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]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Company submission with revised economic case**
   - Company's submission with updated PAS

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Breast Cancer Now
   - United Kingdom Breast Cancer Group
   - NHS England

4. **Evidence Review Group critique to company's revised economic case**
   - Evidence Review Group critique after factual accuracy correction
   - Addendum to ERG critique including updated PAS

5. **ERG response to factual accuracy check**
   - Erratum to ERG critique
   - ERG addendum
   - ERG addendum (post factual check)
   - ERG addendum on updated PAS

6. **Comments on the Appraisal Consultation Document received through the NICE website**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical experts and patient experts – Nominated experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Confidential until publication

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Pfizer	Thank you for giving us the opportunity to comment on the Appraisal Consultation Document (ACD) for the above named appraisal. We are disappointed that a pragmatic solution to the methodological challenges which prevent palbociclib from demonstrating cost-effectiveness has not yet been found, given the transformative clinical value that has been recognised. As this first-in-class medicine allows metastatic breast cancer patients to experience a median PFS in excess of 2 years for the first time, yet the list price of the medicine is consistent with previous therapies in the area, the decision to not recommend palbociclib is unacceptable. Despite the lack of flexibility suggested in the ACD, we remain open to dialogue with the NHS and NICE and are fully committed to finding a solution which can bring this transformative medicine to patients in England and Wales. However, it is essential to acknowledge that the hurdle to access cannot not solely be overcome through reductions to price. We thoroughly welcome the conclusion of the committee, in line with the clinical experts and the patient testimony, that palbociclib is a clinically effective treatment. This follows formal recognition by the MHRA that it is promisingly innovative. That palbociclib serves key patient needs of prolonging progression-free survival (PFS) and delaying the need for chemotherapy and the associated patient-experience cannot be understated. However, shortcomings within the methods of cost-effectiveness evaluation prevent palbociclib from achieving an ICER below the required threshold have remained barriers to palbociclib's recommendation. The presence of these barriers in the context of such transformational clinical benefit	Comments noted. The committee discussed the proposals put forward by the company regarding adopting flexibility in NICE methodology. The committee concluded that the assumption of an alternative more expensive, hypothetical comparator treatment was not appropriate. The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib. The committee noted that the Medicines and Healthcare products Regulatory Agency recognises palbociclib as a promising innovative medicine and agreed that there is a clinical need for this patient group. It recognised that no weight had been given in the cost-effectiveness analysis to the specific benefit of delaying chemotherapy with its attendant side effects, which patients consider important (see FAD section 4.15).

Consultee	Comment [sic]	Response
	necessitates a more flexible application of the evaluation methods, so that the assessment accounts for the full value of palbociclib. The ACD rightly notes the value to patients of increased PFS. Clinical expert and patient opinion as expressed in the written submissions and at the committee meeting was unanimous: increases to PFS – which bring with them the ability to sustain a normal life – are as important to women with terminal breast cancer as increases to overall survival (OS). By contrast, however, the ICERs on which the committee made their decision value OS nearly two-and-a-half times higher than they do PFS. It is clear that we must seek to harmonize the mathematics with the patient experience, so as to prevent discord between patients' reality and the resource allocation decisions which affect them. By way of example, if PFS and OS were valued equally within the palbociclib analyses, the ICER could conceivably reduce by up to £46,000 per QALY lower than currently. The imperfections within traditional cost-effectiveness evaluation that prevent add-on therapies such as palbociclib from demonstrating a cost-effective ICER, and which therefore severely limit the extent to which an ICER can reflect the true value of the medicine, must not be ignored. These issues have arisen in metastatic breast cancer appraisals previously, and will continue to in the future. Such issues are illustrated when the economic evaluation instead compares palbociclib to the average cost of previously appraised therapies, rather than to generic letrozole; the result is a cost-effective ICER. Pfizer implores the committee to consider the merits of the scenarios presented within this response as these better align to the way patients and clinicians value the disease and this medicine. If such flexibility is not adopted, palbociclib – and more importantly, the women for whom it may be an appropriate treatment option – are left in an unacceptable position. Pfizer is aware that even transformative clinical benefit must be balanced against cost pressures. For this reason, the UK list price of palbociclib is among the lowest	

Consultee	Comment [sic]	Response
	of published European markets. At this price, if the full value of the medicine is pragmatically accounted for, palbociclib is a cost-effective use of NHS resources.	
Pfizer	**The need for flexibility in the methods of evaluation** We thoroughly welcome that the ACD[1] so clearly reflects the great importance patients place on staying in a progression-free state as long as is possible, and on delaying time to chemotherapy. Similarly, we welcome the conclusion that palbociclib has a clear and important benefit in improving progression-free survival. These conclusions by the committee are of great significance with respect to the considerations of cost-effectiveness, and will therefore be addressed in more detail in later sections. The committee conclusion that all plausible ICERs were above the level that could be considered a cost-effective use of NHS resources fails to acknowledge that the traditional assumptions of cost-effectiveness evaluation severely limit the extent to which palbociclib can achieve an ICER near the required threshold, almost irrespective of price. Situations such as this necessitate judicious flexibility in the methods of evaluations, so as to ensure the complete value of the medicine is accounted for and that no medicine is denied access to routine commissioning simply because of artefacts of analysis. In the assessment of palbociclib, prudent flexibility is required in three areas: estimation of the expected overall survival; the valuation of progression-free survival relative to overall survival; and the cost of the comparator. The following sections of this document address each of the issues in turn. Consideration of these issues – both cumulatively and in isolation – make clear that the ACD neither fully acknowledges the drivers of the ICER, nor fully accounts for the value of palbociclib offered to patients, and by extension, to the NHS.	Comment noted. The committee discussed the expected overall survival, the relationship between progression-free survivals and overall survival and concluded that although it is possible that the overall survival gain might be better than that in PALOMA-1, there is no evidence to support an assumption of overall survival gain equal to the progression-free survival gain without further overall survival data from PALOMA-2 (see FAD sections 4.6 and 4.10).

Consultee	Comment [sic]	Response
Pfizer	**Expected overall survival benefit** The ACD makes clear that the relationship between PFS and OS is complex, but nevertheless agrees with the clinical experts by recognising that the significant improvements seen with palbociclib in progression-free survival will likely result in improvements to overall survival. The committee ultimately concluded that the plausible overall survival gain is within a range bounded on one side by the immature OS from PALOMA-1 (mean of 6.6 months) and on the other by estimate where improvements in PFS from PALOMA-2 translated to improvements in OS (mean of 11.2 months). The clinical expert testimony during the committee meeting made clear that a 1-to-1 translation of PFS benefit to unconfounded OS benefit was a reasonable assumption, noting no current evidence to suggest otherwise. However, experts also noted that, by sheer virtue of the randomness of response post-progression, the mature data may still fail to show the medicine's true OS benefit. Given this testimony, it is therefore not unreasonable to assume that the unconfounded OS benefit is at least greater than the lower bound of the committee's currently preferred range. The higher value noted in the ACD should therefore be considered most appropriate for decision making. The committee agreed the populations in both the PALOMA-1 and PALOMA-2 trials were similar to the patient population seen in clinical practice in England, and ultimately considered both mixed trial data and PALOMA-1-only data in its evaluation of cost-effectiveness. Although both trials are immature, PALOMA-1 has had longer follow-up to date and, given that the primary outcomes from PALOMA-1 and PALOMA-2 are consistent, use of the PALOMA-1 data to extrapolate and estimate outcomes may provide more accurate results.	Comments noted. The committee discussed the expected overall survival and concluded that although it was possible that the overall survival gain might be better than that in PALOMA-1, there was no evidence to support an assumption of overall survival gain equal to the progression-free survival gain (see FAD section 4.10).
Pfizer	**The undervaluing of progression-free survival with the QALY** As made clear by the ACD, the patient testimonial presented to the committee stressed the value patients and their families place on remaining progression-free,	Comments noted. The committee concluded that it is difficult to precisely predict the quality of life of someone with progression-free disease who is taking endocrine therapy and agreed to explore a range of utility values for progression-free disease

Consultee	Comment [sic]	Response
	and the associated ability to continue with normal life. This was reinforced by statements from the clinical experts, which emphasised the importance of PFS as a key treatment goal. The delay to subsequent chemotherapy that is a result of PFS was notably cited in the ACD as key for patients in the case of palbociclib. Following the committee meeting, Pfizer sought further input on this issue through an advisory board consisting of 8 leading UK clinical experts. This advisory board discussed not only the qualitative value of PFS in relation to OS, but also the quantitative utilities that are typically applied in modelled health states in metastatic breast cancer, including in this appraisal for palbociclib. Feedback at this advisory board was unanimous: improving time spent progression-free is as important to patients as improvements in time spent alive, thus the utility elicited to remaining progression-free (as opposed to progressing) should be similar to that related to giving life extension to reflect the real value of these outcomes. In this instance, it is clear that the metric by which the appropriateness of a utility value should be judged is whether or not it aligns, in principal, with the value described by clinical experts and patients themselves. As noted by Pfizer at the committee meeting, **the base case utility values OS almost two-and-a-half times greater than it values PFS** in the modelling (see Appendix A for further details); this is a stark contrast to clinical and patient perception of PFS and OS, which considers them of similar value. As such, the utility values informing the ICERs discussed in the ACD fail to reflect the full value of PFS for this disease and patient population. The ACD indeed notes that aspects of the patient experience, such as the desire to avoid future events, specifically treatment with chemotherapy, is not captured by the EQ-5D. In this respect, the valuation of PFS relative to OS represents a shortcoming of the methods of cost-effectiveness evaluation. Such a conclusion is not unique to this appraisal: for example, in the NICE appraisal of abiraterone[2] and the SMC appraisal of everolimus[3], the benefits of delaying	(0.72 to 0.77) for its deliberation on the cost effectiveness of palbociclib. (see FAD sections 4.12 and 4.13).

Consultee	Comment [sic]	Response
	chemotherapy through extending progression-free survival were noted as not being fully captured in the modelling. **Adjusting the utility values so that the benefit of remaining progression-free aligns with the patient experience, as described above, moves the ICER downwards by between £30,000 and £46,000 per QALY**, dependant on the committee's preference for the modelled base case. This adjustment removes the OS valuation that is nearly two-and-a-half times greater than PFS, and instead allowing time spent progression-free to produce a comparable QALY benefit to remaining alive (see Appendix A for full details). Although this solution to the methodological shortcoming noted above may itself be imperfect, insofar as it limits incongruences between the model and a patient's reality, such a departure from the traditional method is appropriate, pragmatic, and necessary.	
Pfizer	**The acquisition cost of the comparator when comparing incrementally** The committee concludes in the ACD that the assumption of a higher cost for the comparator treatment than the current cost for generic letrozole was not appropriate and could not be considered, noting that the committee cannot calculate cost-effectiveness based on a hypothetical comparator. For the avoidance of doubt, let us make clear that Pfizer appreciates that the committee cannot make real-life resource allocation decisions based on hypothetical scenarios. However, of almost singular importance in the appraisal of palbociclib is the limited ability of this drug to demonstrate cost-effectiveness within the confines of the current methodological framework. A key shortcoming is evident in the assessment of incremental cost. As palbociclib is an add-on to current treatment, there is no cost offset, making its *entire* treatment cost 'incremental'. This makes the numerator of the ICER sufficiently large that it cannot be overcome unless unrealistic assumptions (such as greater than 5 years OS gain or 10 years PFS gain) are adopted with respect to the denominator (i.e., the benefit). Moreover, the notable lack of access in the UK to innovative first-line treatment options in this subtype has left patients with a choice of either generic aromatise inhibitors or generic chemotherapies, in effect creating nearly the same mathematic challenge with regard to incremental cost even if palbociclib were not an add-on therapy. Palbociclib's ability to demonstrate cost-	Comments noted. The committee concluded that the assumption of an alternative more expensive, hypothetical comparator treatment was not appropriate. The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib. The committee noted that the Medicines and Healthcare products Regulatory Agency recognises palbociclib as a promising innovative medicine and agreed that there is a clinical need for this patient group. It recognised that no weight had been given in the cost-effectiveness analysis to the specific benefit of delaying chemotherapy with its attendant side effects, which patients consider important (see FAD section 4.15).

Consultee	Comment [sic]	Response
	effectiveness is in fact so effected by the cost of the comparator that if we consider cost comparisons versus other treatments in metastatic breast cancer, particularly recent innovative therapies, palboclicib could be deemed cost-effective. Indeed, this is not an issue that solely affects palbociclib, but is one that has impacted several previously appraisals in metastatic breast cancer and will continue to impact future appraisals; neglect of this issue in this appraisal will not solve the wider problem. Across all NICE appraisals, guidance has been produced for 13 medicines in metastatic breast cancer – including chemotherapies and targeted therapies – appraised at an average of £2,485 per month (at list price), equating to £22,745 per total course of treatment (see Appendix B for details).[4-15] In comparison, the monthly cost of letrozole is £32 per total course of treatment[16]. If the innovation seen across metastatic breast cancer in the last two decades were applied to this appraisal and the cost of the comparator in the model was instead **the average cost of all NICE appraised metastatic breast cancer medicines, it is possible for the ICER to fall to below £50,000 per QALY**. This strikingly illustrates the extent to which lack of access to innovative treatments today limits the likelihood of access to future innovations tomorrow. Although the current assessment framework was built on the idea of cost-effectively allocating future resources, in truth it may actually serve to increase inequality in access medicines between disease areas, penalising patients if their illness happens to be one in which new innovative treatments bring benefits as add-on therapies, or if we have simply reached the point where current therapy is generic. The ultimate result for palbociclib is unacceptable, as the expectation (falsely) remains that the hurdle to access can be overcome exclusively through reductions to palbociclib's price. Pfizer is aware that even transformation clinical benefit must be balanced against cost pressures. It is for this reason that the UK list price of palbociclib is among the lowest of all published European markets, at the time of press. Noting this, it is further important to not only consider this cost against the unprecedented effectiveness of the treatment, but against wider services too. **When the changes brought about through the re-valuation of PFS are coupled with a comparison versus the cost of the average treatment for metastatic breast cancer than NICE has appraised, the ICER can be reduced between £57,000 and £107,000 per QALY lower than at current**, dependent on the committee's preference for the modelled base case. The result is an ICER produced that is around the £30,000 per QALY threshold (see Appendix B for details).	

Consultee	Comment [sic]	Response
	Acknowledgment of these key limitations illustrates that palbociclib should be deemed a cost-effective use of NHS resources. As well as a delay to chemotherapy, the ACD also cites the potential reduction to first-line chemotherapy from the introduction of palbociclib, in line with comments at the scoping stage suggesting a large proportion of patients currently receiving chemotherapy could benefit from treatment with endocrine therapy[18] (however, chemotherapy was removed as a comparator from the final scope). Although relevant chemotherapy is now generic, it carries a higher cost burden than the current comparator, letrozole, due to the management of adverse events and the HRG tariffs related to both oral and IV chemotherapy administration. Further, with the chemotherapy outcomes being lower[17] than letrozole[16], the ICER for palbociclib versus chemotherapy would be expected to be lower than versus the current comparator.	
Pfizer	For UK patients requiring first-line treatment for HER2- ER+ metastatic breast cancer, access to innovation has stagnated. Artefacts of the current analysis framework mean that palbociclib (as an add-on therapy offering significant progression-free survival [PFS] gain versus a generic comparator) cannot be expected to be cost-effective, even if priced comparably to previously recommended therapies. Indeed, there is no clinically plausible survival advantage that the drug could offer which would change this. Given the lack of NHS access to innovation in this particular treatment space, the appraisal of palbociclib draws close attention to the Institute's responsibility to recognise the potential for long term benefits to the NHS of innovation. The technical issues which overlap and interact to create this access hurdle are complex; nevertheless, we have proposed simplifying, illustrative modifications to the methods which seek to address what we consider the primary issues: the relative importance of PFS, and issues relating to the comparator. The Institute has agreed to consider flexibility with respect to the methods in these areas, and the ERG has undertaken a critique of our proposals. This document outlines our response to those considerations and critique. In response to a concurrent request from the Institute, further detail regarding the structured discussions that were had	Comments noted. The committee discussed the proposals put forward by the company regarding adopting flexibility in NICE methodology at the second meeting, however, the company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib.

Consultee	Comment [sic]	Response
	with clinical experts concerning the relative value of PFS accompanies this response, as does the most recent update to the PALOMA-1 overall survival data. It bears repeating that the PALOMA-1 overall survival (OS) data have the same caveats of those interim final PALOMA-1 data already considered by the committee, meaning a range of survival estimates, as previously agreed following expert advice at the first committee meeting, is still appropriate. In addition to previous analyses exploring the relative value of PFS and comparisons with other first-line chemotherapy, we have included here a more robust comparison with medicines launched (and in instances recommended) for the wider population of metastatic breast cancer. In doing so, we demonstrate the inequity of access opportunity within metastatic breast cancer. It is a fairer comparison to view the cost-effectiveness of palbociclib in relation to other innovations in metastatic breast cancer, rather than to an insurmountable, low cost comparator which also is added-on to. Such a comparison makes clear the extent to which treatments like palbociclib are, and will be, unduly penalised because of the sustained lack of access to innovation in the HER2- ER+ treatment space. As part of this response, Pfizer have also included a confidential Patient Access Scheme, which will make palbociclib available to the NHS at a discounted price. Taking into account the Patient Access Scheme and the new survival data, whether assuming an approach that either compares to other NICE-approved metastatic breast cancer medicines, or alternatively re-values PFS and considers current chemotherapy use, the ICER can fall to between [redacted] and [redacted] per QALY. Regardless of the flexibilities the committee deems most appropriate in this instance, palbociclib can represent a cost-effective use of NHS resource.	

Consultee	Comment [sic]	Response
Pfizer	**Updated Overall Survival (OS) data from PALOMA-1** In the company submission, OS data were provided from the interim cut of PALOMA-1 (conducted in 2013). The primary outcome in the PALOMA-1 trial was PFS and although data on OS were also collected, the trial was not powered for OS. No OS data were available from PALOMA-2 as the number of events specified in the protocol as required for analysis had not yet been reached, with Pfizer blinded to the results. Since submission, the final OS data-cut from PALOMA-1 has become available, and is provided here. PALOMA-2 OS data remain unavailable, for the reasons noted above. In the final analysis (30th December 2016), the stratified hazard ratio for overall survival was 0.897 (95% CIs: 0.623,1.294, p=0.281), based upon 116 deaths from 165 patients.[1] This hazard ratio has increased slightly from the interim datacut, although broadly similar (interim HR=0.813, 95% CIs: 0.492, 1.345).[2] The updated median OS in the palbociclib plus letrozole arm was 37.5 months (95% CIs: 31.4, 47.8) and in the letrozole alone arm was 34.5 months (95% CI: 27.4, 42.6).[1] Survival probability at 1 year was [redacted] in the palbociclib plus letrozole arm, and [redacted] in the letrozole alone arm [redacted] and at 2 years was [redacted] in the palbociclib plus letrozole arm, and [redacted] in the letrozole alone arm [redacted] At 3 years, survival probability was [redacted] in the palbociclib plus letrozole arm, and [redacted] in the letrozole alone arm [redacted][1] The ACD makes clear that the relationship between PFS and OS is complex, but nevertheless recognizes that the significant improvements seen with palbociclib in PFS will likely result in improvements to OS. The committee therefore concluded that the expected OS would range from that observed in PALOMA-1 (with this initial conclusion based on the interim OS data) as a lower bound, to that which equates with a 1-to-1 translation of PFS gain-to-OS gain as an upper bound. Although these new data address the lower bound of this range, the rationale for the upper bound remains unchanged. Expert testimony at the meeting stated that a	Comment noted. The committee considered the final analysis of overall survival data from PALOMA-1 trial (see FAD section 4.10)

Consultee	Comment [sic]	Response
	number of factors (post-progression treatments, randomness of subsequent response, etc.) prevent PALOMA-1 from providing an entirely unconfounded estimate of the benefit to OS associated with palbociclib, and its usefulness may therefore be limited. It is therefore still appropriate to consider the "true" OS as falling within a range. With these new data, and using the ERG's PALOMA-1 modelled base case, the lower bound of the mean range in OS is now 4.0 months (previously 6.2 months). The upper bound in the ERG's modelled PALOMA-1 base case is 10.7 months (previously 11.2 months when using the company's original model). This range in OS, 4.0 months to 10.7 months, is reflective of using either PALOMA-1 data as the basis for extrapolation, or the relationship between PFS gain to OS gain. The revised ICERs related to this range in OS are £105,117 to £159,064 per QALY. With the Patient Access Scheme (PAS) [redacted] this new range is [redacted] per QALY to [redacted] per QALY. Importantly, however, these ICERs (included here only for completeness) are not a true representation of the cost-effectiveness of palbociclib, for reasons discussed on the following pages.	
Pfizer	**Methodological Hurdles to Access** Despite the unprecedented efficacy afforded by palbociclib, the base case estimate of cost-effectiveness in the initial submission far exceeded the traditional threshold. This was acknowledged in both the submission itself and the Pfizer ACD response. That palbociclib is simultaneously an add-on therapy, given until progression, and compared with a generic treatment, combines to create a significant barrier to access. The Pfizer ACD response focused on two elements of the current methodology which, if flexed in recognition of the barriers they create in this instance, illustrate that palbociclib can indeed be deemed a cost-effective use of NHS resources. This included the relative value of PFS, and issues relating to the comparator. **(i) <u>Relative Value of Progression-Free Survival</u>** The ERG has reviewed Pfizer's approach to re-valuing the utility benefit associated with PFS, stating such an approach would have merit if:	Comments noted. The committee discussed the proposals put forward by the company regarding adopting flexibility in NICE methodology (at the second meeting), however, the company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib.

Consultee	Comment [sic]	Response
	a) additional PFS benefit should be valued equally to additional OS benefit (gained as extra PPS at the end of life); **and** b) the treatment of interest has greater PFS and lower OS (and, therefore, lower PPS) than one of the treatments it is being compared against. Pfizer consider the condition outlined in point (a) to be satisfied. Pfizer consulted multiple experts across a variety of relevant disciplines, including key clinicians, within the UK metastatic breast cancer community to understand the value of additional PFS, relative to additional OS. The feedback has been unanimous that a treatment bringing extensions to PFS in this treatment space is as valuable as one bringing extensions to OS. This feedback is in line with both the clinical expert statements and the patient testimonial that featured during the committee meeting, and detailed further in the accompanying report from a structured discussion since that meeting.[3] The ERG suggests that the equality of additional PFS and OS benefit might not apply in situations where disease progression does not have much of a negative impact on quality of life. The evidence included in the Pfizer submission regarding the value of "normality", as well as the patient and clinician testimonials provided to date, indicate that this is not the case within first-line metastatic breast cancer. As set out in the original company submission, retaining normality (which includes caring for a family, continuing in a job, not having to rely on informal care, a delay to, and not having to undergo, chemotherapy, etc.) can be greatly impacted once symptoms cross a certain threshold after progression. This negative impact on quality of life can be substantial, albeit not in ways necessarily captured by traditional metrics. Indeed, previous NICE and SMC appraisals have already concluded that that at least one element of "normality" listed above (that is, the value to delaying chemotherapy) is not captured in current QALY estimates.	

Consultee	Comment [sic]	Response
	The ERG posits in point (b) that one can argue QALY benefit from PFS gain is undervalued with respect to OS gain effectively *only* when all PFS gains are made at the expense of post-progression survival (PPS) gain, and it provides illustrative scenarios as a means of explanation. The ERG conclude that there is no need to re-examine the value awarded to PFS in this specific case, because PFS gain is not made at the expense of PPS gain (as depicted in ERG Scenario 3.) In this way the ERG states, *"the benefit of additional PFS is already equal to the QALY benefit of additional OS*". In the ERG's illustrative 'Scenario 1' (presented in **Error! Reference source not found.** below), Intervention 1 leaves the PFS benefit of standard of care unchanged, but extends overall survival versus standard care by extending PPS (resulting in a QALY gain from that life extension of 0.51 [*i.e.,* 0.51 in PPS versus 0 at death]). By contrast, Intervention 2 extends PFS but reduces PPS by an equal amount, thereby leaving overall survival versus standard of care unaffected. This increases QALYs versus standard of care by 0.21 (0.72 – 0.51). Scenario 2 provides an alternate illustration of the concept presented in Scenario 1, so is therefore not re-presented in this response. Scenario 3 extends PFS versus standard of care, but leaves PPS unaffected, thereby increasing the overall survival by a length of time equal to the increase in PFS. In this respect, Scenario 3 illustrates both an extension to both PFS and to OS. As depicted in the ERG diagram, the QALY gain here is 0.72 QALYs. The ERG states that OS and PFS are of equal benefit within Scenario 3 (and therefore valued equally within the resulting ICER) because *"incremental OS is gained in PFS".* In this way, the ERG conceptualises this +0.72 QALY gain as coming from one discrete benefit: the addition of time to PFS. Pfizer consider it more appropriate to conceptualise this +0.72 as the result of two benefits to the patient at two independent points in their lives: 0.21 from the improvement to quality of life from the retention of a 'normal' state for longer at that time, added to the 0.51 from the life extension at the end of life; these QALY	

Consultee	Comment [sic]	Response
	benefits are accrued separately. Figure 3 below presents Scenario 3, but with added detail to better reflect these two independent effects in terms of QALYs. It is that these two benefits are not equally valued, despite them being for the same amount of time, that is at odds with how clinical experts and patient perceive outcomes in reality, as the improvements from PFS produce fewer additional QALYs than those for OS. Of the total QALY gain, 71% is driven by extensions to OS (0.51 of 0.72), yet only 29% by extensions to PFS (0.21 of 0.72). These percentages translate to OS being valued 2.43 times higher than PFS (0.51/0.21) in the calculation of the incremental QALY gain. It is important to the note that implicit in the discussion of Scenario 3 above as it applies to palbociclib is that PFS gain translates directly into OS gain. The committee has concluded that this assumption represents the plausible upper bound of survival benefit, but Pfizer are mindful that this OS assumption has on one hand been dismissed by the ERG as not appropriate for use in the base case, and is now on the other hand provided as rationale to dismiss our position regarding PFS valuation. Separate to the above conditions, the ERG writes that the inequality in additional PFS and PPS benefit described in the Pfizer ACD response is purely an artefact of the utility values used in the model. This is true. The ERG is correct to point out that the principle of adjusted relative value between PFS and OS can be achieved by either: adjusting the **PFS** value, keeping the PPS value unchanged (i.e., using 1.0 and 0.5); or by adjusting the **PPS** value and leaving the PFS value unchanged (using 0.72 and 0.36). The comments from the preceding page regarding patient benefit during PFS not being captured by current metrics suggest that “undervalued” PFS is perhaps best corrected for with changes to the PFS value itself, rather than forcibly down-weighting PPS utility. Nevertheless, ICERs are presented on the following pages that reflect both approaches. By presenting both approaches, changes to the PPS or PFS values create upper and lower bounds of an ICER range which reflects an equal valuation of PFS and OS.	

Consultee	Comment [sic]	Response
	It is lastly important to point out that Pfizer are aware that the approach described above is necessarily simplifying. However, it is equally important to point out that the approach is akin in this respect to the assumptions made within the End-of-Life (EoL) criteria. The EoL criteria give "greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age." This assumption (about full quality of life) is not a reflection of reality, but rather one which allows for a more simplified application of the principle in question. Bearing in mind the Institute's responsibility to recognise the potential for long term benefits to the NHS of innovation, the approach provided here is a simplified illustration of how methodological flexibility can address the access hurdle for patients and medicines in this treatment space. Taking into account the Patient Access Scheme, the cost per QALY which incorporates the above utility adjustments ranges from [redacted] per QALY to [redacted] per QALY, reflective of the range in adjustments described above, and the range in OS in line with the committee's preference.	
Pfizer	**(ii) <u>Comparator Selection</u>** As previously stated, artefacts of the current analysis framework mean that any new medicine for women with HER2-HR+ metastatic breast cancer with similar characteristics to palbociclib (that is, an add-on therapy offering significant progression-free survival gain versus a generic comparator) is not expected to be cost-effective. This is due, in part, to the choice of the comparator. That a more expensive comparator makes cost-effectiveness easier to establish is neither a complicated nor controversial point. But we do not make this point here to argue that in all instances a comparison versus a generic creates a hurdle to access. Appraisals in other disease areas have made clear this is not the case. What we do wish to illustrate is the inequity within metastatic breast cancer with respect to *access opportunity*, created by the sustained lack of approved innovation in this	Comments noted. The committee discussed the proposals put forward by the company regarding adopting flexibility in NICE methodology (at the second meeting), however, the company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib.

Consultee	Comment [sic]	Response
	specific treatment area. By way of example, if palbociclib were instead compared to other treatments recommended by NICE in the broader metastatic breast cancer space, the ICER for palboclicib would differ greatly to that which comes from its comparison with letrozole, falling to below £50,000 per QALY at list price with no adjustments to PFS *and* assuming the conservative bound of OS. As an early illustration of the point regarding comparator cost, Pfizer previously noted that, in the company base case, unless currently implausible gains to OS are assumed (between 5 and 10 years), the price required to achieve a cost-effective ICER versus the current comparator would be around £500 per cycle; this is a lower monthly price than *all* 13 previously-appraised metastatic breast cancer medicines (**Error! Reference source not found.**). When one considers that an efficacious treatment such as palbociclib must, in one comparison, require either implausible efficacy assumptions or a monthly cost lower than all previously appraised therapies before being deemed cost effective, and yet in another comparison to other therapies in metastatic breast cancer produce ICERs that could be deemed cost-effective, it becomes clear that the currently chosen comparator is significantly restricting the possibility of a new therapy ever becoming available in first-line HER2- ER+ metastatic breast cancer. Below we explore the impact of adjusting the treatment costs and outcomes against which palbociclib is compared in more detail, using two scenarios: comparison within metastatic breast cancer more broadly, and versus first-line chemotherapy within HER2- ER+ metastatic breast cancer. ***(a) <u>Comparison within metastatic breast cancer</u>*** Given the hurdle to access created by the current comparator, a fairer comparison considers the cost-effectiveness of palbociclib in relation to other innovations in metastatic breast cancer. Pfizer have explored the costs and outcomes of previous metastatic breast cancer medicines appraised by NICE, with a view to understanding the impact on the palbociclib ICER if any of these medicines had	

Consultee	Comment [sic]	Response
	served as the comparator in place of letrozole. This builds on the analysis presented in the original ACD response, furthered in recent productive discussions with NICE, now providing a more comprehensive comparison. Pfizer have calculated the average monthly price at around £2,530 (total treatment cost £25,248) across the 13 metastatic breast medicines in which NICE have completed appraisals, at the time of appraisal (noting these figures are updated from Table 2 in the initial *Response to ACD*), associated with an average of 1.38 QALYs (2.31 LYs).[5-16] These 13 treatments include those for other subtypes within metastatic breast cancer, and for different lines[1]. An initial comparison in the response to ACD showed that if the incremental costs of palbociclib were calculated with reference to this cost (that is, the average of previously appraised therapies) rather than the current comparator, the ICER could be dramatically reduced, highlighting the difficulties in achieving traditional cost-effectiveness within this patient population. Following critique from the ERG and discussions with the Institute noting that the comparison in the ACD response excluded considerations of the comparator effectiveness, and the presence of Patient Access Schemes for many of the medicines, this comparison has been updated and presented below. Comparing the incremental benefit and incremental cost for palbociclib versus other therapies in metastatic breast cancer produces a much lower estimate of cost-effectiveness than when palbociclib is evaluated as an add-on therapy with a low cost comparator arm. The average ICER versus these therapies is displayed in Table 3 versus all 13 therapies, and then in Table 4 when considering only the seven therapies which NICE have recommended. [6,10-17] When compared at list price to the seven therapies which NICE have recommended, the ICER for palbociclib would fall to between £45,092 per QALY (if	

[1] It should be noted that when comparing treatments from different previous appraisals, treatments do differ in effectiveness as a consequence of different subtypes of mBC, subgroups of patients, or the lines in which the treatments are used. However, the cost of treatments also differs in the same way, and as such is relative to the benefit. For example, with a treatment which treats till progression, it does not matter whether the associated PFS is 5 or 15 months, as the consideration of cost and benefits are proportionate (*e.g.,* 5 months PFS and 5 months cost, or 15 months PFS and 15 months cost, each will result in the same cost-to-benefit ratio).

Consultee	Comment [sic]	Response
	assuming PFS translates to OS gain), and [redacted] per QALY (if using the updated OS from PALOMA-1). With the confidential PAS for palbociclib, these ICERs drop to between [redacted] and [redacted] per QALY. If those comparators which offered a PAS were assumed [redacted], the ICER would change by under £1,000 per QALY illustrating that, even if those comparators had a larger PAS, this would be expected to minimally impact the average ICER.	
Pfizer	The difference between these ICERs and the committee's originally preferred ICER range in the ACD (£132,000 to £213,000 per QALY) illustrates the extent to which letrozole insurmountably blocks access to long-term innovation in this treatment space. These exploratory analyses also suggest that the women comprising the population of this appraisal are less likely to access new innovative treatments than those with other forms of metastatic breast cancer and/or requiring a different line of treatment, even though the costs and benefits of new interventions in different spaces within metastatic breast cancer may actually be equal. When utility is adjusted so that incremental PFS accrues the same amount of QALYs as incremental OS, the ICERs for palbociclib versus other therapies within metastatic breast cancer differ further. **Error! Reference source not found.** and **Error! Reference source not found.** present these ICERs versus the 13 previously appraised therapies, and the seven recommended therapies, respectively.	Comments noted. The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib.
Pfizer	***(a) Comparison with chemotherapy*** For completeness, an adjustment based on the assumption that the introduction of palbociclib may reduce the need for first-line chemotherapy (as originally noted in the ACD) is presented below. Market research and recently consulted clinical expert opinion suggests around 50% of the first-line HER2- ER+ metastatic population receive endocrine therapy, with the other 50% receiving chemotherapy as their treatment, even though experts estimate only around 20% have life threatening disease; this implies that 30% of patients eligible for palbociclib in combination with an aromatase inhibitor currently receive chemotherapy. Clinical feedback indicates this 30% receiving chemotherapy who	Comments noted. The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib.

