NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pertuzumab for adjuvant treatment of early HER2-positive breast cancer [ID1192]

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

1. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Roche Products
     - Response
     - Appendix
   - Breast Cancer Care
   - Breast Cancer Now
   - UK Breast Cancer Group (UKBCG)
   - NHS England

2. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Alistair Ring, clinical expert nominated by Roche

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

4. **ERG response to the company's updated analysis**

5. **Expert personal perspectives** from:
   - Professor Jayant S Vaidya – clinical expert, nominated by BASO
   - Professor Andrew Wardley - clinical expert, nominated by Roche

6. **ERG addendum produced following second committee meeting**

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

Pertuzumab for adjuvant treatment of HER2-positive early breast cancer [ID1192]

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Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 6 July 2018 **, upload to NICE Docs**

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Roche Products Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	**Tom Loughran** ***Health Economist at Roche Products Ltd.***

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Comment number	Comments
1	Whilst disappointed with the decision, Roche is cognisant of the challenges associated with this appraisal. In response to the Committee's preliminary recommendation, Roche has provided formal comments in the table below. The comments raised, centre on several key themes that span both the clinical and cost-effectiveness elements of this appraisal. Regarding clinical effectiveness, Roche has focussed its comments on addressing the following key issues: The Committee's perception of "marginal" benefit in the intention-to-treat population of the APHINITY trial, the selection of the pre-specified subgroups, and the magnitude of effectiveness in the high-risk population. Considering the ongoing discussions regarding the clinical effectiveness, Roche believes it critical that at least one clinical expert be in attendance at the second appraisal committee meeting. In addition, Roche has also addressed key aspects surrounding the cost-effectiveness of pertuzumab. Specifically, the treatment effect duration of pertuzumab, incorporation of trastuzumab biosimilars, and the suggested "overestimation" of overall survival (OS). As part of this discussion, revised cost-effectiveness estimates and scenario analyses have also been presented in a supplementary appendix. Further to adjustments in the modelling assumptions, Roche have also [redacted] Revised cost-effectiveness estimates included in this response have been generated using this improved offer. The results provided in the appendix serve to illustrate that pertuzumab, in the adjuvant setting, can be regarded as a cost-effective use of scarce NHS resources in all plausible scenarios. The company trusts that the information provided within this response will mind the Committee to reconsider its provisional recommendation, thus allowing high-risk patients to access to adjuvant pertuzumab on the NHS. Roche is committed to ensuring patient access to its innovative medicines and is therefore open to exploring all possible routes of funding. Should any further information be required, Roche would be happy to provide it in order to aid the Committee's decision making.
2	**The Committee's provisional recommendations are not suitable for the NHS** **The provisional recommendations are not sound nor suitable for guidance to the NHS. The ACD does not capture the wider impact of HER2-positive breast cancer and the remaining risk in node-positive eBC patients despite improvements in prognosis with adjuvant trastuzumab. In particular, the curative intent when initiating treatment in the eBC setting has not been acknowledged.** The long-term implications for these high risk node-positive patients need to be considered: • There is no cure in the metastatic breast cancer (mBC) setting and more than 50% of patients will die in 5 years despite receiving the most effective treatment currently available • Adjuvant treatment with trastuzumab has been the standard of care for decades worldwide • The addition of pertuzumab in this adjuvant setting further reduces the risk of recurrence by 23% compared to the current standard of care Of the patients diagnosed with HER2-positive metastatic breast cancer in the UK, approximately 71.2% initially present with early disease and subsequently relapse, with a median duration from eBC to mBC diagnosis of four years. (Wardley *et al.*, 2018) Despite treatment with pertuzumab in the metastatic setting, more than 50% of mBC patients will die within 5 years. (Swain *et al.*, 2015) As the median age of patients presenting with HER2-positive breast cancer is mid-50s, around five years younger than the general breast cancer population, it is of utmost importance that patients have access to the best possible treatment options to further reduce their risk of recurrence, so that they can continue living their lives and

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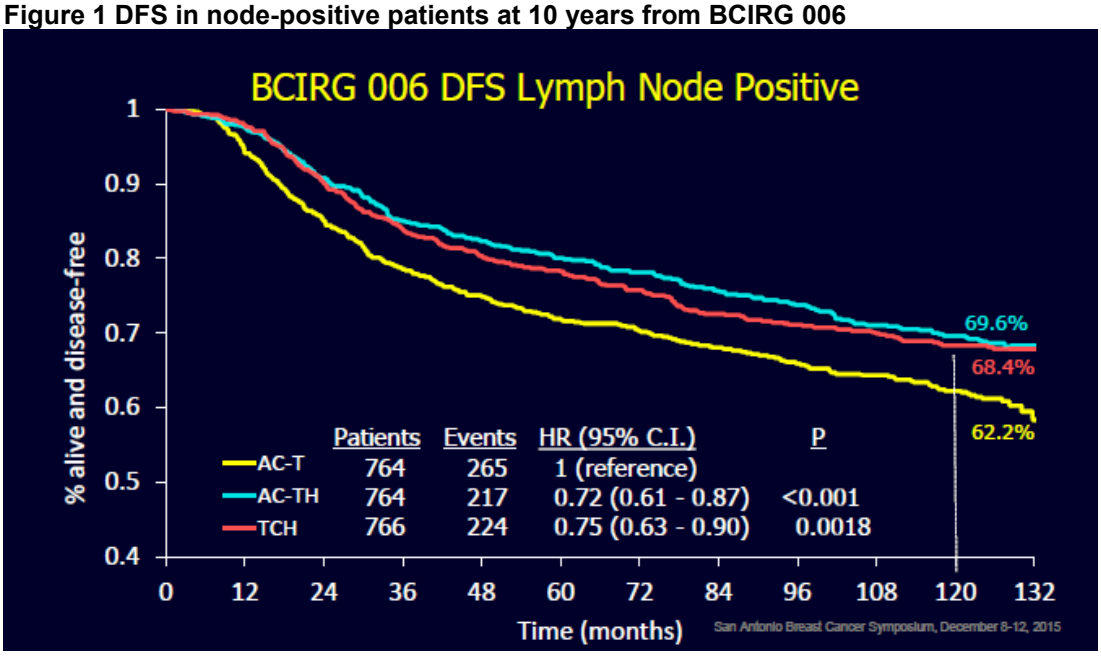
	contributing to wider society as a whole. The improvement seen in the APHINITY study in the node-positive subgroup should to be considered in the context that despite treatment with adjuvant trastuzumab, 30% of node-positive patients will go on to experience a recurrence within ten years (Slamon *et al.*, 2015). Further emphasising that these high risk patients should have the opportunity to benefit from the addition of pertuzumab in the adjuvant setting. **Figure 1 DFS in node-positive patients at 10 years from BCIRG 006**  By not providing patients with a treatment proven to further reduce their risk of recurrence, the most effective treatment will not be available to eBC patients in this curative setting. Roche recommends the broader context of treating in the eBC setting is considered. Without the broader context, the positive benefits that adjuvant pertuzumab can provide cannot be fully captured. We request that this be addressed by the Committee in its reconsideration of all the evidence presented. **Given the clinical aspects highlighted in the ACD, we feel that further clarity from clinical experts would be beneficial at the next Committee meeting.**
3	**Nodal-positive subgroup is the most clinically relevant subgroup** **The summaries regarding selection of subgroups are not accurate interpretations of the evidence that was submitted. Nodal status was included as a stratification factor in the APHINITY study (ensuring balance in baseline characteristics between the two arms). It is an objective and independent prognostic factor in eBC. Indeed, within the ACD, the Committee acknowledges that node-positive patients have a higher risk of recurrence.** Whilst tumour size is regarded as a clinical factor used to determine prognosis in eBC, studies have shown that hormone receptor-negative status and node-positive status are the most influential for risk determination overall. (Strasser-Weippl *et al.*, 2015; Cameron *et al.*, 2017; Cortazar *et al.*, 2014) These references were provided as part of the response to the evidence review group's (ERG) clarification question on why other high risk groups were excluded. The ERG had reviewed the citations and noted that the clarification response was acceptable. In addition, the ERG clinical advisor agreed that node-positive and hormone receptor-negative eBC are higher-risk subgroups.

