NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]

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. **Consultee and commentator comments on the Appraisal Consultation Document from:**
   - Roche
   - Breast Cancer Now

3. **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

Pertuzumab for treating HER2 positive 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 companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

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 appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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
Roche	**1. Has all of the relevant evidence been taken into account?** <u>HER2+ Metastatic breast cancer treatments</u> As mentioned in the cover letter, there is complexity regarding the inclusion of CDF funded treatments within this appraisal, which has a significant impact on the ICER. Within the ACD the Committee noted that they would like to see scenarios which exclude the CDF funded metastatic breast cancer treatments of Kadcyla and Perjeta. These are presented below. We would like to make the Committee aware that the inclusion of Kadcyla and Perjeta as metastatic treatments within the modelled patient pathway was discussed with NICE at the decision problem meeting in December 2015, at which time no questions or concerns were raised. In addition, at the same meeting we sought advice from NICE as to how to incorporate confidential discounts for metastatic treatments that are in place within the CDF. The advice given, and followed, was to include the metastatic treatments at list price and present a threshold analysis showing the percentage discount that would need to be in place to take the ICER up to £30,000. In the worst case scenario, if funding were lost during the CDF rapid review for both Kadcyla and Perjeta as metastatic treatments, the ICER rises to £22,696 and £37,281 under the Roche and ERG base cases, with 62% and 28% chance of being cost-effective respectively at a £30,000 WTP. Roche are committed to exploring all avenues to allow patients to continue to benefit from these transformational medicines and it is our belief and hope that they will remain available to patients in the longer term. In the more optimistic scenario where funding is retained for both metastatic treatments, the discounts on these drugs would need to be as high as 40% to raise the ICER to £30k, (applied to the ERG base case). Alternatively, using the Roche base case, even with a 100% discount on these metastatic drugs, the ICER would not reach £30,000. This approach has been necessary to protect the confidential agreement between Roche and NHS England that already exist within the CDF. With the agreement of NHS England we are willing to disclose the effective discount on CDF funded treatment in line with section 3 of the NICE guidance “Handling of products on the CDF”.	Thank you for your comments. Please see FAD section 4.12.

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>As mentioned in the cover letter we would like to signal our intention to offer a risk mitigation strategy against a change in funding or price of the CDF funded medicines. Details will be provided by 16th June as agreed with the Programme Director for Technology Appraisals.

Table 1: Scenarios assuming loss of mBC treatment funding
<table>
<tr><td></td><td></td><td></td><td colspan="2">PSA % Chance CE at £30,000 per QALY gained</td></tr>
<tr><td></td><td>Roche</td><td>ERG</td><td>Roche</td><td>ERG</td></tr>
<tr><td>Kadcyla and Perjeta mBC treatments not available*</td><td>£23,985</td><td>£37,281</td><td>62%</td><td>28%</td></tr>
</table>
Table 2: Threshold analysis regarding CDF funded metastatic breast cancer treatments
<table>
<tr><td></td><td>ICER</td><td>% discount required for CDF funded mBC treatments to raise ICER to £30k</td></tr>
<tr><td>Roche Base case</td><td>£8,215</td><td>100% = £26,324 ICER</td></tr>
<tr><td>ERG Base case</td><td>£23,467</td><td>40%</td></tr>
</table></td><td></td></tr>
<tr><td>Roche</td><td><u>CTNeoBC meta-analysis - population</u>

The Committee noted within the ACD that they would like to see the results both using the HER2-positive population from CTNeoBC meta-analysis and also using the total population. These ICERs have already been presented in the appraisal to date. The ICER is £8,215 using the HER2-positve population and £19,939 using the total population.
We consider that the HER2-positive population is the most appropriate, and it was always our intention to use this. It is our understanding that the ERG supports this position as did the clinical advisors who</td><td>Thank you for your comments.</td></tr>
</table>

Consultee	Comment [sic]	Response
	attended the Committee meeting.	
Roche	**2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** <u>Substantial limitations of the comparative data</u> The committee commented on the limitations of data from the phase II, open-label trials NeoSphere and TRYPHAENA studies and concluded it has substantial limitations. Whilst we agree that the points noted in the ACD are factually correct (including small patient numbers, open label, lack of long term efficacy data). We would like to highlight that blinding is almost universally absent from oncology trials, mainly due to the nature of the interventions (cytotoxic drugs) and the associated toxicities and method of administration and additionally both NeoSphere and TRYPHAENA had met the criteria set by the EMA where approval of medicines is based on pCR. (Further detail provided in Appendix 2); based on this, Perjeta as neoadjuvant treatment in HER2-positive early breast cancer was subsequently granted its EU licence. (Further detail provided in Appendix 2). This serves to highlight the regrettable mismatch between the regulatory process which seeks to bring novel therapies to market faster to benefit patients, and the HTA process, which is often unable to make a positive recommendation given the above mentioned data limitations.	Thank you for your comments. Please see FAD section 4.3. Please see FAD section 4.12.
Roche	<u>Totality of evidence base for Perjeta</u> In the neoadjuvant setting it is correct that the only relevant comparative data is NeoSphere and TRYPHAENA. However there is a strong totality of evidence base for Perjeta which has been referenced within the submission. Although TRYPHAENA was primarily designed as a cardiac safety study, tpCR rates for all 3 arms in this study were high (>50%). These results are important, as this provides clinical evidence on the efficacy and safety of adding Perjeta to the most commonly used Herceptin-based chemotherapy regimens in the UK., which differs to the regimens evaluated from the pivotal study NOAH (patietns received 11 cycles of Herceptin-based neoadjuvant treatment prior to surgery). Traditional endpoints such as DFS, EFS and OS only represent one of the goals of neoadjuvant treatment and do not reflect tumour re-staging or improved cosmesis. To predefine survival outcomes	Thank you for your comments. Please see FAD section 4.3.

Consultee	Comment [sic]	Response
	in neoadjuvant clinical trials is almost impossible due to the short duration of treatment before surgery, compared to the long duration (years) of treatment required to evaluate survival outcomes, such as from adjuvant clinical trials. The evaluation of novel breast cancer therapies in the neoadjuvant setting thus depend on improvements in intermediate endpoints transforming into clinically meaningful increases in survival rates. Prior to obtaining the neoadjuvant licence for the treatment of early HER2-positive breast cancer prior to surgery, the importance and clinical benefits of dual HER2 blockade with anti-HER2 targeted therapies have been demonstrated from the CLEOPATRA study. This was a phase III, randomised, placebo-controlled trial in 808 patients which evaluated the combination of 2 anti-HER2 targeted therapies, Perjeta and Herceptin, with docetaxel versus Herceptin, docetaxel and placebo in HER2-positive metastatic breast cancer. Results of this study showed superior survival benefits versus the placebo arm; this large study also generated sufficient safety data to enable the EMA to grant an EU licence in metastatic indication. Based on the totality of evidence presented on the clinical benefits of dual HER2 blockade with 2 targeted therapies, as well as confirmatory survival data from the ongoing APHINITY study, we believe that there is sufficient comparative clinical evidence regarding the efficacy and safety of Perjeta across its licenced indications, including, as neoadjuvant treatment in HER2-positive early breast cancer.	

Consultee	Comment [sic]	Response
Roche	<u>Pathological Complete Response</u> The committee has expressed concerns over the wide confidence intervals for pathological complete response (pCR) in both the intervention and the comparator arms, and their associated uncertainty. It should be noted that this uncertainty in the pCR ranges is incorporated in the Probabilistic Sensitivity analysis (PSA) and also tested within deterministic sensitivity analysis. We acknowledge that varying the pCR rates has the ability to significantly move the ICER from a low of £6k to a high of £76k (using ERG base case); this analysis shows the impact of varying each arm individually to the extremes of the confidence interval. There is no reason to believe the lower end of the range is any less plausible than the upper end. Several studies in HER2-positive early breast cancer have demonstrated the positive association of achieving pCR and improvement in long-term outcomes such as event-free survival (EFS). These include: **NOAH** study (Gianni et al): in patients who received Herceptin neoadjuvant treatment, pCR was strongly associated with improved EFS versus patients who did not received Herceptin treatment. This study was also included as part of the CTNeoBC meta-analysis by Cortazar et al. **HannaH** study (Jackisch et al): Patients who achieved tpCR had a >60% reduction in the risk of an EFS event compared with those who did not: HR 0.38 (95% CI 0.22e0.65) in the subcutaneous arm and 0.32 (95% CI 0.18e0.60) in the intravenous arm. Results of the meta-analysis of 5,768 patients with HER2-positive early breast cancer by Broglio et al also provides further evidence of the association of pCR with improved long-term outcomes such as EFS in patients with early disease.	Thank you for your comments. Please see FAD section 4.5.
Roche	<u>Overestimation of treatment effect in NeoSphere</u> The ACD notes that the treatment effect may have been overestimated in NeoSphere “because not all major treatments were given in the neoadjuvant setting (for example anthracyclines).” We are unclear from the description in the ACD how this conclusion was reached and disagree that this is the case The NeoSphere study was designed to isolate the treatment effect of the addition of Perjeta to Herceptin from potential confounding additional chemotherapy, including antracyclines. Considering that NeoSphere clearly demonstrates that the addition of Perjeta to Herceptin has a positive impact on pCR, then it is entirely reasonable to assume based on the pCR results in TRYPHEANA that the	Thank you for your comments. This text has now been removed from the final appraisal determination.