Consultee	Comment [sic]	Response
	would be eligible for palbociclib receive predominantly capecitabine (sometimes a taxane). On this basis, an ICER has been generated for palbociclib versus capecitabine, and proportionately blended with the current aromatase inhibitor comparison (30/50) (reflects 30% chemotherapy use, 50% aromatase inhibitor use, but excludes the 20% of patients who receive chemotherapy due to life threatening disease); the result is an estimate of cost-effectiveness versus "standard of care" as a general category. A naïve comparison was conducted to account for efficacy by taking the costs and QALYs from the cost-effectiveness evaluation of capecitabine to produce an ICER (see Appendix A), but adjusted to reflect the current cost of capecitabine. At list price, the estimated ICER for palbociclib in combination with letrozole versus capecitabine is £49,478 to £54,020 per QALY (the range reflective of palbociclib's OS), falling to [redacted] to [redacted] per QALY with the PAS. Incremental cost-effectiveness ratios for this blended comparison reflecting standard of care are presented below, with and without the relative PFS adjustments described above (including the upper and lower bounds created by adjusting either PPS or PFS).	
Pfizer	**Summary** Despite the unprecedented efficacy afforded by palbociclib, the base case estimate of cost-effectiveness in the initial submission far exceeded the traditional willingness-to-pay threshold. This ICER results from the interaction of particular characteristics of the drug (that it is an add-on therapy, given until progression, and compared with a low cost, generic alternative) with the current methodological framework for assessment, and in so doing, butts against a significant barrier to access. The Pfizer ACD response focused on two elements of the current methodology which, if flexed in recognition of the barriers they create in this instance, illustrate that palbociclib can indeed be deemed a cost-effective use of NHS resources. This	Comments noted. The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib. The committee noted that the Medicines and Healthcare products Regulatory Agency recognises palbociclib as a promising innovative medicine and agreed that there is a clinical need for this patient group. It recognised that no weight had been given in the cost-effectiveness analysis to the specific benefit of delaying chemotherapy with its attendant side effects, which patients consider important (see FAD section 4.15).

Consultee	Comment [sic]	Response
	included the relative value of PFS, and issues relating to the comparator. The Institute has agreed to consider flexibility with respect to the methods in these areas, and the ERG has undertaken a critique of our proposals. Following the ERG critique, we have modified our approach to PFS utility adjustment so as to now present an ICER range which incorporates the patient and clinician feedback that PFS is equally valuable to OS in this treatment space. Pfizer have also explored the cost and outcomes of other breast cancer medicines approved and/or appraised by NICE, with a view to understanding the impact on the palbociclib ICER if any of these medicines had served as the comparator in place of letrozole. Comparing the incremental benefit and incremental cost for palbociclib versus other therapies in the wider category of metastatic breast cancer produces a much lower estimate of cost-effectiveness than when palbociclib is compared to letrozole. The same can be said for comparison of palbociclib versus a weighted average of letrozole and first-line chemotherapy. The difference between the ICERs from these comparisons and the committee's preferred ICER range in the ACD illustrates to extent to which, specifically in this treatment space, the current comparator insurmountably blocks patient access to long-term innovation. Failure to recognise this will only result in an ever-increasing gap between the outcomes achieved among HER2- ER+ patients in England and Wales, and those achieved in other developed countries. It should be noted that this barrier effects only those treatments requiring a comparison with letrozole, within this patient population. Once an innovative treatment is approved in this treatment space, it is expected to displace letrozole monotherapy, and this block to innovation is thereby removed. Future treatments will now incrementally compare to this new treatment, and traditional consideration of cost-effectiveness can resume. However, for as long as this issue fails to be addressed, no new treatments are likely to achieve cost-effectiveness, meaning no new treatment will be available to the women considered in this appraisal. In	

Consultee	Comment [sic]	Response
	comparison to other subtypes or lines where innovative treatments are already available, this represents significant inequity with respect to access opportunity. The changes in the ICER with respect to of issues described above are summarised below in **Error! Reference source not found.**. Bearing in mind the Institute's responsibility to recognise the potential for long term benefits to the NHS of innovation, the approach provided here represents a simplified illustration of how methodological flexibility can address the access hurdle for patients and medicines in this treatment space. When these flexibilities are considered alongside the newly-offered Patient Access Scheme, the impact on the ICER is significant. Regardless of which flexibilities the committee deems most appropriate in this instance, palbociclib can represent a cost-effective use of NHS resources.	
Breast Cancer Now	Breast Cancer Now welcomes the opportunity to respond to the Appraisal Consultation Document (ACD) for palbociclib with an aromatose inhibitor for previously untreated metastatic hormone receptor-positive, HER2 negative breast cancer, published by NICE on 3 February 2017. The Committee has provisionally rejected palbociclib with an aromatose inhibitor as it does not consider it to be a cost-effective use of NHS resources. The Committee notes in the ACD that the Incremental Cost Effectiveness Ratio's (ICERs) presented are considerably above the range normally considered by NICE. Breast Cancer Now is calling on Pfizer to reconsider its decision not to offer any form of discount on palbociclib. However, there are a number of other factors contributing to the high ICERs presented that highlight some serious issues with the appraisal system. We believe these mean that the Committee's recommendation is not sound, nor a suitable basis for guidance to the NHS. These issues – which are set out in more detail below, in our answers to the question posed by NICE in the ACD – are that: • palbociclib is enabling patients to live so much longer without their condition progressing that little overall survival data is currently available. Perversely, this	Comments noted. The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib.

Consultee	Comment [sic]	Response
	counts against it as the system gives less weight to progression free survival data than overall survival data; • although clinically-effective, a new, branded, medicine like palbociclib can never hope to be considered cost-effective when compared to a generic treatment like letrozole; and • although metastatic breast cancer is an incurable condition, palbociclib has not been considered under the 'end of life' criteria.	
Breast Cancer Now	Has all of the relevant evidence been taken into account? Breast Cancer Now has received several statements from women who have either been treated with palbociclib, or who have the type of metastatic breast cancer for which palbociclib would be an effective treatment. These statements are at Annex A. They highlight in particular the value that patients attach to the delay in progression of their disease, and ability to carry on a relatively normal life, that palbociclib provides. We would like the Committee to take account of these statements in making its final decision.	The committee took into account the consultation comments received emphasising how patients' value delaying disease progression and therefore deferring start of chemotherapy (see FAD section 4.2).
Breast Cancer Now	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Breast Cancer Now believes the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence under the current appraisal system. However we also believe that there are serious issues with the system that mean this recommendation is not sound, nor a suitable basis for guidance to the NHS.	The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib.
Breast Cancer Now	Are the recommendations sound and a suitable basis for guidance to the NHS? A number of factors have contributed to this recommendation that highlight some serious issues with the current appraisal system. Breast Cancer Now believes this means the recommendation is not sound, nor a suitable basis for guidance to the NHS. Firstly, patients are much living longer on palbociclib with letrozole (the aromatose inhibitor used in the clinical trials) without their condition progressing than on	Comments noted. According to the Guide to the methods of technology appraisal 2013 section 1.4.2 'a technology can be considered to be cost effective if its health benefits are greater than the opportunity costs of programmes displaced to fund the new technology, in the context of a fixed NHS budget. In other words, the general consequences for the wider group of patients in the NHS are considered

Consultee	Comment [sic]	Response
	letrozole alone – a median of an additional 10 months. We know that patients value delayed progression: it means more quality time with loved ones during which they may be able to lead a more or less normal daily life, as well as a delay to starting second line treatment of chemotherapy, which is traditionally associated with more severe side effects and a poorer quality of life. However, because patients are living longer without their condition progressing, very little data is currently available on how long palbociclib extends survival overall. The appraisal system gives less weight to progression free survival than overall survival, meaning treatments without overall survival data do not do as well against the cost-effectiveness threshold. Furthermore, the current treatment option for patients that would be eligible for palbociclib (letrozole) is available generically and is therefore much cheaper. It is virtually impossible for new medicines such as palbociclib to be considered cost-effective when they are compared to generic treatments. Based on the cost of palbociclib included in the ACD, treatment with palbociclib and letrozole will cost in the region of £29,533 for the median 10 months of progression free survival shown in the clinical trials. Treatment with letrozole alone for this period will cost in the region of £33.[2] Finally, despite the fact that metastatic breast cancer is an incurable condition, palbociclib has not been considered under the 'end of life criteria' which allow NICE to use a higher cost-effectiveness threshold. Palbociclib is an important new treatment option for patients with hormone positive, HER2 negative metastatic breast cancer, substantially improving upon current treatment options. It is available in several other countries, including Germany and the USA. However, the issues outlined above suggest that palbociclib is unlikely to be approved for routine use in the NHS in England. Unless patients are able to access clinically effective drugs such as palbociclib we will never achieve the ambition set out in the Cancer Strategy to close the gap in cancer outcomes with other countries in Europe and further afield.	alongside the effects for those patients who may directly benefit from the technology'. The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib. The committee noted that the Medicines and Healthcare products Regulatory Agency recognises palbociclib as a promising innovative medicine and agreed that there is a clinical need for this patient group. It recognised that no weight had been given in the cost-effectiveness analysis to the specific benefit of delaying chemotherapy with its attendant side effects, which patients consider important (see FAD section 4.15).

[2]The recommended dose of palbociclib is 125mg once daily for 21 consecutive days followed by 7 days off treatment to make up a complete cycle of 28 days. The cost of a 21 capsule pack of 125mg capsules of palbociclib is £2,950. The British National Formulary lists the recommended dose of letrozole as 2.5mg daily, and the cost of a 28 tab pack of 2.5mg of generic letrozole as £3.32.

Consultee	Comment [sic]	Response
Breast Cancer Now	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? We are not aware of any aspects that require particular consideration to avoid unlawful discrimination.	Comment noted.
UK Breast Cancer Group	**Effectiveness of palbociclib in combination with an aromatase inhibitor** Not since the introduction of hormone therapy with tamoxifen, over 40 years ago, has there been a trial that has shown an incremental benefit for this most common type of breast cancer of the size that is seen in the Paloma 1 and 2 trials. Investigator and independently assessed progression-free survival was nearly doubled with a 10 month improvement and there was a consistent improvement in the hazard ratios for progression in both trials. This level of benefit is unprecedented for this group of patients with estrogen receptor positive HER2-negative breast cancer. The improvement in response rates of the combination compared with aromatase inhibition alone was associated with a reduction in the symptomatic burden faced by these patients and is comparable, or better, than would be expected for chemotherapy. The toxicity of palbociclib is noted and is mainly neutropenia, but unlike the neutropenia seen with chemotherapy, was of little clinical relevance with a neutropenic sepsis rate of 1%. Other side effects were generally very mild in the trials and the clinical experience with this agent is consistent with the trial data. Clinical experience with palbociclib suggests that patients lead a near normal life whilst on this drug combination. The detriment in quality of life that would be associated with chemotherapy and/or progressive cancer is given very little score in the standard models, but should in our opinion count for more. The standard monitoring in the trials, where safety and recording of toxicity accurately are critical, is more intensive than would occur in routine practice with this	Comment noted. The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib. The committee agreed that palbociclib improved progression-free survival (see FAD section 4.4 and 4.5)

Consultee	Comment [sic]	Response
	intervention. A monthly appointment for three months would be needed, with assessment of response at 3 months. Appointments would then be 3 monthly. Patients on aromatase inhibition alone, as shown by the trial data, would progress on average twice as soon. These patients with hormone-receptor positive cancers would then usually go on to receive chemotherapy, such as weekly paclitaxel or capecitabine, both of which would require much more frequent blood tests and hospital visits for treatment and monitoring, and cause increased toxicity. There is no doubt a hormonal combination would be preferable on all accounts, by delaying the introduction of chemotherapy and maintaining quality of life with minimal meaningful toxicity.	
UK Breast Cancer Group	**Cost-effectiveness** We note the methods used and the various models used to calculate cost-effectiveness. The improvements in PFS are robust, but overall survival data is immature and difficult to account for in the model used. A 10 month improvement in PFS only leads to a 0.17 QALYs. The cost of the drug at full list price would then amount to around £35,000 per year. The cost of being on chemotherapy, the next treatment the patients would be on in the same time period that would still be on letrozole/palbociclib would be similar, if all costs are considered. A QALY of between £132,872-£213,206 for a drug that would cost £35,000 a year at full list price seems bizarre and perversely would mean that even if the drug was free, it would not seem to be cost-effective. A comparison between chemotherapy costs for the difference in PFS after progression on letrozole alone would need to be done for a fair comparison of real NHS costs.	The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib.
UK Breast Cancer Group	**Other effects of a negative appraisal** The UK cancer survival statistics are often shown to be behind other comparable countries. This negative appraisal would serve to widen this gap further, to the detriment of patients with metastatic breast cancer. Other drugs in this setting that have not been approved will also widen this gap. As stated in the Department of health's NHS Outcomes Framework, one of the stated goals is to reduce morbidity and mortality of major illnesses, specifically citing breast cancer. The UK is the highest recruiter in the world to cancer clinical trials on the basis of numbers of patients seen. We should be proud of this and our patients and the	Comment noted. According to the Guide to the methods of technology appraisal 2013 section 1.4.2 'a technology can be considered to be cost effective if its health benefits are greater than the opportunity costs of programmes displaced to fund the new technology, in the context of a fixed NHS budget. In other words, the general consequences for the wider group of patients in the NHS are considered alongside the effects for those patients who may directly benefit from the technology'.

Consultee	Comment [sic]	Response
	wider economy benefits hugely from UK engagement in clinical research. The life sciences are the third biggest contributor to the economy. If the standard of care in the UK falls behind what is internationally recognised, we will be unable to take part in further innovative studies that often offer free drugs, pay the NHS for services used and stimulate academic innovation. The UK economy will suffer as a consequence. We would therefore ask that the committee re-think the negative appraisal to the benefit of all concerned, especially those unfortunate enough to have metastatic breast cancer. I am sure there is room to re-negotiate with all the relevant stakeholders	The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib.

Comments received from clinical experts and patient experts

No comments

Comments received from commentators

Commentator	Comment [sic]	Response
Novartis	Novartis would like to thank the National Institute for Health and Care Excellence (NICE) Technology Appraisal Committee for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. 1. Has all the relevant evidence been taken into account? Novartis considers that all the relevant clinical evidence for this appraisal been taken into account. 2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Novartis considers that that NICE interpretation of the clinical and cost effectiveness evidence is reasonable and fair. Novartis support the committees assertion that given the benefit for improvement in progression-free survival shown by the intervention treatment CDK 4/6 inhibitor palbociclib, it was likely this would result in improvement in overall survival. Additionally, while chemotherapy was not considered an appropriate comparator within this appraisal, it should be noted that recent market research indicates that chemotherapy is used as a first-line treatment in up to 36% of the licenced population assessed within this appraisal. 3. Are the recommendations sound and a suitable basis for guidance to the NHS? Yes	Comment noted. The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib.

Commentator	Comment [sic]	Response
	4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Novartis does not consider that there are any aspects of the recommendations that require particular consideration in this regard.	

Comments received from members of the public

Role*	Comment [sic]	Response
Patient	I have secondary breast cancer - having first been diagnosed with metastatic cancer in 2007 - and was on the Paloma-3 clinical trial via The Royal Marsden Hospital from June 2014 until April 2016 with Fulvestrant as an additional drug and Zoladex. I was fortunate to get the drugs and not be on the placebo trial. Within weeks the latest tumour in my vertabrae had shrunk. I work full time as a national newspaper sports writer and was able within weeks as well to cover the Commonwealth Games in Glasgow. Throughout the period on the drug I worked full-time, in a job which took me as far as China and Brazil for weeks at a time, and paid a higher rate of tax. The side-effects in terms of other drugs I have experienced were minimal making it more cost-effective in my opinion than others. The current drug I am on which is older and not as advanced has already caused a side effect which meant I had to go in an NHS ambulance to the local A&E hospital and have treatment there within weeks of going on the drug and I am told this could happen again - more cost to the system. There are very few drugs on the market for secondary breast cancer patients and as more women are surviving longer with primaries then further down the line they are likely to have secondaries. The drug does not cost much more over two years than older drugs which are not as effective. I was able to have a normal life with no time off work. In addition I had to care for my 86 year old mother with dementia. She is not eligible for state care so again I was and currently	Comment noted. The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib. The committee agreed that people who are having treatment value delaying progression of the disease and an important consideration is delaying the time to chemotherapy (see FAD section 4.2).

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patient', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Comment [sic]	Response
	needed to sort out private care as she deteriorated while I was on this drug. This has saved the NHS money and social services. In terms of OS rates, secondary cancer survival rates are themseleves sketchy and in some health authorities often non-existent. As I understood it Paloma-3 was stopped early because of the early results which meant the drug could be fast-tracked for a licence. I am still living as a result of this drug and believe other women should be able to access it on the NHS. When I was accepted on the trial I remember telling the Royal Marsden staff that it would help other women further down the line. I feel strongly that drugs that have been shown to have clear results with minimal side-effects should be available to as many people as possible, especially as private health companies are in some cases now following NICE guidelines on new drugs too	
Carer	The cost for routine commissioning of Palbociclib is unlikely to be met for some time. My daughter is 32 years old, she has a daughter of her own who is 9 years old. Her breast cancer diagnosis was delayed by 9 months because a biopsy was not offered when she first presented at age 29 with a breast lump to the consultant at our local hospital. I understand that NICE guidelines at the time did not provide for routine biopsy for young patients. There must be other young women in the same situation who have been poorly served by the NICE guidance for diagnosis. The delayed diagnosis is directly related to the progression to the secondary metastases she now has. "Progression free survival state is consistently undervalued in technology appraisals" 10 extra months of progression free survival to a 32 year old woman with a 9 year old daughter would be of great value. If NICE approves the use of Palbociclib where the progression free survival	Comment noted. The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib. The committee agreed that people who are having treatment value delaying progression of the disease and an important consideration is delaying the time to chemotherapy (see FAD section 4.2).

Role*	Comment [sic]	Response
	state would be most beneficial and where patient's do not have other health problems, rather than for routine use, it would provide more evidence on overall survival in an otherwise healthy group of women and would be helpful in assessing the benefits of Palbociclib to overall survival. The fact that Palbociclib is available but too expensive for NHS use adds insult to injury for my daughter whose delayed diagnosis had a profound affect on her well being and will have already shortened her life. It will be a tragedy when my granddaughter loses her mum, if this can be delayed it will be a very good thing for her and if this group of younger patients in similar situations can be helped by the drug Palbciclib then the quality of life for many people will be improved not just the patients themselves. I would appreciate if you could take this into account when you consider the cost to benefit of this new and optimistic line of treatment, thank you.	
NHS Professional	Agree with the committee decision that at this point in time, PFS benefit without OS benefit does not justify the routine use given the high cost involved but it should be reconsidered if better deal can be negotiated with Pfizer even with the PFS benefit as it will save costs in chemotherapy use, the treatment of complications of chemotherapy, less time off work for patients and carer thus contributing to wider financial economy (not taken in to account in current models, therefore resulting in higher costs per QALY than acceptable).	Comment noted. The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib.
Breast Cancer Care	At Breast Cancer Care we hear from people living with secondary breast cancer every day about their hopes for new treatments. It is devastating access to palbociclib is being blocked. We are aware that, in addition to other factors, cost has played a significant role in this draft appraisal decision. Urgent conversations between NICE, NHS England and Pfizer need to take place. We hope that a way forward is found so that people living with the disease can have access to this ground breaking drug.	Comments noted. The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib.

Role*	Comment [sic]	Response
MP	I understand that Palbociclib is a first line treatment option for patients with hormone positive, HER2 negative secondary breast cancer. I also understand that, in clinical trials, palbociclib with letrozole provides around ten additional months of progression-free survival compared to letrozole alone. Secondary breast cancer is incurable, so ten months of extra life represents time in which women with the diagnosis can continue to be with family and friends, to work, and to contribute to the community. The draft recommendation to reject palbociclib comes just weeks after NICE announced its decision to reject Kadcyla, another innovative drug that can extend the lives of women with secondary breast cancer. The provisional decisions to reject these drugs appears to highlight flaws in NICE ineffective drug appraisal process, which is not working for secondary breast cancer patients. In reviewing the draft recommendation to reject palbociclib, I would urge you to consider the flaws in applying NICE's current drug appraisal process, to this treatment: First, progression-free survival is not given sufficient weight in the appraisal system. Because palbociclib allows patients to live longer without their condition progressing, there is, as yet, little data available on overall survival. This lack of overall survival data has contributed to this provisional rejection. The drug is used in many countries and has little side effects and can enable people to live life as normal. The fact that it stops people getting worse when they are not too bad should be more important than drugs which prolong life for people who are suffering greatly. Currently the appraisal process does not give sufficient weighting to quality of life as opposed to quantity of life. Second, comparing new treatments to generic treatments makes it virtually impossible for them to be considered cost effective. It takes ten years for a drug to lose its licence and become generic and thereby usually become cheaper. The average life expectancy for someone with secondary breast cancer is three years. Affected patients cannot wait for these drugs to become generic. Thirdly, ten months may not sound a long time but for someone with a "life limiting" diagnosis in middle age, every day is special. This drug is one of several that is used in sequence, so on its own it is not a huge amount of time	Comment noted. The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib.

Role*	Comment [sic]	Response
	but added to other time that other drugs give, it makes the prognosis slightly more bearable. Finally, there needs to be greater flexibility around the criteria for being considered an end-of-life treatment. NICE has a higher cost threshold for end-of-life treatments, which it defines as treatments used in the final two years of life. This figure appears arbitrary when compared to drug appraisals in Scotland, where end-of-life is defined as the final three years of life. Also, is it not positive to offer drugs that give a decent quality of life to the relatively well?	
Carer	I have seen first hand the good this drug can do as my wife, [redacted], was part of a clinical trial at the Royal Marsden. Just over two years ago, having an original diagnosis of secondary cancer, of origin in either breast or uterus (most likely breast), she was told that the cancer had spread to lymph nodes in the chest and a tumour was growing in her lower back. She was put on the trial for palbociclib at the Marsden and her progress was immediate. The tumour shrank and the drug worked effectively for two years. Its effectiveness having reduced, she was taken off the trial and is now on the next phase of treatment on a different drug. That, though, is two years of good life given by the drug she might not otherwise have had. I therefore urge NICE to reconsider its decision not to make palbociclib more widely available to people, especially as it has, I understand, potential to be used in prostate cancer, which is the most common male cancer and from which I myself suffer. I would like more to benefit from the life extension that my wife has experienced, with the consequent bonus not just for them but all the families and friends around them. I would also like more development of the drug for use on prostate cancer.	Comment noted. The company submitted a revised economic analysis with an updated patient access scheme, and the committee recommended palbociclib. The committee agreed that people who are having treatment value delaying progression of the disease and an important consideration is delaying the time to chemotherapy (see FAD section 4.2).

Pfizer Limited
24th February 2017

Dear Dr. Adam,

Re: Breast cancer (metastatic, hormone-receptor positive, HER2-negative, untreated) – palbociclib

Thank you for giving us the opportunity to comment on the Appraisal Consultation Document (ACD) for the above named appraisal. We are disappointed that a pragmatic solution to the methodological challenges which prevent palbociclib from demonstrating cost-effectiveness has not yet been found, given the transformative clinical value that has been recognised. As this first-in-class medicine allows metastatic breast cancer patients to experience a median PFS in excess of 2 years for the first time, yet the list price of the medicine is consistent with previous therapies in the area, the decision to not recommend palbociclib is unacceptable. Despite the lack of flexibility suggested in the ACD, we remain open to dialogue with the NHS and NICE and are fully committed to finding a solution which can bring this transformative medicine to patients in England and Wales. However, it is essential to acknowledge that the hurdle to access cannot not solely be overcome through reductions to price.

We thoroughly welcome the conclusion of the committee, in line with the clinical experts and the patient testimony, that palbociclib is a clinically effective treatment. This follows formal recognition by the MHRA that it is promisingly innovative. That palbociclib serves key patient needs of prolonging progression-free survival (PFS) and delaying the need for chemotherapy and the associated patient-experience cannot be understated. However, shortcomings within the methods of cost-effectiveness evaluation prevent palbociclib from achieving an ICER below the required threshold have remained barriers to palbociclib's recommendation. The presence of these barriers in the context of such transformational clinical benefit necessitates a more flexible application of the evaluation methods, so that the assessment accounts for the full value of palbociclib.

The ACD rightly notes the value to patients of increased PFS. Clinical expert and patient opinion as expressed in the written submissions and at the committee meeting was unanimous: increases to PFS – which bring with them the ability to sustain a normal life – are as important to women with terminal breast cancer as increases to overall survival (OS). By contrast, however, the ICERs on which the committee made their decision value OS nearly two-and-a-half times higher than they do PFS. It is clear that we must seek to harmonize the mathematics with the patient experience, so as to prevent discord between patients' reality and the resource allocation decisions which affect them. By way of example, if PFS and OS were valued equally within the palbociclib analyses, the ICER could conceivably reduce by up to £46,000 per QALY lower than currently.

The imperfections within traditional cost-effectiveness evaluation that prevent add-on therapies such as palbociclib from demonstrating a cost-effective ICER, and which therefore severely limit the extent to which an ICER can reflect the true value of the medicine, must not be ignored. These issues have arisen in metastatic breast cancer appraisals previously, and will continue to in the future. Such issues are illustrated when the economic evaluation instead compares palbociclib to the average cost of previously appraised therapies, rather than to generic letrozole; the result is a cost-effective ICER. Pfizer implores the committee to consider the merits of the scenarios presented within this response as these better align to the way patients and clinicians value the disease and this medicine. If such flexibility is not adopted, palbociclib – and more importantly, the women for whom it may be an appropriate treatment option – are left in an unacceptable position.

Pfizer is aware that even transformative clinical benefit must be balanced against cost pressures. For this reason, the UK list price of palbociclib is among the lowest of published European markets. At this price, if the full value of the medicine is pragmatically accounted for, palbociclib is a cost-effective use of NHS resources.

Yours sincerely,

[redacted]

For and on behalf of Pfizer UK

1. The need for flexibility in the methods of evaluation

We thoroughly welcome that the ACD[1] so clearly reflects the great importance patients place on staying in a progression-free state as long as is possible, and on delaying time to chemotherapy. Similarly, we welcome the conclusion that palbociclib has a clear and important benefit in improving progression-free survival. These conclusions by the committee are of great significance with respect to the considerations of cost-effectiveness, and will therefore be addressed in more detail in later sections.

The committee conclusion that all plausible ICERs were above the level that could be considered a cost-effective use of NHS resources fails to acknowledge that the traditional assumptions of cost-effectiveness evaluation severely limit the extent to which palbociclib can achieve an ICER near the required threshold, almost irrespective of price. Situations such as this necessitate judicious flexibility in the methods of evaluations, so as to ensure the complete value of the medicine is accounted for and that no medicine is denied access to routine commissioning simply because of artefacts of analysis.

In the assessment of palbociclib, prudent flexibility is required in three areas: estimation of the expected overall survival; the valuation of progression-free survival relative to overall survival; and the cost of the comparator. The following sections of this document address each of the issues in turn. Consideration of these issues – both cumulatively and in isolation – make clear that the ACD neither fully acknowledges the drivers of the ICER, nor fully accounts for the value of palbociclib offered to patients, and by extension, to the NHS.

2. Expected overall survival benefit

The ACD makes clear that the relationship between PFS and OS is complex, but nevertheless agrees with the clinical experts by recognising that the significant improvements seen with palbociclib in progression-free survival will likely result in improvements to overall survival. The committee ultimately concluded that the plausible overall survival gain is within a range bounded on one side by the immature OS from PALOMA-1 (mean of 6.6 months) and on the other by estimate where improvements in PFS from PALOMA-2 translated to improvements in OS (mean of 11.2 months). The clinical expert testimony during the committee meeting made clear that a 1-to-1 translation of PFS benefit to unconfounded OS benefit was a reasonable assumption, noting no current evidence to suggest otherwise. However, experts also noted that, by sheer virtue of the randomness of response post-progression, the mature data may still fail to show the medicine's true OS benefit. Given this testimony, it is therefore not unreasonable to assume that the unconfounded OS benefit is at least greater than the lower bound of the committee's currently preferred range. The higher value noted in the ACD should therefore be considered most appropriate for decision making.

The committee agreed the populations in both the PALOMA-1 and PALOMA-2 trials were similar to the patient population seen in clinical practice in England, and ultimately considered both mixed trial data and PALOMA-1-only data in its evaluation of cost-effectiveness. Although both trials are immature, PALOMA-1 has had longer follow-up to date and, given that the primary outcomes from PALOMA-1 and PALOMA-2 are consistent, use of the PALOMA-1 data to extrapolate and estimate outcomes may provide more accurate results.

3. The undervaluing of progression-free survival with the QALY

As made clear by the ACD, the patient testimonial presented to the committee stressed the value patients and their families place on remaining progression-free, and the associated ability to continue with normal life. This was reinforced by statements from the clinical experts, which emphasised the importance of PFS as a key treatment goal. The delay to subsequent chemotherapy that is a result of PFS was notably cited in the ACD as key for patients in the case of palbociclib.

Following the committee meeting, Pfizer sought further input on this issue through an advisory board consisting of 8 leading UK clinical experts. This advisory board discussed not only the qualitative value of PFS in relation to OS, but also the quantitative utilities that are typically applied in modelled health states in metastatic breast cancer, including in this appraisal for palbociclib. Feedback at this advisory board was unanimous: improving time spent progression-free is as important to patients as improvements in time spent alive, thus the utility elicited to remaining progression-free (as opposed to progressing) should be similar to that related to giving life extension to reflect the real value of these outcomes.

In this instance, it is clear that the metric by which the appropriateness of a utility value should be judged is whether or not it aligns, in principal, with the value described by clinical experts and patients themselves. As noted by Pfizer at the committee meeting, **the base case utility values OS almost two-and-a-half times greater than it values PFS** in the modelling (see Appendix A for further details); this is a stark contrast to clinical and patient perception of PFS and OS, which considers them of similar value. As such, the utility values informing the ICERs discussed in the ACD fail to reflect the full value of PFS for this disease and patient population. The ACD indeed notes that aspects of the patient experience, such as the desire to avoid future events, specifically treatment with chemotherapy, is not captured by the EQ-5D. In this respect, the valuation of PFS relative to OS represents a shortcoming of the methods of cost-effectiveness evaluation. Such a conclusion is not unique to this appraisal: for example, in the NICE appraisal of abiraterone[2] and the SMC appraisal of everolimus[3], the benefits of delaying chemotherapy through extending progression-free survival were noted as not being fully captured in the modelling.

Adjusting the utility values so that the benefit of remaining progression-free aligns with the patient experience, as described above, moves the ICER downwards by between £30,000 and £46,000 per QALY, dependant on the committee's preference for the modelled base case. This adjustment removes the OS valuation that is nearly two-and-a-half times greater than PFS, and instead allowing time spent progression-free to produce a comparable QALY benefit to remaining alive (see Appendix A for full details). Although this solution to the methodological shortcoming noted above may itself be imperfect, insofar as it limits incongruences between the model and a patient's reality, such a departure from the traditional method is appropriate, pragmatic, and necessary.

4. The acquisition cost of the comparator when comparing incrementally

The committee concludes in the ACD that the assumption of a higher cost for the comparator treatment than the current cost for generic letrozole was not appropriate and could not be considered, noting that the committee cannot calculate cost-effectiveness based on a hypothetical comparator. For the avoidance of doubt, let us make clear that Pfizer appreciates that the committee cannot make real-life resource allocation decisions based on hypothetical scenarios. However, of almost singular importance in the appraisal of palbociclib is the limited ability of this drug to demonstrate cost-effectiveness within the confines of the current methodological framework. A key shortcoming is evident in the assessment of incremental cost.

As palbociclib is an add-on to current treatment, there is no cost offset, making its *entire* treatment cost 'incremental'. This makes the numerator of the ICER sufficiently large that it cannot be overcome unless unrealistic assumptions (such as greater than 5 years OS gain or 10 years PFS gain) are adopted with respect to the denominator (i.e., the benefit). Moreover, the notable lack of access in the UK to innovative first-line treatment options in this subtype has left patients with a choice of either generic aromatise inhibitors or generic chemotherapies, in effect creating nearly the same mathematic challenge with regard to incremental cost even if palbociclib were not an add-on therapy. Palbociclib's ability to demonstrate cost-effectiveness is in fact so effected by the cost of the comparator that if we consider cost comparisons versus other treatments in metastatic breast cancer, particularly recent innovative therapies, palboclicib could be deemed cost-effective. Indeed, this is not an issue that solely affects palbociclib, but is one that has impacted several previously appraisals in metastatic breast cancer and will continue to impact future appraisals; neglect of this issue in this appraisal will not solve the wider problem.

Across all NICE appraisals, guidance has been produced for 13 medicines in metastatic breast cancer – including chemotherapies and targeted therapies – appraised at an average of £2,485 per month (at list price), equating to £22,745 per total course of treatment (see Appendix B for details).[4-15] In comparison, the monthly cost of letrozole is £32 per total course of treatment[16]. If the innovation seen across metastatic breast cancer in the last two decades were applied to this appraisal and the cost of the comparator in the model was instead **the average cost of all NICE appraised metastatic breast cancer medicines, it is possible for the ICER to fall to below £50,000 per QALY**. This strikingly illustrates the extent to which lack of access to innovative treatments today limits the likelihood of access to future innovations tomorrow. Although the current assessment framework was built on the idea of cost-effectively allocating future resources, in truth it may actually serve to increase inequality in access medicines between disease areas, penalising patients if their illness happens to be one in which new innovative treatments bring benefits as add-on therapies, or if we have simply reached the point where current therapy is generic. The ultimate result for palbociclib is unacceptable, as the expectation (falsely) remains that the hurdle to access can be overcome exclusively through reductions to palbociclib's price.