	We acknowledge that at this point in time, there are not sufficient events in the node-negative patients to determine the treatment effect in this subgroup. However, that does not invalidate the interpretation of the results seen in the high risk node-positive population. The information that we have at this point in time tells us that the addition of adjuvant pertuzumab provides a clinically meaningful improvement in node-positive patients (HR=0.77, 95% CI 0.62-0.96; p=0.02). The European Commission has now approved the use of pertuzumab in the adjuvant setting for HER2-positive early breast cancer (eBC) patients at high risk of recurrence (EMC, 2018). Within section 5.1 of the summary of product characteristics, based on APHINITY, high risk is defined as lymph node-positive or hormone receptor-negative disease. It is appropriate to focus on a high risk subgroup, defined within our label, when describing the patients who are likely to benefit the most from this treatment. Node-positive patients are at a higher risk of recurrence and are in a greater need of more effective treatments. We feel that further input from clinical experts would be beneficial at the next Committee meeting to provide further reassurance that the node-positive subgroup is a clinically relevant subgroup and appropriate for adjuvant pertuzumab.
4	**Treatment effect in node-positive subgroup is consistent with other therapies that improve standard of care** **The summaries regarding treatment effect in the high risk subgroups are not accurate interpretations of the evidence that was submitted**. **The hazard ratio and absolute differences seen in the node-positive subgroup in APHINITY are in line with other therapies that have improved standard of care in breast cancer.** As the APHINITY study met the primary objective in the ITT population, assessment of key pre-specified subgroups was appropriate to investigate drivers behind the overall ITT effect. In the APHINITY study, patients in the node-positive subgroup appear to be driving the overall treatment effect and this is the most clinically appropriate group who are at greater need of more effective treatments: • **Lymph node-positive subgroup (HR=0.77, 95% CI 0.62-0.96; p=0.02)** - 3-year IDFS: 92.0% vs. 90.2% (difference of 1.8%) - 4-year IDFS: 89.9% vs. 86.7% (difference of 3.2%) Within section 3.5 of the ACD, it states that "the absolute difference in event rates across the treatment arms of all the node-status and hormone receptor status groups was small (range 0.5% to 3.2%)." When focusing on the longer term time points, the absolute difference at 3-years and 4-years were 1.8% to 3.2%, respectively, in the node-positive subgroup. Together with the hazard ratio of 0.77, the results in the node-positive subgroup are considered clinically meaningful in the curative eBC setting. The magnitude of benefit in the node-positive subgroup is similar to other studies where new treatments have been compared to an existing standard of care (i.e. 2nd generation regimens). The incremental gains achieved by these agents have been sufficient to change clinical practice in breast cancer: (Möbus *et al.*, 2017). • **Aromatase inhibitors vs. tamoxifen (HR=0.82 [95% CI: 0.75–0.91]; HR=0.80 [95% CI: 0.73–0.88])** o Reduction in risk of recurrence after 5 years: 2.6% to 3.1% • **Anthracyclines plus taxanes vs anthracyclines (HR=0.86 [95% CI: 0.82–0.91]; HR=0.84 [95% CI: 0.78–0.91])** o Reduction in risk of recurrence at 5 years: 2.8% to 3.6% This has been confirmed by UK clinical experts who have also highlighted this point and acknowledge the benefit of adjuvant pertuzumab for these high risk patients. We would invite the Committee to reconsider its conclusion in the ACD in this regard.

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5	**Totality of the evidence indicate that pertuzumab is clinically effective in the adjuvant setting** **The IDFS estimates at specific time points (e.g. 3-years and 4-years) should be presented in conjunction with the associated HR and p-value to ensure the totality of evidence is taken into account. Additionally, the ACD does not capture the clinical expert's comment during the Committee meeting explaining why it is unreasonable to expect separation of the IDFS curves whilst patients are receiving treatment. The hazard ratio estimates for all pre-specified sensitivity analyses were below 1.00, demonstrating the robustness of the primary efficacy results.** The primary endpoint of APHINITY was tested using the log rank test and the associated treatment effect estimated using the hazard ratio at the primary analysis after a protocol pre-specified number of events. Therefore, the hazard ratio should be included as part of the summary of clinical effectiveness interpretations of the evidence. The hazard ratio describes the treatment effect throughout the whole time period assessed whereas the absolute values (i.e. 3-year, 4-year IDFS) indicate a snapshot of the data at one point in time and do not describe the observed overall benefit of a treatment. APHINITY met its primary efficacy objective, demonstrating a statistically significant and a clinically meaningful 19% reduction of the risk of an IDFS event with pertuzumab compared with placebo in the primary analysis (HR=0.81; 95% CI, 0.66–1.00; log rank test p=0.045). (von Minckwitz *et al.*, 2017) Although there is some evidence of non-proportionality of hazards due to the KM curves not diverging during early time points through to around 18 months, this does not invalidate the interpretation of observed benefit based on the hazard ratio. The ACD does not capture the clinical expert's comment during the Committee meeting explaining that you wouldn't expect to see IDFS events whilst patients are receiving treatment, and that the differences become more apparent when treatment is stopped (which is in line with what we see with the KM curves). Multiple pre-specified sensitivity analyses (provided as part of the reference pack [Roche Products Ltd, 2017]) were conducted to assess the robustness of the primary IDFS analysis in the ITT population to different intercurrent events (such as initiation of non-protocol anticancer therapy or discontinuation of study treatment due to toxicity) and to the stratification factors used in the calculation of the hazard ratio and p-value. The hazard ratio estimates for all analyses were below 1.00, supportive of an improvement in IDFS with pertuzumab when implementing various alternative assumptions in the analysis, demonstrating the robustness of the primary efficacy results. In the node-positive subgroup, patients derived an even greater benefit with a 23% reduction in risk of recurrence or death (HR=0.77, 95% CI 0.62-0.96; p=0.02). An increasing difference is observed at 3 and 4 years (as highlighted in comment 4). Roche believe the summaries of clinical effectiveness included in the ACD need to be re-interpreted with consideration of the totality of the evidence presented in the company submission.
6	**Adjuvant pertuzumab produces a clinically meaningful difference for node-positive eBC patients** **The Committee's use of "marginal efficacy" to describe the efficacy of pertuzumab in the ITT population, in a setting where patients and clinicians are striving for a cure is controversial. "Marginal efficacy" is a subjective term and is not a reasonable interpretation of the evidence submitted.** Treatment in the eBC setting is initiated with curative intent. The value it brings to patients is reiterated in Breast Cancer Now's submission prior to the first Committee meeting that "any treatment that improves outcomes is a welcome step forward for patients". The European Society of Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) offers a rational, structured and consistent approach to assess the clinically meaningful benefit of anti-cancer drugs. The primary IDFS endpoint result from APHINITY meets the criteria for high level of clinical benefit in the curative setting when assessed using the ESMO-MCBS (Cherny *et al.*, 2015).

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	The magnitudes of benefit seen in the node-positive subgroup is even greater and should translate to an even more clinically meaningful improvement for these patients who have a higher risk of their disease returning. For this reason, the company submission is focused on node-positive subgroup as a base case. In recognition of the significant clinical benefit observed in the high-risk population in comparison with existing therapies, the CHMP have also recommended granting an additional year of market protection for pertuzumab. (EMA, 2017) International treatment guidelines have also been updated to reflect pertuzumab as an option for node-positive patients in the adjuvant HER2-positive early breast cancer setting. (Denduluri *et al.*, 2018; Curigliano *et al.*, 2017; NCCN, 2018; AGO, 2018) This position is supported by clinical experts and patient organisation consulted by NICE in advance of the Appraisal Committee Meeting. Roche have consulted clinical experts and professional groups including UKBCG and ABS, who all acknowledge the clinical benefit in the node-positive subgroup. There is broad support from the clinical community for making adjuvant pertuzumab available on the NHS for node-positive, HER2-positive eBC patients. We request that the Committee's consideration reflects this stance. Roche believe the summaries of clinical effectiveness included in the ACD need to be re-interpreted with consideration of the above evidence.
7	**Subgroup statistical tests for interaction** **The current summaries regarding the statistical tests of interaction are ambiguous as they could be interpreted as referring to statistical significance of treatment differences within subgroups, rather than to heterogeneity of treatment differences** (specifically "Finally the committee noted that statistical tests for interaction resulted in p values for invasive disease-free survival of less than 0.05 (p=0.17 for interaction between nodal status and invasive disease-free survival; p=0.54 for interaction between hormone receptor status) suggesting that neither nodal nor hormone receptor status were associated with a statistically significant difference in treatment effect."). The statistical tests for interaction between treatment and key subgroups noted within the ACD (i.e. p=0.17 for nodal status, and p=0.54 for hormone receptor status) provide overall tests of the heterogeneity of the treatment effect across the subgroup's categories. Whilst used to convey additional statistical context, clinical considerations (as described above in comment 3) were used to determine prioritisation of subgroup findings, rather than the interaction test results. The clinical considerations are therefore the reason why the results of the interaction test for menopausal status did not lead to its selection as a prioritised subgroup. This was also confirmed by the clinical expert at the Committee meeting, who confirmed that menopausal status would not be a clinically relevant subgroup for this submission. With regard to exploratory testing for statistical significance between treatment groups within subgroups, p-values for the identified high risk subgroups are presented above and within section B.2.7.1 and B.2.7.2. of the company submission (p=0.02 for node-positive; p=0.085 for hormone receptor-negative subgroups). These were provided as additional information when interpreting the results for these subgroups along with the confidence internals and their clinical relevance to breast cancer. We are concerned around particular focus on the upper limit of the CI which might be contributing to NICE's uncertainty of the data in the node-positive subgroup. With regard to interpreting the confidence intervals, it should be noted that the lower limit of the confidence interval is equally plausible as the upper limit, therefore it is not reasonable to focus only on the upper CI limit. We believe that the benefit seen in the node-positive subgroup is not due to chance when you interpret the results with the clinical rationale that this is the most influential prognostic factor in eBC and was a stratification factor in APHINITY. Roche recommends the Committee reconsiders its provisional recommendation based on the information provided.