Consultee	Comment [sic]	Response
	combination of both anthracycline and non-anthracycline based chemotherapy, Perjeta and Herceptin in the neoadjuvant setting result in at least as positive effect on pCR as that seen in NeoSphere.	
Roche	Number of cycles of Perjeta It is our belief from research carried out with UK clinicians that Perjeta is most likely to be used in combination with FEC-Herceptin and docetaxel for 3 cycles. If Perjeta is used for 6 cycles, it is most likely to be used with the Herceptin, docetaxel and carboplatin regimen, rather than concomitant FEC due to concerns with cardiotoxicity. Four cycles is mostly based on regimens used in US clinical practice and is the number of cycles used in NeoSphere.	Thank you for your comment. Please see FAD section 4.13.
Roche	Breast Conservation Surgery The ACD notes that according to NICE GC80, there is an “increased risk of local recurrence with breast-conserving surgery and radiotherapy compared with mastectomy after systemic therapy “ The last update for NICE CG80 was in 2009, since then there have been many scientific advances. These have evaluated not only the outcomes and safety of breast-conserving surgery (BCS) versus mastectomy, but in particular the use of neoadjuvant therapy, which in some patients, can enable breast-conserving surgery instead of a mastectomy. Recent data presented at the San Antonio Breast Cancer Conference 2015 from a Dutch Cancer Registry of approximately 37,000 patients (where 58% of patients had BCS) showed an improvement in 10-year survival in patients who received BCS compared to mastectomy, at every tumour size and nodal status stage. Although there were cofounding factors such as younger patients with small tumours in the BCS group, these results showed that BCS may in fact improve overall survival (van Maaren et al. 2016).	Thank you for your comments. Reference to the clinical guideline has now been removed.

Consultee	Comment [sic]	Response
Roche	<u>Comparator treatments and generalizability of Neosphere to UK clinical practce</u> Within the ACD is it noted that 25% of HER2-positive patients who receive neoadjuvant treatment do not receive a regimen containing Herceptin. The implication in the ACD is that the treatment received by these patients should be considered as a comparator within this appraisal. Since Perjeta is an additive therapy to Herceptin, it is only those patients who are eligible to receive Herceptin that can be prescribed Perjeta. Therefore we do not consider that the treatments received by these 25% of HER2-positive patients are applicable to this appraisal. The use of docetaxel as the sole chemotherapy partner with Herceptin is challenged as being the sole comparator within this appraisal. We would like to clarify that market research shows that docetaxel is used as part of a treatment regimen in 68% of total HER2-positive neoadjuvant treatments measured across 2015. Herceptin and docetaxel are used in 62% of all regimens. If we consider only the sub-set of patients who are receiving Herceptin (and are therefore eligible to receive Perjeta); docetaxel and Herceptin combination comprises the overwhelming majority of treatments at 79% of the total. Of the remaining patients 9% receive Herceptin in combination with paclitaxel with or without anthracycline and for the remaining 11% the combination partner is a mix of anthracycline, or unknown partner therapy. We therefore acknowledge that there are patients who receive alternative regimens to Herceptin and docetaxel, but that the regimens that make up the total are fragmented and are likely to have limited ability to inform this appraisal. Expert opinion has confirmed that the baseline characteristics of the patient selection for the NeoSphere trial do not differ greatly from the population seen in the UK. This also applies to the patients enrolled in the TRYPHAENA study, which does not differ greatly to the UK population.	Thank you for your comment. Please see FAD section 4.6.
Roche	<u>SMC v NICE</u> A full breakdown of the difference in the parameter values and assumptions between these two submissions is provided in an appendix to this ACD response, together with an explanation of the rationale for each. This provides a step by step analysis of the impact of applying each different parameter or assumption from the NICE cost-effectiveness analysis to the SMC base case. It can be seen that there are five drivers of the differences in QALYs, Costs and ICER (Table 3) and applying the NICE parameters to the SMC model produces near identical ICER, QALYs and Costs Table 3: Reconciliation of ICER. QALY and Costs between SMC and NICE base case	Thank you for your comments. Please see FAD section 4.8.

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>
<table>
<tr><th>Driver</th><th>Parameter</th><th>Impact on SMC ICER</th><th>Impact on SMC Incremental QALY</th><th>Impact on SMC Incremental Costs</th></tr>
<tr><td>1</td><td>Metastatic treatment availability</td><td></td><td></td><td></td></tr>
<tr><td></td><td>Cost of 1L mBC treatments</td><td>-£2,739</td><td>0</td><td>-£833</td></tr>
<tr><td></td><td>Cost of 2L mBC treatments</td><td>-£13,860</td><td>0</td><td>-£4,215</td></tr>
<tr><td></td><td>Transition probabilities from mBC non progressed to progressed</td><td>-£130</td><td>-0.004</td><td>-£190</td></tr>
<tr><td></td><td>Transition probabilities from mBC progressed to death</td><td>+£310</td><td>-0.003</td><td>-£21</td></tr>
<tr><td>2</td><td>Capping of utility values to not exceed that of the general population of the same age</td><td>+£6,351</td><td>-0.048</td><td>£0</td></tr>
<tr><td>3</td><td>Country specific population mortality tables</td><td>-£1,420</td><td>0.013</td><td>-£3</td></tr>
<tr><td>4</td><td>Metastatic progressed utility value</td><td>-£331</td><td>0.003</td><td>0</td></tr>
<tr><td>5</td><td>BSA</td><td>+£4</td><td>0</td><td>£1</td></tr>
<tr><td>1-5</td><td>Impact of applying all</td><td>-£16776</td><td>-0.041</td><td>-£5806</td></tr>
<tr><td></td><td>SMC base case</td><td>£34,100</td><td>0.304</td><td>£10,370</td></tr>
<tr><td></td><td>NICE base case</td><td>£17,297</td><td>0.263</td><td>£4,557</td></tr>
<tr><td></td><td>Difference between base cases</td><td>-£16,803</td><td>-0.041</td><td>-£5,813</td></tr>
</table>
</td><td></td></tr>
<tr><td>Roche</td><td>3. Are the recommendations a sound and suitable basis for guidance to the NHS?
Although, significant uncertainty exists, as described within the ACD and above, much of this is as a result of the difference in the data accepted by the regulatory bodies versus that required by HTA bodies such as NICE. In particular the need for a robust way to predict overall survival required by</td><td>Thank you for your comments. Please see FAD section 4.12.</td></tr>
</table>

Consultee	Comment [sic]	Response
	NICE and other HTA bodies. There are items highlighted within the ACD as driving significant uncertainty which we believe have occurred due to lack of clarity within our company submission, rather than being a source of true uncertainty. These include the differences between the SMC and NICE ICER, QALY and cost values, which we hope have now been justified (Appendix 1). For example the metastatic utility value which was explicitly highlighted in the ACD, drives a minor increase in the ICER of less than £300 if applied to the ERG base case or £100 against the Roche base case. In addition the inclusion of CDF funded treatments within the patient pathway, produces uncertainty regarding the future availability of these treatments. This is a factor of the CDF rapid review process, and we welcome the guidance that NICE has recently provided on how these should be factored into this appraisal. To aid in the decision making we have provided scenarios without these treatments and also threshold analysis (the latter being in line with the advice we received from NICE at the early stage of this appraisal). We hope this will aid the Committees decision making in this respect. The reported ICERs fall within a range typically considered cost-effective and in many cases substantially below that. There is a strong totality of evidence that supports the clinical effectiveness and safety of Perjeta within the HER2-positive breast cancer treatment pathway. Clinical advisors to the Committee agreed that pCR is a good indicator of long term benefit and in addition expressed the importance and benefits of neoadjuvant treatment to patients. Perjeta has held a marketing authorisation in the UK for use as neoadjuvant therapy for HER2-positive early breast cancer since July 2015. In the interim, patients have been unable to benefit from this treatment as no funding route was available. Regrettably the NICE appraisal for this treatment will not produce guidance until September 2016 at the earliest. If the current ACD becomes guidance, patients will still be unable to benefit from this treatment. We would like to signal our intent to offer a risk mitigation scheme for Perjeta against a change in funding situation or price of the CDF funded metastatic breast cancer treatments contained in the patient pathway. We ask the Committee to reconsider the evidence and clarity provided in this response in conjunction with the risk mitigation scheme (which will follow on 13th June), to allow patients in England and Wales to benefit from Perjeta as neoadjuvant treatment.	
Roche	References Gianni L, Eiermann W, Semiglazov V et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 2010; 375: 377–84 Jackisch C, Hegg R, Stroyakovskiy D et al. HannaH phase III randomised study: Association of total	Thank you for your response.