Pfizer is aware that even transformation clinical benefit must be balanced against cost pressures. It is for this reason that the UK list price of palbociclib is among the lowest of all published European markets, at the time of press. Noting this, it is further important to not only consider this cost against the unprecedented effectiveness of the treatment, but against wider services too.

When the changes brought about through the re-valuation of PFS are coupled with a comparison versus the cost of the average treatment for metastatic breast cancer than NICE has appraised, the ICER can be reduced between £57,000 and £107,000 per QALY lower than at current, dependant on the committee's preference for the modelled base case. The result is an ICER produced that is around the £30,000 per QALY threshold (see Appendix B for details). Acknowledgment of these key limitations illustrates that palbociclib should be deemed a cost-effective use of NHS resources.

As well as a delay to chemotherapy, the ACD also cites the potential reduction to first-line chemotherapy from the introduction of palbociclib, in line with comments at the scoping stage suggesting a large proportion of

patients currently receiving chemotherapy could benefit from treatment with endocrine therapy[18] (however, chemotherapy was removed as a comparator from the final scope). Although relevant chemotherapy is now generic, it carries a higher cost burden than the current comparator, letrozole, due to the management of adverse events and the HRG tariffs related to both oral and IV chemotherapy administration. Further, with the chemotherapy outcomes being lower[17] than letrozole[16], the ICER for palbociclib versus chemotherapy would be expected to be lower than versus the current comparator.

5. References

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15) National Institute for Care and Health Excellence. TA371. Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane. 2015. www.nice.org.uk/ta371

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the draft remit and draft scope (pre-referral). 2016. https://www.nice.org.uk/guidance/GID-TA10068/documents/scope-consultation-comments-and-responses

19) Brazier, Ara. Using Health State Utility Values from the General Population to Approximate Baselines in Decision Analytic Models when Condition-Specific Data are Not Available. Volume 14, Issue 4, June 2011, Pages 539–545

Appendix A: The valuation of PFS and resulting ICER change

Currently, extensions to OS are worth nearly two-and-a-half times more than extensions to PFS, in terms of relative QALY gained:

- In the model, the utility score elicited being progression-free was 0.72. After a patient progresses, their utility falls to 0.51. Upon death, utility falls to 0.
- Hence, if a patient's PFS is extended, they will continue to benefit from a utility of 0.72 as opposed to 0.51 (i.e., the value of remaining progression-free for a certain period of time is worth an additional utility of 0.21 to patients compared to if they had progressed during this time).
- If a patient's OS is extended at the end of life, they will continue to benefit from being alive in a progressed (later line) state at utility of 0.51, as opposed to a utility of 0 (i.e., the value of OS is worth an additional utility of 0.51 to patients during the time they have life extended).
- Resultantly, the value of an additional month's OS is worth 2.43 times more QALYs than the value of an additional month's PFS in the model (0.51/0.21 = 2.43). Simply put, this severely mis-aligns with the expert perception that, to patients, additional PFS is as important as additional OS.

To adjust the QALY estimate in line with clinician and patient expert feedback, utility for PFS is adjusted to a score of 1 (applied to both arms) whilst the utility in the progressed state is left at 0.51.

- As such, the QALY impact of remaining progression-free versus progressing (1-0.51 = 0.5) is of a comparable magnitude to remaining alive versus dying (0.51-0 = 0.5).
- Although previous literature has shown a score of 1 is possible with the EQ-5D, despite a patient having multiple conditions may render,[19] it is important to note this adjustment is **not** intended to reflect patients having perfect health; it is acknowledged the health of these patients may still be impacted by the disease. This adjustment departs from the traditional EQ-5D-elicited interpretation of utility where the score is a solely a valuation of physical and emotional health at the point in time the patient completed the questionnaire , and instead is simply a mathematical adjustment so that the value of remaining progression-free within the model aligns with the value to patients in real life. The motive is purely to harmonize decision making with the patient experience for whom these decisions are made.

Table 1. Changes in the ICER when the PFS utility adjustment is applied, reflecting the upper bound of the committee's preference for expected OS gain (11.2 months)

	Original company model	ERG model, PALOMA-1	ERG model, PALOMA-2
Current ICERs	150,869	102,876	158,365
Adjust PFS utility	120,569	70,397	112,450

Adjustments conducted within the model:

- *The above scenarios were run in the model by editing the sheet Utility, cells D12 and D18, setting these to =1*
- *For the ERG model, switches R2-R12 were applied, but excluding R4 (which was set to =0 to allow for pre-progression utility to be over-ridden). R1 was not applied for the table above as these results aim to reflect the upper bound of the OS range.*
- *In the revised company model, ERG modification R5 was applied to set post-progression utility to =0.51 (the other ERG modifications were not applied)*

Appendix B: The cost of comparator and resulting ICER change

Table 2. Cost of previously NICE appraised therapies in metastatic breast cancer, at list price

TA	Technology	Total drug acquisition cost	Monthly drug acquisition	Notes on total treatment cost calculations
TA371	Trastuzumab emtansine[15]	£90,831	£6,624	*Total cost cited in FAD. Monthly cost divided by average duration (14.5 months).*
TA295/ TA421	Everolimus + aromatase inhibitor[14]	£23,166	£2,970	*30 day 10mg tabs cited as £2,970. Multiplied by PFS (7.8 months)*
TA263	Bevacizumab + capecitabine[13]	£31,725	£3,689	*Average monthly cost cited as £3,689, for a median PFS of 8.6 months*
TA257	Lapatinib + aromatase inhibitor[12]	£28,212	£2,197	*£28,212 for 55.2 week treatment duration = £2,197 per month*
TA257	Trastuzumab + aromatase inhibitor[12]	£26,018	£1,735	*£26,018 for 15 month treatment duration = £ per month*
TA250/ TA423	Eribulin[11]	£7,512	£1,788	*£313 per 2mg vial, 1.23mg per m2 = 2.13mg per patient (BSA=1.73m2), thus 2 vials required per dose. Dose administered twice per 21 day cycle (=4 vials x £313 per 21 day cycle, = £1,788 per month) for median of 3.7 months.*
TA239	Fulvestrant[10]	£4,440	£683	*First month cost £1044.82, then subsequent months £522.41. Multiplied by PFS of 6.5 months*
TA214	Bevacizumab + taxane[9]	£37,344	£3,305	*Monthly price cited of £3304.76, multiplied by median PFS of 11.3 months*
TA116	Gemcitabine + paclitaxel[8]	£11,346	£2,701	*Total cost of gemcitabine is £2346 for 6 cycles = £391 per cycle, added to paclitaxel, £1,500 = £1891 per 21 days. Taken for 6 cycles.*
TA54	Vinorelbine[7]	£1,500	£735	*Average cost per patient cited as £1300 to £1800. Average dose is 25 mg/m² once weekly = 43mg per week = 4.3ml. 5mg vials, x4 per month = £735 per month*
TA62	Capecitabine combination[6]	£9,090	£1,990	*Cited in FAD; £1,393 per 21 days*
TA34	Trastuzumab + paclitaxel[5]	£15,500	£1,750	*£15,500 cited in FAD per 38 week course. Per month = £1,750*
TA6/30	Taxanes[4]	£9,000	£2,143	*Cited in FAD; £1,500 per 21 days, for 6 cycles*
Average cost across all appraised therapies		**£22,745**	**£2,485**	
Average cost across innovative therapies (*i.e.*, excluding chemotherapy TA116,54,62,6/30)		**£29,417**	**£2,749**	

Note: costs have not been inflated to current year

It should be noted that the average PFS observed across these other medicines appraisals is actually less than that of letrozole, suggesting the ICER would be even lower if the benefit in the ICER was also adjusted.

Table 3. Changes in the ICER when the cost of comprador is adjusted, and combined with the PFS utility adjustment from Table 1, reflecting the upper bound of the committee's preference for expected OS gain (11.2 months)

	Original company model	ERG model, PALOMA-1	ERG model, PALOMA-2
Current ICERs	150,869	102,876	158,365
1) Adjust monthly comparator cost, combined with adjustment in PFS utility	54,775	34,035	51,492
2) Adjust total comparator cost, combined with adjustment in PFS utility	93,058	45,758	85,805

Adjustments conducted within the model:

- *The above scenario 1) was run in the model by editing the sheet EngineLET_PBO, cells AP9 and AP10, setting these to =2,485*
- *The above scenario 2) was run in the model by editing sheet EngineLET_PBO, cell CH534, setting this to =(CH533-BU534)+(22745*(BU534/AP534)) This formula first deducts the total cost of letrozole, then replaces it with the average cost of £22,745 from Table 2, discounted as letrozole was.*
- *For both scenarios, in the sheet Utility, cells D12 and D18, these were set to =1 (requiring ERG modification R4 set to =0)*

Pfizer UK Ltd
4th May 2017

Dear Dr. Adam (on behalf on the Appraisal Committee) and Prof. Longson (on behalf of the Institute),

Re: Appraisal ID915 – Breast cancer (metastatic, hormone-receptor positive, HER2-negative, untreated) – palbociclib

For UK patients requiring first-line treatment for HER2- ER+ metastatic breast cancer, access to innovation has stagnated. Artefacts of the current analysis framework mean that palbociclib (as an add-on therapy offering significant progression-free survival [PFS] gain versus a generic comparator) cannot be expected to be cost-effective, even if priced comparably to previously recommended therapies. Indeed, there is no clinically plausible survival advantage that the drug could offer which would change this. Given the lack of NHS access to innovation in this particular treatment space, the appraisal of palbociclib draws close attention to the Institute's responsibility to recognise the potential for long term benefits to the NHS of innovation.

The technical issues which overlap and interact to create this access hurdle are complex; nevertheless, we have proposed simplifying, illustrative modifications to the methods which seek to address what we consider the primary issues: the relative importance of PFS, and issues relating to the comparator. The Institute has agreed to consider flexibility with respect to the methods in these areas, and the ERG has undertaken a critique of our proposals. This document outlines our response to those considerations and critique. In response to a concurrent request from the Institute, further detail regarding the structured discussions that were had with clinical experts concerning the relative value of PFS accompanies this response, as does the most recent update to the PALOMA-1 overall survival data. It bears repeating that the PALOMA-1 overall survival (OS) data have the same caveats of those interim final PALOMA-1 data already considered by the committee, meaning a range of survival estimates, as previously agreed following expert advice at the first committee meeting, is still appropriate.

In addition to previous analyses exploring the relative value of PFS and comparisons with other first-line chemotherapy, we have included here a more robust comparison with medicines launched (and in instances recommended) for the wider population of metastatic breast cancer. In doing so, we demonstrate the inequity of access opportunity within metastatic breast cancer. It is a fairer comparison to view the cost-effectiveness of palbociclib in relation to other innovations in metastatic breast cancer, rather than to an insurmountable, low cost comparator which also is added-on to. Such a comparison makes clear the extent to which treatments like palbociclib are, and will be, unduly penalised because of the sustained lack of access to innovation in the HER2- ER+ treatment space.

As part of this response, Pfizer have also included a confidential Patient Access Scheme, which will make palbociclib available to the NHS at a discounted price. Taking into account the Patient Access Scheme and the new survival data, whether assuming an approach that either compares to other NICE-approved metastatic breast cancer medicines, or alternatively re-values PFS and considers current chemotherapy use, the ICER can fall to between [redacted] and [redacted] per QALY. Regardless of the flexibilities the committee deems most appropriate in this instance, palbociclib can represent a cost-effective use of NHS resource.

Yours sincerely,

[redacted]
For and on behalf of Pfizer UK

1. Updated Overall Survival (OS) data from PALOMA-1

In the company submission, OS data were provided from the interim cut of PALOMA-1 (conducted in 2013). The primary outcome in the PALOMA-1 trial was PFS and although data on OS were also collected, the trial was not powered for OS. No OS data were available from PALOMA-2 as the number of events specified in the protocol as required for analysis had not yet been reached, with Pfizer blinded to the results. Since submission, the final OS data-cut from PALOMA-1 has become available, and is provided here. PALOMA-2 OS data remain unavailable, for the reasons noted above.

In the final analysis (30th December 2016), the stratified hazard ratio for overall survival was 0.897 (95% CIs: 0.623,1.294, p=0.281), based upon 116 deaths from 165 patients.[1] This hazard ratio has increased slightly from the interim datacut, although broadly similar (interim HR=0.813, 95% CIs: 0.492, 1.345).[2]

The updated median OS in the palbociclib plus letrozole arm was 37.5 months (95% CIs: 31.4, 47.8) and in the letrozole alone arm was 34.5 months (95% CI: 27.4, 42.6).[1]

Survival probability at 1 year was [redacted] in the palbociclib plus letrozole arm, and [redacted] in the letrozole alone arm [redacted] and at 2 years was [redacted] in the palbociclib plus letrozole arm, and [redacted] in the letrozole alone arm [redacted] At 3 years, survival probability was [redacted] in the palbociclib plus letrozole arm, and [redacted] in the letrozole alone arm [redacted][1]

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

The ACD makes clear that the relationship between PFS and OS is complex, but nevertheless recognizes that the significant improvements seen with palbociclib in PFS will likely result in improvements to OS. The committee therefore concluded that the expected OS would range from that observed in PALOMA-1 (with this initial conclusion based on the interim OS data) as a lower bound, to that which equates with a 1-to-1 translation of PFS gain-to-OS gain as an upper bound.

Although these new data address the lower bound of this range, the rationale for the upper bound remains unchanged. Expert testimony at the meeting stated that a number of factors (post-progression

treatments, randomness of subsequent response, etc.) prevent PALOMA-1 from providing an entirely unconfounded estimate of the benefit to OS associated with palbociclib, and its usefulness may therefore be limited. It is therefore still appropriate to consider the "true" OS as falling within a range.

With these new data, and using the ERG's PALOMA-1 modelled base case, the lower bound of the mean range in OS is now 4.0 months (previously 6.2 months). The upper bound in the ERG's modelled PALOMA-1 base case is 10.7 months (previously 11.2 months when using the company's original model). This range in OS, 4.0 months to 10.7 months, is reflective of using either PALOMA-1 data as the basis for extrapolation, or the relationship between PFS gain to OS gain. The revised ICERs related to this range in OS are £105,117 to £159,064 per QALY. With the Patient Access Scheme (PAS) [redacted] this new range is [redacted] per QALY to [redacted] per QALY. Importantly, however, these ICERs (included here only for completeness) are not a true representation of the cost-effectiveness of palbociclib, for reasons discussed on the following pages.

2. Methodological Hurdles to Access

Despite the unprecedented efficacy afforded by palbociclib, the base case estimate of cost-effectiveness in the initial submission far exceeded the traditional threshold. This was acknowledged in both the submission itself and the Pfizer ACD response.

That palbociclib is simultaneously an add-on therapy, given until progression, and compared with a generic treatment, combines to create a significant barrier to access. The Pfizer ACD response focused on two elements of the current methodology which, if flexed in recognition of the barriers they create in this instance, illustrate that palbociclib can indeed be deemed a cost-effective use of NHS resources. This included the relative value of PFS, and issues relating to the comparator.

(i) Relative Value of Progression-Free Survival

The ERG has reviewed Pfizer's approach to re-valuing the utility benefit associated with PFS, stating such an approach would have merit if:

a) additional PFS benefit should be valued equally to additional OS benefit (gained as extra PPS at the end of life); **and**

b) the treatment of interest has greater PFS and lower OS (and, therefore, lower PPS) than one of the treatments it is being compared against.

Pfizer consider the condition outlined in point (a) to be satisfied. Pfizer consulted multiple experts across a variety of relevant disciplines, including key clinicians, within the UK metastatic breast cancer community to understand the value of additional PFS, relative to additional OS. The feedback has been unanimous that a treatment bringing extensions to PFS in this treatment space is as valuable as one bringing extensions to OS. This feedback is in line with both the clinical expert statements and the patient testimonial that featured during the committee meeting, and detailed further in the accompanying report from a structured discussion since that meeting.[3]

The ERG suggests that the equality of additional PFS and OS benefit might not apply in situations where disease progression does not have much of a negative impact on quality of life. The evidence included in the Pfizer submission regarding the value of "normality", as well as the patient and clinician testimonials

provided to date, indicate that this is not the case within first-line metastatic breast cancer. As set out in the original company submission, retaining normality (which includes caring for a family, continuing in a job, not having to rely on informal care, a delay to, and not having to undergo, chemotherapy, etc.) can be greatly impacted once symptoms cross a certain threshold after progression. This negative impact on quality of life can be substantial, albeit not in ways necessarily captured by traditional metrics. Indeed, previous NICE and SMC appraisals have already concluded that that at least one element of "normality" listed above (that is, the value to delaying chemotherapy) is not captured in current QALY estimates.

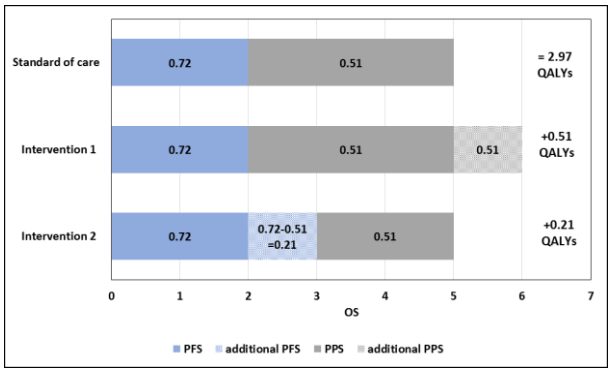
The ERG posits in point (b) that one can argue QALY benefit from PFS gain is undervalued with respect to OS gain effectively *only* when all PFS gains are made at the expense of post-progression survival (PPS) gain, and it provides illustrative scenarios as a means of explanation. The ERG conclude that there is no need to re-examine the value awarded to PFS in this specific case, because PFS gain is not made at the expense of PPS gain (as depicted in ERG Scenario 3.) In this way the ERG states, *"the benefit of additional PFS is already equal to the QALY benefit of additional OS*".

In the ERG's illustrative 'Scenario 1' (presented in Figure 2 below), Intervention 1 leaves the PFS benefit of standard of care unchanged, but extends overall survival versus standard care by extending PPS (resulting in a QALY gain from that life extension of 0.51 [*i.e.,* 0.51 in PPS versus 0 at death]). By contrast, Intervention 2 extends PFS but reduces PPS by an equal amount, thereby leaving overall survival versus standard of care unaffected. This increases QALYs versus standard of care by 0.21 (0.72 – 0.51). Scenario 2 provides an alternate illustration of the concept presented in Scenario 1, so is therefore not re-presented in this response.

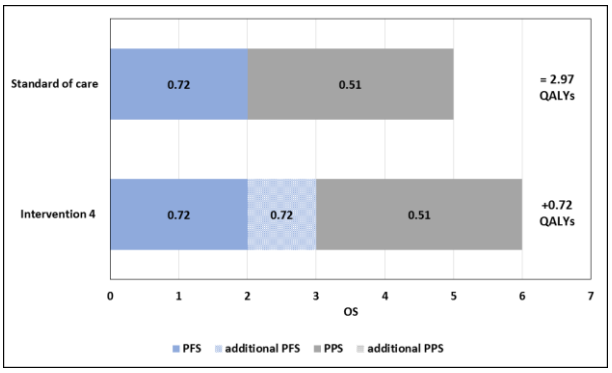
Scenario 3 extends PFS versus standard of care, but leaves PPS unaffected, thereby increasing the overall survival by a length of time equal to the increase in PFS. In this respect, Scenario 3 illustrates both an extension to both PFS and to OS. As depicted in the ERG diagram, the QALY gain here is 0.72 QALYs.

Figure 2. ERG's illustrative scenarios[4]

Scenario 1



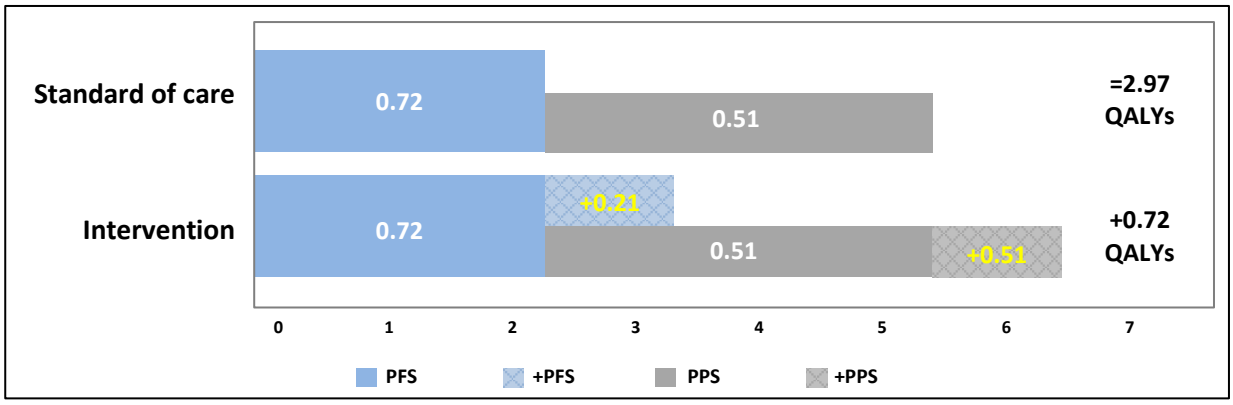
Scenario 3



The ERG states that OS and PFS are of equal benefit within Scenario 3 (and therefore valued equally within the resulting ICER) because *"incremental OS is gained in PFS".* In this way, the ERG conceptualises this +0.72 QALY gain as coming from one discrete benefit: the addition of time to PFS.

Pfizer consider it more appropriate to conceptualise this +0.72 as the result of two benefits to the patient at two independent points in their lives: 0.21 from the improvement to quality of life from the retention of a 'normal' state for longer at that time, added to the 0.51 from the life extension at the end of life; these QALY benefits are accrued separately. Figure 3 below presents Scenario 3, but with added detail to better reflect these two independent effects in terms of QALYs.

Figure 3. Scenario 3, with added detail



It is that these two benefits are not equally valued, despite them being for the same amount of time, that is at odds with how clinical experts and patient perceive outcomes in reality, as the improvements from PFS produce fewer additional QALYs than those for OS. Of the total QALY gain, 71% is driven by extensions to OS (0.51 of 0.72), yet only 29% by extensions to PFS (0.21 of 0.72). These percentages translate to OS being valued 2.43 times higher than PFS (0.51/0.21) in the calculation of the incremental QALY gain.

It is important to the note that implicit in the discussion of Scenario 3 above as it applies to palbociclib is that PFS gain translates directly into OS gain. The committee has concluded that this assumption represents the plausible upper bound of survival benefit, but Pfizer are mindful that this OS assumption has on one hand been dismissed by the ERG as not appropriate for use in the base case, and is now on the other hand provided as rationale to dismiss our position regarding PFS valuation.

Separate to the above conditions, the ERG writes that the inequality in additional PFS and PPS benefit described in the Pfizer ACD response is purely an artefact of the utility values used in the model. This is true. The ERG is correct to point out that the principle of adjusted relative value between PFS and OS can be achieved by either: adjusting the **PFS** value, keeping the PPS value unchanged (i.e., using 1.0 and 0.5); or by adjusting the **PPS** value and leaving the PFS value unchanged (using 0.72 and 0.36).

The comments from the preceding page regarding patient benefit during PFS not being captured by current metrics suggest that “undervalued” PFS is perhaps best corrected for with changes to the PFS value itself, rather than forcibly down-weighting PPS utility. Nevertheless, ICERs are presented on the following pages that reflect both approaches. By presenting both approaches, changes to the PPS or PFS values create upper and lower bounds of an ICER range which reflects an equal valuation of PFS and OS.

It is lastly important to point out that Pfizer are aware that the approach described above is necessarily simplifying. However, it is equally important to point out that the approach is akin in this respect to the assumptions made within the End-of-Life (EoL) criteria. The EoL criteria give “greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age.” This assumption (about full quality of life) is not a reflection of reality, but rather one which allows for a more simplified application of the principle in question.

Bearing in mind the Institute’s responsibility to recognise the potential for long term benefits to the NHS of innovation, the approach provided here is a simplified illustration of how methodological flexibility can address the access hurdle for patients and medicines in this treatment space. Taking into account the

Patient Access Scheme, the cost per QALY which incorporates the above utility adjustments ranges from [redacted] per QALY to [redacted] per QALY, reflective of the range in adjustments described above, and the range in OS in line with the committee's preference.

Table 1. ICERs for palbociclib plus letrozole versus letrozole alone, with adjustments to utility to represent equal weighting for both PFS and OS

	Adjust PFS utility (PFS = 1.0, PPS = 0.51)	**Adjust PPS utility (PFS = 0.72, PPS = 0.36)**
Lower bound OS (PALOMA-1)	[redacted] per QALY	[redacted] per QALY
Upper bound OS (PFS to OS extrapolation)	[redacted] per QALY	[redacted] per QALY

(ii) Comparator Selection

As previously stated, artefacts of the current analysis framework mean that any new medicine for women with HER2-HR+ metastatic breast cancer with similar characteristics to palbociclib (that is, an add-on therapy offering significant progression-free survival gain versus a generic comparator) is not expected to be cost-effective. This is due, in part, to the choice of the comparator. That a more expensive comparator makes cost-effectiveness easier to establish is neither a complicated nor controversial point. But we do not make this point here to argue that in all instances a comparison versus a generic creates a hurdle to access. Appraisals in other disease areas have made clear this is not the case. What we do wish to illustrate is the inequity within metastatic breast cancer with respect to *access opportunity*, created by the sustained lack of approved innovation in this specific treatment area. By way of example, if palbociclib were instead compared to other treatments recommended by NICE in the broader metastatic breast cancer space, the ICER for palboclicib would differ greatly to that which comes from its comparison with letrozole, falling to below £50,000 per QALY at list price with no adjustments to PFS *and* assuming the conservative bound of OS.

As an early illustration of the point regarding comparator cost, Pfizer previously noted that, in the company base case, unless currently implausible gains to OS are assumed (between 5 and 10 years), the price required to achieve a cost-effective ICER versus the current comparator would be around £500 per cycle; this is a lower monthly price than *all* 13 previously-appraised metastatic breast cancer medicines (Table 8).

When one considers that an efficacious treatment such as palbociclib must, in one comparison, require either implausible efficacy assumptions or a monthly cost lower than all previously appraised therapies before being deemed cost effective, and yet in another comparison to other therapies in metastatic breast cancer produce ICERs that could be deemed cost-effective, it becomes clear that the currently chosen comparator is significantly restricting the possibility of a new therapy ever becoming available in first-line HER2- ER+ metastatic breast cancer.

Below we explore the impact of adjusting the treatment costs and outcomes against which palbociclib is compared in more detail, using two scenarios: comparison within metastatic breast cancer more broadly, and versus first-line chemotherapy within HER2- ER+ metastatic breast cancer.

(a) Comparison within metastatic breast cancer

Given the hurdle to access created by the current comparator, a fairer comparison considers the cost-effectiveness of palbociclib in relation to other innovations in metastatic breast cancer. Pfizer have explored the costs and outcomes of previous metastatic breast cancer medicines appraised by NICE, with a view to understanding the impact on the palbociclib ICER if any of these medicines had served as the comparator in place of letrozole. This builds on the analysis presented in the original ACD response, furthered in recent productive discussions with NICE, now providing a more comprehensive comparison.

Pfizer have calculated the average monthly price at around £2,530 (total treatment cost £25,248) across the 13 metastatic breast medicines in which NICE have completed appraisals, at the time of appraisal (noting these figures are updated from Table 2 in the initial *Response to ACD*), associated with an average of 1.38 QALYs (2.31 LYs).[5-16] These 13 treatments include those for other subtypes within metastatic breast cancer, and for different lines[a]. An initial comparison in the response to ACD showed that if the incremental costs of palbociclib were calculated with reference to this cost (that is, the average of previously appraised therapies) rather than the current comparator, the ICER could be dramatically reduced, highlighting the difficulties in achieving traditional cost-effectiveness within this patient population.

Following critique from the ERG and discussions with the Institute noting that the comparison in the ACD response excluded considerations of the comparator effectiveness, and the presence of Patient Access Schemes for many of the medicines, this comparison has been updated and presented below. Comparing the incremental benefit and incremental cost for palbociclib versus other therapies in metastatic breast cancer produces a much lower estimate of cost-effectiveness than when palbociclib is evaluated as an add-on therapy with a low cost comparator arm. The average ICER versus these therapies is displayed in Table 3 versus all 13 therapies, and then in Table 4 when considering only the seven therapies which NICE have recommended. [6,10-17]

When compared at list price to the seven therapies which NICE have recommended, the ICER for palbociclib would fall to between £45,092 per QALY (if assuming PFS translates to OS gain), and £49,768 per QALY (if using the updated OS from PALOMA-1). With the confidential PAS for palbociclib, these ICERs drop to between [redacted] and [redacted] per QALY. If those comparators which offered a PAS were assumed [redacted], the ICER would change by under £1,000 per QALY illustrating that, even if those comparators had a larger PAS, this would be expected to minimally impact the average ICER.

Table 2. ICERs if palbociclib were compared to the previous 13 therapies NICE have fully appraised in metastatic breast cancer

Palbociclib at list price		PAS for palbociclib		PAS for palbociclib, but also the same PAS applied to those comparators offering a PAS	
PALOMA-1 OS gain	**PFS:OS gain**	**PALOMA-1 OS gain**	**PFS:OS gain**	**PALOMA-1 OS gain**	**PFS:OS gain**
£55,222	£45,478	[redacted]	[redacted]	[redacted]	[redacted]

[a] It should be noted that when comparing treatments from different previous appraisals, treatments do differ in effectiveness as a consequence of different subtypes of mBC, subgroups of patients, or the lines in which the treatments are used. However, the cost of treatments also differs in the same way, and as such is relative to the benefit. For example, with a treatment which treats till progression, it does not matter whether the associated PFS is 5 or 15 months, as the consideration of cost and benefits are proportionate (*e.g.,* 5 months PFS and 5 months cost, or 15 months PFS and 15 months cost, each will result in the same cost-to-benefit ratio).

See Appendix A for additional detail

Table 3. ICERs if palbociclib were compared to the previous 7 therapies NICE have recommended in metastatic breast cancer

Palbociclib at list price		PAS for palbociclib		PAS for palbociclib, but also the same PAS applied to those comparators offering a PAS	
PALOMA-1 OS gain	PFS:OS gain	PALOMA-1 OS gain	PFS:OS gain	PALOMA-1 OS gain	PFS:OS gain
£49,768	£45,092	[redacted]	[redacted]	[redacted]	[redacted]

See Appendix A for additional detail

The difference between these ICERs and the committee's originally preferred ICER range in the ACD (£132,000 to £213,000 per QALY) illustrates the extent to which letrozole insurmountably blocks access to long-term innovation in this treatment space. These exploratory analyses also suggest that the women comprising the population of this appraisal are less likely to access new innovative treatments than those with other forms of metastatic breast cancer and/or requiring a different line of treatment, even though the costs and benefits of new interventions in different spaces within metastatic breast cancer may actually be equal.

When utility is adjusted so that incremental PFS accrues the same amount of QALYs as incremental OS, the ICERs for palbociclib versus other therapies within metastatic breast cancer differ further.

Table 6 and Table 7 present these ICERs versus the 13 previously appraised therapies, and the seven recommended therapies, respectively.

Table 4. ICERs if palbociclib were compared to the previous 13 therapies NICE have fully appraised in metastatic breast cancer, with utility values adjusted so that incremental PFS accrues the same QALYs as incremental OS

Palbociclib at list price		PAS for palbociclib		PAS for palbociclib, but also the same PAS applied to those comparators offering a PAS	
PALOMA-1 OS gain	PFS:OS gain	PALOMA-1 OS gain	PFS:OS gain	PALOMA-1 OS gain	PFS:OS gain
£39,254	£35,472	[redacted]	[redacted]	[redacted]	[redacted]

Table 5. ICERs if palbociclib were compared to the previous 7 therapies NICE have recommended in metastatic breast cancer, with utility values adjusted so that incremental PFS accrues the same QALYs as incremental OS

Palbociclib at list price		PAS for palbociclib		PAS for palbociclib, but also the same PAS applied to those comparators offering a PAS	
PALOMA-1 OS gain	PFS:OS gain	PALOMA-1 OS gain	PFS:OS gain	PALOMA-1 OS gain	PFS:OS gain
£38,609	£36,440	[redacted]	[redacted]	[redacted]	[redacted]

(b) Comparison with chemotherapy

For completeness, an adjustment based on the assumption that the introduction of palbociclib may reduce the need for first-line chemotherapy (as originally noted in the ACD) is presented below.

Market research and recently consulted clinical expert opinion suggests around 50% of the first-line HER2- ER+ metastatic population receive endocrine therapy, with the other 50% receiving chemotherapy as their treatment, even though experts estimate only around 20% have life threatening disease; this implies that 30% of patients eligible for palbociclib in combination with an aromatase inhibitor currently receive chemotherapy. Clinical feedback indicates this 30% receiving chemotherapy who would be eligible for palbociclib receive predominantly capecitabine (sometimes a taxane).

On this basis, an ICER has been generated for palbociclib versus capecitabine, and proportionately blended with the current aromatase inhibitor comparison (30/50) (reflects 30% chemotherapy use, 50% aromatase inhibitor use, but excludes the 20% of patients who receive chemotherapy due to life threatening disease); the result is an estimate of cost-effectiveness versus "standard of care" as a general category. A naïve comparison was conducted to account for efficacy by taking the costs and QALYs from the cost-effectiveness evaluation of capecitabine to produce an ICER (see Appendix A), but adjusted to reflect the current cost of capecitabine. At list price, the estimated ICER for palbociclib in combination with letrozole versus capecitabine is £49,478 to £54,020 per QALY (the range reflective of palbociclib's OS), falling to [redacted] to [redacted] per QALY with the PAS.

Incremental cost-effectiveness ratios for this blended comparison reflecting standard of care are presented below, with and without the relative PFS adjustments described above (including the upper and lower bounds created by adjusting either PPS or PFS).

Table **6** presents the ICERs at list price, and Table 7 presents the ICERs with the PAS.