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8	**Adjuvant pertuzumab is now approved for use in node-positive patients in the EU** **The European Commission has now approved the use of pertuzumab in the adjuvant setting for HER2-positive early breast cancer (eBC) patients at high risk of recurrence (EMC, 2018). Within section 5.1 of the summary of product characteristics, based on APHINITY, high risk is defined as those with lymph node-positive or hormone receptor-negative disease.** The clinical evidence submitted to the EMA for the adjuvant pertuzumab label was the same evidence presented within the company submission. The EMA accepted that the analysis methods for the time to event endpoints were appropriate and was satisfied with the level of clinical evidence provided for the high risk subgroups. There were no challenges regarding the clinical effectiveness, or safety, of adding pertuzumab to trastuzumab plus chemotherapy for the node-positive subgroup. The EMA has recognised the need to further improve systemic therapy in the eBC setting with pertuzumab, whilst there is still a chance of curing these high risk patients. The APHINITY study was designed to test a single primary objective (IDFS) and not co- (or multiple) primary objectives, therefore a multiplicity adjustment where the alpha is split between different (primary) objectives wasn't relevant for study design. In agreement with health authorities, adjustment for multiple testing of primary and key pre-specified secondary endpoints (IDFS, IDFS-SPNBC, DFS, OS) was incorporated using a fixed sequence testing hierarchy providing type I error control at 5% significance level for the above endpoints and allows appropriate statistical interpretation for labelling. Pertuzumab as adjuvant treatment for patients with HER2-positive early breast cancer at high risk of recurrence has been granted a licence in multiple countries worldwide including the US. In recognition of the significant clinical benefit observed in the high-risk population in comparison with existing therapies, the CHMP have also recommended granting an additional year of market protection for pertuzumab. (EMA, 2017) We request the Committee reviews its recommendation in recognition of the clinical benefit in node-positive patients, in line with health authorities and guidelines worldwide.
9	**Updated ASCO guidelines recommend the use of adjuvant pertuzumab in node-positive patients** Since the Committee meeting, ASCO has updated their guidelines to recommend the use of adjuvant pertuzumab in HER2-positive early breast cancer patients at high risk of recurrence. The ASCO Expert Panel preferentially supports the recommendation for pertuzumab in the node-positive subgroup. (Denduluri *et al.*, 2018) This reflects their recognition of the importance of reducing the risk of recurrence whilst in the HER2-positive eBC setting and the benefit adjuvant pertuzumab could bring to these node-positive patients who still have an opportunity to achieve a cure. The update to ASCO guidelines follows other treatment guidelines that have been updated since APHINITY data was published (Curigliano *et al.*, 2017; NCCN, 2018; AGO, 2018), all of which have recommended the use of adjuvant pertuzumab for patients with node-positive disease and are in-line with the base case focused on in the Roche submission. This position is supported by clinical experts and patient organisation consulted by NICE in advance of the Appraisal Committee Meeting. Roche have consulted clinical experts and professional groups including UKBCG and ABS, who all acknowledge the clinical benefit in the node-positive subgroup. There is broad support from the clinical community for making adjuvant pertuzumab available on the NHS for HER2-positive eBC. We request that the Committee's consideration reflects this stance. Roche believe the summaries of clinical effectiveness included in the ACD need to be re-interpreted with consideration of the above evidence.

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10	**Parameterisation of the "cure" model in the cost-effectiveness analysis** Analyses of the long-term data from the HERA (Cameron *et al.*, 2017) and BCIRG 006 (Slamon *et al.*, 2011) studies show that recurrence rates in the HER2+ adjuvant breast cancer population begin relatively high, before sharply decreasing, and finally stabilising (at approximately 120 months). This trend is assumed to also be reflected in the APHINITY trial (von Minckwitz *et al.*, 2017). In Roche's base case economic analysis, the trend described above has been replicated by assuming that from 48 months onwards, the proportion of patients being "cured" (no longer at risk of recurrence and only subject to background mortality) increases linearly with time from 0% at 48 months to 90% at 120 months. Forty-eight months was preferred to 36 months in the base case, as APHINITY data are available up until this timepoint (48 months). In their report, the ERG agreed with the principle of the cure model, however, they suggested a different starting point and maximum cure rate. According to the ERG, the cure rate should increase linearly with time from 0% at 36 months up to 95% at 120 months. In short, Roche agrees with the ERG's revised start point and maximum cure rate. Starting the cure model from 36 months as opposed to 48 months appears to more accurately reflect the change in hazard, as supported by the smoothed hazard plots. When using a 95% maximum cure rate the proportion of patients experiencing a recurrence after 10 years is more in-line with the data published by Takeuchi *et al.* (Takeuchi *et al.*, 2009) Please see the Section B.3.3.1 of the company submission and Section 5.2.6 of the ERG report for a more in-depth discussion on this aspect of the economic analysis.
11	**Proportion of metastatic and non-metastatic recurrences** In Roche's economic base case, any recurrence that occurred within 18 months of treatment initiation was assumed to be managed as a metastatic event (in terms of prognosis and treatment options). The proportion of recurrences that were metastatic and non-metastatic in the post-18-month period were then derived directly from the APHINITY trial data (von Minckwitz *et al.*, 2017). The ERG noted that the percentage of recurrences that were metastatic and non-metastatic were calculated using the entirety of the APHINITY data (pre-18 months and post-18 months), but were then only applied to the post-18-month period in the model (as 100% of recurrences pre-18 months are assumed to be managed as a metastatic event in the model). As a result of this discrepancy, the ERG attempted to re-calculate these post-18 month percentages using only the corresponding (post-18 month) APHINITY data. The results of Roche's original approach and the ERG's approach are given below: **Table 1 Proportion of metastatic and non-metastatic events used in the economic analysis – node positive population**

	Roche base case (combined arms)	ERG analysis (combined arms)
Pre-18 month period		
% of recurrences that were non-metastatic	0%	0%
% of recurrences that were metastatic	100%*	100%*
Post-18 month period		
% of recurrences that were non-metastatic	18.93%	27.60%
% of recurrences that were metastatic	81.07%	72.40%

* All recurrences that occur less than 18 months following treatment initiation are managed as a metastatic event (in terms of

treatment and prognosis)

Although the ERG's methodology appeared to be an improvement on the original calculations, the company noted that several key assumptions had been made. Following the first committee meeting, Roche has conducted further analysis on the observed APHINITY data, the results of which are presented in Table 2 below.

Table 2 Proportion of metastatic and non-metastatic events from the supplementary analysis of the APHINITY data – node positive population

	Additional analysis of APHINITY data
Pre-18 month period	
% of recurrences that were non-metastatic	24.42%
% of recurrences that were metastatic	75.58%
Post-18 month period	
% of recurrences that were non-metastatic	20.62%
% of recurrences that were metastatic	79.38%

The use of the observed APHINITY data is the most robust way of estimating these parameter values. Therefore, the figures reported in Table 2 have been incorporated into the revised economic analysis (see comment 15).

12

Incorporation of trastuzumab biosimilars

At the time of the company's original submission, trastuzumab biosimilars were not yet commercially available in the UK. Despite this, the launch of these drugs was expected imminently. Roche therefore submitted the cost-effectiveness results of a scenario analysis which did incorporate trastuzumab biosimilars as part of the decision problem. Though the impact of trastuzumab biosimilars was recognised by the ERG in their report, they failed to incorporate this impact when quoting their own cost-effectiveness estimates. Subsequently, the Committee also failed to incorporate the impact of biosimilars on the decision problem in the appraisal consultation document (ACD).

The omission of biosimilars from the ACD was particularly surprising given both the company's and Professor Peter Clark's (Consultant Medical Oncologist and current Chair of the Chemotherapy Clinical Reference Group) comments during the first committee meeting in May. In summary, Professor Clark noted that the "company was correct" in its incorporation of biosimilars in the cost-effectiveness modelling. In addition, he also offered insights into both the expected market share and price of these drugs (see below). These comments served to confirm that trastuzumab biosimilars are expected to become a significant part of HER2+ breast cancer practice in the UK.

At the time of writing, both the price and the market share of biosimilars are not definitively known. Nevertheless, based on comments from Professor Clark, NHSE publications, and market intelligence collected by Roche, plausible ranges have been identified for both of these parameters.

In the first committee meeting, Professor Clark stated that he expects the market share of trastuzumab biosimilars in this indication to be between 90% and 100% of the trastuzumab IV market before the publication of final guidance. This expectation is also in-line with a commissioning paper published by NHSE – "…at least 90% of new patients will be prescribed the best value biological medicine within 3 months of launch of a biosimilar medicine" (NHSE, 2017). On the basis of these comments, cost-effectiveness results have been generated using a range of biosimilar market share values from 90 to 100%.

	In addition, Professor Clark also made reference to the expected price of trastuzumab biosimilars. He noted that the discount offered in comparison to the Herceptin IV list price is "significant". Market intelligence collected by Roche has allowed the company to estimate the discount associated with these drugs. It is the belief of Roche that biosimilars are currently being offered to the NHS at a discount of at least 70% compared to Herceptin IV. As such, the company has provided cost-effectiveness results using a range of discounts from 70% up to 80%. Trastuzumab biosimilars are now available for widespread use in the UK. Consequently, it is the strong belief of Roche that these drugs should be incorporated into estimates of cost-effectiveness in this appraisal. Roche are cognisant of other NICE appraisals (TA329, TA375, TA513, TA509 etc.*)* in which biosimilars have been incorporated explicitly in the decision-making of the committee. Failure to do so here would result in an inconsistency that is potentially unfair and unreasonable in light of the evidence submitted. Furthermore, any incremental cost-effectiveness ratio (ICER) that fails to account for biosimilars is not reflective of the UK environment and is inherently misleading.
13	**Overestimation of OS in the cost-effectiveness model** Both the ERG and the Committee have commented that the cost-effectiveness model overestimates OS in the base case analysis. The response below outlines the justification for three key issues which either the committee or the ERG have previously highlighted: • *Poor fit of the modelled OS curve compared to the observed data from APHINITY* • *Overestimation of modelled OS compared to older adjuvant trastuzumab trials* • *Steep decline in OS in the modelled curves is not reflected in other long terms studies* In summary, Roche has adjusted the modelled OS to increase generalisability to UK clinical practice. This is the primary reason for the suggested "overestimation" of OS in the model. Roche believes this approach to be robust and methodologically preferable to an unadjusted approach. The response below serves to justify the modelled OS and highlight that the projections are perfectly plausible. ***Poor fit of the modelled OS curve compared to the observed data from APHINITY*** In the ACD, the committee state that the modelled OS data does not fit the observed APHINITY data very well. While this is true, Roche has previously provided the rationale for this poor fit as part of its response to the ERG's clarification questions. In addition, this justification is presented in the ERG report and seems to have been accepted by the ERG as reasonable. Despite making the same assertion regarding the poor fit of OS, the Committee has neglected to report or even consider the company's explanation in the ACD. As a result, the justification for this poor fit has been reiterated below. In the economic analysis, OS is modelled by accounting for the risk of death in each individual health state. Background mortality applies in all health states and is the main cause of death in the IDFS, non-metastatic recurrence, and remission states. The risk of death is significantly higher in the mBC health states. For mBC patients, the risk of death is modelled according to trial data on mBC therapies available to current UK patients. In the UK, the proportion of mBC patients receiving pertuzumab + trastuzumab + chemotherapy (PTC) as a first-line treatment option is significantly higher than in the APHINITY (von Minckwitz *et al.*, 2017), HERA (Cameron *et al.*, 2017), and BCIRG 006 (Slalom *et al.*, 2011) trials – see Table 3. PTC has only recently become a standard of care in this setting of UK practice. It is therefore expected that more patients in the UK today are receiving this regimen than the populations in trials which began over six years ago. These medicines are transformative and have a direct impact on survival outcomes in patients. The percentage of modelled mBC patients receiving these therapies is reflective of the rates seen in UK clinical practice (ESTHER study [Wardley *et al.*, 2018]) rather than the rates seen in APHINITY. Consequently, mBC

patients in the model can expect better overall survival outcomes than the equivalent patients in the APHINITY trial.