Consultee	Comment [sic]	Response
	pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. EU J of Cancer 2016; 62: 62-75 Broglio et al. Association of Pathologic Complete Response to Neoadjuvant Therapy in HER2-Positive Breast Cancer With Long-Term Outcomes. JAMA Oncol. http://oncology.jamanetwork.com/article.aspx?articleid=2492724 van Maaren M, de Munck L, de Bock G, Jobsen J, van Dalen T, Poortmans P, et al. Higher 10-year overall survival after breast conserving therapy compared to mastectomy in early stage breast cancer: A population-based study with 37,207 patients. Cancer Res 2016;76: Abstract nr S3–05) Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. British Journal of Cancer (2006) 95, 683 – 690 Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014; 384(9938): 164-172	
Breast Cancer Now	Breast Cancer Now welcomes the opportunity to comment on the appraisal consultation document regarding the use of pertuzumab for the treatment of primary HER2 positive breast cancer in the neoadjuvant setting. We did not have any comments specific to the questions in the consultation paper but wanted to highlight a few important points arising from this Technology Appraisal.	Thank you for your comments.
Breast Cancer Now	**Neoadjuvant medicines** The level and type of evidence presented by the pharmaceutical company to support the submission for pertuzumab neoadjuvant was the main reason why this drug has been given a draft rejection by NICE: *"The committee concluded that there was considerable uncertainty about whether pathological complete response was a meaningful indicator of long-term survival outcomes, such that it could be viewed as a surrogate marker of long-term benefit."* Whilst we agree that no standard relationship is proven between a complete response rate and overall survival, we believe that this presents a problem for this type of medicines. For breast cancer drugs used in the neoadjuvant setting, overall survival is likely to take at least 15 years to collect. Waiting for this long before making a decision about whether a treatment can be made available on the NHS would means that patients are facing unacceptable delays for potentially innovative treatments. We believe that this is a significant issue for pharmaceutical companies, as exclusivity patents would be very close to expiry by the time overall survival data comes in. This raises a question about how further innovation in these types of drugs would be incentivised in the future. We would like NICE to refer this	Thank you for your comments. Please see FAD section 4.5. Please see FAD section 4.12.

Consultee	Comment [sic]	Response
	question to the NICE Decision Support Unit in order to: 1. produce guidance for companies, which may be working on neoadjuvant cancer drugs of the future, to set out clearly what kinds of evidence companies will need to provide in order to gain a NICE approval 2. assess and analyse the issue of neoadjuvant drugs more broadly to decide whether seeking overall survival is appropriate for these types of medicines, given the very long times frames involved, especially comparing to the level of evidence NICE requires for cancer and other long term conditions and whether this is comparable.	
Breast Cancer Now	**Patient subset** Whilst the patient population set to benefit from this treatment is very small, it could be a very important treatment option. The majority of breast cancers are diagnosed in stages 1 and 2. Furthermore, only around 15% of breast cancers have HER2 positive receptor status. This medicine may be important for a very small group of patients, who are diagnosed with diagnosed with inflammatory or locally advanced HER2 positive breast cancer. Inflammatory breast cancer is very rare but a particularly aggressive form of breast cancer. Patients with this type of cancer are therefore more likely to be diagnosed in later stages. Whilst this type of information was included in the scope of the appraisal, we are not sure whether this was given due weight and consideration in the Committee meeting. For example, patients in whom HER2 positive breast cancer is too advanced to operate on are already given a combination of trastuzumab and chemotherapies with the intention of shrinking the tumour so that it becomes operable. If a tumour is not operable, this is associated with a poor long term prognosis. Therefore a medicine in this setting, which increases the likelihood of good response, means that patients in this very small subsection potentially have better chances of curative treatment.	Thank you for your comments. Please see FAD section 1.1.
Breast Cancer Now	**Cancer Drugs Fund** The purpose of the new Cancer Drugs Fund (CDF) is for use in instances where the evidence is insufficient or the uncertainty is too high to make a routine commissioning decision[1]. Based on the reasons given for this drug's rejection, it would seem that pertuzumab ought to be considered for a place on the new CDF. Whilst we appreciate that it would take a long time to collect additional data on overall survival, we would have liked to have seen it considered for the CDF, in light of the fact that this medicine has produced some impressive results and would be eligible to a very small patient population. Furthermore, the timing of this Technology Appraisal is problematic. At the time of the Appraisal, there was a level of uncertainty caused by the changes to the CDF. This is evident in some of the comments made in the Committee papers: *"The committee considered that it would have liked to have seen an analysis from the company which*	Thank you for your comments. Please see FAD section 4.12.

Consultee	Comment [sic]	Response
	included a scenario in which CDF-funded drugs were excluded." Guidance has not made it clear whether new drugs would be considered in light of medicines currently available via the CDF or whether these are to be excluded from the analysis. Whilst these medicines are not available via routine commissioning at this time, the CDF is part of the access environment in England, even if the future of access to these medicines is uncertain. NICE needs to provide clear guidance to cover the period whilst CDF drugs are re-assessed, so that any new medicines being appraised are assessed fairly. Furthermore, the launch of the new Fund has been delayed by three months, which would have not be been known at the beginning of the appraisal process. This delay has excluded the chances of this drug being considered for use on the CDF, yet it could have been expected to be otherwise, as the new CDF was due to be launched on 1st April 2016 1 CDF consultation document. NHS England and NICE, Nov 2015.	
Breast Cancer Now	**Review period** For the reasons given above and because the assessment of this innovative use of the medicine just missed out on the possibility of having an option to be considered for entry into the new CDF, we would suggest that a review period of 3 years is too long. This is further supported by the fact that a last minute decision was made with regards to the start of the new Cancer Drugs Fund, where this was delayed from the original start date of 1st April to 1st July. The company involved in this appraisal, may well have planned to have the CDF as an option with the timing of their Technology Appraisal. However, before another appraisal happens, we would like the NICE Decision Support Unit to feed back on the two areas we raised as being important to ensure that future medicines in this category have a fair chance of appraisal and so that this type of medicines are appropriately incentivised. This will be important for the benefit of cancer patients, who may well benefit from innovative medicines like these in the future.	Thank you for your comments. Please see FAD section 1.1.

Comments received from clinical experts and patient experts

No comments received.

Comments received from commentators

No comments received.

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Public		I would like to stress the benefits of this combination of drugs. I have stage 4 her2 breast cancer and have been on this combination of drugs (including zometa) since November 2012. I am now on cycle 59. Without this I would not have had the luxury of time with my family which includes 3 children. The youngest two being 6 and 8. I would like to think this treatment options remains available to women like me for the foreseeable future otherwise you are committing us to an early death sentence. Please take the experiences of real people on board before making such devastating decisions.	Thank you for your comments. Please see FAD section 1.1. and 4.12.
Public		Disgraceful recommendation - What is the point of cancer research and testing, if drugs that are discovered, developed and proved to help are always blocked due to expense? Maybe the system and questions by which you make your "informed" decision is out of date and perhaps that should be subjected to a "Fit for purpose" test? Who cares about the overall long term benefits when the short term benefits could mean the difference between a life saving operation or not?	Thank you for your comments. Please see FAD section 1.1 and 4.12.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', '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.

[redacted]
Appraisal Project Manager – Committee A
National Institute for Health and Care Excellence
10 Spring Gardens
SW1A 2BU
London
BY EMAIL

13th June 2016

Re: ID767 Neoadjuvant Perjeta (pertuzumab) for the treatment of HER2-positive early breast cancer

Dear Marcia

Thank you for the opportunity to a comment on the ACD. Despite the disappointing ACD decision, Roche remain committed to working with NICE to reach a positive outcome. The many positive benefits of neoadjuvant treatment were eloquently expressed by the clinical experts and the patient during the first appraisal committee and we are confident that Perjeta as a neoadjuvant treatment provides an important treatment option that improves outcomes for patients with HER2-positive disease.

Challenges of assessing early breast cancer medicines

We acknowledge that significant uncertainty does exist in the modelling of long-term clinical effectiveness, due to the difficulty of evaluating long-term outcomes of medicines in the early breast cancer setting and that much benefit is seen significantly later in the patient pathway.

We appreciate that the assessment of an early breast cancer medicine holds significant challenges within a Health Technology Assessment process. In the case of Perjeta, the pivotal trial (NeoSphere) was not designed for registration purposes, however the strong results led us to seek marketing authorisation to allow patients to benefit from this treatment at the earliest opportunity. We acknowledge that within the NICE assessment process the decision making criteria differs to that used by the regulators and that translating the pathological complete response (pCR) endpoint into long term survival in a robust manner over the lifetime of a patient is particularly challenging.

CDF rapid review

Today we became aware of guidance published by NICE on June 2nd, regarding how CDF funded treatments will be considered in an appraisal such as this. We welcome this clarity, which provides a firm basis for ourselves and the Committee to progress. We have not been able to fully consider the implications of this guidance within this response and are grateful that the offer to provide additional input in this respect has been extended to us through to 16th June. It will be our intention to provide a risk mitigation scheme, and will provide details within these timelines.