Table 6. Blended comparison versus letrozole and chemotherapy, with and without utility adjustments (palbociclib list price)

	No utility adjustment	**Utility adjustment so that incremental PFS and OS carry the same QALY value**	
		Utility lower bound (adjust PPS utility)	Utility upper bound (adjust PFS utility)
OS lower bound	£119,662	£100,491	£70,090
OS upper bound	£84,243	£83,933	£58,315

See Appendix B for additional detail

Table 7. Blended comparison versus letrozole and chemotherapy, with and without utility adjustments (palbociclib PAS)

	No utility adjustment	**Utility adjustment so that incremental PFS and OS carry the same QALY value**	
		Utility lower bound (adjust PPS utility)	Utility upper bound (adjust PFS utility)
OS lower bound	[redacted]	[redacted]	[redacted]
OS upper bound	[redacted]	[redacted]	[redacted]

See Appendix B for additional detail

3. Summary

Despite the unprecedented efficacy afforded by palbociclib, the base case estimate of cost-effectiveness in the initial submission far exceeded the traditional willingness-to-pay threshold. This ICER results from the interaction of particular characteristics of the drug (that it is an add-on therapy, given until progression, and compared with a low cost, generic alternative) with the current methodological framework for assessment, and in so doing, butts against a significant barrier to access.

The Pfizer ACD response focused on two elements of the current methodology which, if flexed in recognition of the barriers they create in this instance, illustrate that palbociclib can indeed be deemed a cost-effective use of NHS resources. This included the relative value of PFS, and issues relating to the comparator. The Institute has agreed to consider flexibility with respect to the methods in these areas, and the ERG has undertaken a critique of our proposals.

Following the ERG critique, we have modified our approach to PFS utility adjustment so as to now present an ICER range which incorporates the patient and clinician feedback that PFS is equally valuable to OS in this treatment space.

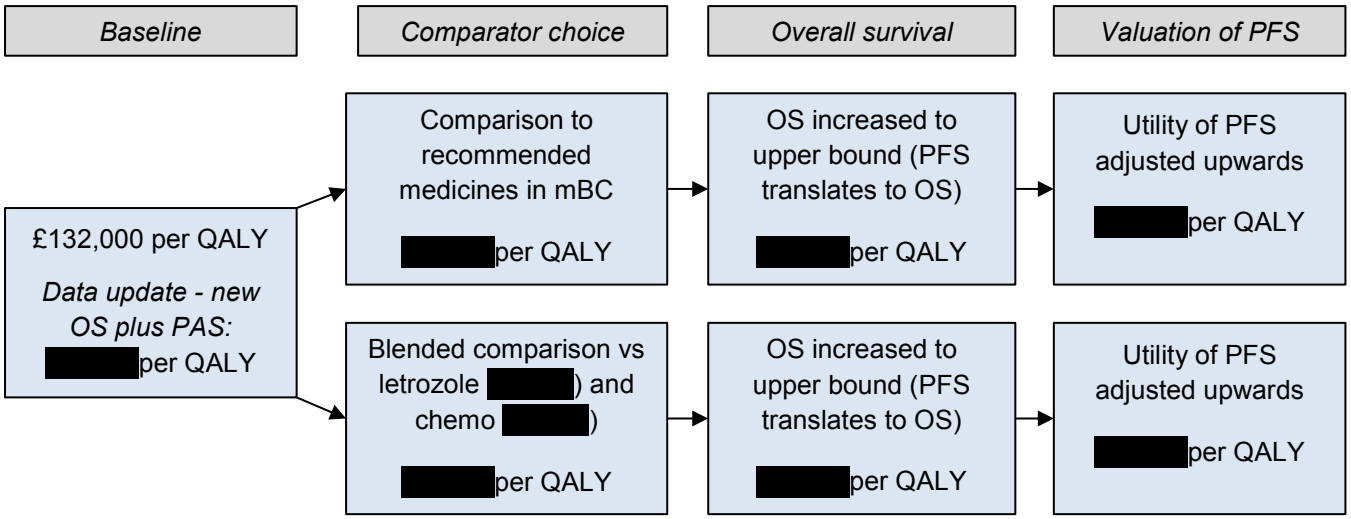
Pfizer have also explored the cost and outcomes of other breast cancer medicines approved and/or appraised by NICE, with a view to understanding the impact on the palbociclib ICER if any of these medicines had served as the comparator in place of letrozole.

Comparing the incremental benefit and incremental cost for palbociclib versus other therapies in the wider category of metastatic breast cancer produces a much lower estimate of cost-effectiveness than when palbociclib is compared to letrozole. The same can be said for comparison of palbociclib versus a weighted average of letrozole and first-line chemotherapy. The difference between the ICERs from these comparisons and the committee's preferred ICER range in the ACD illustrates to extent to which, specifically in this treatment space, the current comparator insurmountably blocks patient access to long-term innovation. Failure to recognise this will only result in an ever-increasing gap between the outcomes achieved among HER2- ER+ patients in England and Wales, and those achieved in other developed countries.

It should be noted that this barrier effects only those treatments requiring a comparison with letrozole, within this patient population. Once an innovative treatment is approved in this treatment space, it is expected to displace letrozole monotherapy, and this block to innovation is thereby removed. Future treatments will now incrementally compare to this new treatment, and traditional consideration of cost-effectiveness can resume. However, for as long as this issue fails to be addressed, no new treatments are likely to achieve cost-effectiveness, meaning no new treatment will be available to the women considered in this appraisal. In comparison to other subtypes or lines where innovative treatments are already available, this represents significant inequity with respect to access opportunity.

The changes in the ICER with respect to of issues described above are summarised below in Figure 4. Bearing in mind the Institute's responsibility to recognise the potential for long term benefits to the NHS of innovation, the approach provided here represents a simplified illustration of how methodological flexibility can address the access hurdle for patients and medicines in this treatment space. When these flexibilities are considered alongside the newly-offered Patient Access Scheme, the impact on the ICER is significant. Regardless of which flexibilities the committee deems most appropriate in this instance, palbociclib can represent a cost-effective use of NHS resources.

Figure 4. Summary of ICER decrements in Scenarios 1 and 2 (with the PAS)



Note: This diagram at list price is presented in Appendix C

4. References

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Appendix A: The cost of comparator and resulting ICER change

Table 8. Cost of previously NICE appraised therapies in metastatic breast cancer, at list price, at the time of appriasal

TA	Year	Technology	NICE decision	Total drug acquisition cost	Monthly treatment cost	Notes on total treatment cost calculations
TA250/ TA423	2016	Eribulin[16]	**Yes**	£10,243	£1,815	*£313 per 2mg vial, 1.23mg/m2 = 2.13mg per patient (BSA=1.73m2), thus 2 vials required per dose. Dose administered twice per 21 day cycle; treat till progression*
TA295/ TA421	2016	Everolimus + aromatase inhibitor[15]	**Yes**	£29,748	£2,714	*30 day 10mg tabs cited as £2,673 in most recent FAD. Plus AI at £1.65 per month; treat till progression*
TA371	2015	Trastuzumab emtansine[14]	No	£90,831	£6,264	*Total cost £90,831 cited in FAD for average duration of 14.5 months.*
TA263	2013	Bevacizumab + capecitabine[13]	No	£36,706	£3,739	*Average monthly cost cited as £3,689; treat till progression*
TA257	2012	Lapatinib + aromatase inhibitor[12]	No	£28,212	£2,222	*£28,212 for 55.2 week treatment duration*
TA257	2012	Trastuzumab + aromatase inhibitor[12]	No	£26,832	£1,789	*£26,018 for 15 month treatment duration*
TA239	2011	Fulvestrant[11]	No	£7,649	£561	*First month cost £1044.82, then subsequent months £522.41; treat till progression*
TA214	2011	Bevacizumab + taxane[10]	No	£41,523	£3,345	*Monthly price cited of £3304.76; treat till progression*
TA116	2007	Gemcitabine + paclitaxel[9]	**Yes**	£11,346	£2,741	*Total cost of gemcitabine is £2346 for 6 cycles = £391 per cycle, added to paclitaxel, £1,500 = £1891 per 21 days. Taken for 6 cycles.*
TA54	2002	Vinorelbine[8]	**Yes**	£1,550	£639	*Average cost per patient cited as £1300 to £1800. Average dose is 25 mg/m² once weekly = 43mg per week = 4.3ml. 5mg vial per week (£147 per vial)*
TA62	2003	Capecitabine combination[7]	**Yes**	£9,490	£2,019	*Cited in FAD; £1,393 per 21 days; continuously treat till progression*
TA34	2002	Trastuzumab + paclitaxel[6]	**Yes**	£25,100	£2,872	*£15,500 cited in FAD per 38 week course (paclitaxel for 6 cycles only)*
TA6/30	2001	Taxanes[5]	**Yes**	£9,000	£2,174	*Cited in FAD; £1,500 per 21 days, for 6 cycles*
Average cost across all appraised therapies				£25,248	£2,530	
Average cost across subgroup of only NICE recommended therapies				£13,782	£2,139	

In the initial response to ACD, median PFS was used to determine some treatment duration whereas now mean is used, in line with the NICE preferred model in each appraisal. Further, the previous table did not include all regimen costs in some instances (only add-on therapy cost for TA34 was included for example); all regimen costs are now included.

Table 9. Effectiveness across NICE appraised therapies in metastatic breast cancer, taken from the committee's final ICER (i.e. the preferred model)

TA	Year	Technology	NICE decision	QALYs for intervention	LYs for intervention	LYs PFS	LYs PPS	Total costs	QALYs re-calculated using same utilities*
TA250/ TA423	2016	Eribulin[16]	**Yes**	0.88	1.39	0.47	0.91	£17,520[+]	0.81
TA295/ TA421	2016	Everolimus + aromatase inhibitor[15]	**Yes**	1.59	2.67	0.91	1.76	£49,748	1.57
TA371	2015	Trastuzumab emtansine[14]	No	1.91	3.16	1.21	1.95	£111,162	1.89
TA263	2013	Bevacizumab + capecitabine[13]	No	1.34	2.23	0.81	1.42	£56,317	1.32
TA257	2012	Lapatinib + aromatase inhibitor[12]	No	2.39	3.40	1.18	2.22	£60,614	2.01
TA257	2012	Trastuzumab + aromatase inhibitor[12]	No	2.02	3.41	1.19	2.22	£54,749	2.01
TA239	2011	Fulvestrant[11]	No	1.70	3.03	1.14	1.89	£35,567	1.81
TA214	2011	Bevacizumab + taxane[10]	No	1.50	2.68	1.04	1.64	£49,403	1.61
TA116	2007	Gemcitabine + paclitaxel[17]	**Yes**	1.20	1.92	0.75	1.17	£30,313	1.15
TA54	2002	Vinorelbine[17]	**Yes**	0.36	0.58	0.48	0.09	£4,900[+]	0.41
TA62	2003	Capecitabine combination[17]	**Yes**	0.77	1.27	0.82	0.45	£19,787	0.85
TA34	2002	Trastuzumab + paclitaxel[6]	**Yes**	1.25	2.50	0.69	1.81	£28,600	1.43
TA6/30	2001	Taxanes[17]	**Yes**	1.09	1.78	0.69	1.08	£23,055	1.07
ID951	2017	Palbociclib (PALOMA-1 OS gain)	-	2.26	3.58	2.09	1.48	£87,028 *(list price)*	2.33
		Palbociclib (PFS translates to OS gain)		2.50	4.05	2.09	1.95	£92,366 *(list price)*	2.56

**The majority of appraisals Lloyd 2006 for utilities, however some did not. For example, lapatinib used an alternative source which had scored utilities over 10% higher for each state. Hence, when comparing between appraisals, a crude comparison of total QALYs is subject to bias (e.g. lapatinib scored 2.39 QALYs, yet trastuzumab in the same appraisals scored 20% lower QALYs, despite having almost identical PFS and PPS time). In order to control for the bias, the average utility was assumed (0.76 PFS and 0.50 PPS), and this was then applied to the LYs spent in each state. The last column displays the revised QALYs for each appraisal, adjusted to remove the data source bias. This column should be used for comparisons. Full workings, assumptions to bridge data gaps, and exact sources from which each piece of data is extracted are included in the accompanying Excel form.*

[+]*Estimates due to data not reported*

Table 4. ICERs for palbociclib versus NICE appraised therapies in metastatic breast cancer, taken from the committee's final ICER (i.e. the preferred model)

TA	Technology	ICERs for palbociclib (list)		ICERs for palbociclib (PAS)		ICERs for palbociclib (PAS)	
		PALOMA-1 OS gain	PFS:OS gain	PALOMA-1 OS gain	PFS:OS gain	PALOMA-1 OS gain	PFS:OS gain
TA250/TA423	Eribulin	£46,002	£42,831	[redacted]	[redacted]	[redacted]	[redacted]
TA295/TA421	Everolimus + aromatase inhibitor	£49,505	£43,069	[redacted]	[redacted]	[redacted]	[redacted]
TA371	Trastuzumab emtansine	*palbo dominates*	*palbo dominates*	[redacted]	[redacted]	[redacted]	[redacted]
TA263	Bevacizumab + capecitabine	£30,655	£29,112	[redacted]	[redacted]	[redacted]	[redacted]
TA257	Lapatinib + aromatase inhibitor	£82,853	£57,182	[redacted]	[redacted]	[redacted]	[redacted]
TA257	Trastuzumab + aromatase inhibitor	£103,790	£68,710	[redacted]	[redacted]	[redacted]	[redacted]
TA239	Fulvestrant	£99,572	£75,400	[redacted]	[redacted]	[redacted]	[redacted]
TA214	Bevacizumab + taxane	£52,641	£45,166	[redacted]	[redacted]	[redacted]	[redacted]
TA116	Gemcitabine + paclitaxel	£48,426	£44,083	[redacted]	[redacted]	[redacted]	[redacted]
TA54	Vinorelbine	£42,869	£40,639	[redacted]	[redacted]	[redacted]	[redacted]
TA62	Capecitabine combination	£45,436	£42,286	[redacted]	[redacted]	[redacted]	[redacted]
TA34	Trastuzumab + paclitaxel	£65,281	£56,355	[redacted]	[redacted]	[redacted]	[redacted]
TA6/30	Taxanes	£50,861	£46,384	[redacted]	[redacted]	[redacted]	[redacted]
Average ICER for palbociclib versus all 13 appraised therapies		**£55,222**	**£45,478**	[redacted]	[redacted]	[redacted]	[redacted]
Average ICER for palbociclib versus the subgroup of only the 7 NICE recommended therapies		**£49,768**	**£45,092**	[redacted]	[redacted]	[redacted]	[redacted]

**Where palbociclib dominates, a value of £0 is used when calculating the average ICER*

Appendix B: Comparison with chemotherapy

In order to conduct a blended comparison of cost-effectiveness versus chemotherapy and letrozole, an ICER for palbociclib versus capecitabine was naively calculated.

In Clinical Guideline 81 for breast cancer, a cost-effectiveness evaluation which replaces previous NICE guidance (including that of capecitabine) is presented for chemotherapies (Appendix 1, CG81, Table A1.14). Table 10 sets out the cost and effectiveness data for capecitabine, taken from Table 9, calculated taken from CG81.

Table 10. Costs, QALYs and LYs for capecitabine plus docetaxel, taken from CG81

QALYs for capecitabine+doc	LYs for capecitabine+doc	LYs PFS	LYs PPS	Total costs	QALYs re-calculated*
0.77	1.27	0.82	0.45	£19,787	0.85

**Re-calculated using the average utility from mBC appraisals to avoid bias, as detailed in the footnote of Table 9*

As the naïve comparison is to capecitabine monotherapy, the costs of docetaxel are removed and current cost of capecitabine used. From capecitabine's total cost of £19,787 (Table 10), the drug acquisition cost is estimated at £9,490 (Table 8). This results in the remaining £10,297 of lifetime costs attributed to non-drug acquisition costs. The current cost of capecitabine till progression (for 0.82 years = 9.9 months) is estimated at £459 (with the licensed dose of capecitabine is 2,500mg/m^2 per day).[18] This produces a current lifetime expected cost of £10,755 for capecitabine, relative to 0.77 QALYs (1.27 LYs). The resulting ICERs at list price and with the PAS are presented in Table 11 and Table 12.

Table 11: Naïve incremental cost-effectiveness results for palbociclib in combination with letrozole versus capecitabine (palbociclib at list price)

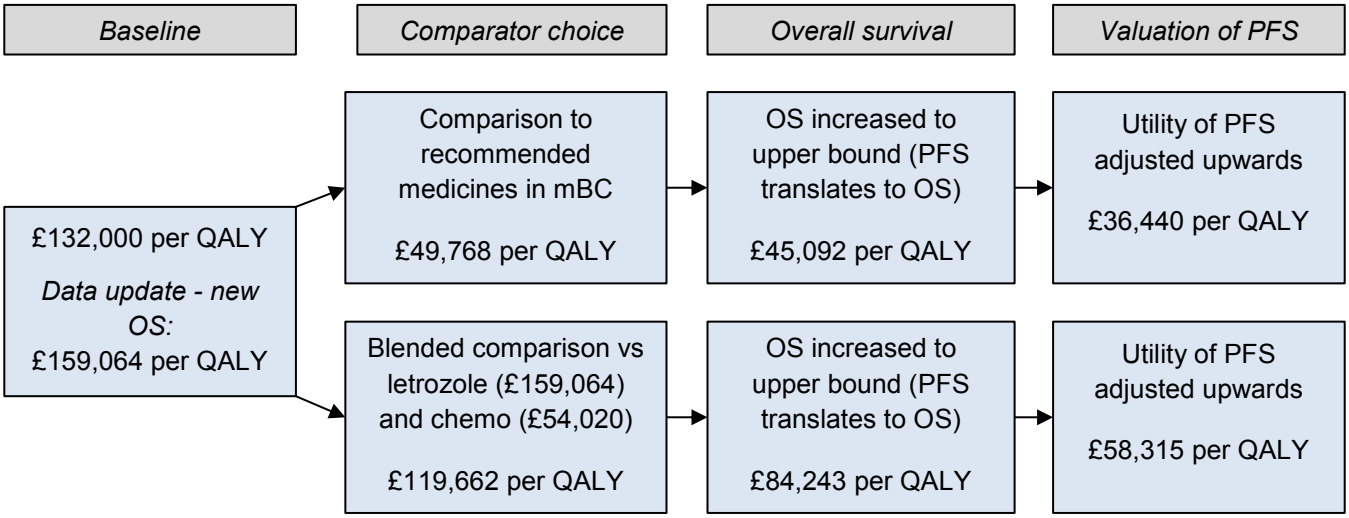
	Costs	QALYs	Incr. costs	Incr. QALYs	ICER
Capecitabine	£10,755	0.85			
Palbociclib plus letrozole *(upper bound of OS)*	£92,366	2.50	£81,611	1.65	£49,478
Palbociclib plus letrozole *(lower bound of OS)*	£87,028	2.26	£76,273	1.41	£54,020

Table 12: Naïve incremental cost-effectiveness results for palbociclib in combination with letrozole versus capecitabine (palbociclib with the PAS price)

	Costs	QALYs	Incr. costs	Incr. QALYs	ICER
Capecitabine	£10,755	0.85			
Palbociclib plus letrozole *(upper bound of OS)*	[redacted]	2.50	[redacted]	1.65	[redacted]
Palbociclib plus letrozole *(lower bound of OS)*	[redacted]	2.26	[redacted]	1.41	[redacted]

Appendix C: Summary of ICERs at list price

Figure 5. Summary of ICER decrements in Scenarios 1 and 2 (at list price)



Note, this figure mirrors Figure 4 which is with PAS

To assist decision making, below are revised ICERs as per Table 2 of the ERG Report (18 May 2017) with the [redacted]. ICERs have been produced with in the ERG's version of the company model, but with the company's extrapolation of new OS data.

Replication of Table 2 from the ERG Report, with the [redacted] PAS (smallest to largest)

Scenario			ICER with PAS
OS	**PFS utility**	**Comparator**	
PFS gain=OS gain	PFS=1, PPS=0.51	13 therapies	[redacted]
PFS gain=OS gain	PFS=1, PPS=0.51	13 therapies (with PAS)	[redacted]
IPD analysis	PFS=1, PPS=0.51	13 therapies	[redacted]
IPD analysis	PFS=1, PPS=0.51	13 therapies (with PAS)	[redacted]
PFS gain=OS gain	PFS=1, PPS=0.51	7 therapies	[redacted]
IPD analysis	PFS=1, PPS=0.51	7 therapies	[redacted]
PFS gain=OS gain	PFS=1, PPS=0.51	7 therapies (with PAS)	[redacted]
IPD analysis	PFS=1, PPS=0.51	7 therapies (with PAS)	[redacted]
PFS gain=OS gain	Base case	13 therapies	[redacted]
PFS gain=OS gain	Base case	13 therapies (with PAS)	[redacted]
PFS gain=OS gain	PFS=0.72, PPS=0.36	13 therapies	[redacted]
PFS gain=OS gain	Base case	7 therapies	[redacted]
PFS gain=OS gain	PFS=0.72, PPS=0.36	13 therapies (with PAS)	[redacted]
IPD analysis	Base case	13 therapies	[redacted]
IPD analysis	PFS=0.72, PPS=0.36	13 therapies	[redacted]
PFS gain=OS gain	Base case	7 therapies (with PAS)	[redacted]
IPD analysis	Base case	13 therapies (with PAS)	[redacted]
IPD analysis	PFS=0.72, PPS=0.36	13 therapies (with PAS)	[redacted]
IPD analysis	Base case	7 therapies	[redacted]
IPD analysis	Base case	7 therapies (with PAS)	[redacted]
PFS gain=OS gain	PFS=0.72, PPS=0.36	7 therapies	[redacted]
IPD analysis	PFS=0.72, PPS=0.36	7 therapies	[redacted]
PFS gain=OS gain	PFS=0.72, PPS=0.36	7 therapies (with PAS)	[redacted]
PFS gain=OS gain	Base case	Capecitabine	[redacted]
IPD analysis	PFS=0.72, PPS=0.36	7 therapies (with PAS)	[redacted]
IPD analysis	Base case	Capecitabine	[redacted]
PFS gain=OS gain	PFS=1, PPS=0.51	Blended LET + chemo	[redacted]
IPD analysis	PFS=1, PPS=0.51	Blended LET + chemo	[redacted]
PFS gain=OS gain	PFS=1, PPS=0.51	Base case	[redacted]
PFS gain=OS gain	PFS=0.72, PPS=0.36	Blended LET + chemo	[redacted]
PFS gain=OS gain	Base case	Blended LET + chemo	[redacted]
IPD analysis	PFS=1, PPS=0.51	Base case	[redacted]
PFS gain=OS gain	PFS=0.72, PPS=0.36	Base case	[redacted]
IPD analysis	PFS=0.72, PPS=0.36	Blended LET + chemo	[redacted]
PFS gain=OS gain	Base case	Base case	[redacted]
IPD analysis	Base case	Blended LET + chemo	[redacted]
IPD analysis	PFS=0.72, PPS=0.36	Base case	[redacted]
IPD analysis	Base case	Base case	[redacted]

Source: Updated company model, using ERG assumptions from the initial ERG Report. ICERs use company's extrapolation of updated OS.

Pfizer UK Ltd
7 August 2017

Dear Dr. Adam,

Re: Appraisal ID915 – Breast cancer (metastatic, hormone-receptor positive, HER2-negative, untreated) – palbociclib

Following the 14 July submission to NICE of new evidence regarding the above-named appraisal and the subsequent referral of the topic back to the committee, we are writing to present the detail of the revised economic case, expanded for committee consideration. As requested by the Institute, the analyses and results presented in this document are a more comprehensive version of those presented in the 14 July letter to Sir Andrew Dillon.

In that letter, the analyses incorporated [redacted] considered by the committee. As part of this more comprehensive presentation of the analyses, the [redacted]

It is crucial for the committee to understand why palbociclib warrants special consideration. Despite the HR+ HER2- subgroup being the most common type of metastatic breast cancer in the UK, NICE have never recommended a medicine targeted in this subgroup for previously untreated patients; current therapy (i.e. with an aromatase inhibitor) has been the same for nearly 20 years. Not only does palbociclib represent a long overdue option for these patients, it is a truly transformative medicine: as a first-in-class CDK 4/6 inhibitor and the first ever therapy to be associated with over two years median PFS in a phase III RCT in HR+ HER2- metastatic breast cancer[1], it was awarded a Promising Innovative Medicines designation by the MHRA for its significant advancement over existing therapies. Palbociclib increases PFS by over 10 months when combined with an aromatase inhibitor versus using an aromatase inhibitor alone, at no detriment to health-related quality of life.[1] In doing so, it delays the burden of advanced disease, helping patients stay healthy for longer. On the basis of these unprecedented benefits, buttressed by the committee's previous acknowledgement that particular benefits (such as the delay of chemotherapy) are not adequately reflected in the ICER, we firmly believe that the committee should be flexible in its application of the cost-effectiveness threshold.

On 5 July 2017, the NICE committee discussed the appraisal for ribociclib (another CDK4/6 inhibitor) in combination with an aromatase inhibitor.[2] In that meeting, the committee verbally concluded the presence of a class effect between ribociclib and palbociclib (with respect to efficacy). Despite this conclusion, the two independent economic models in the palbociclib and ribociclib appraisals estimated different incremental costs and QALYs for the interventions, when each was compared to the use of an aromatase inhibitor alone. Our 14 July letter to NICE compared the appraisals, and estimated an ICER for palbociclib based on a naïve incorporation of the incremental QALYs and (assumed) incremental costs from the ribociclib model into the palbociclib model. The more comprehensive case presented here does not rely on the acceptance of the ribociclib model, but instead independently amends the economic case for palboclicib independently (within the ERG's version of our model), and in doing so provides strong, referenced rationale for simple adjustments in assumptions.

There are three components to these adjustments: (1) a revised PAS; (2) a revised utility value for the PFS health state, better reflecting the value of PFS to patients; and (3) revision to the health state costs in later lines of subsequent therapy adjusted for underestimation with respect to both disease related and drug-related costs post-progression.

We are now confident that the revised ICER for palbociclib in combination with letrozole versus letrozole alone can be robustly considered to lie around [redacted] per QALY, which is reflective of the range in expected OS gain preferred by the committee in the ACD. The ICER for palbociclib is now significantly lower than those previously considered by the committee and should be persuasive in demonstrating that that palbociclib represents a cost-effective use of NHS resources. That the new PAS will provide a truly transformational medicine to patients [redacted] should re-assure the committee that the NHS is getting significant value for money.

Yours sincerely,

[redacted]

For and on behalf of Pfizer UK

Revised economic case for palbociclib

Pfizer acknowledges the appraisals for palbociclib and ribociclib are two independent Single Technology Appraisals (STAs) and are not comparators to one another. The application of QALYs directly from those observed in the ribociclib model[2] to the palbociclib model described in the letter to Sir Andrew Dillon on 14 July was expressly a naïve calculation. This addendum here, prepared for the committee more comprehensively, presents and justifies revised ICERs for palbociclib using the independent palbociclib model and does not directly apply QALYs from the ribociclib appraisal.

Our revised case reflects the increased PAS, together with two simple amends to the input data as described below:

1. Post-progression costs

Patients who progress incur post-progression costs. These can be categorised into two areas: those related to the disease (management, monitoring, CT scans, etc) and those related to subsequent therapy-use (drug acquisition costs, administration costs, adverse event management costs, etc). We have been extremely conservative in the inclusion of these in our original model: firstly, disease-related healthcare costs have been underestimated in comparison to what NICE has now accepted in these patients, and secondly, no later line drug therapy costs were included at all in our base case. Indeed, the ERG highlight this underestimation in their report (p107) and undertake sensitivity analyses that add-in costs to the model post-progression as a proxy for the lack of subsequent drug-related costs.

The estimate originally included in our model for post-progression health-state costs (i.e. in the second-line and beyond) averaged £573 per cycle.[a] This is significantly less than that accepted by NICE in TA421[3] (everolimus + exemestane) published during the course of the palbociclib appraisal (currently the only NICE recommended appraisal in this patient population), which is almost double our estimate, at £1,140 per cycle (when inflated to 2017).[b] For context, it is worth noting that this is the value suggested by the ERG in the ribociclib appraisal, with the committee also considering a higher estimate from the manufacturer in that appraisal.[2]

It is important to note a revised cost estimate of £1,140 per cycle, in line with what NICE has previously accepted, for disease-related costs, still excludes any subsequent drug treatment-related costs; the ERG highlighted that these should have been more thoroughly costed in our model. Table 8 of our response dated 4 May 2017 showed that the average cost of NICE approved (later-line) medicines for these patients is £2,139, per model cycle. All drug-related costs would be higher than this if administration or adverse event management costs were included. Consequently, these two estimates for disease-relate and drug-related costs suggest that the real post-progression costs should easily exceed £3,000 per cycle. However, we have considered a more conservative cost estimate in our revised base case of £2,000. In a scenario analysis we have considered an extremely conservative estimate of only £1,140 per cycle, which excludes subsequent-drug related costs.

This revision to the estimate used for post-progression costs is applied equally to both arms in the palbociclib model by an adjustment to the input estimate for health-care resource within the "progressed" state. As such, the ICER falls to between [redacted] and [redacted] per QALY (the range

[a] In the original palbociclib model, applied second-line costs are £245 per cycle, third-line are £438 per cycle, fourth-line are £639 per cycle, and best supportive care are £975 per cycle. Thus, the average for post-progression (second-line and beyond) = £573.
[b] £800 for progressed disease used in TA295/TA421 in 2012/13, inflated to £1140 by the ERG in ID1026 to reflect 2017.

reflecting the expected OS gain, as per the committee's preference at ACD). The midpoint of this range is [redacted] per QALY.

2. PFS health state utility values

During the appraisal for palboclicib we have continuously argued that the true value to patients from remaining progression-free is not fully captured in the QALY for multiple reasons, with the committee noting one of these reasons in the ACD (the benefit of delaying subsequent chemotherapy whilst progression-free). We have highlighted previously how the patients who are progression-free can continue to live a near-normal life, yet the utility assigned to PFS is 0.72 in the palbociclib model. This is therefore an underestimate of necessary utility, and further, is lower than that observed for palbociclib in the RCT.[4] Therefore, in our revised case, we have simplified our approach to estimating the additional utility benefit associated with PFS. From a review of published NICE appraisals for women with for HR+HER2- women with mBC, we note that NICE have accepted the utility for second-line disease is 0.772 with everolimus plus exemestane (TA421, 2016).[3] As first-line patients are healthier than second-line, the utility applied to palbociclib or letrozole should logically exceed 0.772, in order to be consistent with assumptions NICE have previously accepted.

However, in order to be further conservative, our revised economic case does not exceed 0.772 but rather applies this utility for first-line patients in our model, equally to both arms when progression-free. This further decreases the ICER to between [redacted] per QALY, the range reflecting the expected OS gain and denoted by a midpoint of [redacted] per QALY. Although the utility adjustment has a marginal impact when combined with the adjusted post-progression costs, it is a more appropriate value than that considered before.

The revised base case ICER with the two simple adjustments to input data in our model, as described above, is [redacted] per QALY with the increased PAS. As explained, both of these adjustments are considered conservative and further, we believe that these ICERs still fail to capture fully the true value of PFS and contain no flexibility around issues with innovation in the choice of comparator, as raised in previous documentation. Together, all these points suggest the revised base case is a very conservative estimate of true cost-effectiveness. The revised case with scenario analyses is presented in Table 1 (see Appendix for incremental costs and QALYs). These are significantly lower than those previously considered by the committee, and should be persuasive in demonstrating that that palbociclib represents a cost-effective use of NHS resources.

Table 1. ICERs for palbociclib plus an aromatase inhibitor vs. an aromatase inhibitor at [redacted] PAS in the revised case, considering options for PFS utility and post-progression costs

		PFS utility	
		0.72 current model	**0.77** previously accepted estimate
Post-progression costs per cycle	**£1,140** disease related costs only	[redacted]	[redacted]
	£2,000 also includes subsequent therapy costs	[redacted]	[redacted]

Each ICER is the midpoint of the upper and lower bounds of expected gain in OS. Those bounds are included in the Appendix, along with incremental costs and QALYs for each ICER.

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Appendix: Incremental costs and incremental QALYs in the revised ICER calculations

Tables 2 and 3 present incremental costs and QALYs, calculated through the palbociclib model when adjustments to utility and to post-progression costs are made. Table 2 reflects the lower bound in expected OS gain and Table 3 the upper bound.

Table 2. Incremental costs and QALYs at the lower bound of the OS range (*i.e.* using PALOMA-1 observed OS)

Lower OS bound *(3m gain)*	PFS utility = 0.72			PFS utility = 0.77		
	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Post-progression cost = £1,140	[redacted]	0.36	[redacted]	[redacted]	0.42	[redacted]
Post-progression cost = £2,000	[redacted]	0.36	[redacted]	[redacted]	0.42	[redacted]

Table 3. Incremental costs and QALYs at the upper bound of the OS range (*i.e.* assuming gains in PFS translate to gains in OS)

Upper OS bound *(10m gain)*	PFS utility = 0.72			PFS utility = 0.77		
	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Post-progression cost = £1,140	[redacted]	0.60	[redacted]	[redacted]	0.65	[redacted]
Post-progression cost = £2,000	[redacted]	0.60	[redacted]	[redacted]	0.65	[redacted]

Pfizer UK Ltd
28 September 2017

Dear Dr. Adam,

Re: Appraisal ID915 – Breast cancer (metastatic, hormone-receptor positive, HER2-negative, untreated) – palbociclib

On 26 July 2017, NICE made public a temporary suspension of the appraisal to consider a revised case from Pfizer which included revisions to the economics and a change to the Patient Access Scheme. Following conversations with NICE, a more comprehensive addendum to our revised case was submitted on 7 August. After our case was submitted, it was then confirmed that Appraisal Committee A would meet to discuss the appraisal of ribociclib on 5 September prior to the meeting for palbociclib, scheduled for 4 October. During the public meeting for ribociclib (ID1026), the Appraisal Committee discussed their preference for the two assumptions revised in our latest economic case for palbociclib (healthcare costs related to patients post-progression, and the utility of first-line patients pre-progression). A unique situation occurred in which, between us submitting our revised case for palbociclib (7 August) and the meeting to discuss our case (4 October), the Appraisal Committee have discussed their preferences for our two assumptions within a separate appraisal (ID1026, 5 September). As the Appraisal Committee's decisions on these assumptions are applicable to our appraisal, such discussions and preferences are considered as new evidence in the palbociclib appraisal.