Table 3 Proportion of treatment options on each treatment option in first-line mBC

Treatment option received after distant recurrence	APHINITY trial	ESTHER study
Pertuzumab + trastuzumab + chemotherapy	24.1%	71.2%
Placebo + trastuzumab + chemotherapy	46.7%	22.9%
Chemotherapy alone	29.2%	5.9%

Once the proportion of patients receiving PTC and TC in the mBC states of the model is set equal to the proportions seen in APHINITY, the modelled OS fit to the OS KM curves is improved (Figure 2 and Figure 3). As reported by the ERG, the ESTHER study gives a more accurate representation of current UK practice and therefore the treatment shares reported in that study should be used in the base case of this economic analysis (Wardley *et al.*, 2018).

Figure 2 Modelled OS vs. APHINITY KM data (node-positive population) - Using UK clinical practice mBC treatment use

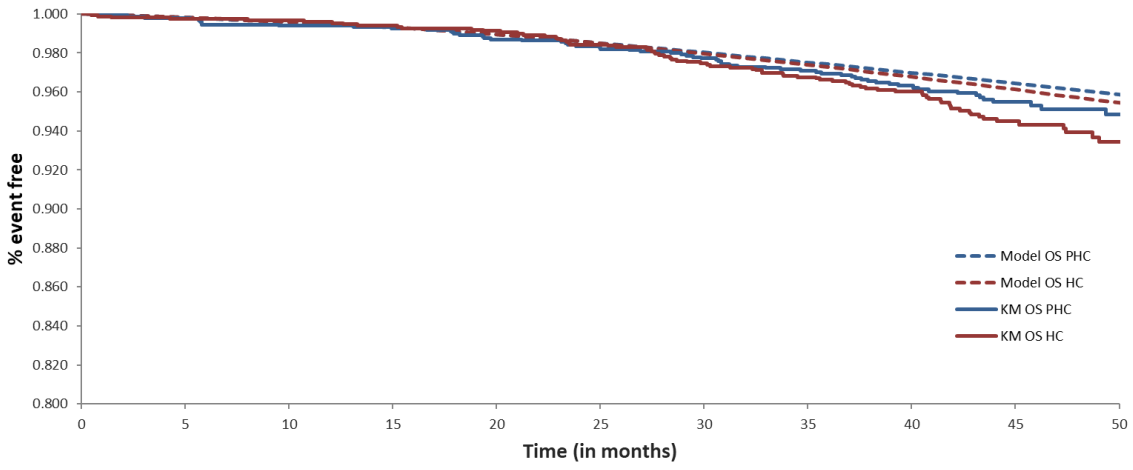

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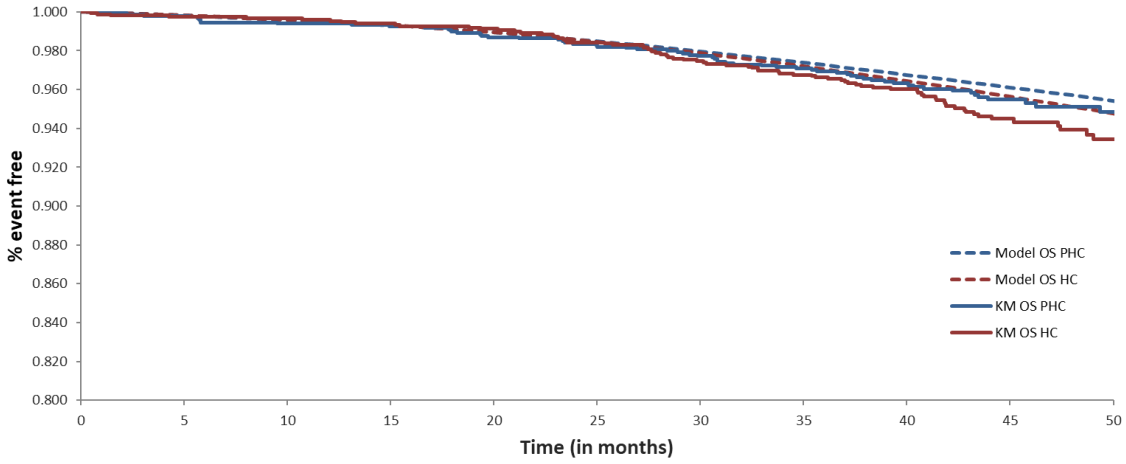
Figure 3 Modelled OS vs. APHINITY KM data (node-positive population) – Using mBC treatment use as seen in APHINITY trial



It is also important to note at this stage that the poor fit is actually a difference of 0.7% and 1.8% at the three and four-year timepoints respectively (placebo arm). Whereas, a difference of 0.4% and 1.2% is observed at the three and four-year time points in the pertuzumab arm. Although the modelled OS is undoubtedly an overestimation in both arms, the difference is indeed negligible.

When using the treatment usage figures reported in APHINITY, the companies base case ICER increases from £34,086 (ESTHER resource use) to £34,963. This is an incremental change of £877 (+2.57%). In terms of the overall cost-effectiveness results, the impact is marginal.

Overestimation of modelled OS compared to older adjuvant trastuzumab trials

The explanation offered in part one of this comment also helps to explain the overestimation of OS at later timepoints. Patients in current UK practice have a level of access to transformative medicines in first-line mBC which patients in the APHINITY (von Minckwitz *et al.*, 2017), HERA (Cameron *et al.*, 2017), and BCIRG 006 (Slalom *et al.*, 2011) trials did not. These transformative medicines have a significant impact on overall survival outcomes in the metastatic setting. Consequently, it is expected that OS outcomes in the modelled patients would be superior to those in the aforementioned trials.

When the first-line mBC treatment shares observed in APHINITY are used in the model, as opposed to the shares observed in UK practice (ESTHER studies), the OS estimates projected by the model are in-line with the values reported in the older adjuvant trials (Table 4). Once again, the company agrees with

the ERG's assessment that the resource use reported in ESTHER is reflective of current UK practice and should therefore be used in the base case of the economic analysis (Wardley *et al.*,2018).

It is also important to note here that the outcomes of the APHINITY study, both in terms of IDFS and OS are the best ever seen in any adjuvant breast cancer trials. Therefore, it follows logic that a model based on this study is likely to provide OS estimates higher than anything observed or modelled in the past.

Table 4 Overall survival comparison

		3 yr	4 yr	5 yr	10 yr	12 yr
Company Extrapolation for N+ Placebo Arm – ESTHER study RU data	Base case population	97.21%	95.64%	93.87%	83.76%	80.28%
Company Extrapolation for N+ Placebo Arm – APHINITY RU data		96.98%	95.03%	92.81%	81.72%	78.60%
Observed APHINITY Trial – N+ Control Arm	Identical to base case population	96.54%*	93.80%*	-	-	-
HERA Trial Full Population – 1Y T arm	Healthier than base case	92.70%	89.30%	86.90%	80.70%	79.40%
HERA Trial HR+ Population – 1Y T arm	Much healthier than base case	94.50%	-	89.10%	82.70%	80.90%
HERA Trial HR- Population – 1Y T arm	Healthier than base case	90.90%	-	84.60%	78.70%	77.90%
BCIRG-006 Full trial population, AC-TH arm	Healthier than base case	97%**	94%**	92%	85.9%	-