Additional complexity within this appraisal has been the timing of the Cancer Drugs Fund (CDF) rapid review for metastatic breast cancer (mBC) treatments (Kadcyla (trastuzumab emtansine) and Perjeta). The concurrent timing is unfortunate, and outside of ours and the Committees control. Metastatic treatments are an inherent part of the treatment pathway for early breast cancer patients and have a significant impact on the ICER. Within the ACD response we supply analysis which shows the impact of

the loss of funding for these medicines has to the ICER for this appraisal. In addition, and as agreed with NICE earlier in the appraisal process, we supply a threshold analysis to show by how much the price of the CDF funded treatments would need to fall to raise the ICER to £30,000 per QALY gained.

Roche consider that predetermining the outcome of the CDF review process and the potential impact on the treatment pathway before it has concluded would seem inappropriate. We are committed to exploring all avenues to allow patients to continue to benefit from these transformational medicines and it is our belief and hope that we can find a solution to secure long term funding.

Differences between the SMC cost effectiveness results and NICE

The Committee has also expressed significant concern regarding the differences between the ICERs in the HTA submission to the SMC and NICE for this indication. Although we provided an explanation upon request on 29th March and offered to supply further detail if required, this was felt to be inadequate by the Committee and had the highly regrettable consequence of casting doubt over the validity of our entire submission and the reputation of Roche.

Further to our letter dated 26th April we would once again like to put it on record that it has never been our intention to withhold evidence or to mislead the Committee in any way - and we are greatly concerned that the Committee and NICE more widely have interpreted our actions in this way.

In an appendix to the ACD response we provide additional clarity on the differences between the two evaluations and hope that this provides the re-assurance the Committee desires. This supports the prior information supplied to NICE that the main drivers of the differences in costs, QALYs and ICERs are the metastatic treatments available in Scotland versus England and in addition the utility cap which was implemented in the NICE submission (which has the effect of increasing the ICER in the NICE analysis).

Seeking Baseline funding

We are seeking baseline funding for this treatment since this provides sustainable access and the potential for all eligible patients to be considered for treatment. We are engaging with clinicians to explore options for data collection that may be able to meet the needs of the new CDF process. If the Committee ultimately feel that the uncertainty in the clinical data remains too great to make a positive recommendation, we would appreciate the opportunity to discuss all options that would result in satisfactory resolution of the adjudged uncertainty.

Although considerable uncertainty exists in the long term survival estimations, in the majority of sensitivity analysis, the ICER remains below £30,000 per QALY gained. It is our intention to submit a risk mitigation scheme as outlined above and hope that this will reduce the uncertainty regarding the impact of the CDF funded medicines upon this appraisal.

We would be happy to supply any further detail that the Committee require to aid their decision making

Yours sincerely

[redacted]

Head of Health Economics and Strategic Pricing

Response to ACD

1. Has all of the relevant evidence been taken into account?

HER2+ Metastatic breast cancer treatments

As mentioned in the cover letter, there is complexity regarding the inclusion of CDF funded treatments within this appraisal, which has a significant impact on the ICER. Within the ACD the Committee noted that they would like to see scenarios which exclude the CDF funded metastatic breast cancer treatments of Kadcyla and Perjeta. These are presented below.

We would like to make the Committee aware that the inclusion of Kadcyla and Perjeta as metastatic treatments within the modelled patient pathway was discussed with NICE at the decision problem meeting in December 2015, at which time no questions or concerns were raised. In addition, at the same meeting we sought advice from NICE as to how to incorporate confidential discounts for metastatic treatments that are in place within the CDF. The advice given, and followed, was to include the metastatic treatments at **list price** and present a threshold analysis showing the percentage discount that would need to be in place to take the ICER up to £30,000.

In the worst case scenario, if funding were lost during the CDF rapid review for both Kadcyla and Perjeta as metastatic treatments, the ICER rises to £22,696 and £37,281 under the Roche and ERG base cases, with 62% and 28% chance of being cost-effective respectively at a £30,000 WTP. Roche are committed to exploring all avenues to allow patients to continue to benefit from these transformational medicines and it is our belief and hope that they will remain available to patients in the longer term.

In the more optimistic scenario where funding is retained for both metastatic treatments, the discounts on these drugs would need to be as high as 40% to raise the ICER to £30k, (applied to the ERG base case). Alternatively, using the Roche base case, even with a 100% discount on these metastatic drugs, the ICER would not reach £30,000.

This approach has been necessary to protect the confidential agreement between Roche and NHS England that already exist within the CDF. With the agreement of NHS England we are willing to disclose the effective discount on CDF funded treatment in line with section 3 of the NICE guidance "Handling of products on the CDF".

As mentioned in the cover letter we would like to signal our intention to offer a risk mitigation strategy against a change in funding or price of the CDF funded medicines. Details will be provided by 16th June as agreed with the Programme Director for Technology Appraisals.

Table 1: Scenarios assuming loss of mBC treatment funding

			PSA % Chance CE at £30,000 per QALY gained	
	Roche	**ERG**	**Roche**	**ERG**
Kadcyla and Perjeta mBC treatments not available*	£23,985	£37,281	62%	28%

Table 2: Threshold analysis regarding CDF funded metastatic breast cancer treatments

	ICER	% discount required for CDF funded mBC treatments to raise ICER to £30k
Roche Base case	£8,215	100% = £26,324 ICER
ERG Base case	£23,467	40%

CTNeoBC meta-analysis - population

The Committee noted within the ACD that they would like to see the results both using the HER2-positive population from CTNeoBC meta-analysis and also using the total population. These ICERs have already been presented in the appraisal to date. The ICER is £8,215 using the HER2-positve population and £19,939 using the total population.

We consider that the HER2-positive population is the most appropriate, and it was always our intention to use this. It is our understanding that the ERG supports this position as did the clinical advisors who attended the Committee meeting.

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

Substantial limitations of the comparative data

The committee commented on the limitations of data from the phase II, open-label trials NeoSphere and TRYPHAENA studies and concluded it has substantial limitations. Whilst we agree that the points noted in the ACD are factually correct (including small patient numbers, open label, lack of long term efficacy data). We would like to highlight that blinding is almost universally absent from oncology trials, mainly due to the nature of the interventions (cytotoxic drugs) and the associated toxicities and method of administration and additionally both NeoSphere and TRYPHAENA had met the criteria set by the EMA where approval of medicines is based on pCR. (Further detail provided in Appendix 2); based on this, Perjeta as neoadjuvant treatment in HER2-positive early breast cancer was subsequently granted its EU licence. (Further detail provided in Appendix 2).

This serves to highlight the regrettable mismatch between the regulatory process which seeks to bring novel therapies to market faster to benefit patients, and the HTA process, which is often unable to make a positive recommendation given the above mentioned data limitations.

Totality of evidence base for Perjeta

In the neoadjuvant setting it is correct that the only relevant comparative data is NeoSphere and TRYPHAENA. However there is a strong totality of evidence base for Perjeta which has been referenced within the submission.

Although TRYPHAENA was primarily designed as a cardiac safety study, tpCR rates for all 3 arms in this study were high (>50%). These results are important, as this provides clinical evidence on the efficacy and safety of adding Perjeta to the most commonly used Herceptin-based chemotherapy regimens in the UK., which differs to the regimens evaluated from the pivotal study NOAH (patietns received 11 cycles of Herceptin-based neoadjuvant treatment prior to surgery).

Traditional endpoints such as DFS, EFS and OS only represent one of the goals of neoadjuvant treatment and do not reflect tumour re-staging or improved cosmesis. To predefine survival outcomes in neoadjuvant clinical trials is almost impossible due to the short duration of treatment before surgery, compared to the long duration (years) of treatment required to evaluate survival outcomes, such as from adjuvant clinical trials. The evaluation of novel breast cancer therapies in the neoadjuvant setting thus depend on improvements in intermediate endpoints transforming into clinically meaningful increases in survival rates.

Prior to obtaining the neoadjuvant licence for the treatment of early HER2-positive breast cancer prior to surgery, the importance and clinical benefits of dual HER2 blockade with anti-HER2 targeted therapies have been demonstrated from the CLEOPATRA study. This was a phase III, randomised, placebo-controlled trial in 808 patients which evaluated the combination of 2 anti-HER2 targeted therapies, Perjeta and Herceptin, with docetaxel versus Herceptin, docetaxel and placebo in HER2-positive metastatic breast cancer. Results of this study showed superior survival benefits versus the placebo arm; this large study also generated sufficient safety data to enable the EMA to grant an EU licence in metastatic indication.

Based on the totality of evidence presented on the clinical benefits of dual HER2 blockade with 2 targeted therapies, as well as confirmatory survival data from the ongoing APHINITY study, we believe that there is sufficient comparative clinical evidence regarding the efficacy and safety of Perjeta across its licenced indications, including, as neoadjuvant treatment in HER2-positive early breast cancer.