We present revised ICERs in Table 1 below with post-progression cost estimates of £1,140 and £2,000 as per our most recent case (7 August). We note the similarities in these estimates with those discussed in the related ribociclib appraisal (ID1026) on 5 September. We also present the estimate from the ERG Report (13 September) which we corrected in the factual accuracy check (20 September) of £1,395. As was set out in our 7 August addendum, we believe £1,140 per cycle represents the most conservative estimate reflecting post-progression costs.

The revised ICERs continue to consider the utility estimates of 0.72 and 0.77 for PFS from our 7 August addendum. Whilst we still believe a value of at least 0.77 is most appropriate for decision making given NICE have already recommended a medicine last December for this subtype with this value applied to the second-line setting (TA421), however we have included the economic impact of applying the midpoint of the range (0.75) for consideration.

[redacted] Pfizer's revised basecase is now [redacted] whilst the most conservative estimate of the assumptions produces an ICER of [redacted] As such, even when considering the most conservative estimates for post-progression costs, and/or pre-progression utility, and/or overall survival, all scenarios are considered cost-effective [redacted], particularly when noting that benefits such as the value of delaying subsequent chemotherapy are not captured in the QALY.

Yours sincerely,

[redacted]
For and on behalf of Pfizer UK

Results

Table 1 displays the ICERs reflective of the midpoint of the expected OS range (the upper and lower bounds as preferred by the Committee in the ACD). These 'midpoint' ICERs are calculated by taking the midpoint of the incremental costs and incremental QALYs from the lower/upper bounds of OS, and estimating an ICER from these.

Table 1. ICERs for palbociclib plus letrozole vs. letrozole at [redacted]

		PFS utility		
		0.72 current model	**0.75*** midpoint of the two estimates	**0.77** previously accepted by NICE
Post-progression costs per 4-week cycle	**£1,140** disease related costs only	[redacted]	[redacted]	[redacted]
	£1,395 ERG estimate of disease + therapy costs, corrected by company in FA check	[redacted]	[redacted]	[redacted]
	£2,000 disease related costs + subsequent therapy costs	[redacted]	[redacted]	[redacted]

**The estimate used in the model is 0.747, the midpoint of 0.772 and 0.721, but rounded to 2 decimal places (0.75) for the table*

The ICERs relating specifically to each bound are included in Table 2, along with incremental costs and QALYs for each ICER. **The ICERs in Table 1 are derived from estimates in Table 2**. Besides the assumptions in question (post-progression costs, PFS utility, OS), the ERG's version of the palbociclib model has been used in all analyses.

Table 2. Detailed overview of incremental costs and QALYs at the upper and lower bound of the OS range, [redacted]

	PFS utility = 0.72			PFS utility = 0.75			PFS utility = 0.77		
	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Lower bound of expected OS gain (PALOMA-1 observed, 3 month median OS gain)									
Post-progression cost = £1,140	[redacted]								
Post-progression cost = £1,395	[redacted]								
Post-progression cost = £2,000	[redacted]								
Upper bound of expected OS gain (direct extrapolation from PFS to OS, 10 month median OS gain)									
Post-progression cost = £1,140	[redacted]								
Post-progression cost = £1,395	[redacted]								
Post-progression cost = £2,000	[redacted]								

Liv Gualda
Project Manager
NICE
10 Spring Gardens
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SW1A 2BU

24 February 2017

Dear Ms Gualda,

Re: Response to Appraisal Consultation Document on palbociclib with an aromatose inhibitor for previously untreated metastatic hormone receptor-positive, HER2 negative breast cancer

Breast Cancer Now welcomes the opportunity to respond to the Appraisal Consultation Document (ACD) for palbociclib with an aromatose inhibitor for previously untreated metastatic hormone receptor-positive, HER2 negative breast cancer, published by NICE on 3 February 2017.

The Committee has provisionally rejected palbociclib with an aromatose inhibitor as it does not consider it to be a cost-effective use of NHS resources. The Committee notes in the ACD that the Incremental Cost Effectiveness Ratio's (ICERs) presented are considerably above the range normally considered by NICE.

Breast Cancer Now is calling on Pfizer to reconsider its decision not to offer any form of discount on palbociclib. However, there are a number of other factors contributing to the high ICERs presented that highlight some serious issues with the appraisal system. We believe these mean that the Committee's recommendation is not sound, nor a suitable basis for guidance to the NHS. These issues – which are set out in more detail below, in our answers to the question posed by NICE in the ACD – are that:

- palbociclib is enabling patients to live so much longer without their condition progressing that little overall survival data is currently available. Perversely, this counts against it as the system gives less weight to progression free survival data than overall survival data;
- although clinically-effective, a new, branded, medicine like palbociclib can never hope to be considered cost-effective when compared to a generic treatment like letrozole; and
- although metastatic breast cancer is an incurable condition, palbociclib has not been considered under the 'end of life' criteria.

Has all of the relevant evidence been taken into account?

Breast Cancer Now has received several statements from women who have either been treated with palbociclib, or who have the type of metastatic breast cancer for which palbociclib would be an effective treatment. These statements are at Annex A. They highlight in particular the value that patients attach to the delay in progression of their disease, and ability to carry on a relatively normal life, that palbociclib provides. We would like the Committee to take account of these statements in making its final decision.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Breast Cancer Now believes the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence under the current appraisal system. However we also believe that there are serious issues with the system that mean this recommendation is not sound, nor a suitable basis for guidance to the NHS.

Are the recommendations sound and a suitable basis for guidance to the NHS?

A number of factors have contributed to this recommendation that highlight some serious issues with the current appraisal system. Breast Cancer Now believes this means the recommendation is not sound, nor a suitable basis for guidance to the NHS.

Firstly, patients are much living longer on palbociclib with letrozole (the aromatose inhibitor used in the clinical trials) without their condition progressing than on letrozole alone – a median of an additional 10 months. We know that patients value delayed progression: it means more quality time with loved ones during which they may be able to lead a more or less normal daily life, as well as a delay to starting second line treatment of chemotherapy, which is traditionally associated with more severe side effects and a poorer quality of life. However, because patients are living longer without their condition progressing, very little data is currently available on how long palbociclib extends survival overall. The appraisal system gives less weight to progression free survival than overall survival, meaning treatments without overall survival data do not do as well against the cost-effectiveness threshold.

Furthermore, the current treatment option for patients that would be eligible for palbociclib (letrozole) is available generically and is therefore much cheaper. It is virtually impossible for new medicines such as palbociclib to be considered cost-effective when they are compared to generic treatments. Based on the cost of palbociclib included in the ACD, treatment with palbociclib and letrozole will cost in the region of £29,533 for the median 10 months of progression free survival shown in the clinical trials. Treatment with letrozole alone for this period will cost in the region of £33.[i]

breast cancer now

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Finally, despite the fact that metastatic breast cancer is an incurable condition, palbociclib has not been considered under the 'end of life criteria' which allow NICE to use a higher cost-effectiveness threshold.

Palbociclib is an important new treatment option for patients with hormone positive, HER2 negative metastatic breast cancer, substantially improving upon current treatment options. It is available in several other countries, including Germany and the USA. However, the issues outlined above suggest that palbociclib is unlikely to be approved for routine use in the NHS in England. Unless patients are able to access clinically effective drugs such as palbociclib we will never achieve the ambition set out in the Cancer Strategy to close the gap in cancer outcomes with other countries in Europe and further afield.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

We are not aware of any aspects that require particular consideration to avoid unlawful discrimination.

Yours sincerely.

[redacted]
Breast Cancer Now

[i] The recommended dose of palbociclib is 125mg once daily for 21 consecutive days followed by 7 days off treatment to make up a complete cycle of 28 days. The cost of a 21 capsule pack of 125mg capsules of palbociclib is £2,950. The British National Formulary lists the recommended dose of letrozole as 2.5mg daily, and the cost of a 28 tab pack of 2.5mg of generic letrozole as £3.32.

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Annex A

Hi, a fellow forum member on breast cancer care said that on a secondary Facebook page (I do not belong to this) you were asking for experiences of Palbociclib. I am a long time patient of the Marsden. I think my history might be relevant so briefly:

Diagnosed primary x3 in R breast 1995, mx, CMF chemo and radio. No lymph node involvement, ER+, HER-. 5 years tamoxifen.
Local recurrence in R axilla 2009, surgery x2, EC chemo, radio, Letrozole.
Further recurrence same area 2011, further surgery x2, Exemestane.
Further recurrence same area 2013, CT scan showed cancer in R hilar lymph node.
Capecitabine for approx 2.5 years
Faslodex 5 months

In 1995 histology showed no BRCA1 or 2 but I have a strong family history, maternal grandmother and mother both had BC. Recently told have some type of mutation, waiting for more information. I was put forward for the PIPA trial which combines Palbociclib with another kinase inhibitor, Taselisib and started this in May 2016. I joined the dose escalation phase and take 125mg for 21 days then 7 days off, and take 2 mg Taselisib continuously. I have now been on the trial for 9 months and scans have shown 30% reduction and stable. The tumour in my axilla no longer shows on scans. I am due a 3 month scan next week.

The side effects I have experienced are some diarrhoea, nausea and mouth ulcers, all manageable with medication and have improved with time. I had a throat infection and voice loss in the first cycle, took antibiotics, never recurred. I have always had good safety bloods and have never delayed a cycle or had a dose reduction. Other side effects have been tiredness, hair/eyelash loss (not complete but noticeable) I don't feel that I can comment on the preliminary PIPA trial findings but I have found Palbociclib to be a lifeline when my options are running out and I'm very grateful to Pfizer (and Roche) for my opportunity to extend PF survival. I am fit and well, still riding my horses and enjoying life.

I believe that this drug is being considered as a first line treatment combined with a hormonal drug. I can only talk about myself. I have been heavily pretreated and am close to running out of further options for secondary breast cancer. Many of my friends do not believe that I have cancer at all! It has been very well controlled and I look and feel almost completely normal. I have enough energy to look after and ride 2 horses, and also have 2 dogs. I socialise and am involved in the lives of my 2 sons and 2 stepchildren. I travel abroad when I am able and I'm happily married.

The part that is really really hard is in your head..."how much more time do I have? Will I be around for my sons weddings?...grandchildren? What will the next scan show?" Yes, I have been around for longer than I imagined... But every month counts, I never thought that life could be so very precious. I thank my lucky stars every day to be on Palbociclib. It has had such good results that it has been fast-tracked for use in U.S. Canada,Europe. Many patients in U.S. have been on it for nearly 16 months or more. So many drugs work for such a short time, if at all, this one has to be considered. Lastly my son is a cancer researcher in London. It is so disheartening when their hard work and dedication doesn't translate into prolonging life. Cancer research is at a very exciting point. Is it right for new drugs to only be available for private patients in UK?

This patient wishes to remain anonymous

I have secondary breast cancer, ER+/HER-, recently put onto Letrozole

Having lived with Advanced Breast Cancer for over 4 years it's so important to know that new drugs like palbociclib will be there in the future, so when other drugs stop working there's still hope. Having lost my own mother to breast cancer when I was 12 years old I was determined to see my son finish school and support him through exams and the trials of teenage life. He'll be off to university this year and my new goal is to see him graduate, maybe even see him get his first job, or get married. This drug has the potential to help me do this, so knowing there's a drug with the potential to extend my life is really exciting and could make a huge difference – to deny it to so many women like me would seem cruel.

[redacted]

My name is and I am 67 years old.

In January 2014, I was diagnosed with breast cancer. After having a full mastectomy in February, I was told that the cancer had spread to most of my near-by lymph nodes. Further investigations and tests in the following months revealed that the cancer had actually spread to my bones. So in April 2014, I was diagnosed with secondary breast cancer. I was transferred to The Christie Hospital Manchester where I was offered to go on a clinical trial called PALOMA-2.

I started taking the drug palbociclob in May 2014 together with letrozole and a calcium supplement. I take 125mg palbociclib for 3 weeks then 1 week off, 2.5mg Letrozole with calcium every day.

There are a few side effects, fatigue being the worst, but that is not all the time so when I am tired, I rest, and when I'm not, I am very active. My hair has gone a lot thinner, I get mouth ulcers quite often but mouth wash usually sorts these out in a couple of days. I am also very cautious about infections as my white blood cells can be low at times. I am monitored every 4 weeks, have a CT scan every 3 months and bone scan every 6 months.

I have been on palbociclib for 32 months and the cancer has not spread at all since I started on the drug. When I was first diagnosed with secondary breast cancer, I was told that I only had 12-18 months life expectancy left and now I'm looking at 3-5 years.

After my diagnosis with secondary breast cancer, I wanted to go back to work just to get some normality back into my life. I continued to work as a driving instructor until December 2015. I was well enough to continue working, but being 66 at the time, I felt it was the right time to retire. I have an active life and swim twice a week and love to go walking. I am able to look after my grandchildren and great-grandchildren, picking them up from school on most days.

It's not just a matter of surviving on this drug but enjoying my life. The side effects are all manageable and the fact that I was able to work and am still able to lead an active life and enjoy family life.

I believe I would not be here now if I had not been offered this trial and would love other women to have the same opportunity as me.

Hi,

I am a 35 year old lady with ER/PR+ MBC and I wanted to email you to express my interest in the campaign to make Palbociclib available on the NHS.

I am currently on weekly Paclitaxel, following progression on Capecitabine. Ibrance (Palbociclib) is a drug that I am aware is used widely in the USA for hormonally positive breast cancers but I do not know of anyone who has managed to access it here in the UK. This is a great shame as it is one of only two targeted therapies that I am aware of that are appropriate for HER2 - breast cancer treatment.

I am a healthy young woman, with a really positive outlook. I have spent most of my thirties fighting breast cancer so I don't have children of my own but I am an aunty, and a god-mother to a number of small people who are very important to me. I am active within my community and I strive to continue to be a productive member of society. In order for me to continue to live my best life there need to be more options on the table for my treatment.

Thanks,

[redacted]

I am a 42 year old woman who has secondary or metastatic breast cancer. The tumour type is hormone positive and HER2 negative.

Palbociclib is a drug which would suit my tumour type.

I am a wife, a daughter and a mother of 3 girls age 68 and 10.

I was diagnosed with the disease in February 2012 (almost exactly 5 yrs ago) aged 37 after suffering from back pain. At the time I was working as a GP in Banbury and it was a junior doctor doing some training with me who pointed out to me that I should get my back pain investigated. My back pain was not preceded by a breast lump. I was and am too busy to be ill.

At the time of my diagnosis my 3 children were all under the age of 5. Every day I have had with my family since then has been important to us and so valuable for the children.

The secondary cancer is only in my bones so far and despite treatment and some pain I have a remarkably good quality of life at the moment. I am on a tablet form of chemotherapy and drugs to help alleviate the side effects from this. If you didn't know my story, no one would be able to tell that there is anything wrong with me.

I am trying to write a statement to explain what the drug palbociclib could or does mean to me.

Quite simply, I want to live. I want to live good years and be with my children and family for as long as possible. I have been closely following the early trials on palbociclib and hoping that it would indeed be a useful drug to extend my life.

It appears that it is the most promising new drug in a long time for hormone receptor positive breast cancer. It is quoted as giving 10 months extra progression free survival but has been deemed too expensive by NICE.

The drug I am currently in is quoted as giving an average of 9 months progression free survival. I have been on it for 21 months. These months have not been months with me lying in bed, groaning with pain and unable to live a good life. I am able to look after my children before and after school and be involved in various types of voluntary work. I have to rest at certain times of my chemo cycle (which has sadly meant my retirement from General Practice). I have outpatient appointments as hospital every couple of months, blood tests with my local surgery every few weeks but apart from that and the occasional set back, I am able to stay away from healthcare.
I haven't had a night in hospital in 5 yrs and even then, it was only 1 night.

When my current drug stops working as it inevitably will, palbociclib is a drug that could enable me to have more time able to continue to do the same. It has very few side effects.

If I were to have to be on a more traditional chemotherapy, I would be spending on average, many more hours in a hospital bed or chemo unit with all the additional costs and complications the treatment entails for the NHS and society. Sure, I would cost the NHS less if I were dead but what extra costs to society for the fact that I am not here supporting my children and enabling my husband to work, pay taxes etc etc? It frustrates me intensely that NICE cost decisions are made solely on the cost of a single drug and don't at all consider the bigger picture of treatment needs and costs for a group of patients.

I am very aware that we have a finite amount of money in the NHS and I hate to have to try and argue that my life is 'more valid', 'more important' etc than anyone else's.

It is however heartbreaking to know that there is a treatment which could well be extremely effective to prolong my life but that I cannot access it due to cost.

Is there no compromise that could be reached between the drug company and the NHS?

Thank you for reading,

I have stage 4 breast cancer that appears to be resistant against any form of hormonal treatment. I think Ibrance may just help a hormone therapy to work for me instead of going down the root of chemo and hopefully allow me to keep working as at the moment if I go down the chemo root I may have to take early retirement which I certainly didn't want to do as my job keeps me focused.

I hope my story might help other women, even though I had to stop taking Palbociclib after a year. However, the effect it had on me during that year was nothing short of miraculous.

By the time I was diagnosed with metastatic breast cancer, I had lost 30 lbs, was extremely short of breath, wheezing, extremely weak, my bones ached & I had to force myself to eat. Within 10 days after starting palbociclib , I started feeling SO much better, regaining my strength & appetite & generally feeling stronger. Over the next few months, my tumor markers went from the 400s to 100s, and I improved to where I was almost back to normal. I would also add that the only side effects I experienced were slight thinning of my hair, & weakened or softer fingernails.

But, cancer being the sneaky devil that it is, showed up on a CT scan as 2 small spots in my liver, so my oncologist immediately took me off the palbociclib & started me on Xeloda, which I am now still taking.

So the palbociclib worked wonderfully for a year & then apparently stopped working. I don't know if this story helps or not, but let me know if I can be of further help. I prefer not to have media contact, but you may use my name. By the way, I am 73, & my initial diagnosis of breast cancer was 18 years ago.

Sincerely,

I was diagnosed with secondary breast cancer in March 2007 and in June 2014 took part in the clinical trial for Palbociclib as a patient at the Royal Marsden Hospital. This was the Paloma-3 trial. It was obvious within days that I was not on the placebo due to a drop in my white blood cells but getting the drug itself. Weeks later I was able to cover the Commonwealth Games in Glasgow as a sports journalist for a national newspaper, leading a team of four journalists there, working long hours and flying back to London just for one day for treatment - arriving back in Glagow in time for the Opening Ceremony. I was on the drug for almost two years until May 2016. Throughout that period I worked full-time with my job taking me throughout Europe and to China and eventually Rio for the Olympics last summer where I was away from home for a month. I contributed to the country paying higher tax at 40 per cent. During that period I also travelled extensively on holidays alone and with my family to Cuba, Qatar, Cairo and again throughout Europe.

The side-effects were minimal and manageable despite the fact I insisted on having the maximum dosage possible each month.

During that period my 86 year-old mother was diagnosed with vascular dementia. She lives 200 miles away but I sorted out her private care as well as driving to see her and supervise carers every 7-10 days. She is not eligible for state care and without me and family earnings would eventually become a burden on the state. Or would have no one to sort out her affairs as I have no brothers or sisters and her only sister also has dementia. When her condition worsened last April I moved her to a private care home three miles from my home. Again I manage all this.

My husband also has secondary prostate cancer and again I help him. Without the extra two year benefit of being on Palbociclib I doubt whether this would have all been possible and the cost to the state would have been extensive as well as distressing for my mother.

Since October 2016 I have been on an older drug which is funded by NICE. Although it is currently working it has already caused major side-effects. In December - a week before Christmas - I was so ill had to go by ambulance to the local A&E department and spend the day there being treated. The following night I had to make another visit to the A&E department for an injection and then spend another day at the Marsden to ascertain the problem - which turned out to be inflammation of the lung as a result of the drug. I have since had to reduce the dosage, effectively reducing my survival chances in terms of fighting the cancer. The cost of this drug is not much lower than Palbociclib yet the side-effects on this one occasion alone meant hundreds of pounds it not thousands spent on hospital scans, treatment and an ambulance. The dosage will probably be increased next month and I am warned that the side-effect could happen again - so more cost to the NHS. My ability to work is also being affected in terms of fatigue and coping with travel and daily life although I am again still working full-time.

I believe that Palcociclib is more effective in terms of survival, side-effects and also more cost-effective than older drugs and cannot be compared with them. I also believe other women should be able to have it on the NHS.

In terms of overall survival rates as I understood it the third trial was halted because the results were so good, hence affecting overall survival data. Survival data is also poor and sketchy in the Uk for secondary breast cancer. I have lived with advanced cancer for a decade now - a fifth of that due to Palbociclib.

Best

UKBCG
UK Breast Cancer Group

UK Breast Cancer Group (UKBCG) Response to NICE ACD:

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

We, as the UK Breast Cancer Group (UKBCG), representing the vast majority of breast oncologists in the UK, wish to express our concerns with this negative appraisal and would like to group these into three main areas:

1. Effectiveness of palbociclib in combination with an aromatase inhibitor

Not since the introduction of hormone therapy with tamoxifen, over 40 years ago, has there been a trial that has shown an incremental benefit for this most common type of breast cancer of the size that is seen in the Paloma 1 and 2 trials. Investigator and independently assessed progression-free survival was nearly doubled with a 10 month improvement and there was a consistent improvement in the hazard ratios for progression in both trials. This level of benefit is unprecedented for this group of patients with estrogen receptor positive HER2-negative breast cancer.

The improvement in response rates of the combination compared with aromatase inhibition alone was associated with a reduction in the symptomatic burden faced by these patients and is comparable, or better, than would be expected for chemotherapy.

The toxicity of palbociclib is noted and is mainly neutropenia, but unlike the neutropenia seen with chemotherapy, was of little clinical relevance with a neutropenic sepsis rate of 1%. Other side effects were generally very mild in the trials and the clinical experience with this agent is consistent with the trial data.

Clinical experience with palbociclib suggests that patients lead a near normal life whilst on this drug combination. The detriment in quality of life that would be associated with chemotherapy and/or progressive cancer is given very little score in the standard models, but should in our opinion count for more.

The standard monitoring in the trials, where safety and recording of toxicity accurately are critical, is more intensive than would occur in routine practice with this intervention. A monthly appointment for three months would be needed, with assessment of response at 3 months. Appointments would then be 3 monthly. Patients on aromatase inhibition alone, as shown by the trial data, would progress on average twice as soon. These patients with hormone-receptor positive cancers would then usually go on to receive chemotherapy, such as weekly paclitaxel or capecitabine, both of which would require much more frequent blood tests and hospital visits for treatment and monitoring, and cause increased toxicity. There is no doubt a hormonal combination would be preferable on all accounts, by delaying the introduction of chemotherapy and maintaining quality of life with minimal meaningful toxicity.

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UKBCG
UK Breast Cancer Group

2. Cost-effectiveness

We note the methods used and the various models used to calculate cost-effectiveness. The improvements in PFS are robust, but overall survival data is immature and difficult to account for in the model used. A 10 month improvement in PFS only leads to a 0.17 QALYs. The cost of the drug at full list price would then amount to around £35,000 per year. The cost of being on chemotherapy, the next treatment the patients would be on in the same time period that would still be on letrozole/palbociclib would be similar, if all costs are considered. A QALY of between £132,872-£213,206 for a drug that would cost £35,000 a year at full list price seems bizarre and perversely would mean that even if the drug was free, it would not seem to be cost-effective. A comparison between chemotherapy costs for the difference in PFS after progression on letrozole alone would need to be done for a fair comparison of real NHS costs.

3. Other effects of a negative appraisal

The UK cancer survival statistics are often shown to be behind other comparable countries. This negative appraisal would serve to widen this gap further, to the detriment of patients with metastatic breast cancer. Other drugs in this setting that have not been approved will also widen this gap. As stated in the Department of health's NHS Outcomes Framework, one of the stated goals is to reduce morbidity and mortality of major illnesses, specifically citing breast cancer.

The UK is the highest recruiter in the world to cancer clinical trials on the basis of numbers of patients seen. We should be proud of this and our patients and the wider economy benefits hugely from UK engagement in clinical research. The life sciences are the third biggest contributor to the economy. If the standard of care in the UK falls behind what is internationally recognised, we will be unable to take part in further innovative studies that often offer free drugs, pay the NHS for services used and stimulate academic innovation. The UK economy will suffer as a consequence.

We would therefore ask that the committee re-think the negative appraisal to the benefit of all concerned, especially those unfortunate enough to have metastatic breast cancer. I am sure there is room to re-negotiate with all the relevant stakeholders

On behalf of the UKBCG

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NHS England submission for the appraisals of palbociclib and ribociclib in the treatment of ER positive her-2 negative locally advanced or metastatic breast cancer

[redacted]

NHS England wishes to make the following observations on the appraisals of palbociclib and ribociclib.

Marketing authorisations and patients on which the evidence is based

Palbociclib is indicated for the treatment of hormone receptor positive her-2 negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor in patients who are or have been rendered postmenopausal. The PALOMA-2 phase III trial combined palbociclib with letrozole and allowed entry to patients with an ECOG performance score of 0, 1 or 2. All patients were previously **untreated** with systemic **endocrine-based** anti-cancer therapy for their **advanced** ER pos her-2 neg disease. Patients had to have completed any prior adjuvant therapy with anastrazole or letrozole with a disease-free interval of at least 12 months achieved off treatment before relapse. Less than 2% of patients in PALOMA-2 were of performance status 2.

Ribociclib is indicated for the treatment of hormone receptor positive her-2 negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor as **initial endocrine based therapy**. The MONALEESA-2 phase III trial combined ribociclib with letrozole and allowed entry to patients with an ECOG performance score of 0 or 1. All patients were previously **untreated** with systemic **endocrine-based** anti-cancer therapy for their **advanced** ER pos her-2 neg disease. Patients had to have completed any prior adjuvant therapy with anastrazole or letrozole with a disease-free interval of at least 12 months achieved off treatment before relapse.

Although the marketing authorisation is worded as being wider for palbociclib, NHS England regards the two drugs to have identical places in the advanced breast cancer treatment pathway: for initial endocrine-based systemic therapy of ER pos her-2 neg locally advanced or metastatic breast cancer in patients who have either de novo presentations of such disease or have relapsed disease and completed any previous adjuvant therapy with anastrazole/letrozole such that a disease-free interval without such treatment of at least 12 months has been achieved.

Extrapolation of progression-free survival (PFS) and time to treatment discontinuation (TTD)

NHS England is fully aware of the unusual, significant and consistent difference observed between TTD and PFS in these trials. NHS England notes that treatment with letrozole was continued after palbociclib/ribociclib had been discontinued without there being evidence of disease progression and examination of the KM plots for both drugs indicates that there is about a 6 month difference between TTD for these two agents and PFS. This will have been partly due to the additional toxicity of the drugs, partly due to trial protocol and partly due to clinician unfamiliarity with the 2 drugs and the substantial neutropenia they cause.

NHS England does not regard there being a good reason (on the basis of present knowledge) for the rate of patients developing progressive disease to increase with time whilst on palbociclib/ribociclib and hence exponential extrapolation of PFS for both drugs seems reasonable. However, whilst the rate of developing progressive disease whilst on palbociclib/ribociclib plus anastrazole/letrozole is determined by the rate at which tumours become resistance to these combinations, the rate of discontinuing palbociclib is not only determined by the rate of developing resistance to such endocrine-based therapy but also other factors: toxicities, the management of such toxicities, clinician familiarity with the management of such toxicities and treatment protocols. There is therefore some justification for considering that the rate of TTD would increase with time and thus preferring the Weibull extrapolation. [redacted]

Drug costs of subsequent 2nd and 3rd line therapies

As has been discussed above, the appropriate group of patients to be treated with an aromatase inhibitor (anastrazole or letrozole) and either palbociclib or ribociclib is those with incurable locally advanced or metastatic ER positive her-2 negative breast cancer who are previously untreated with endocrine-based therapy for their locally advanced or metastatic disease. Patients must be postmenopausal either by having undergone the menopause or by medical imposition of the menopause (usually with LHRH agonists).

When treating women with ER positive advanced breast cancer, oncologists wish to maximise the opportunities of benefitting from hormone therapies before then needing to switch to cytotoxic chemotherapy because of either the development of hormone refractoriness or the development of visceral spread which requires a rapid response to treatment. Oncologists therefore wish to work endocrine-based treatment as hard as

possible before resorting to chemotherapy and there are several lines of hormone treatment for ER pos patients. In determining the likely treatments received by patients failing palbocicblb/ribociclib with nastrazole/letrozole, it must be remembered that patients starting and continuing on palbociclib/ribociclib will be fit (performance status 0 or 1) and will also be closely monitored on therapy. Thus there will be few patients not proceeding to 2nd line therapies. It is however reasonable to assume that later lines of therapy (3rd line and beyond) are associated with significant numbers of patients not proceeding to a further line of treatment and figures of a drop off rate of 20-25% are reasonable.

The response rate data for palbociclib and ribociclib are strikingly similar. The overall response rates for both drugs was 42%; the overall response rate for patients with measurable disease was 55%; and the clinical benefit response rate was 85-90% (this means the percentage of patients having a complete response, a partial response and those that achieved stable disease, the latter having to last at least 24 weeks). Thus the overwhelming majority of patients benefitted from hormone treatment plus palbociclib/ribociclib and thus most of these would proceed to 2nd line hormone therapy and many would still receive hormone treatment as 3rd line treatment. However, as treatment lines proceed for this ER pos group, there is increasing use of chemotherapy.

NHS England in consultation with its experts in the Chemotherapy Clinical Reference Group has estimated the proportions of patients proceeding to various therapies in the 2nd and 3rd line settings. Such estimations are complex as some patients present de novo with locally advanced/metastatic ER pos breast cancer, some will have been treated with previous adjuvant aromatase inhibitors, some with previous adjuvant tamoxifen and many will have had adjuvant chemotherapy with anthracyclines only and some with both anthracyclines and taxanes. In addition, the time since completion of adjuvant chemotherapy and adjuvant hormone therapy are additional considerations in determining the likely next treatment. The routes are therefore very diverse by which patients arrive at the point in the treatment pathway at which palbociclib/ribociclib are indicated.

To further complicate the situation, the commissioning and thus use of fulvestrant is variable across the country (this is commissioned by CCGs). Nevertheless use is widespread, despite the current negative NICE recommendation for relapsed metastatic breast cancer.

<u>2nd line treatment following palbociclib/ribociclib</u>

1. 100% of patients should be assumed to proceed to 2nd line therapy. A cohort of 100 patients will be used to determine 2nd line treatment costs.
2. Approximately 67 will have further hormone therapy
3. Approximately 33 will switch to chemotherapy at least in the first instance
4. Of the 67 patients having further hormone treatment, 27 will have the combination of everolimus and exemestane, 17 will have tamoxifen, 17 will have fulvestrant and 6

will have exemestane. No patients will receive anastrazole or letrozole as they have just progressed on it

5. Of the 33 patients having chemotherapy, 17 will have single agent capecitabine, 8 a taxane and usually weekly paclitaxel and 8 anthracyclines/other treatments
6. Only everolimus as a 2nd line treatment option has a confidential Patient Access Scheme and both the outcomes with its list and PAS prices will be presented
7. Fulvestrant has a loading dose schedule and this has been incorporated into its cost. It is sometimes administered by hospitals and a worst case scenario is assumed which has 100% hospital administration
8. Tamoxifen and single agent exemestane are prescribed by GPs and thus have no HRG administration costs
9. Relevant chemotherapy HRG administration costs (2017/18) are as follows: £120 for oral administration (everolimus plus exemestane [monthly] and also for 3-weekly capecitabine but calculated monthly); £150 for simple parenteral administration (fulvestrant and given monthly); and £301 for complex parenteral administration per visit but calculated monthly (weekly paclitaxel for 3 weeks out of 4, 3-weekly anthracyclines/other regimens)
10. It should be noted that the only high cost agents in this 2nd line setting are everolimus and fulvestrant. All the rest are generic and therefore inexpensive. NHS England does therefore not recognise the large proportion of patients having expensive chemotherapy regimens under the category of 'other' as outlined in the LRIG commentary.

Drug	Drug cost £	Admin cost £	No. patients	Total cost £
Evero +exem	2673 (LP) + 4	120	27	75519
Tamoxifen	1	0	17	17
Fulvestrant	603	150	17	12801
Exemestane	4	0	6	24
Capecitabine	27	156	17	3111
Paclitaxel	36	903	8	7512
Anthra/other	45	391	8	3488

This gives an average drug cost per patient of £1025 for 2nd line therapy. However if the PAS for everolimus is incorporated into the calculation, the average cost per patient for 2nd line treatment drops to [redacted]. These figures are illustrative but informative as to the likely approximate drug costs of 2nd line treatment, it being known that different case mixes of patients will cause costs to increase/decrease.

<u>3rd line treatment following palbociclib/ribociclib</u>

1. 75% of patients should be assumed to proceed to 3rd line therapy. Of those proceeding, a cohort of 100 patients will be used to determine 3rd line treatment costs.
2. Approximately 50 will have further hormone therapy
3. Approximately 50 will have chemotherapy at least in the first instance
4. Of the 50 patients having further hormone treatment, 13 will have the combination of everolimus and exemestane, 15 will have tamoxifen, 18 will have fulvestrant and 4 will have exemestane. No patients will receive anastrazole or letrozole as they have already progressed on it
5. Of the 50 patients having chemotherapy, 20 will have single agent capecitabine, 13 a taxane and usually weekly paclitaxel, 13 eribulin and 4 anthracyclines/other treatments
6. Everolimus and eribulin have confidential Patient Access Schemes and both the outcomes with their list and PAS prices will be presented
7. Fulvestrant has a loading dose schedule and this has been incorporated into its cost. It is sometimes administered by hospitals and a worst case scenario is assumed which has 100% hospital administration
8. Tamoxifen and single agent exemestane are prescribed by GPs and thus have no HRG administration costs
9. Relevant chemotherapy administration costs (2017/18) are as follows: £120 for oral administration (everolimus plus exemestane [monthly] and also for 3-weekly capecitabine but calculated monthly); £150 for simple parenteral administration (fulvestrant and given monthly); and £301 for complex parenteral administration per visit and calculated monthly (weekly paclitaxel for 3 weeks out of 4, 3-weekly anthracyclines/other regimens, eribulin given twice every 3 weeks)
11. It should be noted that the only high cost agents in these settings are everolimus, fulvestrant and eribulin. All the rest are generic and therefore inexpensive. NHS England does therefore not recognise the large proportion of patients having expensive chemotherapy regimens in the category 'other' as outlined in the LRIG commentary.

