first 21 cycles of each arm, so can be considered reliable).
  - For further details of the EQ-5D response rate and results per cycle see figure 19 (EQ-5D utility values and completion rates) of the ERG report

- ERG noted that EQ-5D data was from the PALOMA-2 trial ITT population when using values collected from just the European population would have been more relevant to the NHS

ERG critique – Further changes

- ERG included a half-cycle correction
- For adverse event costs the company uses a proportion of the relevant NHS Reference Cost (i.e. assumed an hourly rate)
  - ERG amended to apply the full NHS Reference Cost
- Two amendments for calculating the incidence of adverse events:
  - company used the median rather than mean time on treatment to calculate the probability of an adverse events
  - the company has applied annual rather than cycle AE probabilities to each cycle in the model
  - Amending these increases the time on treatment for both arms and reduces the probability of adverse events
- Company applied the 3.5% discount per cycle (28 days)
  - ERG applied the 3.5% discount annually
- Company assume 364 days per year
  - ERG amendment to 365.25 days per year

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- Adverse event costs – Not justified to use a proportion of the relevant NHS Reference Cost to represent a meeting of 20 minutes (Grade 3) or 30 minutes (Grade 4) with a consultant oncologist. This is because NHS Reference Costs provide a currency for payment for the average patient and do not represent an hourly cost (unless that is how much of the resource the average patient uses).

Impact of ERG changes to the ICER

Model scenario ERG revision	Incremental Cost (£)	 QALYs	ICER £/QALY	ICER Change
A. Company original base case	£94,853	0.629	***£150,869***	-
ERG OS estimates based on data from PALOMA-1	£90,977	0.481	£189,310	***+£38,441***
ERG PFS estimates based on data from PALOMA-1	£81,928	0.675	£121,408	***-£29,461***
ERG TTD estimates based on data from PALOMA-1	£64,712	0.629	£102,928	***-£47,941***
ERG recalculated pre-progression utility values from PALOMA-2 trial	£94,853	0.566	£167,727	***+£16,858***
ERG recalculated post-progression utility values	£94,853	0.628	£151,146	***+£277***
Use mid-cycle correction	£93,433	0.628	£148,687	***-£2,182***
Use full reference costs for AEs	£95,861	0.629	£152,472	***+£1,603***
Correct AE incidence calculation	£94,317	0.629	£150,015	***-£854***
Change discounting to annual	£96,262	0.639	£150,710	***-£159***
Use 365.25 days per year	£94,854	0.629	£150,871	***+£2***
B. ERG revised base case	£59,934	0.451	*£132,872*	***-£17,997***

Source: table 34; page 111 of the ERG report

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For total and incremental costs, life years and QALYs see the full table

ERG scenario analyses – PALOMA-2 data

- Company, ERG, and EMA consider PALOMA-2 trial to be of lower risk of bias
- ERG considered mixing PALOMA-1/2 to introduce methodological flaws
  - ERG have presented a scenario analyses of the company's preferred method of including PALOMA-2 PFS, incorporating the ERG's changes to methodology

Source: Figure 20 (ERG revised PFS model), page 105 of the ERG report

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- The ERG notes that the findings from a final analysis of cohort 1 from the PALOMA-1 trial shows large differences between investigator assessed PFS and BICR assessed PFS. These findings were reported by the EMA. According to the EMA, these results indicate that findings from cohort 1 may be significantly biased to the extent that the findings from the PALOMA-1 trial are not suitable for licensure. The EMA also conclude that only findings from cohort 2 should be considered relevant to the efficacy assessment.