Pathological Complete Response

The committee has expressed concerns over the wide confidence intervals for pathological complete response (pCR) in both the intervention and the comparator arms, and their associated uncertainty. It should be noted that this uncertainty in the pCR ranges is incorporated in the Probabilistic Sensitivity analysis (PSA) and also tested within deterministic sensitivity analysis. We acknowledge that varying the pCR rates has the ability to significantly move the ICER from a low of £6k to a high of £76k (using ERG base case); this analysis shows the impact of varying each arm individually to the extremes of the confidence interval. There is no reason to believe the lower end of the range is any less plausible than the upper end.

Several studies in HER2-positive early breast cancer have demonstrated the positive association of achieving pCR and improvement in long-term outcomes such as event-free survival (EFS).

These include:

NOAH study (Gianni et al): in patients who received Herceptin neoadjuvant treatment, pCR was strongly associated with improved EFS versus patients who did not received Herceptin treatment. This study was also included as part of the CTNeoBC meta-analysis by Cortazar et al.

HannaH study (Jackisch et al): Patients who achieved tpCR had a >60% reduction in the risk of an EFS event compared with those who did not: HR 0.38 (95% CI 0.22e0.65) in the subcutaneous arm and 0.32 (95% CI 0.18e0.60) in the intravenous arm.

Results of the meta-analysis of 5,768 patients with HER2-positive early breast cancer by Broglio et al also provides further evidence of the association of pCR with improved long-term outcomes such as EFS in patients with early disease.

Overestimation of treatment effect in NeoSphere

The ACD notes that the treatment effect may have been overestimated in NeoSphere "because not all major treatments were given in the neoadjuvant setting (for example anthracyclines)." We are unclear from the description in the ACD how this conclusion was reached and disagree that this is the case

The NeoSphere study was designed to isolate the treatment effect of the addition of Perjeta to Herceptin from potential confounding additional chemotherapy, including antracyclines. Considering that NeoSphere clearly demonstrates that the addition of Perjeta to Herceptin has a positive impact on pCR, then it is entirely reasonable to assume based on the pCR results in TRYPHEANA that the combination of both anthracycline and non-anthracycline based chemotherapy, Perjeta and Herceptin in the neoadjuvant setting result in at least as positive effect on pCR as that seen in NeoSphere.

Number of cycles of Perjeta

It is our belief from research carried out with UK clinicians that Perjeta is most likely to be used in combination with FEC-Herceptin and docetaxel for 3 cycles. If Perjeta is used for 6 cycles, it is most likely to be used with the Herceptin, docetaxel and carboplatin regimen, rather than concomitant FEC due to concerns with cardiotoxicity.
Four cycles is mostly based on regimens used in US clinical practice and is the number of cycles used in NeoSphere.

Breast Conservation Surgery

The ACD notes that according to NICE GC80, there is an "increased risk of local recurrence with breast-conserving surgery and radiotherapy compared with mastectomy after systemic therapy "

The last update for NICE CG80 was in 2009, since then there have been many scientific advances. These have evaluated not only the outcomes and safety of breast-conserving surgery (BCS) versus mastectomy, but in particular the use of neoadjuvant therapy, which in some patients, can enable breast-conserving surgery instead of a mastectomy. Recent data presented at the San Antonio Breast Cancer Conference 2015 from a Dutch Cancer Registry of approximately 37,000 patients (where 58% of patients had BCS) showed an improvement in 10-year survival in patients who received BCS compared to mastectomy, at every tumour size and nodal status stage. Although there were cofounding factors such as younger patients with small tumours in the BCS group, these results showed that BCS may in fact improve overall survival (van Maaren *et al*. 2016).

Comparator treatments and generalizability of Neosphere to UK clinical practce

Within the ACD is it noted that 25% of HER2-positive patients who receive neoadjuvant treatment do not receive a regimen containing Herceptin. The implication in the ACD is that the treatment received by these patients should be considered as a comparator within this appraisal.

Since Perjeta is an additive therapy to Herceptin, it is only those patients who are eligible to receive Herceptin that can be prescribed Perjeta. Therefore we do not consider that the treatments received by these 25% of HER2-positive patients are applicable to this appraisal.

The use of docetaxel as the sole chemotherapy partner with Herceptin is challenged as being the sole comparator within this appraisal. We would like to clarify that market research shows that docetaxel is used as part of a treatment regimen in 68% of total HER2-positive neoadjuvant treatments measured across 2015. Herceptin and docetaxel are used in 62% of all regimens. If we consider only the sub-set of patients who are receiving Herceptin (and are therefore eligible to receive Perjeta); docetaxel and Herceptin combination comprises the overwhelming majority of treatments at 79% of the total. Of the remaining patients 9% receive Herceptin in combination with paclitaxel with or without anthracycline and for the remaining 11% the combination partner is a mix of anthracycline, or unknown partner therapy.

We therefore acknowledge that there are patients who receive alternative regimens to Herceptin and docetaxel, but that the regimens that make up the total are fragmented and are likely to have limited ability to inform this appraisal.

Expert opinion has confirmed that the baseline characteristics of the patient selection for the NeoSphere trial do not differ greatly from the population seen in the UK. This also applies to the patients enrolled in the TRYPHAENA study, which does not differ greatly to the UK population.

SMC v NICE

A full breakdown of the difference in the parameter values and assumptions between these two submissions is provided in an appendix to this ACD response, together with an explanation of the rationale for each. This provides a step by step analysis of the impact of applying each different parameter or assumption from the NICE cost-effectiveness analysis to the SMC base case. It can be seen that there are five drivers of the differences in QALYs, Costs and ICER (Table 3) and applying the NICE parameters to the SMC model produces near identical ICER, QALYs and Costs

Table 3: Reconciliation of ICER. QALY and Costs between SMC and NICE base case

Driver	Parameter	Impact on SMC ICER	Impact on SMC Incremental QALY	Impact on SMC Incremental Costs
1	**Metastatic treatment availability**			
	Cost of 1L mBC treatments	-£2,739	0	-£833
	Cost of 2L mBC treatments	-£13,860	0	-£4,215
	Transition probabilities from mBC non	-£130	-0.004	-£190

	progressed to progressed			
	Transition probabilities from mBC progressed to death	+£310	-0.003	-£21
2	**Capping of utility values to not exceed that of the general population of the same age**	+£6,351	-0.048	£0
3	**Country specific population mortality tables**	-£1,420	0.013	-£3
4	**Metastatic progressed utility value**	-£331	0.003	0
5	**BSA**	+£4	0	£1
1-5	**Impact of applying all**	**-£16776**	**-0.041**	**-£5806**
	SMC base case	£34,100	0.304	£10,370
	NICE base case	£17,297	0.263	£4,557
	Difference between base cases	**-£16,803**	**-0.041**	**-£5,813**

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

Although, significant uncertainty exists, as described within the ACD and above, much of this is as a result of the difference in the data accepted by the regulatory bodies versus that required by HTA bodies such as NICE. In particular the need for a robust way to predict overall survival required by NICE and other HTA bodies.

There are items highlighted within the ACD as driving significant uncertainty which we believe have occurred due to lack of clarity within our company submission, rather than being a source of true uncertainty.

These include the differences between the SMC and NICE ICER, QALY and cost values, which we hope have now been justified (Appendix 1). For example the metastatic utility value which was explicitly highlighted in the ACD, drives a minor increase in the ICER of less than £300 if applied to the ERG base case or £100 against the Roche base case.

In addition the inclusion of CDF funded treatments within the patient pathway, produces uncertainty regarding the future availability of these treatments. This is a factor of the CDF rapid review process, and we welcome the guidance that NICE has recently provided on how these should be factored into this appraisal. To aid in the decision making we have provided scenarios without these treatments and also threshold analysis (the latter being in line with the advice we received from NICE at the early stage of this appraisal). We hope this will aid the Committees decision making in this respect.

The reported ICERs fall within a range typically considered cost-effective and in many cases substantially below that. There is a strong totality of evidence that supports the clinical effectiveness and safety of Perjeta within the HER2-positive breast cancer treatment pathway. Clinical advisors to the Committee agreed that pCR is a good indicator of long term benefit and in addition expressed the importance and benefits of neoadjuvant treatment to patients.

Perjeta has held a marketing authorisation in the UK for use as neoadjuvant therapy for HER2-positive early breast cancer since July 2015. In the interim, patients have been unable to benefit from this treatment as no funding route was available. Regrettably the NICE appraisal for this treatment will not produce guidance until September 2016 at the earliest. If the current ACD becomes guidance, patients will still be unable to benefit from this treatment.

We would like to signal our intent to offer a risk mitigation scheme for Perjeta against a change in funding situation or price of the CDF funded metastatic breast cancer treatments contained in the patient pathway. We ask the Committee to reconsider the evidence and clarity provided in this response in conjunction with the risk mitigation scheme (which will follow on 13th June), to allow patients in England and Wales to benefit from Perjeta as neoadjuvant treatment.