Drug	Drug cost £	Admin cost £	No. patients	Total cost £
Evero +exem	2673 (LP) + 4	120	13	36361
Tamoxifen	1	0	15	15
Fulvestrant	603	150	18	13553
Exemestane	4	0	4	16
Capecitabine	27	156	20	3660
Paclitaxel	36	903	13	12207
Eribulin	2347	783	13	40690
Anthra/other	45	391	4	1744

This gives an average cost per patient of £1082 for 3rd line therapy. However if the PAS prices for everolimus and eribulin are incorporated into the calculation, the average cost per patient for 3rd line treatment drops to [redacted]. These figures are illustrative but informative as to the likely approximate drug costs of 3rd line treatment, it being known that different case mixes of patients will cause costs to increase/decrease.

4th line treatment following palbociclib/ribociclib

In such a line of therapy, there will be much less hormone therapy and little use of everolimus and exemestane, this combination being the main cost driver of hormone therapy. There would be more use of eribulin, the main cost driver of chemotherapy in the 3rd line setting and also some use of oral vinorelbine. The end result is likely to be a modest increase on 3rd line treatments costs but unlikely to be in excess of [redacted] once the PAS price of eribulin has been taken into consideration.

Post progression health state costs

NHS England agrees with the assumption that health state costs of progressed disease (other than the drug costs associated with active treatment) will progressively increase with each line of therapy as there is escalating need for diagnostic tests, blood tests, palliative radiotherapy, palliative care, out patients visits etc.

Prof Peter Clark

NHS England National Chemotherapy Lead and National Clinical Lead for the Cancer Drugs Fund

30 September 2017

ADDENDUM

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 20 March 2017

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

PALBOCICLIB IN COMBINATION WITH AN AROMATASE INHIBITOR FOR PREVIOUSLY UNTREATED METASTATIC, HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE BREAST CANCER [ID915]

ERG CRITIQUE OF COMPANY'S RESPONSE TO THE ACD

1.1 Appendix A

1.1.1 Critique of justification for amending PFS utility value

The company's argument in Appendix A has some merit only in the specific circumstances where the committee accepts that:

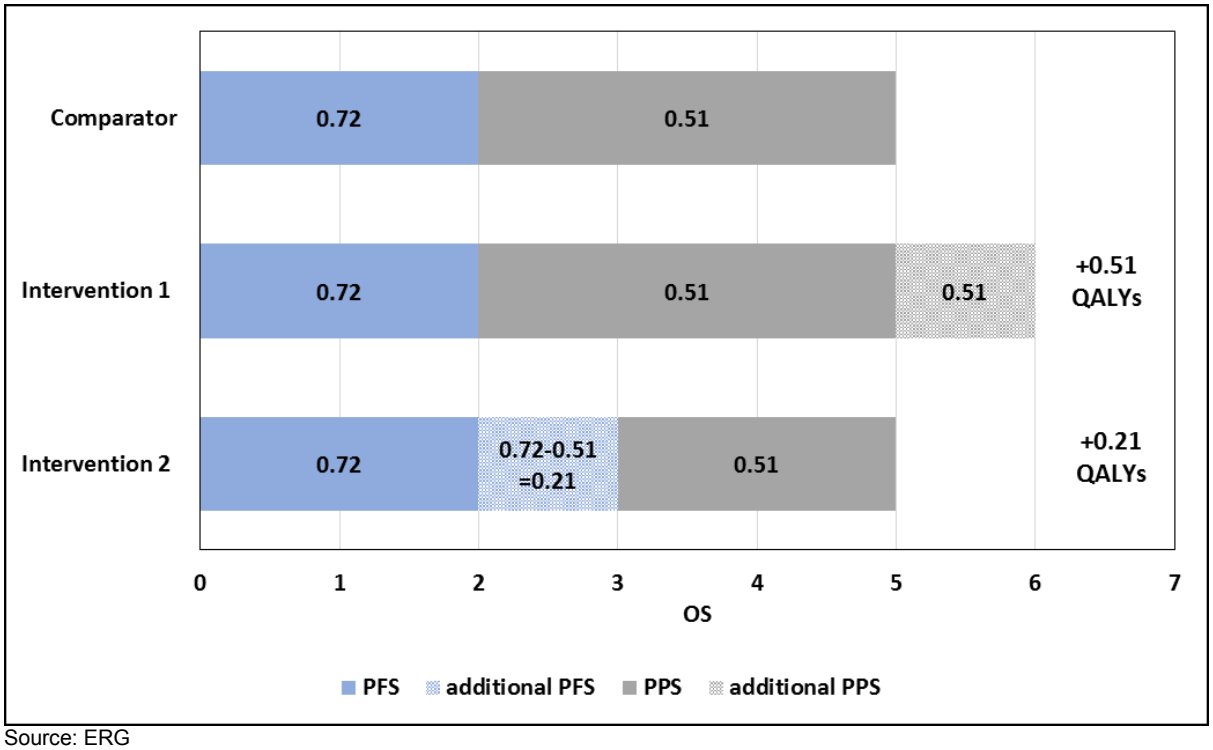
a) additional PFS benefit should always be valued equally to additional OS benefit; and

b) the balance of PFS, PPS and OS between treatments reflects either:

   i. a comparison of three treatments where one treatment extends PPS versus the comparator and one extends PFS versus the comparator (Figure 1); or

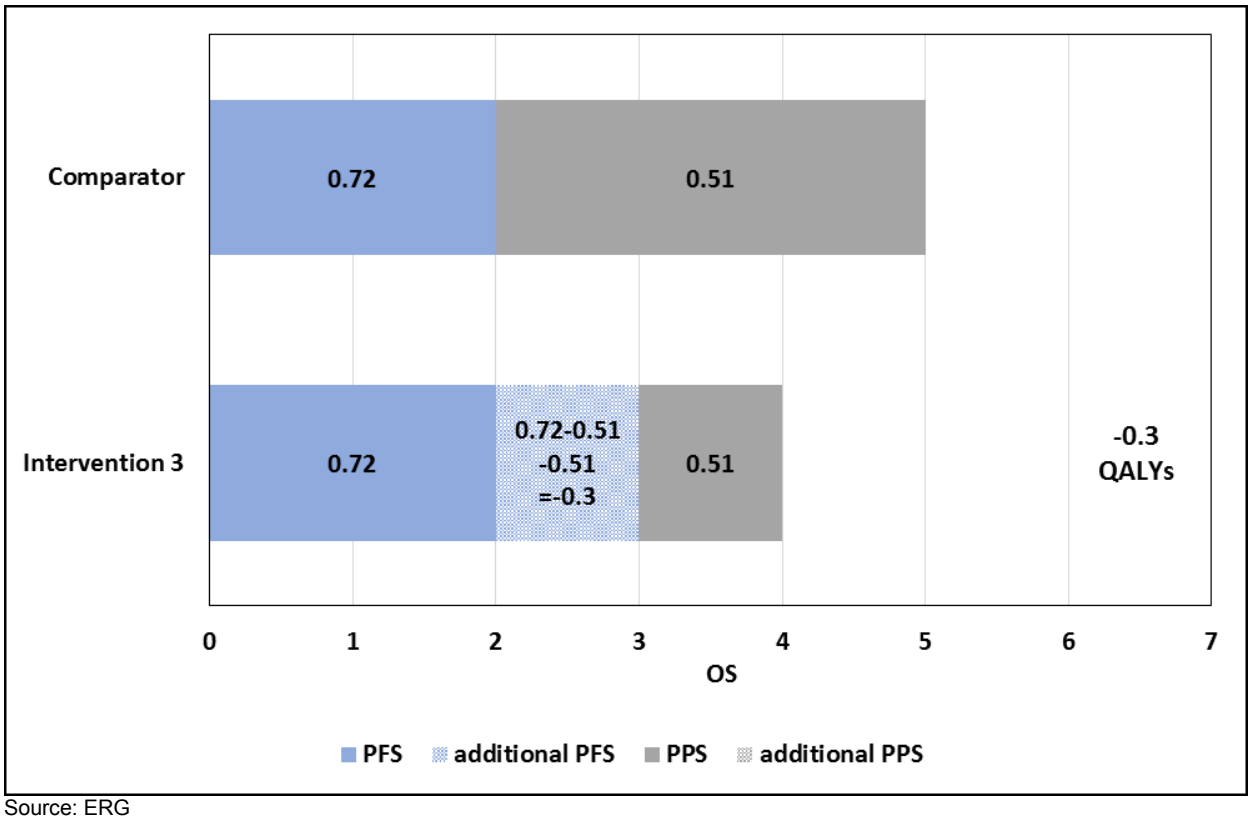
   ii. a comparison of two treatments where the intervention extends PFS but reduces OS versus the comparator (Figure 2).

The ERG does not consider the company's justification for adjusting the PFS utility value to be appropriate in this instance. Point a) would impact upon all technology appraisals, as it requires a new weighting of the benefits of extended PFS and PPS. This would require serious consideration, as there are many complex issues involved including potential conflicts with the weighting of end of life. Plus, it is fairly straightforward to imagine situations in which patients might prefer additional PPS to additional PFS, such as where progression does not have much of a negative impact on quality of life. Point b) is not applicable to the current STA according to the evidence submitted; Figure 3 is an example of the balance of PFS, PPS and OS in the company's original model.



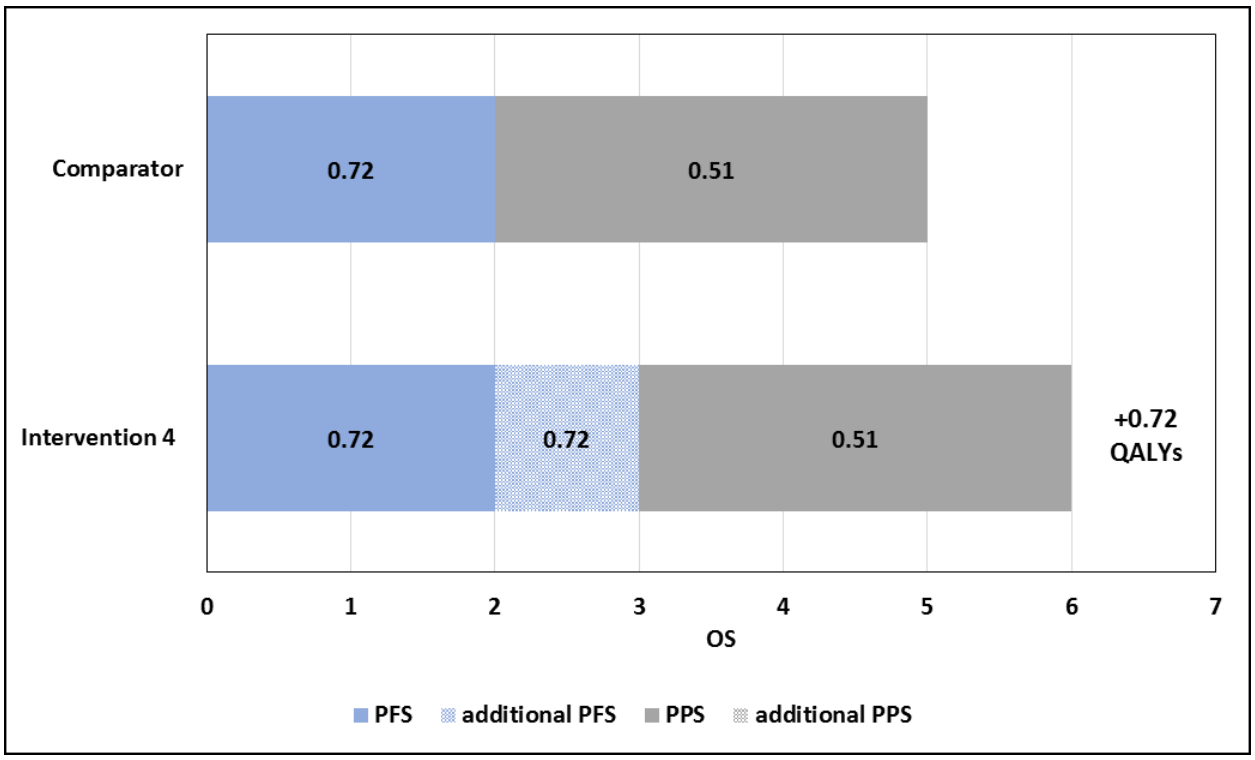
Source: ERG

Figure 1 Example impact on health-related quality of life for three treatments where one intervention extends PPS and one intervention extends PFS



Source: ERG

Figure 2 Example impact on health-related quality of life for two treatments where the intervention extends PFS but reduces OS



Source: ERG

Figure 3 Example impact on health-related quality of life for two treatments where the intervention extends PFS and maintains PPS

1.1.2 Critique of the implementation PFS utility value amendment

The ERG considers the company's attempt to equalise incremental benefit by applying a pre-progression utility value of 1 to be methodologically flawed. The company's implementation of this 'fix' is flawed for three key reasons:

1) the inequality in additional PFS and PPS benefit is purely an artefact of the utility values used in their model. For instance, had the PPS utility been 0.36 (i.e. 0.72 / 2), then there would not be an incremental difference in the additional QALYs gained from spending an extra unit of time in the pre-progression state versus the post-progression state. Any number of amendments to the pre- and post-progression utility values could have been applied in order to meet the requirement for equal incremental benefit and all of these would have different effects on the ICERs per QALY gained;

2) increasing the pre-progression utility value to 1 weights the entirety of PFS for both treatments and not just the additional time spent in the pre-progression state;

3) as noted by the company, it results in implausible values for quality of life. Trial-based utility values are ignored and it is implied that additional time spent in PFS is not only equal to additional time spent in OS but also to full health.

1.1.3 Use of company rather than ERG OS

It should be noted that the company's ICER calculations in Table 1 of Appendix A each use the company's original OS model, even when all the other ERG revisions are applied. This means that the ICERs are all 'best case scenarios', as the ERG's revised approach to modelling OS decreased OS gain for PAL+LET versus the company's model.

1.2 Appendix B

The ICERs given in Appendix B Table 3 of the company's response to the ACD include an uplift in the cost of the comparator to represent the average cost of therapies used to treat metastatic breast cancer; however, no adjustment is made to the effectiveness of the comparator. Also, there is a PAS in operation for a number of the therapies listed in Table 2, which means that average costs based on list price will be overstated.

Additionally, the ICERs in Table 3 include the adjustment to PFS utility discussed in the ERG response to Appendix A and so are subject to the same methodological flaws outlined above.

ADDENDUM 2

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 18 May 2017

CONTAINS COMMERCIAL IN CONFIDENCE AND ACADEMIC IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

PALBOCICLIB IN COMBINATION WITH AN AROMATASE INHIBITOR FOR PREVIOUSLY UNTREATED METASTATIC, HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE BREAST CANCER [ID915]

ERG CRITIQUE OF COMPANY'S REVISED RESPONSE TO THE ACD

1 INTRODUCTION

The company's revised response to the Appraisal Consultation Document (ACD) includes data related to: a proposed Patient Access Scheme (PAS) and updated overall survival (OS) data from the PALOMA-1 trial. Additionally, the company has put forward a methodological argument outlining what it perceives as flaws in the approach taken by NICE to the conduct of technology appraisals and why it believes that the Appraisal Committee (AC) should give this appraisal special consideration.

The ERG has analysed the impact of the PAS and updated OS data from the PALOMA-1 trial on the cost effectiveness of this new intervention. It has summarised the methodological arguments included in the company's response (proposals to change the valuing of progression free survival (PFS) and the cost of the comparator used in the appraisal) but has not commented on its merits or demerits, as these arguments are out of the remit of the ERG as outlined in the NICE Guide to Methods of Technology Appraisal.

2 PATIENT ACCESS SCHEME

The company has included in its revised response an updated model, which includes a PAS in the form of a simple discount ([redacted]) on the price of palbociclib (PAL). The PAS had not been approved by the time of writing; however, the ERG has followed advice from NICE and included the company's PAS in its estimations of incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained.

3 REVISED COMPANY BASE CASE

The company has included in its revised base case all the amendments from the ERG's original critique except for the original remodelling of OS. These include:

- ERG PFS estimates based on data from PALOMA-1
- ERG time to treatment discontinuation estimates based on data from PALOMA-1
- ERG recalculated pre-progression utility values from PALOMA-2 trial (0.721)

- ERG recalculated post-progression utility values using Lloyd 2006 (0.5052)
- Use of mid-cycle correction
- Use of full reference costs for adverse events
- Correct AE incidence calculation
- Change of discounting to annual
- Use of 365.25 days per year

The revised company base case incorporates two estimates of survival: a 'lower bound' based on parametric modelling of the individual patient data (IPD) from the final OS analysis of the PALOMA-1 trial; and an 'upper bound' based on parametric modelling of the IPD for both treatments and then applying an adjustment to the palbociclib+letrozole (PAL+LET) model to increase OS gain to match PFS gain.

Without the PAS, the revised company base case ICER per QALY gained using the 'lower bound' OS is £159,064 and the revised company base case ICER per QALY gained using the 'upper bound' OS is £105,117.

With the PAS, the revised company base case ICER per QALY gained using the 'lower bound' OS is £[redacted] and the revised company base case ICER per QALY gained using the 'upper bound' OS is £[redacted].

4 UPDATED OVERALL SURVIVAL DATA FROM PALOMA-1 TRIAL

The ERG considers the data from the final OS analysis from the PALOMA-1 trial to be the best available evidence for OS for treatment with PAL+LET versus letrozole (LET). Data from the final OS analysis are 85% complete in each arm and do not show evidence of a significant difference in survival for treatment with PAL+LET versus LET (log rank p=0.356, Mann-Whitney U p=0.435).

In its original report, the ERG concluded that there was no evidence of a survival benefit for PAL+LET versus LET; however, given the immaturity of the data available from the interim analysis, it modelled a small survival benefit for treatment with PAL+LET based on the assumption that the separation of the curves evident in the early data would continue. Visual inspection of the K-M curves (Figure 1) demonstrates that the separation of the curves did not continue and that OS follows very similar trajectories for both treatments.

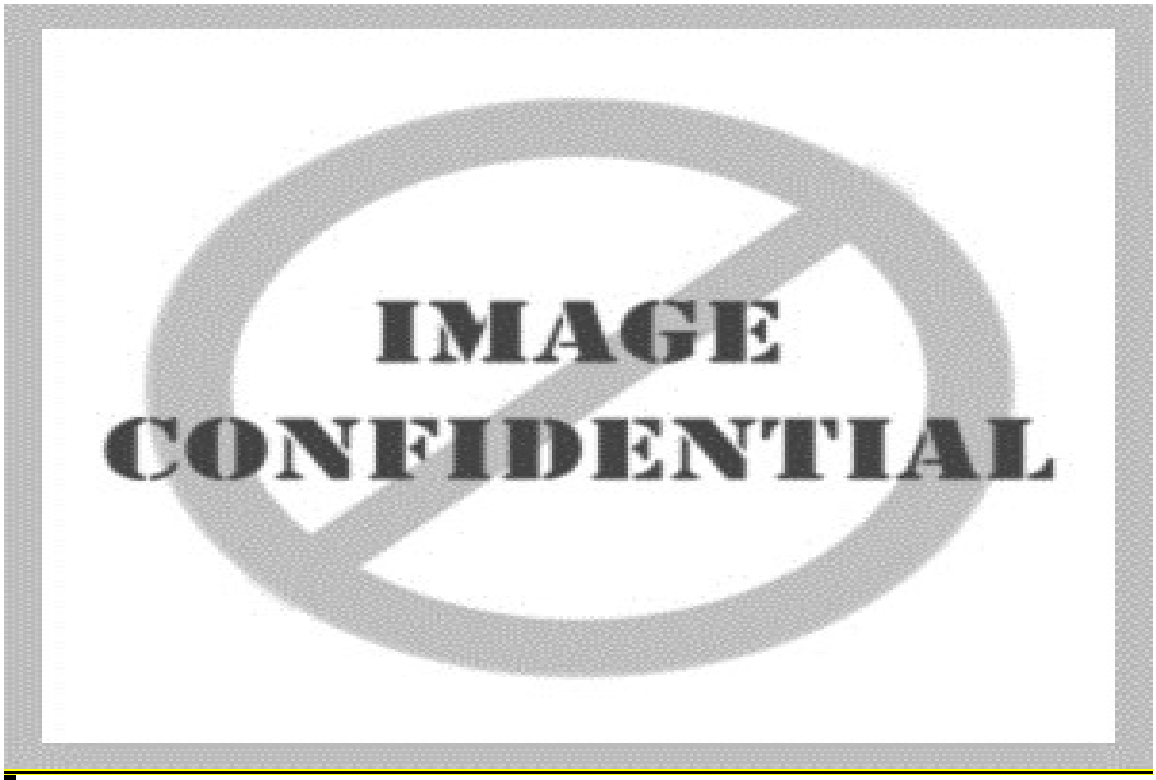


Figure 1 OS K-M curves from PALOMA-1 final analysis: PAL+LET vs LET

Source: Figure 1, Company revised response to ACD

The company notes that the AC concluded it should take into account a range of OS outcomes after the first AC meeting, from the ERG's estimates based on PALOMA-1 K-M data at the lower bound to an upper bound where PFS gain is realised entirely in OS gain. The company argues in its revised response to the ACD that the AC should continue to consider a range of values for OS, as it suggests that the data from PALOMA-1 are unreliable due to potential confounding by post progression treatments, randomness of response and others.

The ERG acknowledges that the updated OS data from PALOMA-1 may be limited due to the size of the trial, but notes that this is at least a mature data set and is the best evidence available for OS for treatment with PAL+LET versus LET. The ERG does not agree with the company that the OS data are unreliable due to the potential confounding factors suggested. The company has not provided any evidence to show that subsequent treatments or any other factors it deems to be potential confounders were any different in the PALOMA-1 trial than might be expected in UK clinical practice.

The ERG has remodelled OS using the updated OS data from the PALOMA-1 trial. Since there is insufficient evidence of a statistically significant difference between OS for the two arms of the PALOMA-1 trial, it may be appropriate to pool the data in order to benefit from a larger data set when projecting survival beyond the end of the available K-M data. However, the ERG could not pool OS from the two treatments, as the data set was not made available

to the ERG in the appropriate format. The ERG has instead estimated survival for the treatments separately; however, the resulting estimate of OS gain should be treated with caution given that there is insufficient evidence of any difference in OS within the final OS analysis data set.

Inspection of the cumulative OS hazard plot (Figure 2) reveals clear linear trends for both treatments from 23 months onwards. This means that exponential curves are an appropriate approximation of the survival trend for treatment with PAL+LET and LET for 68% and 71% of the available data points respectively.

Figure 2 Cumulative OS hazard plot for treatment with PAL+LET vs LET

Source: Revised company response to ACD

The ERG's exploratory analysis of the final OS data cut from the PALOMA-1 trial results in estimates of mean OS gain that are very similar to, and slightly higher than, those generated by the company's fully parametric modelling of the IPD data (referred to as the 'lower bound' of OS in the company's revised response to the ACD). Table 1 gives mean OS and OS gain from the ERG's analysis of the final OS data cut from the PALOMA-1 trial alongside mean OS and OS gain from the company's two OS modelling scenarios. Figure 3 shows a comparison of OS K-M data for both treatments from the final analysis of the PALOMA-1 trial, ERG exponential extrapolation from the end of the K-M data and the company's parametric model based on the IPD data.

Table 1 Mean OS and OS gain: PALOMA-1 final analysis

Survival model (final OS data)	PAL+LET (months)	LET (months)	OS gain (months)
ERG	43.83	40.35	3.47*
Company 'lower bound' (IPD)	42.92	39.54	3.38
Company 'upper bound' (PFS gain=OS gain)	48.56	39.54	9.02

Source: ERG calculations; Updated company model
ERG=Evidence Review Group; IPD=individual patient data; OS=overall survival
* treat with caution, as there is insufficient evidence of a statistically significant OS gain in the K-M data

Figure 3 OS: final analysis K-M data, ERG extrapolation and company IPD model

Source: Updated company model; ERG calculations
IPD=individual patient data; OS=overall survival

Without the proposed PAS included, applying the ERG's updated survival estimates to the revised company base case results in an ICER of £157,120 per QALY gained, which is a decrease of £1,944 versus the revised company base case using the 'lower bound' IPD survival model and increase of £52,004 versus the revised company base case using the 'upper bound' PFS gain=OS gain survival model.

5 WITH THE PROPOSED PAS INCLUDED, APPLYING THE ERG'S UPDATED SURVIVAL ESTIMATES TO THE REVISED COMPANY BASE CASE RESULTS IN AN ICER OF [redacted] PER QALY GAINED, WHICH IS A DECREASE OF [redacted] VERSUS THE REVISED COMPANY BASE CASE USING THE 'LOWER BOUND' IPD SURVIVAL MODEL AND INCREASE OF [redacted] VERSUS THE REVISED COMPANY BASE CASE USING THE 'UPPER BOUND' PFS GAIN=OS GAIN SURVIVAL MODEL. COMPANY'S METHODOLOGICAL PROPOSALS

The company's methodological argument is motivated by its contention that it is unlikely that new treatments will ever be deemed cost effective for this indication using the current comparator, LET which is both effective and inexpensive, and the existing methodological framework for appraising new technologies. This, it argues, is a barrier to innovation. The company contends that this barrier to innovation amounts to an inequity of access opportunity for women with untreated metastatic HR+, HER2-negative breast cancer, as patients with other types of breast cancer are able to access innovative new treatments for their diseases.

The company proposes that NICE should accept two changes to current cost effectiveness methodology for appraisals in this indication where treatment is being compared against LET. These changes, it argues, would allow a new treatment to be considered cost effective according to standard NICE thresholds and therefore remove the barrier to innovation in this indication. The company suggests that, once this new treatment has been approved, the existing cost effectiveness methodology would be reinstated. The company has not suggested that these two proposed changes to cost effectiveness methodology should be applied generally to other appraisals. The two methodological changes proposed by the company are: to change the relative value of the PFS and PPS health states; and to change the comparator.

6 COMPANY ICERS PER QALY GAINED

The ERG has attempted to replicate all the ICERs per QALY gained included in the company's revised response to the ACD, but has not been able to successfully replicate them all. The ICERs per QALY gained shown in Table 2 are the result of ERG systematically amending the updated company model with all the combinations of scenarios (OS, utility values and comparators) proposed by the company. Including the PAS, the lowest ICER per QALY gained is [redacted] for the scenario where PFS gain is entirely realized in OS gain ('upper bound' OS), PFS utility=1 and PPS utility=0.51, and the comparator is assumed to cost the average of 13

previously appraised therapies for metastatic breast cancer. Including the PAS, the highest ICER per QALY gained is [redacted] for the scenario where the IPD data is modelled for OS ('lower bound' OS) and both the utility values and comparator are as per the base case.

Table 2 ICERs per QALY gained for each scenario in company revised response (smallest to largest)

Scenario			ICER	
OS	PFS utility	Comparator	With PAS	Without PAS
PFS gain=OS gain	PFS=1, PPS=0.51	13 therapies	[redacted]	£44,368
PFS gain=OS gain	PFS=1, PPS=0.51	13 therapies (with PAS)	[redacted]	
PFS gain=OS gain	Base case	13 therapies	[redacted]	£45,478
PFS gain=OS gain	PFS=0.72, PPS=0.36	13 therapies	[redacted]	£45,599
PFS gain=OS gain	Base case	13 therapies (with PAS)	[redacted]	
PFS gain=OS gain	PFS=0.72, PPS=0.36	13 therapies (with PAS)	[redacted]	
PFS gain=OS gain	PFS=1, PPS=0.51	7 therapies	[redacted]	£44,168
PFS gain=OS gain	Base case	7 therapies	[redacted]	£45,092
PFS gain=OS gain	PFS=1, PPS=0.51	7 therapies (with PAS)	[redacted]	
PFS gain=OS gain	PFS=0.72, PPS=0.36	7 therapies	[redacted]	£45,358
PFS gain=OS gain	Base case	7 therapies (with PAS)	[redacted]	
PFS gain=OS gain	PFS=0.72, PPS=0.36	7 therapies (with PAS)	[redacted]	
IPD analysis	PFS=1, PPS=0.51	7 therapies	[redacted]	£48,526
IPD analysis	PFS=1, PPS=0.51	13 therapies	[redacted]	£53,238
IPD analysis	Base case	7 therapies	[redacted]	£49,768
IPD analysis	PFS=1, PPS=0.51	7 therapies (with PAS)	[redacted]	
IPD analysis	PFS=0.72, PPS=0.36	7 therapies	[redacted]	£49,878
IPD analysis	PFS=1, PPS=0.51	13 therapies (with PAS)	[redacted]	
IPD analysis	PFS=0.72, PPS=0.36	13 therapies	[redacted]	£54,842
IPD analysis	Base case	7 therapies (with PAS)	[redacted]	
IPD analysis	Base case	13 therapies	[redacted]	£55,222
IPD analysis	PFS=0.72, PPS=0.36	7 therapies (with PAS)	[redacted]	
IPD analysis	PFS=0.72, PPS=0.36	13 therapies (with PAS)	[redacted]	
IPD analysis	Base case	13 therapies (with PAS)	[redacted]	
PFS gain=OS gain	PFS=1, PPS=0.51	Blended LET + chemo	[redacted]	£58,321
PFS gain=OS gain	Base case	Capecitabine	[redacted]	£59,545
IPD analysis	Base case	Capecitabine	[redacted]	£63,491
IPD analysis	PFS=1, PPS=0.51	Blended LET + chemo	[redacted]	£70,098
PFS gain=OS gain	PFS=1, PPS=0.51	Base case	[redacted]	£71,211
PFS gain=OS gain	PFS=0.72, PPS=0.36	Blended LET + chemo	[redacted]	£83,947
IPD analysis	Base case	Blended LET + chemo	[redacted]	£84,252
IPD analysis	PFS=1, PPS=0.51	Base case	[redacted]	£89,018
PFS gain=OS gain	PFS=0.72, PPS=0.36	Base case	[redacted]	£98,587
IPD analysis	PFS=0.72, PPS=0.36	Blended LET + chemo	[redacted]	£100,457
PFS gain=OS gain	Base case	Base case	[redacted]	£105,117
PFS gain=OS gain	Base case	Blended LET + chemo	[redacted]	£119,672
IPD analysis	PFS=0.72, PPS=0.36	Base case	[redacted]	£122,637
IPD analysis	Base case	Base case	[redacted]	£159,064

Source: Updated company model
ERG=Evidence Review Group; IPD=individual patient data; OS=overall survival; PFS=progression free survival

Table 1 ERG cost effectiveness results for each scenario in company revised response (smallest to largest)

Scenario			ICER	
OS	PFS utility	Comparator	With PAS	Without PAS
PFS gain=OS gain	PFS=1, PPS=0.51	13 therapies	[redacted]	£44,368
PFS gain=OS gain	PFS=1, PPS=0.51	13 therapies (with PAS)	[redacted]	
PFS gain=OS gain	Base case	13 therapies	[redacted]	£45,478
PFS gain=OS gain	PFS=0.72, PPS=0.36	13 therapies	[redacted]	£45,599
PFS gain=OS gain	Base case	13 therapies (with PAS)	[redacted]	
PFS gain=OS gain	PFS=0.72, PPS=0.36	13 therapies (with PAS)	[redacted]	
PFS gain=OS gain	PFS=1, PPS=0.51	7 therapies	[redacted]	£44,168
PFS gain=OS gain	Base case	7 therapies	[redacted]	£45,092
PFS gain=OS gain	PFS=1, PPS=0.51	7 therapies (with PAS)	[redacted]	
PFS gain=OS gain	PFS=0.72, PPS=0.36	7 therapies	[redacted]	£45,358
PFS gain=OS gain	Base case	7 therapies (with PAS)	[redacted]	
PFS gain=OS gain	PFS=0.72, PPS=0.36	7 therapies (with PAS)	[redacted]	
IPD analysis	PFS=1, PPS=0.51	7 therapies	[redacted]	£48,526
IPD analysis	PFS=1, PPS=0.51	13 therapies	[redacted]	£53,238
IPD analysis	Base case	7 therapies	[redacted]	£49,768
IPD analysis	PFS=1, PPS=0.51	7 therapies (with PAS)	[redacted]	
IPD analysis	PFS=0.72, PPS=0.36	7 therapies	[redacted]	£49,878
IPD analysis	PFS=1, PPS=0.51	13 therapies (with PAS)	[redacted]	
IPD analysis	PFS=0.72, PPS=0.36	13 therapies	[redacted]	£54,842
IPD analysis	Base case	7 therapies (with PAS)	[redacted]	
IPD analysis	Base case	13 therapies	[redacted]	£55,222
IPD analysis	PFS=0.72, PPS=0.36	7 therapies (with PAS)	[redacted]	
IPD analysis	PFS=0.72, PPS=0.36	13 therapies (with PAS)	[redacted]	
IPD analysis	Base case	13 therapies (with PAS)	[redacted]	
PFS gain=OS gain	Base case	Capecitabine	[redacted]	£59,545
IPD analysis	Base case	Capecitabine	[redacted]	£63,491
PFS gain=OS gain	PFS=1, PPS=0.51	Blended LET + chemo	[redacted]	£58,321
IPD analysis	PFS=1, PPS=0.51	Blended LET + chemo	[redacted]	£70,098
PFS gain=OS gain	PFS=1, PPS=0.51	Base case	[redacted]	£71,211
PFS gain=OS gain	PFS=0.72, PPS=0.36	Blended LET + chemo	[redacted]	£83,947
PFS gain=OS gain	Base case	Blended LET + chemo	[redacted]	£119,672
IPD analysis	PFS=1, PPS=0.51	Base case	[redacted]	£89,018
PFS gain=OS gain	PFS=0.72, PPS=0.36	Base case	[redacted]	£98,587
IPD analysis	PFS=0.72, PPS=0.36	Blended LET + chemo	[redacted]	£100,457
PFS gain=OS gain	Base case	Base case	[redacted]	£105,117
IPD analysis	Base case	Blended LET + chemo	[redacted]	£84,252
IPD analysis	PFS=0.72, PPS=0.36	Base case	[redacted]	£122,637
IPD analysis	Base case	Base case	[redacted]	£159,064

Source: Updated company model
ERG=Evidence Review Group; IPD=individual patient data; OS=overall survival; PFS=progression free survival

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 implementation group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Wednesday 20 September 2017** 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.

