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]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/194/07

Erratum completed 14 December 2016

CONTAINS [redacted] AND [redacted] DATA

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]



[redacted]

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.