References

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Appendix 1: Comparison of the SMC and NICE cost effectiveness analysis

Introduction

The purpose of this addendum is to provide the NICE Committee with a detailed breakdown of the differences between the economic analyses provided to NICE compared to the first SMC submission made in September 2015.

The effect of each different assumption or parameter on the ICER, incremental cost and QALYS are presented in turn and the rationale for the difference explained. Finally all differences are applied together.

The starting point for the reconciliation is between the SMC ICER of **£34,100** and the original NICE base case of **£17,297**. These are selected since they both incorporated the population error from the CTNeoBC-meta analysis, identified by the ERG during the course of the NICE appraisal. In addition analysis comparing to this original base case was specifically mentioned within the ACD.

The additional parameter/assumption changes which produce the following range of ICERS are also provided:

- **£19,939 Roche Revised Base Case 1** subcutaneous Herceptin was incorporated into the base case
- **£8,215 Roche Revised Base Case 2** as above plus correction to the population used to estimate EFS (error identified by ERG)
- **£23,467 ERG base case**, includes population error correction plus subcutaneous Herceptin , in addition log normal parametric distribution applied to survival analysis and switch to general population mortality at 50 years

Background

The Roche SMC submission for neoadjuvant pertuzumab was made on 7th September 2015 and expected to conclude in March 2016, these dates were noted within the NICE submission (12th January 2016). At this time the SMC submission was still ongoing and the SMC meeting had not yet taken place. The SMC decision was published, as expected on 7th March 2016.

Our rationale for not providing the detail on the SMC cost-effectiveness results within our NICE submission is twofold. Firstly, as a matter of principle we consider details of submissions to other jurisdictions to be confidential until published, since the SMC appraisal was ongoing we considered it inappropriate to include detail at this juncture. Secondly, although there are few appraisals where the SMC submission occurs first, we followed the same approach previously for TA343 (obinutuzumab). Similarly, during that appraisal we noted the dates of the SMC appraisal within the NICE submission, but did not provide any further detail – no further details of the SMC submission were requested by the Committee. Hence when we followed a similar approach for this current appraisal - on the basis of our previous experience we did not consider it as an inappropriate action.

Upon receipt of a request on 29th March 2016 from NICE to explain the differences between the SMC and NICE cost-effectiveness results, we provided this information on 5th April 2016 and offered to provide additional detail if required. We note that our response of 5th April did form part of the Committee papers; however we were not asked to provide any further detail. It only became apparent during the Appraisal Committee Meeting on 19th April 2016 that the level of detail provided was

viewed as insufficient. In addition we did not become aware of the serious concerns of the Committee regarding withholding details of the SMC submission, until this meeting.

At the Committee meeting on 19th April it was clear that the Committee had drawn an adverse view of our submission as a result of the absence of details of the SMC submission. We trust that the above explanation will reassure the Committee that this was the result of an obligation of confidentiality prior to 7th March 2016 and following an established course of action as under TA343.

A re-submission was made to the SMC on 2nd May 2016, we are currently waiting for confirmation of appraisal timelines. The revised submission incorporates preferences expressed by the SMC during the course of the first appraisal and corrects the population error from the CTNeoBC- meta analysis.

Results Summary

A detailed summary of the differences in the results between original NICE base case and SMC first submission are shown below.

Table 4: Base case result comparison

Results table NICE original submission				Results Table SMC first submission				Incremental differences		
	PHD	HD	Incremental		PHD	HD	Incremental	PHD	HD	Incremental
Life year Gain (LYG)	**16.719**	**16.353**	**0.365**	**Life year Gain (LYG)**	**16.209**	**15.847**	**0.362**	**0.510**	**0.506**	**0.003**
EFS	14.708	14.111	0.597	EFS	14.359	13.781	0.579	0.349	0.330	0.018
Locoreg, Recurr	0.115	0.128	-0.013	Locoreg, Recurr	0.113	0.126	-0.013	0.002	0.002	0.000
Remission	0.847	0.944	-0.098	Remission	0.822	0.919	-0.097	0.025	0.025	-0.001
Metastatic not progressed	0.457	0.509	-0.053	Metastatic not progr	0.387	0.432	-0.045	0.070	0.077	-0.008
Metastatic progressed	0.592	0.661	-0.068	Metastatic progresse	0.528	0.590	-0.062	0.064	0.071	-0.006
QALY Gain	**11.499**	**11.236**	**0.263**	**QALY Gain**	**12.287**	**11.983**	**0.304**	**-0.788**	**-0.747**	**-0.041**
EFS	10.179	9.763	0.415	EFS	11.039	10.589	0.451	-0.860	-0.826	-0.036
Locoreg, Recurr	0.08	0.089	-0.009	Locoreg, Recurr	0.078	0.087	-0.009	0.002	0.002	0.000
Remission	0.66	0.736	-0.076	Remission	0.640	0.716	-0.075	0.020	0.020	-0.001
Metastatic not progressed	0.313	0.349	-0.036	Metastatic not progr	0.265	0.296	-0.031	0.048	0.053	-0.005
Metastatic progressed	0.268	0.299	-0.031	Metastatic progresse	0.264	0.295	-0.031	0.004	0.004	0.000
Costs	**104,575**	**100,018**	**4,557**	**Costs**	**53,798**	**43,428**	**10,370**	**50777**	**56590**	**-5813**
EFS	38,308	26,122	12,185	EFS	38,354	26,170	12,184	-46	-48	1
Locoreg, Recurr	2,516	2,806	-290	Locoreg, Recurr	2,480	2,771	-291	36	35	1
Remission	690	769	-79	Remission	669	748	-79	21	21	0
Metastatic not progressed	20,950	23,361	-2,412	Metastatic not progr	10,646	11,897	-1250	10304	11464	-1162
Metastatic progressed	42,112	46,960	-4,848	Metastatic progresse	1,649	1,842	-194	40463	45118	-4654
Cost Per LYG			**£12,471**	**Cost Per LYG**			**£28,673**			**-16,202**
Cost per QALY			**£17,297**	**Cost per QALY**			**£34,100**			**-16,803**

LYG, QALYs Costs all discounted and 1/2 cycle corrected. PHD - Perjeta, Herceptin and Docetaxel, PH = Perjeta and Herceptin

Costs

Overall the incremental cost difference between SMC and NICE is £5831; all of this difference excluding £3 is due to costs incurred in the metastatic health states.

For the metastatic health states the difference in costs are significant due to the different treatments available for metastatic disease in Scotland; predominantly Kadcyla (trastuzumab emtansine) and Perjeta, which are not routinely available in Scotland for HER2 positive metastatic breast cancer, but available in England via the Cancer Drugs Fund.

Patients in the comparator arm progress to metastatic disease faster and remain in those health states for longer than those in the intervention arm; therefore the cost of metastatic breast cancer (mBC) treatment has a significant effect on the ICER. The higher mBC treatment costs in England reduce the ICER as patients treated with Perjeta spend less time in the mBC health states compared to the comparator arm, reducing spend on mBC treatments.

If the same monthly mBC treatment cost are applied to the SMC model as are used in the NICE submission, this has the impact of reducing the incremental cost difference by £5,048 and consequently reduces the ICER by £16,600

The available mBC treatments also impact the transition probabilities between the health states metastatic non-progressed to metastatic progressed and between metastatic progressed to death. The transition probabilities are higher in Scotland since the available treatments for metastatic disease are less effective.

If the same transition probabilities are used within the SMC model as were used in the NICE model, this has the impact of changing the LYG and QALYs in the main, the knock on effect to costs and ICER are of lowering the SMC costs by £311 and reducing ICER by £179

The net impact of applying both the costs and transition probabilities from the NICE base case to the SMC model is to reduce the incremental cost difference by £5,788 and reducing the ICER by £18,640.

Details of the different input parameters are shown below.

Table 5: Metastatic treatment costs and transitions

	SMC	**NICE**
1L mBC treatment Avg. monthly cost	£2,295 Comprises weighted average of Herceptin + docetaxel, plus supportive care	£3,822 Comprises weighted average of Herceptin + taxane, Perjeta + Herceptin + docetaxel, Herceptin + other, plus supportive care
2L mBC treatment Avg. monthly cost	£260 Comprises weighted average of capecitabine, vinorelbine, plus supportive care costs	£5,923 Comprises weighted average of Kadcyla, Perjeta, Herceptin + docetaxel, other (5% of total), plus supportive care
Transition probability: Metastatic non progressed to Metastatic progressed	4.7% Based on Herceptin + docetaxel	4.024% Based on weighted avg. of Herceptin + docetaxel and Perjeta, Herceptin and docetaxel
Probability of death from metastatic	3.148% Based on Herceptin + docetaxel	2.814% Based on weighted avg. of Herceptin +

progressed health state		docetaxel and Perjeta, Herceptin and docetaxel

Other reasons for minor differences in costs are:

- Small difference in body surface area used has a very minor impact since Perjeta is not dosed based on BSA. The reason for the difference is that the SMC submission used the average from NeoSphere, whereas the NICE submission used data on women aged 45 – 54 from the Health & Social Care Information Centre. (Table 95 from submission document). The impact on costs is less than £10
- Population mortality tables applied as relevant to the each country. Scottish mortality rates are higher in general, this impacts the time spent in each health state. The main impact is on LYG and QALYs, the impact on costs is less than £10

Life Years Gained (LYG)

Discounted incremental Life years gained (LYG) are 0.003 lower in the SMC submission, comprising 0.510 less for the Perjeta arm and 0.506 less for the comparator.