Pfizer has included factual inaccuracies below which demonstrate that the ERG's basecase should actually be an ICER of [redacted] per QALY gained, not [redacted] per QALY gain which the ERG cites in its report.

However, even with this corrected ICER, it should be noted that Pfizer disagrees with the ERG's approach which rejected of our estimate of post-progression costs and pre-progression utilities included in the revised submission (7 August), which were adjusted in line with NICE's preferences from related appraisals.

Issue 1 Inaccuracies in the treatment costs calculated in Table 2

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr><td>Table 2 details the acquisition and administration costs related to a variety of later-line therapies. However, there are inaccuracies in several of these calculations.</td><td colspan="2">Details of the proposed amendments and the justification for the amendments are included in the footnote of the below table. The Table is extracted from the ERG Report and pasted here, with the exact inaccurate highlighted using footnotes. We have presented this issue in this format for clarity. Below this table we have included the proposed amendments to the Table with the accurate costs.</td><td rowspan="2">Table 2 amended as follows:

1. ERG has amended the estimated drug cost of capecitabine to £30.58 per month to reflect the dosing schedule.
• 500mg = £19.55 per 120 (eMIT) = £0.16 per tab * 4 = £0.65 per dose * 2 = £1.30 per day * 14 = £18.25 per 3-wk cycle * (52/3) = £316.28 per year / 12 = £26.36 per month
• 250mg = £3.13 per 60 (eMIT) = £0.05 per tab * 2 = £0.10 per dose * 2 = £0.21 per day * 14 = £2.92 per 3-wk cycle * (52/3) = £50.64 per year / 12 = £4.22 per month
• Total drug costs per month = £26.36+£4.22 = £30.58</td></tr>
<tr><td colspan="3">Extracted from ERG Report: Table 1 ERG estimated costs for second- and third-line therapies
<table>
<tr><th>Treatment</th><th>Regimen</th><th>Admin method</th><th>Treatment cost per month</th><th>Admin cost per month</th><th>% of patients</th><th>Total cost per month per patient</th></tr>
<tr><td colspan="7">Second line</td></tr>
<tr><td>Exemestane</td><td>1x25mg per day</td><td>Oral</td><td>£4.16</td><td>£0.00</td><td>17</td><td>£0.71</td></tr>
<tr><td>Capecitabine</td><td>2x1250mg per day</td><td>Oral</td><td>£24.44[1]</td><td>£0.00[2]</td><td>12</td><td>£2.93</td></tr>
<tr><td>Tamoxifen</td><td>1 x 20mg per day</td><td>Oral</td><td>£1.44</td><td>£0.00</td><td>8</td><td>£0.12</td></tr>
<tr><td>Anastrazole</td><td>1 x 1mg per day</td><td>Oral</td><td>£0.75</td><td>£0.00</td><td>7.5</td><td>£0.06</td></tr>
<tr><td>Letrozole</td><td>1 x 2.5mg per day</td><td>Oral</td><td>£1.55</td><td>£0.00</td><td>7</td><td>£0.11</td></tr>
</table></td></tr>
</table>

Docetaxel	1 x 75mg/m^2 every 3 weeks	IV	£30.95[3]	£236.19[3]	7	£18.70
Everolimus	1 x 10mg per day	Oral	£2,673	£0.00	7	£187.11
Paclitaxel	1 x 260mg/m^2 every 3 weeks	IV	£43.10[3]	£236.19[3]	6.5	£18.15
Fulvestrant	2 x 250mg per month	Injection	£522.41[4]	£0.00[5,6]	5	£26.12
Other	N/A	N/A	£2,000	£236.19[7]	23	£514.32
Total						£768.33
Third line						
Capecitabine	2 x 1250mg per day	Oral	£24.44[1]	£0.00[2]	31	£7.58
Fulvestrant	2 x 250mg per month	Injection	£522.41[4]	£79.79[6]	13	£78.29
Tamoxifen	1 x 20mg per day	Oral	£1.44	£0.00	10	£0.14
Exemestane	1 x 25mg per day	Oral	£4.16	£0.00	8	£0.33
Eribulin	2 x 1.23mg/m^2 every 3 weeks	IV	£1083.00	£236.19	7	£92.34
Anastrazole	1 x 1mg per day	Oral	£0.75	£0.00	5	£0.04
Other	N/A	N/A	£2,000	£236.19[7]	26	£581.41
					Total	£760.13

Inaccuracies around the cost calculations in the table, together with description of the correct costs:

1. The monthly cost of capecitabine should be estimated at £49.86.
    - Required dose is 2225mg per admin. Hence, actual dose: 4*500mg (24.7p per tab, eMIT) + 2*150mg (12.9p per tab, eMIT). The cost per admin = £1.24. The treatment is administered twice a day = £2.46 per day. Schedule is 2 weeks on treatment then the third week off. £2.46 x 2/3 x 30.4 = £49.86 per month

2. The administration costs related to oral capecitabine should be £265.64
    - Administration costs from NHS Reference Costs have been applied to IV chemotherapy but not oral chemotherapy. NHS Reference Costs provide an administration cost specifically for oral

2. ERG has amended admin cost of capecitabine to include £265.05 per month
    - Oral chemotherapy = £183.5 per cycle * (52/3) = £3180.67 per year / 12 = £265.05 per month

3. ERG has amended the acquisition cost of docetaxel to £29.78 per month.
    - based on average BSA of 1.75m2 (Sacco 2010) and dose of 75mg/m2, average dose is 131.35mg
    - using 140mg vial size = £20.62 (eMIT) per 3-wk cycle * (52/3) = £357.41 per year / 12 = £29.78 per month

4. ERG has amended the acquisition cost of paclitaxel to £49.59 per month.
    - based on average BSA of 1.75m2 (Sacco 2010) and dose of 175mg/m2, average dose is 306mg
    - using 300mg vial size = £34.33 (eMIT) per 3-wk cycle * (52/3) = £595.05 per year / 12 = £49.59 per month

5. ERG has amended docetaxel and paclitaxel admin costs to £236.19 * (52/3) / 12 = £341.16 per month

chemotherapy: *SB11Z: "Deliver exclusively oral chemotherapy" NHS Reference costs 2015/16.* • This Reference Cost is £183.50, and is applied every 3 weeks. This equates to £265.64 per month. 3. The costs for both drug acquisition and administration are for 21 day cycles. As there are 30.4 days in a month, these costs should be 1.45 times greater in the "per month" cost column. • Docetaxel acquisition cost of £30.95 equates to £44.80 per month • Paclitaxel acquisition cost of £43.10 equates to £62.39 per month • Docetaxel and paclitaxel administration costs of £236.19 equates to £341.91 per month 4. The acquisition cost for fulvestrant omits the increased dose in the first cycle • TA239 is cited as the source for the fulvestrant data; the FAD (Section 2.3) explains how fulvestrant is administered twice in the first month. That FAD (Section 3.3) also states that time to progression is 6.5 months. • Hence, double dose is administered for 1 month, then single dose for 5.5 months. The average cost per month is thus £602.78 5. Fulvestrant carries an administration costs being an intramuscular injection. The "third-line" section of the table includes an admin cost, but it is missing from the "second-line" section. 6. Similar to point 4, the administration cost for fulvestrant omits the increased administration cost in the first cycle • Double dose is administered for 1 month, then single dose for 5.5 months (see point 4). The average administration cost per month is thus £92.07 7. It is assumed this cost is applied from the lines for docetaxel and paclitaxel. If so, this should be updated when those are corrected (see point 3). **Proposed amendment: Updated table with accuracies corrected:**	6. ERG has amended fulvestrant acquisition cost to £602.78 7. ERG has amended fulvestrant admin cost to £92.07

Treatment	Regimen	Admin method	Treatment cost per month	Admin cost per month	% of patients	Total cost per month per patient
Second line						
Exemestane	1x25mg per day	Oral	£4.16	£0.00	17	£0.71
Capecitabine	2x1250mg per day	Oral	£49.86	£265.64	12	£37.86
Tamoxifen	1 x 20mg per day	Oral	£1.44	£0.00	8	£0.12
Anastrazole	1 x 1mg per day	Oral	£0.75	£0.00	7.5	£0.06
Letrozole	1 x 2.5mg per day	Oral	£1.55	£0.00	7	£0.11
Docetaxel	1 x 75mg/m^2 every 3 weeks	IV	£44.80	£341.91	7	£27.07
Everolimus	1 x 10mg per day	Oral	£2,673	£0.00	7	£187.11
Paclitaxel	1 x 260mg/m^2 every 3 weeks	IV	£62.39	£341.91	6.5	£26.28
Fulvestrant	2 x 250mg per month	Injection	£602.78	£92.07	5	£34.74
Other	N/A	N/A	£2,000	£341.91	23	£538.64
Total						£852.69
Third line						
Capecitabine	2 x 1250mg per day	Oral	£49.86	£265.64	31	£97.81
Fulvestrant	2 x 250mg per month	Injection	£602.78	£92.07	13	£90.33
Tamoxifen	1 x 20mg per day	Oral	£1.44	£0.00	10	£0.14
Exemestane	1 x 25mg per day	Oral	£4.16	£0.00	8	£0.33
Eribulin	2 x 1.23mg/m^2 every 3 weeks	IV	£1,083.00	£236.19	7	£92.34
Anastrazole	1 x 1mg per day	Oral	£0.75	£0.00	5	£0.04
Other	N/A	N/A	£2,000	£341.91	26	£608.90
					Total	£889.89

Issue 1b Update of results in ERG Report following corrections in Issue 1

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>ERG response</th></tr>
<tr>
<td>Following corrections in Issue 1 (see above), Table 3 needs to be updated, as do the ERG's ICERs</td>
<td>
Amended Table: Table 2 ERG estimated post-progression costs
<table>
<tr><th>Line of therapy</th><th>Treatment cost</th><th>Health-state cost (company original model)</th><th>Total cost</th></tr>
<tr><td>Second</td><td>£852.69</td><td>£245.22</td><td>£1,097.91</td></tr>
<tr><td>Third</td><td>£889.89</td><td>£437.88</td><td>£1,327.77</td></tr>
<tr><td>Fourth</td><td>As third line</td><td>£636.98</td><td>£1,526.87</td></tr>
<tr><td>BSC</td><td>N/A</td><td>£975.38</td><td>£975.38</td></tr>
<tr><td colspan="3">Average</td><td>£1,231.98</td></tr>
</table>

The ICERs cited on page 4, [redacted] and [redacted] gained, should be updated to [redacted] and [redacted], respectively.

The ICER cited as the ERG's basecase on page 7, [redacted], should be updated to [redacted].
</td>
<td>Superseded by issue 2</td>
</tr>
</table>

Issue 2 Inaccurate estimation of post-progression average treatment costs applicable to this population

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Patients in the first-line in this model receive aromatase inhibitor based therapy, either as monotherapy or with palbociclib. These patients would not then receive an aromatise inhibitor again as a second or third line treatment once they have failed on it in the first line. As such, including these treatments in the calculation of the average later line treatment cost is factually inaccurate as it does not reflect practice.</td>
<td>Table 2 and Table 3 from the ERG Report need to be updated, and the ICERs also. Incorporating the corrections in Issue 1, the amended Tables without aromatase inhibitors are as follows:
Table 2 from the ERG Report
This table has had aromatise inhibitors removed, and the % of patients column re-calculated to add to 100% based on the proportions in the table originally.
<table>
<tr><th>Treatment</th><th>Regimen</th><th>Admin method</th><th>Treatment cost per month</th><th>Admin cost per month</th><th>% of patients</th><th>Total cost per month per patient</th></tr>
<tr><td colspan="7">Second line</td></tr>
<tr><td>Capecitabine</td><td>2x1250mg per day</td><td>Oral</td><td>£49.86</td><td>£265.64</td><td>18</td><td>£55.27</td></tr>
<tr><td>Tamoxifen</td><td>1 x 20mg per day</td><td>Oral</td><td>£1.44</td><td>£0.00</td><td>12</td><td>£0.17</td></tr>
<tr><td>Docetaxel</td><td>1 x 75mg/m^2 every 3 weeks</td><td>IV</td><td>£44.80</td><td>£341.91</td><td>10</td><td>£39.52</td></tr>
<tr><td>Everolimus</td><td>1 x 10mg per day</td><td>Oral</td><td>£2,673</td><td>£0.00</td><td>10</td><td>£273.15</td></tr>
<tr><td>Paclitaxel</td><td>1 x 260mg/m^2 every 3 weeks</td><td>IV</td><td>£62.39</td><td>£341.91</td><td>9</td><td>£38.36</td></tr>
<tr><td>Fulvestrant</td><td>2 x 250mg per month</td><td>Injection</td><td>£602.78</td><td>£92.07</td><td>7</td><td>£50.72</td></tr>
<tr><td>Other</td><td>N/A</td><td>N/A</td><td>£2,000</td><td>£341.91</td><td>34</td><td>£786.33</td></tr>
<tr><td colspan="6">Total</td><td>£1,243.53</td></tr>
<tr><td colspan="7">Third line</td></tr>
<tr><td>Capecitabine</td><td>2 x 1250mg per day</td><td>Oral</td><td>£49.86</td><td>£265.64</td><td>36</td><td>£112.42</td></tr>
<tr><td>Fulvestrant</td><td>2 x 250mg per month</td><td>Injection</td><td>£602.78</td><td>£92.07</td><td>15</td><td>£103.83</td></tr>
</table>
</td>
<td>Letrozole is the comparator and is used to reflect this class of treatments, but as noted in the company submission and also by the EMA in the EPAR for palbociclib, the three aromatase inhibitors are considered similar (letrozole, anastrozole, exemestane). Once a patient fails on first-line therapy (either palbociclib in combination with letrozole or letrozole alone), they would not be offered an aromatase inhibitor again; there is no evidence</td>
<td>Text deleted on page 3:
Using the results of a study[6] that analysed real-world treatment patterns of postmenopausal women with ER+/HER2- metastatic breast cancer in the UK, the ERG has estimated second- and third-line treatments in this population to cost £768 and £760 respectively (Table 2). The ERG estimates that the average cost of post-progression treatment, including the ERG's estimate of the cost of subsequent therapy and the company's estimate of health-state costs, is £1,146 (Table 3).
Additional text on page 3:
The ERG has investigated the use of post-progression</td>
</tr>
</table>

Tamoxifen	1 x 20mg per day	Oral	£1.44	£0.00	11	£0.17
Exemestane	1 x 25mg per day	Oral	£4.16	£0.00	8	£106.14
Eribulin	2 x 1.23mg/m^2 every 3 weeks	IV	£1,083.00	£236.19	30	£699.88
Other	N/A	N/A	£2,000	£341.91	36	£112.42
					Total	£1,022.44

Table 3 from the ERG Report

Line of therapy	Treatment cost	Health-state cost (company original model)	Total cost
Second	£1,243.53	£245.22	£1,488.75
Third	£1,022.44	£437.88	£1,460.32
Fourth	As third line	£636.98	£1,659.42
BSC	N/A	£975.38	£975.38
		Average	£1,395.96

The ICERs cited on page 4 should be updated to [redacted] and [redacted], respectively.

The ICER cited as the ERG's basecase on page 7 should be updated to [redacted].

supporting this. As such, including letrozole, anastrazole and exemestane in the model as subsequent treatments leads to an inaccurate estimate of the cost of later line therapies in this population.

treatments in the population being considered in this appraisal to find a justifiable figure to use in the model. It used the results of a study[6] that analysed real-world treatment patterns of postmenopausal women with ER+/HER2- metastatic breast cancer in the UK as a base and took into account clinical advice that it is realistic to assume that this population would receive capecitabine, taxanes (docetaxel and paclitaxel), fulvestrant and other endocrine therapies (tamoxifen and exemestane) in approximately equal proportions, with a small proportion (~5%) receiving everolimus+exemestane and the rest other treatments. Based on this analysis, the ERG has estimated post-progression treatments in this population to cost £760 per month (Table

			2). The ERG estimates that the average cost of the subsequent therapy lines (including the ERG's estimate of the cost of subsequent therapy and the company's estimate of health-state costs by line of therapy) is £1,200 (Table 3). The ERG has retained the company's estimate of BSC resource use and costs for patients receiving BSC. Table 2 amended to remove aromatase inhibitors and redistribute proportions based on clinical input. Table 3 amended based on results of table 2. ICERs amended on page 4 to [redacted] and [redacted] per QALY gained

Issue 3 Inaccurate reflection of clinical practice through application of later-line treatment costs into the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The application of costs within the model is not suitable and likely leads to an inaccurate reflection of practice.	Noting the corrections from Issues 1 and 2, the average cost of £1,395.96 should be applied as an average to all post-progression lines rather than individually applying the cost per line. The ICERs cited on page 4 should be updated to [redacted] and [redacted], respectively. The ICER cited as the ERG's basecase on page 7 should be updated to [redacted].	The model is not prepared to look at all subsequent lines in detail: 1. The model does not allow for consideration of fifth line or sixth line (or beyond). In practice, patients often have more than four lines of treatment. 2. The model uses an average (and somewhat arbitrary) estimate to suggest how long patients remain in subsequent lines (that is not treatment specific), i.e. the number of months in second line, third lien, etc. These are not treatment specific treatment durations and are not reflective of the average treatment duration of the treatments listed in the ERG's Table 2. 3. The model arbitrarily assumes that 25% of patients move to BSC after each line rather than continuing treatment (i.e. 25% of first line patients still alive do not progress to second line treatment but instead move to BSC; and likewise during second line to third line	The ERG has amended the model to include average costs of £1,199.89 for subsequent treatment lines, but not for BSC (see table 3). The most important issue here is that treatment costs should not be included for patients receiving BSC. Given the structure of the company's model, BSC should be considered separately from the second-, third- and fourth-line treatments. The company assumption that 25% of patients move to BSC after progression on a previous line of therapy was based on clinical opinion it received (CS, section 5.2.2). The ERG has not seen any evidence on which to base a revision of this evidence this estimate. It does not consider it plausible that 100% of patients would move to subsequent lines of therapy. The ERG has not amended this assumption. Text deleted on page 7:

		transition 25% proceed straight to BSC, and likewise from third line to fourth line in the model). The current model is sensitive to this input and application of detailed treatment costs per line interacts with this arbitrary assumption. Hence, considering the model is better set up to accommodate averages applied to later line treatment costs, the ERG's method of applying treatment related costs to each line specifically, rather than an average, conflicts with the above 3 points. As such, this can lead to factually inaccurate results. Furthermore, the model still does not consider any treatment related costs for the subsequent treatments such as adverse event management or additional monitoring, which leads to inaccurate costs if attempting to apply these in detail. It is thus more in line with the current model structure and can be considered a less inaccurate if an average treatment cost is applied to all lines, rather than a specific cost to each line. Hence, the average cost of £1,395.96 should be applied to all lines equally post-progression. This impacts the ICER, bringing the	the ERG's estimate of post-progression costs applied by line of therapy, and Additional text on page 7: the ERG's estimate and application of post-progression costs, and ICER amended on page 7 to [redacted].

		EERG's basecase to [redacted] when corrections in the other Issues are also considered (page 7 of the ERG Report).	

Additional note on model sensitivity to level of post-progression costs:

The ICER per QALY gained is sensitive to the cost of post-progression treatments, since treatment with PAL+LET in the model results in less time spent in the post-progression state than treatment with LET. This means that the longer the time spent in the post-progression state, the greater the proportionate cost of treatment with LET compared to treatment with PAL+LET, which results in lower ICERs per QALY gained for treatment with palbociclib (and vice versa).

The sensitivity of the model to the level of post-progression costs can be tested by removing all post-progression costs from the model (but retaining QALYs generated after progression). When using the company's unadjusted modelling of OS, removing all post-progression costs yields an ICER of [redacted] per QALY gained [redacted] greater than when the ERG's post-progression cost estimates are included). When using the company's adjusted modelling of OS (which decreases the difference in time spent in the post-progression state between the two treatments) removing all post-progression costs yields an ICER of [redacted] per QALY gained [redacted] greater than when the ERG's post-progression cost estimates are included).

ADDENDUM 3

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 13 September 2017

CONTAINS [redacted] DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

INTRODUCTION

This addendum contains critique of the revised economic case submitted to NICE by the company on the 7th August 2017 for the appraisal of palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer.

The company has made three changes to the cost-effectiveness model since its submission was last considered by the Appraisal Committee (AC) on the 8th July 2017: i) an increased Patient Access Scheme (PAS) discount on the price of palbociclib for use in the NHS; ii) increased post-progression costs; and iii) a higher utility value for the pre-progression health state.

Throughout this new submission, the company has used the AC's preferred modelling assumptions from the Appraisal Consultation Document (ACD) except where otherwise noted. Since the AC concluded in the ACD that it was plausible that overall survival (OS) gain might lie within a range of estimates, the company has provided ICERs per QALY gained based on two different methods for modelling OS: i) unadjusted modelling of the updated OS data as presented in its response to the ACD; and ii) adjusted modelling of OS (where OS gain equals progression-free survival [PFS] gain). The ERG prefers the unadjusted OS model, but has also provided revised ICER estimates using the adjusted OS model for completeness.

1 PATIENT ACCESS SCHEME DISCOUNT

The company's revised analysis includes a [redacted] discount on the palbociclib list price, which reduces the price per pack from £2,950 to [redacted]. All ICERs in this document include the company's updated PAS.

Applying the PAS to the company's cost-effectiveness model using the company's unadjusted modelling of OS yields an ICER of [redacted] per quality adjusted life year (QALY) gained. Applying the PAS to the company's cost-effectiveness model using the company's adjusted modelling of the updated OS data, so that OS gain equals PFS gain, yields an ICER of [redacted] per QALY gained.

2 POST-PROGRESSION COSTS

The ERG has identified two issues with the company's revised application of post-progression costs in its cost-effectiveness model: i) the company's revised estimate of post-progression health-state costs cannot be verified and ii) the company has included subsequent therapy

costs (e.g. drug acquisition costs, drug administration costs, etc) for patients receiving best supportive care (BSC), i.e. patients who are not receiving active therapy.

2.1 Post-progression health-state costs

The company quotes an updated resource use cost of £1,140 per cycle for the post-progression health-state, which the ERG has not been able to verify or replicate. This updated value is used in a scenario analysis in which only disease costs (e.g. monitoring, CT scans, etc) are included for patients in the post-progression health state. This scenario reflects the company's original base case; that is, only disease costs were included in the original model for patients in the post-progression state. The post-progression health-state costs from the original model are given in Table 1 for comparison.

Table 1 Post-progression health-state costs: original base case and updated scenario analysis

Line of treatment	Post-progression health-state costs	
	Original base case	Updated scenario analysis
Second	£245.22	£1,140
Third	£437.88	£1,140
Fourth	£636.98	£1,140
BSC	£975.38	£1,140
Average	***£573.86***	***£1,140***

Source: Company model

The company states that £1,140 is the cost of progressed disease given in NICE TA421[1] inflated to 2017 prices. NICE TA421[1] was published in late 2016 and is a review of NICE TA295,[2] which was published in 2013. The cost for progressed disease given in TA295,[2] at 2011 prices, was £802 per month. The company does not detail the methods it has used to increase £802 to £1,140, and the ERG has been unable to replicate the cost inflation using the Hospital and Community Health Services pay and price inflation index.[3] The company notes that the ERG involved in NICE ID1026[4] has suggested this uplifted cost for that appraisal. The documents for ID1026[4] were not publicly available at the time of writing this addendum, so the ERG has been unable to verify the values used in ID1026[4] or check whether they are applicable to this appraisal.

Without access to the assumptions or methods behind the company's updated post-progression health-state cost, the ERG is unable to identify the source of the difference between the company's original and updated post-progression health-state costs. The company's original cost estimates were based on Package 2 from NICE Clinical Guideline 81,[5] which was also the basis for the post-progression health-state costs used in TA295.[2] These were then updated with input from clinical nurse specialists in 2016. This means that

resource use and costs in the company's original submission were verified with current clinical experts. The company has not given any reasons for the discrepancy between the estimated resource use by its clinical expert panel and that which underlies its new cost estimate for the post-progression health-state, nor has it justified why the new figure is more appropriate. In the absence of any further evidence or justification for the new value, the ERG considers the company's original post-progression health-state costs to be more appropriate than its new estimate.

2.2 Subsequent therapy costs

The company has also amended post-progression costs in the model to include an estimate of the cost of subsequent therapies, which were not included in its original analysis. The ERG agrees that subsequent therapy costs should be included in the model. However, the company has added a cost for subsequent therapies for patients receiving BSC as well as for patients receiving treatment in lines two to four. This means that the company has included drug acquisition and administration costs for patients who are not receiving active therapy. The ERG considers it more appropriate to estimate the cost of BSC using only health-state costs.

The company estimates in its new base case that subsequent treatments cost £2,000 per cycle. cycle. This estimate is based on the company's analysis of the cost of later-line treatments for metastatic breast cancer that have previously been approved by NICE. The ERG notes that these treatments do not represent all subsequent treatments received by patients being treated treated for metastatic breast cancer. Using the results of a study[6] that analysed real-world treatment patterns of postmenopausal women with ER+/HER2- metastatic breast cancer in the UK, the ERG has estimated second- and third-line treatments in this population to cost £768 and £760 respectively (

Table 2). The ERG estimates that the average cost of post-progression treatment, including the ERG's estimate of the cost of subsequent therapy and the company's estimate of health-state costs, is £1,146 (Table 3).

Table 2 ERG estimated costs for second- and third-line therapies

Treatment	Regimen[7]	Admin method	Treatment cost per month	Admin cost per month	% of patients [6]	Total cost per month per patient
Second line						
Exemestane	1x25mg per day	Oral	£4.16[8]	£0.00*	17	£0.71
Capecitabine	2x1250mg per day	Oral	£24.44[8]	£0.00*	12	£2.93
Tamoxifen	1 x 20mg per day	Oral	£1.44[8]	£0.00*	8	£0.12
Anastrazole	1 x 1mg per day	Oral	£0.75[8]	£0.00*	7.5	£0.06
Letrozole	1 x 2.5mg per day	Oral	£1.55[8]	£0.00*	7	£0.11
Docetaxel	1 x 75mg/m^2 every 3 weeks[x]	IV	£30.95[8]	£236.19[9]	7	£18.70
Everolimus	1 x 10mg per day	Oral	£2,673[10]	£0.00*	7	£187.11
Paclitaxel	1 x 260mg/m^2 every 3 weeks[x]	IV	£43.10[8]	£236.19[9]	6.5	£18.15
Fulvestrant	2 x 250mg per month	Injection	£522.41[11]	£0.00*	5	£26.12
Other	N/A	N/A	£2,000[+]	£236.19[9]	23	£514.32
Total						£768.33
Third line						
Capecitabine	2 x 1250mg per day	Oral	£24.44[8]	£0.00*	31	£7.58
Fulvestrant	2 x 250mg per month	Injection	£522.41[12]	£79.79[11]	13	£78.29
Tamoxifen	1 x 20mg per day	Oral	£1.44[8]	£0.00*	10	£0.14
Exemestane	1 x 25mg per day	Oral	£4.16[8]	£0.00*	8	£0.33
Eribulin	2 x 1.23mg/m^2 every 3 weeks[x]	IV	£1083.00[13]	£236.19[9]	7	£92.34
Anastrazole	1 x 1mg per day	Oral	£0.75[8]	£0.00*	5	£0.04
Other	N/A	N/A	£2,000[+]	£236.19[9]	26	£581.41
					Total	£760.13

* Oral therapies are assumed to have no administration cost, although some pharmacy cost will apply
[+] Assumption based on company's analysis of the cost treatments recommended by NICE for metastatic breast cancer
[x] Body surface area assumed to be 1.75m^2 (average breast cancer)[14]
Source: Kurosky et al. 2015; NHS Reference Costs 2014/2015, eMIT; BNF; ERG calculations

Table 3 ERG estimated post-progression costs

Line of therapy	Treatment cost	Health-state cost (company original model)	Total cost
Second	£768.33	£245.22	£1,013.55
Third	£760.13	£437.88	£1,198.01
Fourth	As third line	£636.98	£1,397.11
BSC	N/A	£975.38	£975.38
		Average	£1,146.01

Source: Company model; this report, Table 2

When using the company's unadjusted modelling of OS, applying the ERG's estimated post-progression costs to the company's amended model yields an ICER of [redacted] per QALY gained. When using the company's adjusted modelling of OS (OS gain=PFS gain), applying the ERG's post-progression costs yields an ICER of [redacted] per QALY gained.

3 PRE-PROGRESSION HEALTH-STATE UTILITY VALUE

The company has increased the pre-progression health-state utility value to 0.772 (from 0.72), which it argues is more representative of the utility benefit associated with PFS in this indication. The ERG does not consider this updated utility value to be as appropriate as the AC preferred utility value (0.72). The AC preferred utility value for pre-progression is derived from the PALOMA-2 trial which, although a different trial to the trial from which survival data was taken (PALOMA-1), includes the same population and intervention as is being considered in this appraisal. The new value is taken from a trial for a different intervention and a different line of therapy than is being considered in this appraisal.[1]

The company has taken the value of 0.772 from NICE TA421,[1] which concerned a similar indication (women with HR+, HER-2 negative, metastatic breast cancer) to this appraisal but was related to second-line treatment rather than first line. The company argues that patients in pre-progression receiving treatment in the first line should logically have a utility value at least as high as patients who have progressed after first-line treatment and are now receiving second-line treatment. Therefore, patients in the pre-progression state in this appraisal should have a utility at least as high as patients in the pre-progression state in TA421.[1]

The ERG does not consider this argument to be robust enough to justify using another value from the literature instead of a utility value derived from a clinical trial that - although not the same trial as survival data were taken from - looked at the same intervention and the same population as is being considered in this appraisal.

4 CALCULATION OF ICER RANGE MIDPOINTS

Various ICERs in the company's new submission document are given as the midpoint of ranges, calculated as the arithmetic mean of two ICERs. The ERG does not consider these ICERs to be meaningful since the arithmetic mean of a range of ICERs yields only a mean of those ICERs and not a mean ICER, due to the statistical properties of ratios. Taking a mean of ICERs derived from varying the assumptions in a single model does not give the same result as calculating an ICER from the mean of the costs and mean of the QALYs generated by varying the same assumptions. When considering uncertainty in a single cost-effectiveness comparison, it is important to understand the relationship between the mean costs and mean benefits that arise from changing the parameters in a single model, as is reflected in the ICER. In contrast, a mean of ICERs would be appropriate for comparing, say, base case cost-effectiveness results across a number of appraisals.

The company has provided the range of ICERs used to calculate its midpoint ICERs in Table 2 and Table 3 of the appendix to its revised submission of the 7th August 2017. These ICERs are shown in Table 4 and Table 5 of this document. The ERG has verified the ICERs from these tables in the company model. The ERG considers these company ICERs to be more appropriate for decision making than the company's midpoint ICERs given elsewhere in its document.

The ERG notes that the upper and lower bound ICERs given in section 1 of the company's document ([redacted] and [redacted]) are not repeated in the company's appendix tables. The ERG has not been able to replicate these two ICERs in the company model.

Table 4 Company revised ICERs using unadjusted OS modelling

Lower OS bound	PFS utility = 0.72			PFS utility = 0.77		
	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Post-progression cost = £1,140	[redacted]	0.36	[redacted]	[redacted]	0.42	[redacted]
Post-progression cost = £2,000	[redacted]	0.36	[redacted]	[redacted]	0.42	[redacted]

Source: Table 2, Company revised economic case, 7 August 2017

Table 5 Company revised ICERs using adjusted OS modelling (OS gain = PFS gain)

Upper OS bound	PFS utility = 0.72			PFS utility = 0.77		
	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Post-progression cost = £1,140	[redacted]	0.60	[redacted]	[redacted]	0.65	[redacted]
Post-progression cost = £2,000	[redacted]	0.60	[redacted]	[redacted]	0.65	[redacted]

Source: Table 3, Company revised economic case, 7 August 2017

5 CONCLUSION

The ERG does not consider the company's revised post-progression health-state cost or revised pre-progression utility value to be appropriate. The ERG accepts the need to apply an estimate of subsequent therapy costs, but questions the company's estimate of these costs and their application in the model. The ERG maintains its position regarding the modelling of

the updated OS data, namely that the company's unadjusted OS model is more appropriate than the company's adjusted model where OS gain equals PFS gain.

In light of the company's revised economic case, the ERG's revised base case includes:

- the company's unadjusted OS model,
- the ERG's estimate of post-progression costs applied by line of therapy, and
- the AC's preferred pre-progression utility value of 0.72.

Taking into account the updated PAS, the ERG's revised base case ICER is [redacted] per QALY gained.

6 REFERENCES

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ADDENDUM 3 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 28 September 2017

CONTAINS [redacted] DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The company identified three issues in relation to factual inaccuracies in the original Evidence Review Group (ERG) report. These issues were cumulative and all related to the calculation of costs given in Table 2 of the ERG Addendum 3. 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.

INTRODUCTION

This addendum contains critique of the revised economic case submitted to NICE by the company on the 7th August 2017 for the appraisal of palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer.