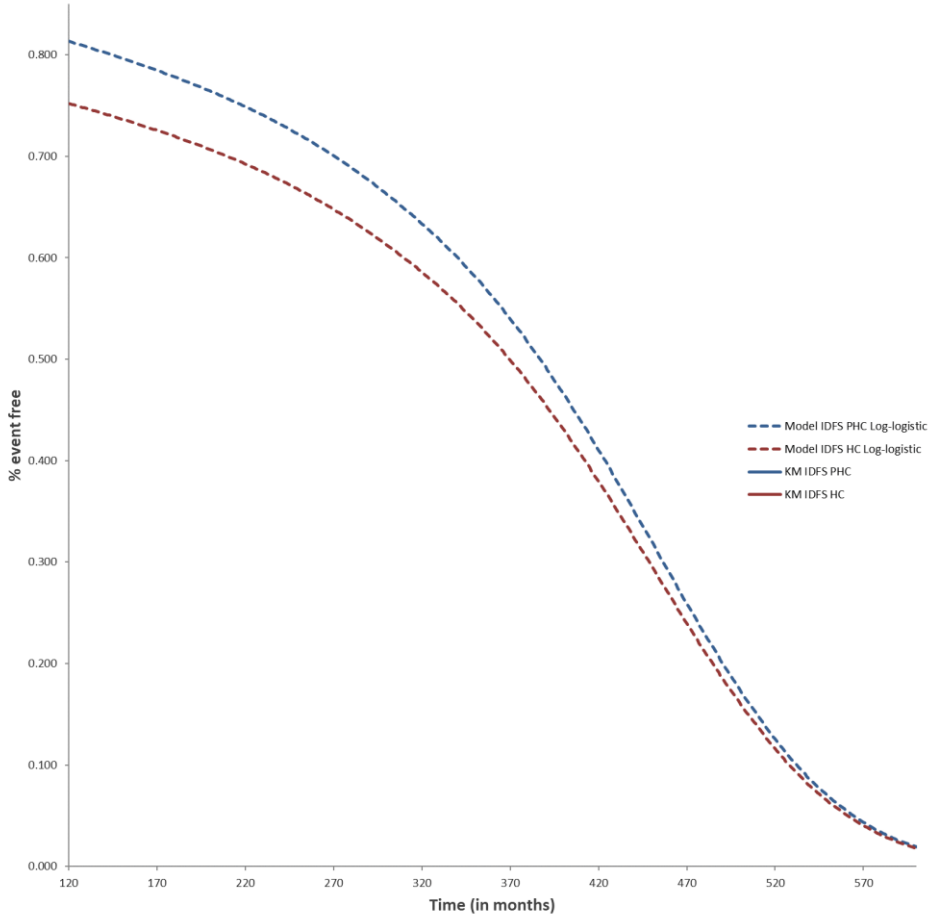
*approximate, extracted from economic model. **approximate, extracted from KM plot.

In addition, a recent surrogate endpoint validation study (manuscript in preparation) was conducted to estimate the trial and patient-level correlation between DFS and OS in HER2+ eBC (please see the original submission appendices for more information on the methodology). Based on the estimated correlation equation, a longer term OS HR in a "new" study (i.e. in APHINITY) can be predicted based upon the observed DFS HR in the same study. The observed IDFS HR at four years in the node-positive population of APHINITY was 0.77, therefore the predicted OS HR (using the correlation equation) would be estimated to be 0.775. The OS HR predicted by the model at 10 years is 0.80 (under the company's base case assumptions). In summary, the model projection can be considered to be broadly in line with the predicted OS HR from the correlation equation. Furthermore, given that the modelled OS HR is superior to the equation prediction, the model can potentially be considered to be underestimating the OS benefit in the pertuzumab arm.

	It is important to note here that the predicted value quoted above will be associated with considerable confidence intervals. In the meta-analysis study used to derive the correlation equation, the DFS definition was broad, and data availability meant that no analyses could be performed for an IDFS endpoint. The OS outcomes in the economic model have been generated by modelling IDFS and not DFS. However, it should be acknowledged that the IDFS definition is more "restrictive" than DFS (i.e. excludes second primary non-breast cancers) and that the HR between DFS and IDFS were very similar in APHINITY. Irrespective of the disparity in endpoints, the OS HR predicted by the regression model (based on DFS) can be considered comparable with the OS HR predicted by the cost-effectiveness model (based on IDFS). Despite the associated uncertainty, Roche believes the methodology used in this endpoint validation study to be very robust. The correlation between DFS and OS in this study has been echoed by other authors and academic groups (Savina *et al.,* 2017). In conclusion, the results from said study help to, once again, prove that the model is not "overestimating" OS outcomes. ***Steep decline in OS in the modelled curves is not reflected in other long terms studies*** The ERG commented that the steep decline in modelled OS between years 5 and 10 is not reflected in any of the other adjuvant studies (Figure 19, ERG report). The justification for this sharp change in trajectory in the modelled OS curve is once again related to access to transformative medicines (outlined fully in part one of this comment). In the first five years, background mortality is the principle cause of death in the APHINITY model. The access to transformative therapies means that mBC deaths are delayed in comparison to the older adjuvant trials. Instead of the mBC deaths occurring steadily over the first five years (as in the older trials), they have been delayed. Consequently, the death events have "built up" and now occur rapidly in quick succession. At 10 years, background mortality once again becomes the principle cause of death in the model, hence the stabilisation of the curve after this timepoint. In other words, the improved survival outcomes in mBC patients helps to explain why OS is higher in the first 5 years, before decreasing rapidly and plateauing at approximately year-10. In summary, the issues regarding the overestimation of OS can all be traced back to the evolution of clinical practice in HER2+ breast cancer. A greater proportion of current UK patients (and modelled patients) have access to better medicines than patients enrolled in clinical trials over five years ago. It therefore follows logic that modelled patients have better survival outcomes and are not directly comparable to the older clinical trial populations.
14	**Pertuzumab treatment effect duration** In section 5.2.6 of their report, the ERG provides a critique of the company's assumptions on the incremental treatment effect duration of pertuzumab in the model. The ERG disagrees with Roche's base case assumption that a treatment effect will exist until year 7 before waning and ceasing completely at year 10. Instead, the authors preferred to assume that there is a full treatment effect until year 4 before ceasing completely at year 7. The company agrees with the clinical expert's comments during the first committee meeting, the ERG's assumption is far too conservative and not at all reflective of clinical practice. Throughout their critique, the ERG uses phrases such as "minimal further divergence" or "no widening of separation" when describing the KM curves reported in previous HER2+ eBC trials (Cameron *et al.*, 2017) (Slalom *et al.*, 2011). The company is concerned that the presence of parallel curves in previous studies may be being interpreted as evidence of no treatment effect. The company believes that this is a misinterpretation and that parallel curves are actually reflective of a treatment effect that is constant. If there was indeed no treatment effect, then the curves would begin to converge. A prime example of this is the modelled IDFS curves in the post-10-year period, presented in Figure 4 below. After 10-years, the hazard rates in both arms are equal and therefore the treatment effect has completely ceased. If the

ERG's interpretation was correct, then we would expect to see no change in separation (parallel curves) from this time point onwards. It can be seen quite clearly that these curves are not running parallel, but are in-fact converging. Thus, we can infer that no further separation is not in fact indicative of no treatment effect. The mechanics behind this convergence are as follows: there is a greater number of patients at risk in the PTC arm, therefore, although the hazard rates are equal, the absolute decrease in IDFS is greater, which results in the PTC curve dropping more sharply and the curves converging. Broadly speaking, the curves in HERA (Cameron *et al.*,2017) and BCIRG 006 (Slalom *et al.*, 2011) are parallel at later time points which can be reasonably interpreted as evidence of a persisting albeit constant treatment effect.

Figure 4 Company base case IDFS curves – node positive population



Evidence of this persisting treatment effect can be further substantiated by examining the hazard ratios in the node-positive population in each trial. Hazard ratios between year 7 and year 10 of the HERA and BCIRG 006 trial are shown to be 0.803 and 0.801, respectively. The fact that this hazard ratio is still below 1.00 across this time period can be interpreted as evidence of a long-term treatment effect.

Data from the HERA trial have been routinely cited as an analogue for the treatment effect of pertuzumab in this indication. It is however important to note that any conclusions drawn from this trial data should be

considered under the following caveat: 52% of patients originally randomised to the placebo arm crossed over to the intervention arms of the study. Naturally, the outcomes seen in the placebo arm were greatly improved once patients began receiving trastuzumab and as a result the treatment effect at later timepoints is vastly underestimated. (Cameron *et al.*, 2017)

Comment 13 (and the company submission appendices) discusses the prediction of a 10-year OS HR based on the 4-year IDFS HR seen in the node-positive population of the APHINITY trial. As described above, the companies base case assumptions around treatment effect duration, results in a modelled 10-year OS HR which is broadly in-line with the ratio predicted by the regression equation (0.80 and 0.77, respectively). Using the ERG's assumptions around treatment effect results in a modelled OS HR of 0.843. The ERG's modelled OS HR is significantly superior to the equation-predicted value. This disparity in OS HRs once again serves to suggest that the ERG's assumptions around treatment effect duration are implausibly conservative.

The ERG have previously presented KM curves reported in the PHEREXA (Urruticoechea *et al.*, 2017) and CLEOPATRA trials (Swain *et al.*, 2015). Both of these trials evaluate the use of pertuzumab in mBC patients. Metastatic breast cancer and eBC are completely different settings and are associated with vastly differing outcomes. Naturally, mBC is far more aggressive and patients die far quicker than in the adjuvant setting. Results in these populations are not at all comparable and it is therefore impossible to relate an efficacy pattern seen in one indication to the other. Figure 14,15 and the related prose in the ERG report are largely irrelevant. The company agrees with the comments of the clinical expert in the first committee meeting, who confirmed that results from these trials should not factor into the decision making on this parameter of the analysis.