ERG scenario analyses – PALOMA-2 data

	Company base-case	ERG base-case model	ERG scenario
PFS gain (months)	10.7	13.3	11.5
Time on treatment PAL+LET (months)	30.9	20.7	29.2*
Time on treatment LET (months)	20.2	12.9	18.3*

Source: section 5.6.13, page 97, 100, and 105 of the ERG report; * ERG model

ERG revision	Incremental		ICER	ICER
	Cost (£)	QALYs	£/QALY	Change
A. Company original base case	***£94,853***	***0.629***	***£150,869***	-
ERG PFS estimates based on data from PALOMA-2	£101,238	0.645	£156,984	+£6,115
ERG time on treatment estimates based on data from PALOMA-2	£91,942	0.629	£146,238	-£4,631
ERG scenario (incorporating all other ERG base-case changes)	***£88,452***	***0.415***	***£213,206***	***+£62,337***

Source: table 34, page 111 of the ERG report

ERG sensitivity analyses

- ERG does not agree with the company that it is reasonable to omit drug acquisition costs for subsequent treatments
- Changes the ERG made increase treatment costs – indicating the model is sensitive to the cost of subsequent treatments when post-progression survival is not equal

	Total subsequent treatment costs		
	PAL+LET	LET	Difference
Company base case	[redacted]	[redacted]	[redacted]
Using ERG preferred PFS and OS estimates	[redacted]	[redacted]	[redacted]

Source: Table 32, page 107 of the ERG report

- The ERG has calculated a revised difference in PPS for treatment of -6.7 months, and applied various drug acquisition and administration costs per cycle

Drug acquisition and administration cost	Total subsequent treatment costs			ICER per QALY gained	Difference from base-case
	PAL+LET	LET	Difference		
£100	[redacted]	[redacted]	[redacted]	£147,262	-£3,606
£1,000	[redacted]	[redacted]	[redacted]	£141,222	-£9,646
£10,000	[redacted]	[redacted]	[redacted]	£80,822	-£70,047

Source: Table 33, page 107 of the ERG report

- The ERG's revised PFS and OS estimates increase time spent in PPS, and thus the cost of PPS, substantially more for patients treated with LET than they do for patients treated with PAL+LET, which indicates that the model is sensitive to the cost of subsequent treatments when PPS is not assumed to be equal for the intervention and comparator. The ERG was not able to perform a full costing of post-progression treatments, so carried out a simple sensitivity analysis to investigate the magnitude of the impact of adding drug costs to the subsequent therapy calculations.

- The ICER per QALY gained decreases with an increase in subsequent treatment costs because the analysis uses ERG estimates of PFS and OS in order that the model includes a mean PPS loss for treatment with PAL+LET. This reduces the time spent both on first-line and subsequent treatment for patients receiving PAL+LET in particular, which substantially reduces the total cost of treatment for these patients. However, the key conclusion of the sensitivity analysis is that the ICER per QALY gained changes substantially depending on the cost of subsequent treatment. The ERG thus considers that the company should have included a more through costing of post-progression treatments in its model.

Innovation, Equality, and End-of-Life

Innovation:

- The company considers palbociclib innovative because it is:
  - A novel therapy, which addresses current clinical unmet need: increasing PFS and delaying the need for chemotherapy
  - An innovative therapy recognised at the regulatory level
  - A first-in-class targeted therapy with a new mechanism of action
- For full details see section 2.5 of the company submission

Equality

- Company: no equality issues were raised
- Consultees: no equality issues were raised

End-of-life criteria

- The company has not proposed this drug meets the end-of-life criteria

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Key issues for consideration

Clinical

- Where would treatment with palbociclib likely be used in clinical practice?
- Is the comparison with letrozole generalisable for other aromatase inhibitors?
- What is the benefit of improved PFS to patients, and has this been captured?
- Can improved OS be assumed from evidence of improved PFS?

Cost

- Does the committee consider the company base-case robust?
  - What is the committee's view of the changes made by the ERG?
- Does the committee consider it more appropriate to use PALOMA-1 or PALOMA-2 PFS data for the cost-effectiveness analysis?
- What is the committee's view on the company scenarios which explored:
  - The OS gain of treatment with palbociclib
  - Acquisition costs of the comparator treatment
  - Health-related quality of life of the pre-progression state
- What is the committee's view on the most plausible ICER?

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