The company has made three changes to the cost-effectiveness model since its submission was last considered by the Appraisal Committee (AC) on the 8th July 2017: i) an increased Patient Access Scheme (PAS) discount on the price of palbociclib for use in the NHS; ii) increased post-progression costs; and iii) a higher utility value for the pre-progression health state.

Throughout this new submission, the company has used the AC's preferred modelling assumptions from the Appraisal Consultation Document (ACD) except where otherwise noted. Since the AC concluded in the ACD that it was plausible that overall survival (OS) gain might lie within a range of estimates, the company has provided ICERs per QALY gained based on two different methods for modelling OS: i) unadjusted modelling of the updated OS data as presented in its response to the ACD; and ii) adjusted modelling of OS (where OS gain equals progression-free survival [PFS] gain). The ERG prefers the unadjusted OS model, but has also provided revised ICER estimates using the adjusted OS model for completeness.

1 PATIENT ACCESS SCHEME DISCOUNT

The company's revised analysis includes a *** discount on the palbociclib list price, which reduces the price per pack from £2,950 to ******. All ICERs in this document include the company's updated PAS.

Applying the PAS to the company's cost-effectiveness model using the company's unadjusted modelling of OS yields an ICER of ******* per quality adjusted life year (QALY) gained. Applying the PAS to the company's cost-effectiveness model using the company's adjusted modelling of the updated OS data, so that OS gain equals PFS gain, yields an ICER of ******* per QALY gained.

2 POST-PROGRESSION COSTS

The ERG has identified two issues with the company's revised application of post-progression costs in its cost-effectiveness model: i) the company's revised estimate of post-progression health-state costs cannot be verified and ii) the company has included subsequent therapy

costs (e.g. drug acquisition costs, drug administration costs, etc) for patients receiving best supportive care (BSC), i.e. patients who are not receiving active therapy.

2.1 Post-progression health-state costs

The company quotes an updated resource use cost of £1,140 per cycle for the post-progression health-state, which the ERG has not been able to verify or replicate. This updated value is used in a scenario analysis in which only disease costs (e.g. monitoring, CT scans, etc) are included for patients in the post-progression health state. This scenario reflects the company's original base case; that is, only disease costs were included in the original model for patients in the post-progression state. The post-progression health-state costs from the original model are given in Table 1 for comparison.

Table 1 Post-progression health-state costs: original base case and updated scenario analysis

Second	£245.22	£1,140
Third	£437.88	£1,140
Fourth	£636.98	£1,140
BSC	£975.38	£1,140
Average	***£573.86***	***£1,140***

Source: Company model

The company states that £1,140 is the cost of progressed disease given in NICE TA421[1] inflated to 2017 prices. NICE TA421[1] was published in late 2016 and is a review of NICE TA295,[2] which was published in 2013. The cost for progressed disease given in TA295,[2] at 2011 prices, was £802 per month. The company does not detail the methods it has used to increase £802 to £1,140, and the ERG has been unable to replicate the cost inflation using the Hospital and Community Health Services pay and price inflation index.[3] The company notes that the ERG involved in NICE ID1026[4] has suggested this uplifted cost for that appraisal. The documents for ID1026[4] were not publicly available at the time of writing this addendum, so the ERG has been unable to verify the values used in ID1026[4] or check whether they are applicable to this appraisal.

Without access to the assumptions or methods behind the company's updated post-progression health-state cost, the ERG is unable to identify the source of the difference between the company's original and updated post-progression health-state costs. The company's original cost estimates were based on Package 2 from NICE Clinical Guideline 81,[5] which was also the basis for the post-progression health-state costs used in TA295.[2] These were then updated with input from clinical nurse specialists in 2016. This means that

resource use and costs in the company's original submission were verified with current clinical experts. The company has not given any reasons for the discrepancy between the estimated resource use by its clinical expert panel and that which underlies its new cost estimate for the post-progression health-state, nor has it justified why the new figure is more appropriate. In the absence of any further evidence or justification for the new value, the ERG considers the company's original post-progression health-state costs to be more appropriate than its new estimate.

2.2 Subsequent therapy costs

The company has also amended post-progression costs in the model to include an estimate of the cost of subsequent therapies, which were not included in its original analysis. The ERG agrees that subsequent therapy costs should be included in the model. However, the company has added a cost for subsequent therapies for patients receiving BSC as well as for patients receiving treatment in lines two to four. This means that the company has included drug acquisition and administration costs for patients who are not receiving active therapy. The ERG considers it more appropriate to estimate the cost of BSC using only health-state costs.

The ERG has investigated the use of post-progression treatments in the population being considered in this appraisal to find a justifiable figure to use in the model. It used the results of a study[6] that analysed real-world treatment patterns of postmenopausal women with ER+/HER2- metastatic breast cancer in the UK as a base and took into account clinical advice that it is realistic to assume that this population would receive capecitabine, taxanes (docetaxel and paclitaxel), fulvestrant and other endocrine therapies (tamoxifen and exemestane) in approximately equal proportions, with a small proportion (~5%) receiving everolimus+exemestane and the rest other treatments. Based on this analysis, the ERG has estimated post-progression treatments in this population to cost £760 per month (Table 2). The ERG estimates that the average cost of the subsequent therapy lines (including the ERG's estimate of the cost of subsequent therapy and the company's estimate of health-state costs by line of therapy) is £1,200 (Table 3). The ERG has retained the company's estimate of BSC resource use and costs for patients receiving BSC.

Table 2 ERG estimated costs for post-progression therapies

Treatment	Regimen	Admin method	Treatment cost per month	Admin cost per month	% of patients	Total cost per month per patient
Capecitabine	2500mg/day for 2 weeks out of 3	Oral	£30.58[g]	£265.05[e]	20	£59.13
Docetaxel	1 x 75mg/m^2 every 3 weeks[d]	IV	£29.78[g]	£341.16[f]	10	£37.09
Paclitaxel	1 x 175mg/m^2 every 3 weeks[d]	IV	£49.59[g]	£341.16[f]	10	£39.08
Fulvestrant	2 x 250mg per month (double in first month)	Injection	£602.78[12]	£92.07	20	£138.97
Tamoxifen	1 x 20mg per day	Oral	£1.44[g]	£0.00[a]	10	£0.14
Exemestane	1 x 25mg per day	Oral	£4.16[g]	£0.00[a]	10	£0.42
Everolimus+ exemestane	Everolimus: 1x10mg/day Exemestane: 1x25mg/day	Oral	£2,673[c] £4.16[g]	£0.00[a]	5	£133.86
Other	N/A	N/A	£2,000[b]	£341.16[f]	15	£351.17
					Total	£759.86

[a] Assumed to have no administration cost, although some pharmacy cost will apply
[b] Assumption based on company's analysis of the cost treatments recommended by NICE for metastatic breast cancer
[c] BNF list price; however everolimus is available at a confidential discount to the NHS
[d] Body surface area assumed to be 1.75m^2 (average breast cancer)[14]
[e] NHS reference cost SB11Z Deliver exclusively oral chemotherapy £183.50 per cycle
[f] NHS reference cost SB12Z Deliver Simple Parenteral Chemotherapy at First Attendance £236.19 per cycle
[g] eMIT
Source: NHS Reference Costs 2014/2015, NICE TA239; eMIT; BNF; ERG calculations; clinical opinion

Table 3 ERG estimated post-progression costs

Line of therapy	Treatment cost	Health-state cost (company original model)	Total cost
Second	£759.86	£245.22	£1,005.08
Third	£759.86	£437.88	£1,197.74
Fourth	£759.86	£636.98	£1,396.84
		Average for treatment lines	£1,199.89
BSC	N/A	£975.38	£975.38

Source: Company model; this report, Table 2

When using the company's unadjusted modelling of OS, applying the ERG's estimated post-progression costs to the company's amended model yields an ICER of [redacted] per QALY gained. When using the company's adjusted modelling of OS (OS gain=PFS gain), applying the ERG's post-progression costs yields an ICER of [redacted] per QALY gained.

3 PRE-PROGRESSION HEALTH-STATE UTILITY VALUE

The company has increased the pre-progression health-state utility value to 0.772 (from 0.72), which it argues is more representative of the utility benefit associated with PFS in this indication. The ERG does not consider this updated utility value to be as appropriate as the AC preferred utility value (0.72). The AC preferred utility value for pre-progression is derived from the PALOMA-2 trial which, although a different trial to the trial from which survival data was taken (PALOMA-1), includes the same population and intervention as is being considered in this appraisal. The new value is taken from a trial for a different intervention and a different line of therapy than is being considered in this appraisal.[1]

The company has taken the value of 0.772 from NICE TA421,[1] which concerned a similar indication (women with HR+, HER-2 negative, metastatic breast cancer) to this appraisal but was related to second-line treatment rather than first line. The company argues that patients in pre-progression receiving treatment in the first line should logically have a utility value at least as high as patients who have progressed after first-line treatment and are now receiving second-line treatment. Therefore, patients in the pre-progression state in this appraisal should have a utility at least as high as patients in the pre-progression state in TA421.[1]

The ERG does not consider this argument to be robust enough to justify using another value from the literature instead of a utility value derived from a clinical trial that - although not the same trial as survival data were taken from - looked at the same intervention and the same population as is being considered in this appraisal.

4 CALCULATION OF ICER RANGE MIDPOINTS

Various ICERs in the company's new submission document are given as the midpoint of ranges, calculated as the arithmetic mean of two ICERs. The ERG does not consider these ICERs to be meaningful since the arithmetic mean of a range of ICERs yields only a mean of those ICERs and not a mean ICER, due to the statistical properties of ratios. Taking a mean of ICERs derived from varying the assumptions in a single model does not give the same result as calculating an ICER from the mean of the costs and mean of the QALYs generated by varying the same assumptions. When considering uncertainty in a single cost-effectiveness comparison, it is important to understand the relationship between the mean costs and mean benefits that arise from changing the parameters in a single model, as is reflected in the ICER. In contrast, a mean of ICERs would be appropriate for comparing, say, base case cost-effectiveness results across a number of appraisals.

The company has provided the range of ICERs used to calculate its midpoint ICERs in Table 2 and Table 3 of the appendix to its revised submission of the 7th August 2017. These ICERs are shown in Table 4 and Table 5 of this document. The ERG has verified the ICERs from these tables in the company model. The ERG considers these company ICERs to be more appropriate for decision making than the company's midpoint ICERs given elsewhere in its document.

The ERG notes that the upper and lower bound ICERs given in section 1 of the company's document ([redacted] and [redacted]) are not repeated in the company's appendix tables. The ERG has not been able to replicate these two ICERs in the company model.

Table 4 Company revised ICERs using unadjusted OS modelling

	[redacted]	0.36	[redacted]	[redacted]	0.42	[redacted]
	[redacted]	0.36	[redacted]	[redacted]	0.42	[redacted]

Source: Table 2, Company revised economic case, 7 August 2017

Table 5 Company revised ICERs using adjusted OS modelling (OS gain = PFS gain)

	[redacted]	0.60	[redacted]	[redacted]	0.65	[redacted]
	[redacted]	0.60	[redacted]	[redacted]	0.65	[redacted]

Source: Table 3, Company revised economic case, 7 August 2017

5 CONCLUSION

The ERG does not consider the company's revised post-progression health-state cost or revised pre-progression utility value to be appropriate. The ERG accepts the need to apply an estimate of subsequent therapy costs, but questions the company's estimate of these costs and their application in the model. The ERG maintains its position regarding the modelling of

the updated OS data, namely that the company's unadjusted OS model is more appropriate than the company's adjusted model where OS gain equals PFS gain.

In light of the company's revised economic case, the ERG's revised base case includes:

- the company's unadjusted OS model,
- *the ERG's estimate and application of post-progression costs, and*
- the AC's preferred pre-progression utility value of 0.72.

Taking into account the updated PAS, the ERG's revised base case ICER is [redacted] per QALY gained.

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ADDENDUM 3

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 13 September 2017
With corrected text 28 September 2017
(following response to company's factual error check)

CONTAINS [redacted] DATA

UNIVERSITY OF LIVERPOOL
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP
A MEMBER OF THE RUSSELL GROUP

INTRODUCTION

This addendum contains critique of the revised economic case submitted to NICE by the company on the 7th August 2017 for the appraisal of palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer.

The company has made three changes to the cost-effectiveness model since its submission was last considered by the Appraisal Committee (AC) on the 8th July 2017: i) an increased Patient Access Scheme (PAS) discount on the price of palbociclib for use in the NHS; ii) increased post-progression costs; and iii) a higher utility value for the pre-progression health state.

Throughout this new submission, the company has used the AC's preferred modelling assumptions from the Appraisal Consultation Document (ACD) except where otherwise noted. Since the AC concluded in the ACD that it was plausible that overall survival (OS) gain might lie within a range of estimates, the company has provided ICERs per QALY gained based on two different methods for modelling OS: i) unadjusted modelling of the updated OS data as presented in its response to the ACD; and ii) adjusted modelling of OS (where OS gain equals progression-free survival [PFS] gain). The ERG prefers the unadjusted OS model, but has also provided revised ICER estimates using the adjusted OS model for completeness.

1 PATIENT ACCESS SCHEME DISCOUNT

The company's revised analysis includes a [redacted] discount on the palbociclib list price, which reduces the price per pack from £2,950 to [redacted]. All ICERs in this document include the company's updated PAS.

Applying the PAS to the company's cost-effectiveness model using the company's unadjusted modelling of OS yields an ICER of [redacted] per quality adjusted life year (QALY) gained. Applying the PAS to the company's cost-effectiveness model using the company's adjusted modelling of the updated OS data, so that OS gain equals PFS gain, yields an ICER of [redacted] per QALY gained.

2 POST-PROGRESSION COSTS

The ERG has identified two issues with the company's revised application of post-progression costs in its cost-effectiveness model: i) the company's revised estimate of post-progression

health-state costs cannot be verified and ii) the company has included subsequent therapy costs (e.g. drug acquisition costs, drug administration costs, etc) for patients receiving best supportive care (BSC), i.e. patients who are not receiving active therapy.

2.1 Post-progression health-state costs

The company quotes an updated resource use cost of £1,140 per cycle for the post-progression health-state, which the ERG has not been able to verify or replicate. This updated value is used in a scenario analysis in which only disease costs (e.g. monitoring, CT scans, etc) are included for patients in the post-progression health state. This scenario reflects the company's original base case; that is, only disease costs were included in the original model for patients in the post-progression state. The post-progression health-state costs from the original model are given in Table 1 for comparison.

Table 1 Post-progression health-state costs: original base case and updated scenario analysis

Line of treatment	Post-progression health-state costs	
	Original base case	Updated scenario analysis
Second	£245.22	£1,140
Third	£437.88	£1,140
Fourth	£636.98	£1,140
BSC	£975.38	£1,140
Average	***£573.86***	***£1,140***

Source: Company model

The company states that £1,140 is the cost of progressed disease given in NICE TA421[1] inflated to 2017 prices. NICE TA421[1] was published in late 2016 and is a review of NICE TA295,[2] which was published in 2013. The cost for progressed disease given in TA295,[2] at 2011 prices, was £802 per month. The company does not detail the methods it has used to increase £802 to £1,140, and the ERG has been unable to replicate the cost inflation using the Hospital and Community Health Services pay and price inflation index.[3] The company notes that the ERG involved in NICE ID1026[4] has suggested this uplifted cost for that appraisal. The documents for ID1026[4] were not publicly available at the time of writing this addendum, so the ERG has been unable to verify the values used in ID1026[4] or check whether they are applicable to this appraisal.

Without access to the assumptions or methods behind the company's updated post-progression health-state cost, the ERG is unable to identify the source of the difference between the company's original and updated post-progression health-state costs. The company's original cost estimates were based on Package 2 from NICE Clinical Guideline 81,[5] which was also the basis for the post-progression health-state costs used in TA295.[2]

These were then updated with input from clinical nurse specialists in 2016. This means that resource use and costs in the company's original submission were verified with current clinical experts. The company has not given any reasons for the discrepancy between the estimated resource use by its clinical expert panel and that which underlies its new cost estimate for the post-progression health-state, nor has it justified why the new figure is more appropriate. In the absence of any further evidence or justification for the new value, the ERG considers the company's original post-progression health-state costs to be more appropriate than its new estimate.

2.2 Subsequent therapy costs

The company has also amended post-progression costs in the model to include an estimate of the cost of subsequent therapies, which were not included in its original analysis. The ERG agrees that subsequent therapy costs should be included in the model. However, the company has added a cost for subsequent therapies for patients receiving BSC as well as for patients receiving treatment in lines two to four. This means that the company has included drug acquisition and administration costs for patients who are not receiving active therapy. The ERG considers it more appropriate to estimate the cost of BSC using only health-state costs.

The ERG has investigated the use of post-progression treatments in the population being considered in this appraisal to find a justifiable figure to use in the model. It used the results of a study[6] that analysed real-world treatment patterns of postmenopausal women with ER+/HER2- metastatic breast cancer in the UK as a base and took into account clinical advice that it is realistic to assume that this population would receive capecitabine, taxanes (docetaxel and paclitaxel), fulvestrant and other endocrine therapies (tamoxifen and exemestane) in approximately equal proportions, with a small proportion (~5%) receiving everolimus+exemestane and the rest other treatments. Based on this analysis, the ERG has estimated post-progression treatments in this population to cost £760 per month (Table 2). The ERG estimates that the average cost of the subsequent therapy lines (including the ERG's estimate of the cost of subsequent therapy and the company's estimate of health-state costs by line of therapy) is £1,200 (Table 3). The ERG has retained the company's estimate of BSC resource use and costs for patients receiving BSC.

Table 2 ERG estimated costs for post-progression therapies

Treatment	Regimen	Admin method	Treatment cost per month	Admin cost per month	% of patients	Total cost per month per patient
Capecitabine	2500mg/day for 2 weeks out of 3	Oral	£30.58[g]	£265.05[e]	20	£59.13
Docetaxel	1 x 75mg/m^2 every 3 weeks[d]	IV	£29.78[g]	£341.16[f]	10	£37.09
Paclitaxel	1 x 175mg/m^2 every 3 weeks[d]	IV	£49.59[g]	£341.16[f]	10	£39.08
Fulvestrant	2 x 250mg per month (double in first month)	Injection	£602.78[12]	£92.07	20	£138.97
Tamoxifen	1 x 20mg per day	Oral	£1.44[g]	£0.00[a]	10	£0.14
Exemestane	1 x 25mg per day	Oral	£4.16[g]	£0.00[a]	10	£0.42
Everolimus+ exemestane	Everolimus: 1x10mg/day Exemestane: 1x25mg/day	Oral	£2,673[c] £4.16[g]	£0.00[a]	5	£133.86
Other	N/A	N/A	£2,000[b]	£341.16[f]	15	£351.17
					Total	£759.86

[a] Assumed to have no administration cost, although some pharmacy cost will apply
[b] Assumption based on company's analysis of the cost treatments recommended by NICE for metastatic breast cancer
[c] BNF list price; however everolimus is available at a confidential discount to the NHS
[d] Body surface area assumed to be 1.75m^2 (average breast cancer)[14]
[e] NHS reference cost SB11Z Deliver exclusively oral chemotherapy £183.50 per cycle
[f] NHS reference cost SB12Z Deliver Simple Parenteral Chemotherapy at First Attendance £236.19 per cycle
[g] eMIT
Source: NHS Reference Costs 2014/2015, NICE TA239; eMIT; BNF; ERG calculations; clinical opinion

Table 3 ERG estimated post-progression costs

Line of therapy	Treatment cost	Health-state cost (company original model)	Total cost
Second	£759.86	£245.22	£1,005.08
Third	£759.86	£437.88	£1,197.74
Fourth	£759.86	£636.98	£1,396.84
		Average for treatment lines	£1,199.89
BSC	N/A	£975.38	£975.38

Source: Company model; this report, Table 2

When using the company's unadjusted modelling of OS, applying the ERG's estimated post-progression costs to the company's amended model yields an ICER of [redacted] per QALY gained. When using the company's adjusted modelling of OS (OS gain=PFS gain), applying the ERG's post-progression costs yields an ICER of [redacted] per QALY gained.

3 PRE-PROGRESSION HEALTH-STATE UTILITY VALUE

The company has increased the pre-progression health-state utility value to 0.772 (from 0.72), which it argues is more representative of the utility benefit associated with PFS in this indication. The ERG does not consider this updated utility value to be as appropriate as the AC preferred utility value (0.72). The AC preferred utility value for pre-progression is derived from the PALOMA-2 trial which, although a different trial to the trial from which survival data was taken (PALOMA-1), includes the same population and intervention as is being considered in this appraisal. The new value is taken from a trial for a different intervention and a different line of therapy than is being considered in this appraisal.[1]

The company has taken the value of 0.772 from NICE TA421,[1] which concerned a similar indication (women with HR+, HER-2 negative, metastatic breast cancer) to this appraisal but was related to second-line treatment rather than first line. The company argues that patients in pre-progression receiving treatment in the first line should logically have a utility value at least as high as patients who have progressed after first-line treatment and are now receiving second-line treatment. Therefore, patients in the pre-progression state in this appraisal should have a utility at least as high as patients in the pre-progression state in TA421.[1]

The ERG does not consider this argument to be robust enough to justify using another value from the literature instead of a utility value derived from a clinical trial that - although not the same trial as survival data were taken from - looked at the same intervention and the same population as is being considered in this appraisal.

4 CALCULATION OF ICER RANGE MIDPOINTS

Various ICERs in the company's new submission document are given as the midpoint of ranges, calculated as the arithmetic mean of two ICERs. The ERG does not consider these ICERs to be meaningful since the arithmetic mean of a range of ICERs yields only a mean of those ICERs and not a mean ICER, due to the statistical properties of ratios. Taking a mean of ICERs derived from varying the assumptions in a single model does not give the same result as calculating an ICER from the mean of the costs and mean of the QALYs generated by varying the same assumptions. When considering uncertainty in a single cost-effectiveness comparison, it is important to understand the relationship between the mean costs and mean benefits that arise from changing the parameters in a single model, as is reflected in the ICER. In contrast, a mean of ICERs would be appropriate for comparing, say, base case cost-effectiveness results across a number of appraisals.

The company has provided the range of ICERs used to calculate its midpoint ICERs in Table 2 and Table 3 of the appendix to its revised submission of the 7th August 2017. These ICERs are shown in Table 4 and Table 5 of this document. The ERG has verified the ICERs from these tables in the company model. The ERG considers these company ICERs to be more appropriate for decision making than the company's midpoint ICERs given elsewhere in its document.

The ERG notes that the upper and lower bound ICERs given in section 1 of the company's document ([redacted] and [redacted]) are not repeated in the company's appendix tables. The ERG has not been able to replicate these two ICERs in the company model.

Table 4 Company revised ICERs using unadjusted OS modelling

Lower OS bound	PFS utility = 0.72			PFS utility = 0.77		
	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Post-progression cost = £1,140	[redacted]	0.36	[redacted]	[redacted]	0.42	[redacted]
Post-progression cost = £2,000	[redacted]	0.36	[redacted]	[redacted]	0.42	[redacted]

Source: Table 2, Company revised economic case, 7 August 2017

Table 5 Company revised ICERs using adjusted OS modelling (OS gain = PFS gain)

Upper OS bound	PFS utility = 0.72			PFS utility = 0.77		
	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Post-progression cost = £1,140	[redacted]	0.60	[redacted]	[redacted]	0.65	[redacted]
Post-progression cost = £2,000	[redacted]	0.60	[redacted]	[redacted]	0.65	[redacted]

Source: Table 3, Company revised economic case, 7 August 2017

5 CONCLUSION

The ERG does not consider the company's revised post-progression health-state cost or revised pre-progression utility value to be appropriate. The ERG accepts the need to apply an estimate of subsequent therapy costs, but questions the company's estimate of these costs and their application in the model. The ERG maintains its position regarding the modelling of the updated OS data, namely that the company's unadjusted OS model is more appropriate than the company's adjusted model where OS gain equals PFS gain.

In light of the company's revised economic case, the ERG's revised base case includes:

- the company's unadjusted OS model,
- *the ERG's estimate and application of post-progression costs, and*
- the AC's preferred pre-progression utility value of 0.72.

Taking into account the updated PAS, the ERG's revised base case ICER is [redacted] per QALY gained.

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ADDENDUM 4
With PAS from 28/09/17

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 02 October 2017

CONTAINS [redacted] DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 PATIENT ACCESS SCHEME DISCOUNT

The final company case (dated 28 September 2017) includes a [redacted] discount on the palbociclib list price, which reduces the price per pack from £2,950 to [redacted]. All ICERs in this document refer to the company's updated PAS.

2 POST-PROGRESSION COSTS

When using the company's unadjusted modelling of OS and the company's PFS utility value (0.772), applying the ERG's estimated post-progression costs to the company's amended model yields an ICER of [redacted] per QALY gained. When using the company's adjusted modelling of OS (OS gain=PFS gain) and the company's PFS utility value, applying the ERG's post-progression costs yields an ICER of [redacted] per QALY gained.

3 CONCLUSION

In light of the company's revised economic case, the ERG's revised base case includes:

- the company's unadjusted OS model,
- the ERG's estimate and application of post-progression costs (£1,200 to lines two to four and £975 to BSC), and
- the AC's preferred pre-progression utility value of 0.72.

Taking into account the PAS from 28 September 2017, the ERG's revised base case ICER is [redacted] per QALY gained.

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
[redacted]	Patient		I have secondary breast cancer - having first been diagnosed with metastatic cancer in 2007 - and was on the Paloma-3 clinical trial via The Royal Marsden Hospital from June 2014 until April 2016 with Fulvestrant as an additional drug and Zoladex. I was fortunate to get the drugs and not be on the placebo trial. Within weeks the latest tumour in my vertabrae had shrunk. I work full time as a national newspaper sports writer and was able within weeks as well to cover the Commonwealth Games in Glasgow. Throughout the period on the drug I worked full-time, in a job which took me as far as China and Brazil for weeks at a time, and paid a higher rate of tax. The side-effects in terms of other drugs I have experienced were minimal making it more cost-effective in my opinion than others. The current drug I am on which is older and not as advanced has already caused a side effect which meant I had to go in an NHS ambulance to the local A&E hospital and have treatment there within weeks of going on the drug and I am told this could happen again - more cost to the system. There are very few drugs on the market for secondary breast cancer patients and as more women are surviving longer with primaries then further down the line they are likely to have secondaries. The drug does not cost much more over two years than older drugs which are not as effective. I was able to have a normal life with no time off work. In addition I had to care for my 86 year old mother with dementia. She is not eligible for state care so again I was and currently needed to sort out private care as she deteriorated while I was on this drug. This has saved the NHS money and social services. In terms of OS rates, secondary cancer survival rates are themseleves sketchy and in some health authorities often non-existent. As I understood it Paloma-3 was stopped early because of the early results which meant the drug could be fast-tracked for a licence. I am still living as a result of this drug and believe other women should be able to access it on the NHS. When I was accepted on the trial I remember telling the Royal Marsden staff that it would help other women further down the line. I feel strongly that drugs that have been shown to have clear results with minimal side-effects should be available to as many people as possible, especially as private health companies are in some cases now following NICE guidelines on new drugs too	Sports Journalist	England	No

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[redacted]	Carer		The cost for routine commissioning of Palbociclib is unlikely to be met for some time. My daughter is 32 years old, she has a daughter of her own who is 9 years old. Her breast cancer diagnosis was delayed by 9 months because a biopsy was not offered when she first presented at age 29 with a breast lump to the consultant at our local hospital. I understand that NICE guidelines at the time did not provide for routine biopsy for young patients. There must be other young women in the same situation who have been poorly served by the NICE guidance for diagnosis. The delayed diagnosis is directly related to the progression to the secondary metasteses she now has. "Progression free survival state is consistently undervalued in technology appraisals" 10 extra months of progression free survival to a 32 year old woman with a 9 year old daughter would be of great value. If NICE approves the use of Palbociclib where the progression free survival state would be most beneficial and where patient's do not have other health problems, rather than for routine use, it would provide more evidence on overall survival in an otherwise healthy group of women and would be helpful in assessing the benefits of Palbociclib to overall survival. The fact that Palbociclib is available but too expensive for NHS use adds insult to injury for my daughter whose delayed diagnosis had a profound affect on her well being and will have already shortened her life. It will be a tragedy when my granddaughter loses her mum, if this can be delayed it will be a very good thing for her and if this group of younger patients in similar situations can be helped by the drug Palbciclib then the		Wales	No

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			quality of life for many people will be improved not just the patients themselves. I would appreciate if you could take this into account when you consider the cost to benefit of this new and optimistic line of treatment, thank you.			
[redacted]		NHS Professional	Agree with the committee decision that at tis point in time, PFS benefit without OS benefit does not justify the routine use given the high cost involved but it should be reconsidered if better deal can be negotiated with Pfizer even with the PFS benefit as it will save costs in chemotherapy use, the treatment of complications of chemotherapy, less time off work for patients and carer thus contributing to wider financial economy (not taken in to account in current models, therefore resulting in higher costs per QALY than acceptable).	Consulatnt Medical Oncologist	England	No

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
[redacted]	Patient organisation	Breast Cancer Care	At Breast Cancer Care we hear from people living with secondary breast cancer every day about their hopes for new treatments. It is devastating access to palbociclib is being blocked. We are aware that, in addition to other factors, cost has played a significant role in this draft appraisal decision. Urgent conversations between NICE, NHS England and Pfizer need to take place. We hope that a way forward is found so that people living with the disease can have access to this ground breaking drug.	Policy Manager	England	N/A
[redacted]	Pharmaceutical Industry	Novartis Pharmaceuticals UK Ltd	"At Breast Cancer Care we hear from people living with secondary breast cancer every day about their hopes for new treatments. It is devastating access to palbociclib is being blocked. We are aware that, in addition to other factors, cost has played a significant role in this draft appraisal decision. Urgent conversations between NICE, NHS England and Pfizer need to take place. We hope that a way forward is found so that people living with the disease can have access to this ground breaking drug. " "Novartis would like to thank the National Institute for Health and Care Excellence (NICE) Technology Appraisal Committee for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. 1. Has all the relevant evidence been taken into account? Novartis considers that all the relevant clinical evidence for this appraisal been taken into account. 2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Novartis considers that that NICEâ€™s interpretation of the clinical and cost effectiveness evidence is reasonable and fair.	Health Economics & Outcomes Research Manager	England	NO

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			Novartis support the committeeâ€™s assertion that given the benefit for improvement in progression-free survival shown by the intervention treatment CDK 4/6 inhibitor palbociclib, it was likely this would result in improvement in overall survival. Additionally, while chemotherapy was not considered an appropriate comparator within this appraisal, it should be noted that recent market research indicates that chemotherapy is used as a first-line treatment in up to 36% of the licenced population assessed within this appraisal. 3. Are the recommendations sound and a suitable basis for guidance to the NHS? Yes 4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Novartis does not consider that there are any aspects of the recommendations that require particular consideration in this regard.			
[redacted] (Concerns raised by constituents)	MP	Government	I understand that Palbociclib is a first line treatment option for patients with hormone positive, HER2 negative secondary breast cancer. I also understand that, in clinical trials, palbociclib with letrozole provides around ten additional months of progression-free survival compared to letrozole alone. Secondary breast cancer is incurable, so ten months of extra life represents time in which women with the diagnosis can continue to be with family and friends, to work, and to contribute to the community.			

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			The draft recommendation to reject palbociclib comes just weeks after NICE announced its decision to reject Kadcyla, another innovative drug that can extend the lives of women with secondary breast cancer. The provisional decisions to reject these drugs appears to highlight flaws in NICEâ€™s ineffective drug appraisal process, which is not working for secondary breast cancer patients. In reviewing the draft recommendation to reject palbociclib, I would urge you to consider the flaws in applying NICEâ€™s current drug appraisal process, to this treatment: First, progression-free survival is not given sufficient weight in the appraisal system. Because palbociclib allows patients to live longer without their condition progressing, there is, as yet, little data available on overall survival. This lack of overall survival data has contributed to this provisional rejection. The drug is used in many countries and has little side effects and can enable people to live life as normal. The fact that it stops people getting worse when they are not too bad should be more important than drugs which prolong life for people who are suffering greatly. Currently the appraisal process does not give sufficient weighting to quality of life as opposed to quantity of life. Second, comparing new treatments to generic treatments makes it virtually impossible for them to be considered cost effective. It takes ten years for a drug to lose its licence and become generic and thereby usually become cheaper. The average life expectancy for someone with secondary breast cancer is three years. Affected patients cannot wait for these drugs to become generic. Thirdly, ten months may not sound a long time but for someone with a "life limiting" diagnosis in middle age, every day is special. This drug is one of several that is used in sequence, so on its own it is not a huge amount of			

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			time but added to other time that other drugs give, it makes the prognosis slightly more bearable. Finally, there needs to be greater flexibility around the criteria for being considered an end-of-life treatment. NICE has a higher cost threshold for end-of-life treatments, which it defines as treatments used in the final two years of life. This figure appears arbitrary when compared to drug appraisals in Scotland, where end-of-life is defined as the final three years of life. Also, is it not positive to offer drugs that give a decent quality of life to the relatively well?			
[redacted]	Carer		I have seen first hand the good this drug can do as my wife, [redacted] was part of a clinical trial at the Royal Marsden. Just over two years ago, having an original diagnosis of secondary cancer, of origin in either breast or uterus (most likely breast), she was told that the cancer had spread to lymph nodes in the chest and a tumour was growing in her lower back. She was put on the trial for palbociclib at the Marsden and her progress was immediate. The tumour shrank and the drug worked effectively for two years. Its effectiveness having reduced, she was taken off the trial and is now on the next phase of treatment on a different drug. That, though, is two years of good life given by the drug she might not otherwise have had. I therefore urge NICE to reconsider its decision not to make palbociclib more widely available to people, especially as it has, I understand, potential to be used in prostate cancer, which is the most common male cancer and from which I myself suffer.			

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			I would like more to benefit from the life extension that my wife has experienced, with the consequent bonus not just for them but all the families and friends around them. I would also like more development of the drug for use on prostate cancer. [redacted]			