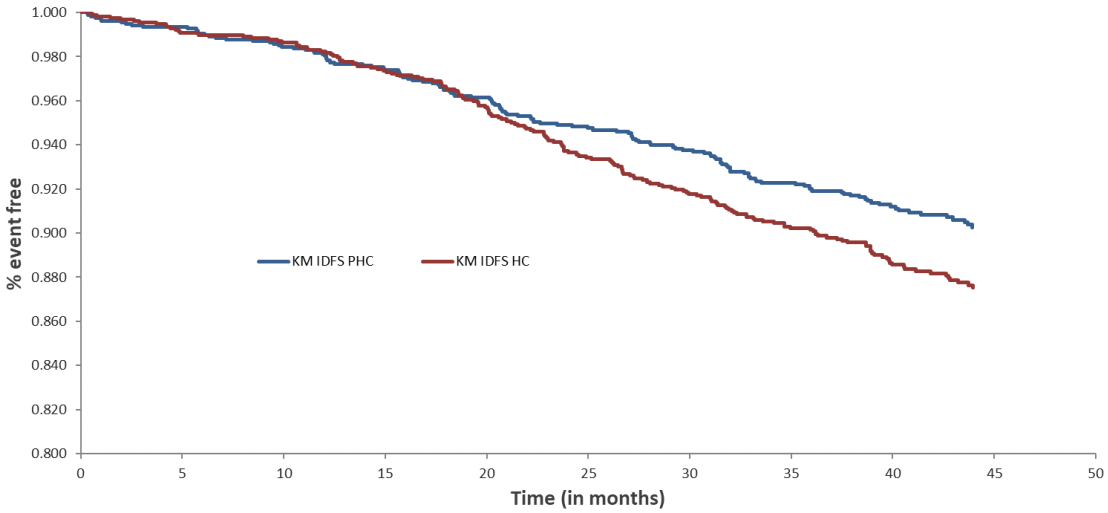
Furthermore, the ERG's assertion that the pertuzumab treatment effect begins to wane after only four years does not appear to be substantiated by the currently available APHINITY data (von Minckwitz *et al.*, 2017). The annualized hazard ratios of the APHNITY KM data are presented in Table 5 below:

Table 5 Annualized hazard ratios in APHINITY data - Node positive population

Time period	Annualized hazard ratio
Year 0-1	1.00
Year 1-2	0.79
Year 2-3	0.75
Year 3-4	0.59

The values in Table 5 clearly show that the hazard ratio is lessening year by year and the treatment effect is therefore increasing over time. This trend seems directly contradictory to the ERG's assumption that the treatment effect would begin to lessen after four years. Admittedly, median follow-up in the node-positive population is at 44.5 months and in year 3-4 significant censoring occurs. This particular ratio can therefore be associated with a larger degree of uncertainty. Nevertheless, if the KM IDFS curves are capped at median follow-up, before the bulk of the censoring occurs, we can see that the greatest separation in the curves occurs at 44.5 months – Figure 5. This, once again, points to the fact that the treatment effect is still increasing at median follow-up and that to assume 3.5 months later that this trend suddenly reverses seems unfounded and illogical.

Figure 5 APHINITY KM IDFS curves – capped at 44.5 months – node positive population



The company agrees with the ERG that this aspect of the analysis is highly uncertain. The currently available evidence does not definitively point to a specific duration of effect. Revised cost-effectiveness results, across a range of treatment effect duration scenarios, have therefore been provided as part of this response – see supplementary appendix. For completeness, both the company's base case assumptions (7-10 years) and the ERG's preferred assumptions (4-7 years) have been included as scenarios in the appendix. Furthermore, the treatment effect duration used in the neoadjuvant pertuzumab appraisal (runs for 7 years and ceases immediately) has also been included.

Irrespective of the uncertainty surrounding this aspect of the model, the evidence provided above strongly suggests that the true treatment effect of pertuzumab is unlikely to be reflected in the ERG's preferred assumptions.

15

Revised cost-effectiveness analysis

As part of this response, revised cost-effectiveness results have been generated. A detailed overview of these results has been provided as a supplementary appendix to this response. The results quoted in the supplementary appendix incorporate the following changes from the originally submitted base case analysis:

- Cure model begins at 36 months and increases linearly with time until reaching a maximum cure rate of 95% at 120 months – see comment 10 for more details
- Revised figures relating to the proportion of recurrences that are metastatic and non-metastatic – see comment 11 for more details
- Correction of an error associated with accounting for non-metastatic recurrences in the pre-18-month period of the Markov traces (impact on the final ICER of 1.5% approximately)
- Incorporation of trastuzumab biosimilars (in-line with the NHS England perspective) into the cost-effectiveness analysis
- Roche have [redacted]. All other confidential discounts in the base case analysis remain unchanged
- Results have been generated for a range of possible treatment effect duration scenarios

Across all plausible scenarios, the resulting ICER ranges from a maximum of £23,928 down to a minimum of £13,215. As mentioned above, the ERG's overly conservative assumptions around the pertuzumab effect duration are implausible, nevertheless, the ICER in this scenario is still approximately £30,000 and can therefore be broadly considered as cost-effective. In conclusion, these revised results serve to

	illustrate that, when incorporating the specified changes, pertuzumab can be regarded as a cost-effective use of NHS resources in all plausible scenarios.
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	Slamon et al. BCIRG 006: 10-Yr Follow-up of Adjuvant AC -> T Compared With AC -> TH and TCH for HER2+ Early BC. Oral presentation presented at San Antonio Breast Cancer Symposium; 8-12 December 2015, San Antonio, Texas Strasser-Weippl K, Horick N, Smith IE, et al. Long-term hazard of recurrence in HER2+ breast cancer patients untreated with anti-HER2 therapy. Breast Cancer Res 2015;17:56. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. NEJM 2015;372:724-734. Takeuchi H, et al. - Clinicopathological characteristics of recurrence more than 10 years after surgery in patients with breast carcinoma. Anticancer Res. 2009 Aug;29(8):3445-8. Urruticoechea et al. - Randomized Phase III Trial of Trastuzumab Plus Capecitabine With or Without Pertuzumab in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer Who Experienced Disease Progression During or After Trastuzumab-Based Therapy - Journal of Clinical Oncology 2017 35:26, 3030-3038 von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. NEJM 2017;377:122-31. http://dx.doi.org/10.1056/NEJMoa1703643 Wardley A, Fredriksson J, Leslie I, et al. Anti-cancer resource use in the initial management of advanced HER2+ breast cancer: an interim analysis of the UK ESTHER study. EBCC-0377. Poster presented at European Breast Cancer Consortium; 21-23 March 2018, Barcelona, Spain.

Pertuzumab for adjuvant treatment of HER2-positive early breast cancer [ID1192]

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Cost-effectiveness appendix

As part of this response, revised estimations of cost-effectiveness have been provided. The changes from the company original base case have been summarised in the body of the main response and are outlined in full below.

This appendix is split into two components a) definitive changes and b) key areas of uncertainty. Part a) (definitive changes) details the changes that have been made or agreed upon by the company since the first appraisal committee meeting. These revised parameter values are believed to be the best available evidence and most relevant to the discussion moving forward. Part b) presents scenario analyses on two key areas of uncertainty. These two key areas are the assumptions around trastuzumab biosimilars and the treatment effect duration of pertuzumab.

For completeness, both the company's and the ERG's base case ICERs are reported in Table 1 and Table 2 below.

Table 1 Cost-effectiveness results - company base case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£ per QALY gained)
HC (trastuzumab + chemotherapy)	[redacted]	12.95	[redacted]	0.606	£34,087
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	13.56			

Table 2 Cost-effectiveness results - ERG preferred assumptions

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£ per QALY gained)
HC (trastuzumab + chemotherapy)	[redacted]	13.267	[redacted]	0.384	£60,679
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	13.652			

Part a) - Definitive changes

As outlined in the main body of the response, the company has modified its assumptions regarding the cure model, proportion of metastatic and non-metastatic recurrences, and the discount offered on pertuzumab in this indication. For clarity, the specific changes and the resulting impact on the company base case ICER have been reported in Table 3 and Table 4 below.

Table 3 Changes made to company base case following first appraisal committee meeting

Parameter	Values in company's original submission	ERG's preferred value	Value used in company's revised estimates
"Cure" adjustments			
Time point at which cure model begins	48 months	36 months	36 months
Maximum cure rate	90%	95%	95%
Time point at which cure model ends	120 months	120 months	120 months
Percentages of disease recurrence			
Metastatic recurrence – Pre 18 months	100%	100%	75.58%
Non-metastatic recurrence – Pre 18 months	0%	0%	24.42%
Metastatic recurrence – Post 18 months	18.93%	72.40%	79.38%
Non-metastatic recurrence – Post 18 months	81.07%	27.60%	20.62%
Confidential PAS discounts			
Discount on [redacted]	[redacted]	N/A	[redacted]

Table 4 Effect of changes outlined in Table 3 on Roche's original base case cost-effectiveness results

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£ per QALY gained)
Original base case					
HC (trastuzumab + chemotherapy)	[redacted]	12.91	[redacted]	0.611	£33,857
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	13.52			
Revised estimates (incorporating changes highlighted in part a)					
HC (trastuzumab + chemotherapy)	[redacted]	13.20	[redacted]	0.556	£30,561
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	13.76			

Part b) - Key areas of uncertainty

As described in the main body to this response, sizable uncertainty still exists in two aspects of the cost-effectiveness analysis.

- **Assumptions around trastuzumab biosimilars**
  - Market share = 90%-100%
  - Discount vs. Herceptin IV = 70%-80%
- **Incremental treatment effect duration of pertuzumab**
  - 4-7 years – ERG assumptions
  - 5-8 years
  - 7 years – Neoadjuvant appraisal
  - 6-9 years
  - 7-10 years – Roche base case

In attempt to mitigate this uncertainty the company has generated cost-effectiveness results that encompass plausible input ranges in both of these aspects. The main body of this response provides more details on how these plausible ranges have been decided upon.

Please note, the ICERs quoted in the subsequent tables have been generated after the incorporation of the changes highlighted in part a) of this appendix.