This is partly explained by differences in the general population mortality tables used for each country. Mortality rates are higher in Scotland compared to England for the population relevant to this analysis.

As mentioned in the cost section, the available metastatic treatments in Scotland also impact LYG. The LYG in the metastatic health states is lower in the SMC analysis than for NICE.

Quality Adjusted Life Years (QALYs)

Quality adjusted life years are higher in the SMC resubmission compared NICE (total incremental difference is 0.041 higher for SMC, with 0.036 of this coming from the EFS health state).

A summary of the utility values used are shown below. The utility values in the SMC submission were identical to those used for NICE, with the exception of metastatic progressed health state.

Within the SMC submission 0.50 utility value was used and within NICE 0.452. This difference is due to a recalculation of this utility during the course of the NICE appraisal when it was identified that the patient age from the Cleopatra trial instead of NeoSphere had been used to calculate this value using the Lloyd et al 2006 mixed model. This error was not spotted in time for the SMC submission. The impact of using the 0.452 utility within the SMC submission has a minimal impact of reducing the ICER by £331 and increases the incremental QALYs by 0.003.

Table 6: Comparison of utility values by health state (SMC v NICE)

Health States	SMC Original Submission	NICE Base Case
EFS	0.696	0.696
Logo regional	0.696	0.696
EFS >yr1	0.779	0.779
Met Not Prog	0.685	0.685
Met Prog	0.5	0.452
Remission	0.779	0.779

Within the NICE submission a cap was placed on the utility values so that they could not be higher than the general population utility for the same age. This was implemented following advice from an external health economics expert post the original SMC submission. This has the impact of reducing the QALYs and raising the ICER. If this were applied to the SMC submission it would have the impact of decreasing the QALY gain by 0.048 and raising the ICER by £6,331.

In addition the Scottish specific mortality rates previously mentioned, also impact the QALYs. If the mortality rates in Scotland were equal to those in England the impact would be to increase the QALY gain by 0.013 and reduce the ICER by £1,420.

Input Parameters

Table 7 presents a comparison of the SMC analysis with all NICE parameters included, it can be seen that the results agree as detailed above

Table 7: Comparison of NICE original Base Case v SMC (with NICE parameters applied)

Results table NICE original submission

	PHD	HD	Incremental
Life year Gain (LYG)	**16.719**	**16.353**	**0.365**
EFS	14.708	14.111	0.597
Locoreg, Recurr	0.115	0.128	-0.013
Remission	0.847	0.944	-0.098
Metastatic not progressed	0.457	0.509	-0.053
Metastatic progressed	0.592	0.661	-0.068
QALY Gain	**11.499**	**11.236**	**0.263**
EFS	10.179	9.763	0.415
Locoreg, Recurr	0.080	0.089	-0.009
Remission	0.660	0.736	-0.076
Metastatic not progressed	0.313	0.349	-0.036
Metastatic progressed	0.268	0.299	-0.031
Costs	**104,575**	**100,018**	**4,557**
EFS	38,308	26,122	12,185
Locoreg, Recurr	2,516	2,806	-290
Remission	690	769	-79
Metastatic not progressed	20,950	23,361	-2,412
Metastatic progressed	42,112	46,960	-4,848
Cost Per LYG			**£12,471**
Cost per QALY			**£17,297**

Results Table SMC model with NICE parameters applied

	PHD	HD	Incremental
Life year Gain (LYG)	**16.719**	**16.353**	**0.365**
EFS	14.708	14.111	0.597
Locoreg, Recurr	0.115	0.128	-0.013
Remission	0.847	0.944	-0.098
Metastatic not progressed	0.457	0.509	-0.053
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QALY Gain	**11.499**	**11.236**	**0.263**
EFS	10.179	9.763	0.415
Locoreg, Recurr	0.080	0.089	-0.009
Remission	0.660	0.736	-0.076
Metastatic not progressed	0.313	0.349	-0.036
Metastatic progressed	0.268	0.299	-0.031
Costs	**104,515**	**99,951**	**4,564**
EFS	38,308	26,122	12,185
Locoreg, Recurr	2,516	2,806	-290
Remission	690	769	-79
Metastatic not progressed	20,950	23,361	-2412
Metastatic progressed	42,052	46,893	-4841
Cost Per LYG			**£12,490**
Cost per QALY			**£17,324**

Table 8 below provides a comparison of the input parameters between the SMC resubmission and NICE submission (where differences exist) and shows the impact of individually applying the NICE parameters to the SMC model, and finally applying all NICE parameters. When all parameters are applied the QALYs agree exactly and the ICER is different by £27.

Not all parameters used within the NICE submission are appropriate for the SMC, however this table is presented to demonstrate the impact of each parameter on the costs, QALYs and ICER.

The results show in Table 8 support the fact that the main drivers of the costs, QALYs and ICERs differences are the metastatic treatments available in Scotland versus England and in addition the utility cap which was implemented in the NICE submission, which has the effect of increasing the ICER in the NICE analysis. All other differences between the ICER submitted to Scotland £34,100 and the original ICER submitted to NICE £17,297 have a small impact on the ICER. This is in line with the previous information supplied to the Committee in written and verbal form.

Table 8: Reconciliation between SMC first Base Case and NICE ICERS

		SMC value	NICE value	ICER	Incr. Cost	Incr. QALY	Difference in ICER (from SMC Base)	Rationale
Roche	**BASE CASE SMC**			**£34,100**	**£10,370**	**0.304**		
1	Utility in metastatic progressed health state	0.5	0.452	£33,769	£10,370	0.307	-£331	QoL calculation used the patient's age from the Lloyd's study rather than the patient's the age from the Cleopatra trial
2	Body surface area (BSA)	1.73	1.79	£34,104	£10,371	0.304	£4	NICE used UK average women aged 45-54, SMC average BSA from NeoSphere
3	Population mortality	Scottish	English	£32,680	£10,367	0.317	-£1,420	relevant jurisdiction population mortality tables used
4	Capping utility values	No	Yes	£40,451	£10,370	0.256	£6,351	Following external advice, a cap on the utilities was incorporatedinto NICE submission to prevent patients from having utilities higher than England population norm at any health state and/or cycle
5	Impact of metastatic treatments (1L and 2L)							
	Cost 1L metastatic treatments	£2,295	£3,824	£31,361	£9,537	0.304	-£2,739	Applied appropriate mBC treatments relevant for each country - see table 2 for detail
	Cost 2L metastatic treatments	£2,295	£5,923	£20,240	£6,155	0.304	-£13,860	
	probability of transition from mBC non progressed to progressed health state	4.70%	4.02%	£33,970	£10,180	0.300	-£130	
	probability of transition to death from mBC progressed health state	3.15%	2.81%	£34,410	£10,349	0.301	£310	
	Total impact of all changes			**£17,324**	**£4,564**	**0.263**		
Roche	**Original BASE CASE NICE**			**£17,297**	**£4,557**	**0.263**		
	difference			**-£27**	**-£7**	**0**		
		SMC value	**NICE value**	**ICER**	**Incr. Cost**	**Incr. QALY**	**Difference in ICER (from original NICE base)**	
	Include subcutaneous Herceptin	scenario only - 0% SC in base case	[redacted]					
Roche	**Updated BASE CASE NICE**			**£19,939**	**£5,253**	**0.263**	**£2,642**	
	Herceptin SC plus corrected the population error from CTNeo	total population	HER2 postive population only					
Roche	**Updated BASE CASE NICE**			**£8,215**	**£2,859**	**0.35**	**-£9,082**	
	As above plus apply log normal to EFS estimation and swtich to background mortaltiy at 50 years	Gamma distribution / 7 years switch	Log normal distribution/ 50 years switch					
ERG	**ERG BASE CASE**			**£23,467**	**£6,784**	**0.262**	**£6,170**	

Appendix 2: EMA guidance on clinical trials where approval based on pCR is acceptable

The European Medicines Agency (EMA) and FDA acknowledged that 'currently available data do not allow prediction of DFS/OS effect from a certain pCR effect**'**; however, the EMA has recognised that it can take a long time to confirm survival outcomes from clinical trials, therefore there is a need for 'new surrogate endpoint for efficacy which would allow the assessment of time-to-event for a given therapy at an earlier time point and would therefore potentially bring novel therapies faster to market for patients' benefit.

EMA has developed the guidance below on 5 key considerations for clinical trials where approval based on pCR is acceptable; we also demonstrate how Perjeta as neoadjuvant treatment met this criteria for approval.