Table 5 Treatment effect – Runs for 4 years before waning and ceasing completely at 7 years – ERG preferred assumption

		Trastuzumab biosimilar discount compared to branded trastuzumab list price (%)					
		70%	72%	74%	76%	78%	80%
Trastuzumab biosimilar market share (%)	90%	£30,344	£29,470	£28,597	£27,723	£26,850	£25,977
	95%	£29,371	£28,449	£27,527	£26,605	£25,683	£24,761
	100%	£28,398	£27,427	£26,457	£25,487	£24,516	£23,546

Table 6 Treatment effect – Runs for 5 years before waning and ceasing completely at 8 years

		Trastuzumab biosimilar discount compared to branded trastuzumab list price (%)					
		70%	72%	74%	76%	78%	80%
Trastuzumab biosimilar market share (%)	90%	£23,928	£23,187	£22,446	£21,704	£20,963	£20,221
	95%	£23,102	£22,319	£21,537	£20,754	£19,971	£19,189
	100%	£22,275	£21,452	£20,628	£19,804	£18,980	£18,156

Table 7 Treatment effect – Runs for 7 years ceases completely at 7 years – Neoadjuvant pertuzumab appraisal

		Trastuzumab biosimilar discount compared to branded trastuzumab list price (%)					
		70%	72%	74%	76%	78%	80%
Trastuzumab biosimilar market share (%)	90%	£21,511	£20,819	£20,128	£19,436	£18,744	£18,052
	95%	£20,740	£20,010	£19,279	£18,549	£17,819	£17,089
	100%	£19,968	£19,200	£18,431	£17,662	£16,894	£16,125

Table 8 Treatment effect – Runs for 6 years before waning and ceasing completely at 9 years

		Trastuzumab biosimilar discount compared to branded trastuzumab list price (%)					
		70%	72%	74%	76%	78%	80%
Trastuzumab biosimilar market share (%)	90%	£20,202	£19,536	£18,871	£18,205	£17,540	£16,874
	95%	£19,460	£18,757	£18,055	£17,352	£16,650	£15,947
	100%	£18,718	£17,978	£17,239	£16,499	£15,760	£15,020

Table 9 Treatment effect – Runs for 7 years before waning and ceasing completely at 10 years – Company base case

		Trastuzumab biosimilar discount compared to branded trastuzumab list price (%)					
		70%	72%	74%	76%	78%	80%
Trastuzumab biosimilar market share (%)	90%	£18,062	£17,439	£16,817	£16,194	£15,572	£14,950
	95%	£17,367	£16,710	£16,053	£15,396	£14,739	£14,082
	100%	£16,673	£15,981	£15,290	£14,598	£13,907	£13,215

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

Name	[redacted]
Role	Patient organisation representative
Other role	
Organisation	Breast Cancer Care
Location	England
Conflict	yes
Notes	
Comments on the ACD:	
Page 4-5 section 3.1 "As highlighted in this section, at Breast Cancer Care we know that fear of recurrence is a common concern for many people being treated for breast cancer. This fear can be a cause of great anxiety, having a significant impact on a personâ€™s wellbeing and ability to move forward after breast cancer. Additional treatment options, such as pertuzumab, that reduce the risk of breast cancer returning, are therefore highly valuable to patients. "	

Pertuzumab for adjuvant treatment of HER2-positive early breast cancer [ID1192]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Breast Cancer Now
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Pertuzumab for adjuvant treatment of HER2-positive early breast cancer [ID1192]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	It is disappointing that NICE has not been able to recommend pertuzumab for the adjuvant treatment of early HER2 positive breast cancer with trastuzumab and chemotherapy. The data from the APHINITY trial presented in the Committee meeting shows a further improvement in invasive disease free survival (IDFS) at 4 years of follow-up in those with node positive disease (1.8% at 3 years and 3.2% at 4 years) and hormone receptor negative disease (1.6% at 3 years and 2.3% at 4 years). Whilst improvements in IDFS are incremental to the current standard of care, much progress has been made in breast cancer over the years through incremental improvements. For example, the addition of a taxane to an anthracycline chemotherapy regime reduces the absolute risk of recurrence by 4.6% and of overall mortality by 3.2% at 8 years.[1] The use of aromatase inhibitors compared with tamoxifen in postmenopausal women reduces the absolute risk of recurrence by 3.6%, and overall mortality by 2.7% at 10 years.[2] Any improvement in outcomes is welcomed by patients and their loved ones. As noted in the ACD, the risk of breast cancer recurring or spreading to other parts of the body, where it becomes incurable, can be a cause of stress and anxiety. Around one in four patients with early HER2 positive breast cancer will experience a recurrence. The impact of a diagnosis of metastatic breast cancer – which has an average life expectancy of 2 to 3 years - is devastating, as the Committee is aware from its work on breast cancer drug appraisals in this setting.
2	I feel that some of the comments I made in the Committee meeting have not been used in context in the ACD. In section 3.1, the comment that 'not all people would consider the additional treatment benefit of pertuzumab in the APHINITY trial to be worthwhile' was intended to reflect the fact that the trial results suggest greater benefit in those at higher risk of recurrence, in line with the marketing authorisation for pertuzumab. Also - whilst it will depend on the individual patient - I said that I thought that most, rather than some, patients would consider a reduced risk of recurrence worth the inconvenience of spending longer in hospital to receive treatment.
3	We agree with the Committee's conclusion in section 3.2 that patients that have had neoadjuvant treatment with pertuzumab should be considered as part of this appraisal, to reflect clinical practice in the UK.
4	In section 3.5 the ACD highlights the small number of events in the node negative subgroup. Although the Committee felt it was not reasonable to conclude that pertuzumab did not benefit node negative patients on this basis, we wonder whether node negative patients would generally be considered at higher risk of recurrence, and therefore fall within the marketing authorisation for adjuvant pertuzumab.

[1] Early Breast Cancer Trialists' Collaborative Group. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. *Lancet* 2012; 379: 432-44. Available at: DOI: 10.1016/S0140-6736(11)61625-5.

[2] Early Breast Cancer Trialists' Collaborative Group. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet* 2015; 386:1341-52. Available at: DOI 10.1016/S0140-6736(15)61074-1

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5	We understand that the majority of patients currently receiving trastuzumab with chemotherapy for early breast cancer will receive it as a subcutaneous injection, which reduces both the time taken to administer treatment and the level of discomfort associated with it. However, when given with pertuzumab, trastuzumab must also be given intravenously. As set out in comment 2 above, most patients are likely to be willing to spend longer in hospital to receive treatment if their risk of recurrence is reduced. Since this appraisal began, several biosimilars of intravenous trastuzumab have become available, and several more are expected to be launched in the coming months. The list price of these biosimilars is cheaper than that for Herceptin, and we understand that confidential discounts have also been agreed for some of them. This may make a positive difference to the cost-effectiveness of pertuzumab in this setting.
6	The overall survival (OS) data that is currently available from the APHINTY trial shows no difference in the intention to treat population at 3 years, but is immature - which is often the case for cancer drugs being appraised by NICE. In the absence of mature OS data, the Committee has accepted IDFS as acceptable for decision making. Whilst the final analysis of OS data from the APHINITY trial is due in 2023, we understand that the next analysis of data is due next year. This may help provide greater certainty for the Committee in relation to the data on IDFS and OS, if any improvement in the cost-effectiveness of pertuzumab in this setting (see comment 5 above) made it a candidate for the CDF.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Pertuzumab for adjuvant treatment of HER2-positive early breast cancer [ID1192]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK Breast Cancer Group (UKBCG)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	UK Breast Cancer Group (UKBCG)

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1	**Has all of the relevant evidence been taken into account?** From the clinical evidence the committee concluded that whilst an improvement in IDFS was observed in the intention-to-treat population of the APHINITY[1] study, any incremental treatment benefit of pertuzumab is likely to be small in this population. The APHINITY trial had a positive result in terms of reduction in invasive disease-free survival at an early time point (median follow-up 45.4 months) in an event driven analysis. In the BCIRG006 trial of adjuvant trastuzumab among node-positive patients receiving a year of adjuvant trastuzumab 5-year rates of disease-free survival, which were 80% in the group receiving AC-T plus trastuzumab and 78% in the group receiving TCH (Table 1A in the Supplementary Appendix)[2,3]. Benefit of trastuzumab in node-positive patients at highest risk for recurrence (i.e., those with ≥4 positive nodes), the 5-year rate of disease-free survival was 73% in the group receiving AC-T plus trastuzumab and 72% in the group receiving TCH, (Table 1A in the Supplementary Appendix)[3]. In the HERA trial the 10-year disease free survival rates for patients who received 1 and 2 years of trastuzumab respectively according to lymph node involvement 0, 1-3 nodes and 4+ nodes involved were 80.1/80.3%, 74.5/73% and 54.5/53.6% respectively[4]. In the hormone-receptor-positive cohort, the 10-year disease-free survival was 72% in the 1-year trastuzumab and 70% in the 2-years trastuzumab groups (figure 2C). In the hormone-receptor-negative cohort, the 10-year disease-free survival rates were lower; 59% for the observation group, 67% for 1-year trastuzumab group, and 67% for 2-years trastuzumab group. In view of this considerable risk of recurrence beyond the time course of the current follow-up for APHINITY it is likely that the magnitude of absolute benefit for pertuzumab in early breast cancer will be considerably greater than that seen at this early time point.
2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Consideration of sub-groups should relate to the overall trial result, which is statistically significantly better than chemotherapy, trastuzumab and placebo alone. The sub-groups are not individually powered to show a difference. The hazard ratios for node-positive and hormone receptor negative sub-groups indicate a greater magnitude of benefit than the overall trial result. It is likely that the confidence intervals will reduce with time as this is seen in all other data sets. Duration of treatment effect of pertuzumab: there is a considerable difference between the cost-effectiveness model from the company, in which the treatment effect started to wane from 7 years and stopped at 10 years, compared to the ERG model in which the treatment effect started the waning from 4 years. In the HERA trial The HR for disease-free survival for 1-year trastuzumab versus observation, remained stable from 4-year median follow-up (HR 0·76figure 3). This suggests a robust and persistent improvement in disease-free survival effected by anti-HER-2 therapy, despite the effect of selective crossover in HERA (52% of patients)[4].
3	**Are the recommendations sound and a suitable basis for guidance to the NHS?** Pertuzumab represents a major advance in the treatment of HER-2 positive breast cancer. It improves overall survival by 42% used in first-line treatment for metastatic breast cancer and increases the chance of pathological complete response by 57% when used as primary medical therapy for 4 cycles. In view of the large difference between the company and ERG assessments of cost effectiveness we as a clinical community would request that considerations be given to how this difference can be bridged so that an highly effective treatment can be made available to benefit breast cancer patients in England, Wales and NI. We routinely use risk assessment and outcome