1. **Well known mechanism of action**
   The mechanism of action of Perjeta as part of dual anti-HER2 targeted therapy is well known through its action to block ligand-depend heterodimerisation of HER2 with other HER2 families such as EGFR, HER3 and HER4; together with Herceptin significantly augments anti-tumour activity in HER2-overexpressing xenograft models and provides more comprehensive blockade of HER2-driven signalling with 2 anti-HER2 targeted therapies. Perjeta also medicates antibody-dependent cell-mediated cytotoxicity (ADCC).
2. **Add-on to an established (neo) adjuvant regimen**
   This has been demonstrated through the pivotal studies NeoSphere and TRYPHAENA where Perjeta is added to Herceptin-based regimens which are used in clinical practice in the UK (TRYPHAENA) and the US (NeoSphere)
3. **Major effect on pCR in the neoadjuvant breast cancer setting**
   There was a significant increase in pCR rates in patients who received Perjeta, Herceptin and docetaxel for 4 cycles prior to surgery in NeoSphere compared to patients who received Herceptin and docetaxel. Patients in the TRYPHAENA study who received Perjeta, Herceptin and chemotherapy also achieved high pCR rates.
4. **Well established safety profile, minor increase in toxicity**
   As discussed previously, the safety profile on the use of Perjeta in clinical practice is based on the clinical evidence from the large phase III CLEOPATRA trial, which also evaluated the safety of Perjeta in combination with Herceptin and docetaxel in patients with HER2-positive metastatic breast cancer.
5. **Confirmatory Adjuvant trial ongoing**
   From the large confirmatory trial APHINITY, to evaluate the efficacy and safety of Perjeta as adjuvant treatment in HER2-positive breast cancer, which is ongoing

Clarification of costs of metastatic treatments included in the ID767 pertuzumab neoadjuvant submission
14th June 2016

Within the pertuzumab neoadjuvant submission, both trastuzumab emtansine and pertuzumab as metastatic breast cancer treatments currently funded via the CDF are included in the model at **list price**.

This is discussed in the ACD response with an explanation of how we came to take this approach and also within the submission document (p276).
We are seeking agreement from NHS England today to disclose these discounts to NICE.

The costs of the metastatic treatments within our model are fully detailed within our submission (p236-245).

In Summary:
Excluding trastuzumab emtansine and pertuzumab the drugs included within the metastatic treatments are as follows

- Trastuzumab list price (no PAS in place). Metastatic treatment is all included at the intravenous formulation list price
- Lapatinib - list price [costed for 4% of patients only within the metastatic progressed health state which contributes 2.2%/ £134 of the monthly cost for this health state]

- The other products are all generics and prices were taken from EMIT:

Docetaxel
Fluoruracil
Epirubicin
Cyclophosphamide
Carboplatin
Vinorelbine
Capecitabine

Marcia Miller
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13 June 2015

Dear Ms Miller,

Re: ACD on neoadjuvant pertuzumab

Breast Cancer Now welcomes the opportunity to comment on the appraisal consultation document regarding the use of pertuzumab for the treatment of primary HER2 positive breast cancer in the neoadjuvant setting. We did not have any comments specific to the questions in the consultation paper but wanted to highlight a few important points arising from this Technology Appraisal.

Neoadjuvant medicines

The level and type of evidence presented by the pharmaceutical company to support the submission for pertuzumab neoadjuvant was the main reason why this drug has been given a draft rejection by NICE:

"The committee concluded that there was considerable uncertainty about whether pathological complete response was a meaningful indicator of long-term survival outcomes, such that it could be viewed as a surrogate marker of long-term benefit."

Whilst we agree that no standard relationship is proven between a complete response rate and overall survival, we believe that this presents a problem for this type of medicines. For breast cancer drugs used in the neoadjuvant setting, overall survival is likely to take at least 15 years to collect. Waiting for this long before making a decision about whether a treatment can be made available on the NHS would means that patients are facing unacceptable delays for potentially innovative treatments. We believe that this is a significant issue for pharmaceutical companies, as exclusivity patents would be very close to expiry by the time overall survival data comes in. This raises a question about how further innovation in these types of drugs would be incentivised in the future. We would like NICE to refer this question to the NICE Decision Support Unit in order to:

1. produce guidance for companies, which may be working on neoadjuvant cancer drugs of the future, to set out clearly what kinds of evidence companies will need to

provide in order to gain a NICE approval

2. assess and analyse the issue of neoadjuvant drugs more broadly to decide whether seeking overall survival is appropriate for these types of medicines, given the very long times frames involved, especially comparing to the level of evidence NICE requires for cancer and other long term conditions and whether this is comparable.

Patient subset

Whilst the patient population set to benefit from this treatment is very small, it could be a very important treatment option. The majority of breast cancers are diagnosed in stages 1 and 2. Furthermore, only around 15% of breast cancers have HER2 positive receptor status. This medicine may be important for a very small group of patients, who are diagnosed with diagnosed with inflammatory or locally advanced HER2 positive breast cancer. Inflammatory breast cancer is very rare but a particularly aggressive form of breast cancer. Patients with this type of cancer are therefore more likely to be diagnosed in later stages. Whilst this type of information was included in the scope of the appraisal, we are not sure whether this was given due weight and consideration in the Committee meeting. For example, patients in whom HER2 positive breast cancer is too advanced to operate on are already given a combination of trastuzumab and chemotherapies with the intention of shrinking the tumour so that it becomes operable. If a tumour is not operable, this is associated with a poor long term prognosis. Therefore a medicine in this setting, which increases the likelihood of good response, means that patients in this very small sub-section potentially have better chances of curative treatment.

Cancer Drugs Fund

The purpose of the new Cancer Drugs Fund (CDF) is for use in instances where the evidence is insufficient or the uncertainty is too high to make a routine commissioning decision.[1] Based on the reasons given for this drug's rejection, it would seem that pertuzumab ought to be considered for a place on the new CDF. Whilst we appreciate that it would take a long time to collect additional data on overall survival, we would have liked to have seen it considered for the CDF, in light of the fact that this medicine has produced some impressive results and would be eligible to a very small patient population.

Furthermore, the timing of this Technology Appraisal is problematic. At the time of the Appraisal, there was a level of uncertainty caused by the changes to the CDF. This is evident in some of the comments made in the Committee papers:

"The committee considered that it would have liked to have seen an analysis from the company which included a scenario in which CDF-funded drugs were excluded."

[1] CDF consultation document. NHS England and NICE, Nov 2015.

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Guidance has not made it clear whether new drugs would be considered in light of medicines currently available via the CDF or whether these are to be excluded from the analysis. Whilst these medicines are not available via routine commissioning at this time, the CDF is part of the access environment in England, even if the future of access to these medicines is uncertain. NICE needs to provide clear guidance to cover the period whilst CDF drugs are re-assessed, so that any new medicines being appraised are assessed fairly.

Furthermore, the launch of the new Fund has been delayed by three months, which would have not be been known at the beginning of the appraisal process. This delay has excluded the chances of this drug being considered for use on the CDF, yet it could have been expected to be otherwise, as the new CDF was due to be launched on 1st April 2016.

Review period

For the reasons given above and because the assessment of this innovative use of the medicine just missed out on the possibility of having an option to be considered for entry into the new CDF, we would suggest that a review period of 3 years is too long. This is further supported by the fact that a last minute decision was made with regards to the start of the new Cancer Drugs Fund, where this was delayed from the original start date of 1st April to 1st July. The company involved in this appraisal, may well have planned to have the CDF as an option with the timing of their Technology Appraisal.

However, before another appraisal happens, we would like the NICE Decision Support Unit to feed back on the two areas we raised as being important to ensure that future medicines in this category have a fair chance of appraisal and so that this type of medicines are appropriately incentivised. This will be important for the benefit of cancer patients, who may well benefit from innovative medicines like these in the future.

Yours sincerely,

breast cancer now

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Comments on the ACD Received from the Public through the NICE Website

Author name	Role	Organisation	Comment	Job Title	Location	Declared Interest	Disclosure
[redacted]			I would like to stress the benefits of this combination of drugs. I have stage 4 her2 breast cancer and have been on this combination of drugs (including zometa) since November 2012. I am now on cycle 59. Without this I would not have had the luxury of time with my family which includes 3 children. The youngest two being 6 and 8. I would like to think this treatment options remains available to women like me for the foreseeable future otherwise you are committing us to an early death sentence. Please take the experiences of real people on board before making such devastating decisions.	retired	England	No	

Author name	Role	Organisation	Comment	Job Title	Location	Declared Interest	Disclosure
[redacted]			Disgraceful recommendation - What is the point of cancer research and testing, if drugs that are discovered, developed and proved to help are always blocked due to expense? Maybe the system and questions by which you make your "informed" decision is out of date and perhaps that should be subjected to a "Fit for purpose" test? Who cares about the overall long term benefits when the short term benefits could mean the difference between a life saving operation or not?		England	No	