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	predictive tools when deciding treatment options for patients. Is there a level of risk/risk reduction at which pertuzumab becomes cost effective? In view of the ongoing high event rate in the trials of adjuvant trastuzumab it is likely that a larger absolute difference and a greater confidence in the difference consequent on pertuzumab treatment will emerge with time. In view of this we would support inclusion on the CDF.
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?** No
	References [1] von Minckwitz G et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med 2017; 377:122-131 [2] Slamon D et al. BCIRG 006 - Phase III Trial Comparing AC→T with AC→TH and with TCH in the Adjuvant Treatment of HER2-Amplified Early Breast Cancer Patients: 10-year Follow-up analysis. SABCS 2015; S5-04 [3] Slamon D et al N Engl J Med. 2011 Oct 6;365(14):1273-83. doi: 10.1056/NEJMoa0910383. [4] Cameron D, et al, Lancet. 2017 Mar 25;389(10075):1195-1205. doi: 10.1016/S0140-6736(16)32616-2. Epub 2017 Feb 17

Insert extra rows as needed

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NHS England submission in July 2018 gor the 2nd meeting on the NICE appraisal of adjuvant pertuzumab in combination with chemotherapy and trastuzumab in early breast cancer

This submission contains information that is commercial in confidence

1. NHS England notes that the evidence base for the use of pertuzumab in the adjuvant setting (ie after definitive breast cancer surgery) lies in combination with adjuvant chemotherapy that is either sequential anthracycline and taxane chemotherapy or the combination of docetaxel/carboplatin. If NICE recommends adjuvant pertuzumab in combination with chemotherapy and trastuzumab, NHS England would wish to commission use of adjuvant pertuzumab in combination with only these types of chemotherapy as that is where the evidence base lies for pertuzumab's licensing by the EMA and the NICE appraisal of clinical and cost effectiveness.
2. Since pertuzumab has to be given intravenously, NHS England would wish to commission its use in combination with intravenous trastuzumab (which can be administered over a 30 minute period). The reason for this is that intravenous trastuzumab is now available as several biosimilar preparations and thus there is an opportunity for making considerable savings. Use of biosimilar trastuzumab in NHS England will be subject to a CQUIN which expects to deliver 90% use of biosimilar intravenous trastuzumab by the end of October 2018. The cost of biosimilar intravenous trastuzumab ([redacted] discounts on list price and the outcomes of a tendering procurement process soon to be known) is therefore in a state of flux. NHS England has used [redacted] on the list price of branded intravenous trastuzumab with which to calculate the budget impact of intravenous trastuzumab in this indication for the rest of the calendar year 2018 following a potential NICE recommendation for pertuzumab in the adjuvant setting. The figure of [redacted] on the list price of branded intravenous trastuzumab has been used for budget impact cost calculations for 2019. These [redacted] figures have been agreed by both NHS England and Roche.
3. If NICE recommends the use of adjuvant pertuzumab, a further reason for NHS England wishing to only commission intravenous trastuzumab (rather than subcutaneous trastuzumab) in combination with intravenous pertuzumab is because the use (and cost) of intravenous trastuzumab is part of the case made by the manufacturer for approval of adjuvant pertuzumab. Although subcutaneous trastuzumab is licensed for use with pertuzumab, Roche did not have the use of (and the higher cost of) subcutaneous trastuzumab in combination with pertuzumab as part of its case to NICE.
4. NHS England has previously submitted that Roche had used incorrect administration costs for pertuzumab and trastuzumab for the remaining treatment time after chemotherapy has been completed. The NHS England chemotherapy delivery tariff in 2017/18 for subcutaneous trastuzumab (ie the comparator for which the tariff is SB12Z) should be £150 per cycle and not £260 per cycle. Roche has used a figure of £310 for the administration of pertuzumab and trastuzumab (tariff SB13Z) and the figure should be £301. It is unclear as to whether these errors have been corrected in the Roche submission for the July 2018 NICE TA meeting.

[redacted]

Chair NHS England Chemotherapy Clinical Reference Group and CDF National Clinical Lead for the Cancer Drug Fund

July 2018

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

Name	Alistair Ring
Role	NHS Professional
Other role	
Organisation	
Location	England
Conflict	Yes
Notes	I have received honoraria for advisory boards and lectures from the manufacturer (Roche)

Comments on the ACD:

"1) To clarify: the focus is the node positive population. Nodal status is a well-established dominant risk factor in determining risk of early recurrence in early breast cancer. It is this group (and not other subgroups) where we should be considering this intervention. Whilst this does represent a subgroup of the ITT population: it is a legitimate and highly relevant sub-group for consideration.
2) The fact that Pertuzumab is available in the neoadjuvant setting should not preclude discussion of treatment in the adjuvant setting: these are distinct clinical scenarios. "

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

Name	
Role	NHS Professional
Other role	
Organisation	Mount Vernon Cancer Centre (East and North Herts NHS Trust)
Location	England
Conflict	no
Notes	I have received honoraria for advisory board meetings organised by Roche/Genentech and other pharmaceutical companies

Comments on the ACD:

The inclusion of trastuzumab in the treatment of HER2-positive early stage breast cancer has and a significant effect on the outcome of people with this type of breast cancer. Nevertheless, despite these improvements, people still relapse and die of this disease. In the context of metastatic breast cancer the addition of pertuzumab to trastuzumab and chemotherapy, led to an unprecedented improvement in survival. The testing of pertuzumab in early-stage disease was a logical extension of the sum of knowledge of this effective therapy and was the subject of the APHINITY trial. Patients included in the trial initially included those at relatively low risk disease (nb, slide 18 is incorrect, those with tumours less than 1cm were required to have ER and PR (hormone) receptor NEGATIVE (not positive). Even with relatively short follow-up, the objective of the trial was achieved demonstrating and improvement in invasive disease-free survival. It is axiomatic that as the prognosis of patients improve, it becomes even more challenging to demonstrate further improvements in outcome. Nevertheless, this has clearly been achieved. Unsurprisingly and in line with other interventions in the adjuvant setting, those patients at highest risk of relapse attain the greatest benefit of the intervention. People in the APHINITY study were stratified by nodal status and hormone-receptor status and analyses in these subgroups is statistically valid and clinically relevant. Irrespective of the use of neoadjuvant HER2-directed therapy, the APHINITY data represent the most reliable evidence that the use of pertuzmab in early-stage, HER2-positive breast cancer improves outcome in people with this hitherto more aggressive, poorer prognosis type of great cancer.

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

Name	
Role	NHS Professional
Other role	
Organisation	royal cornwall hospital
Location	England
Conflict	no
Notes	I have received travel grant from roche
Comments on the ACD:	
affinity study met it's primary end point with a significant improvement in DFS with a HR of 0.81. However I agree with that treating all patients as per protocol/inclusion criteria would be over treatment for the low risk population, in whom de escalation trials should be encouraged. The pre planned subset analysis showed all subgroups benefitted. However the node positive subgroup had the highest event rate, and therefore, in the absence of biological predictive markers, seems the most sensible subgroup to go for. This group still has a significant relapse risk, despite chemotherapy and trastuzumab. The follow up is relatively short for the affinity trial, but the separation of the dfs is clear already, and likely to be greater with greater follow up. The icer seems to be cost effective for this group and it would be unreasonable in my opinion and my colleagues to disadvantage these patients from this new therapy that adds very little acute and almost no long term significant toxicity	

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

Name	
Role	NHS Professional
Other role	
Organisation	
Location	England
Conflict	no
Notes	I have received honoraria/travel and meeting expenses from the manufacturer of this technology.
Comments on the ACD:	
"Subgroup analyses fro the Aphinity demonstrate that node positive patients derive the most benefit from the addition of pertuzumab in the adjuvant setting. The benefit seen in node patients in the APHINITY study represents a magnitude of benefit in line with what we have seen for other practice changing 3rd generation regimens in the adjuvant breast cancer setting e.g. aromatase inhibitors and taxanes (MÃ¶bus V et al. Assessing the Clinical Benefit of Systemic Adjuvant Therapies for Early Breast Cancer. Geburtsh Frauenheilk 2017; 77. 1079â€“1087). This improvement in outcomes represents a clinically meaningful benefit in the curative setting and adjuvant pertuzumab should be an option for patients at high risk of recurrence"	

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

Name	
Role	NHS Professional
Other role	
Organisation	
Location	England
Conflict	N/A
Notes	I do not work for but have received an honorarium for speaking at educational events from Roche.

Comments on the ACD:

"With the dramatic improvements seen over the past 15 years in the survival outcomes of breast cancer, especially within the HER2 positive group of patients, it is going to become increasingly difficult to develop therapies which give large magnitudes of benefit over a whole patient population. If novel therapies which because of this progress cannot demonstrate spectacular gains in outcome are ignored then marginal gains will be missed and the improvements in outcome will plateau. These marginal gains seen over a population are absolute gains for an individual patient where recurrence is prevented.

Perjeta is a highly active and effective anti-cancer treatment as demonstrated by the improvement in pCR rate when added to standard therapy in the neo-adjuvant setting. In the adjuvant setting the HER2 positive patient in the APHINITY study treated with standard anti Her2 therapy did incredibly well with an invasive disease free survival over 90%, higher than seen in the original adjuvant Herceptin trials. Despite the challenge of a high event free survival being set by the control arm Perjeta did demonstrate an improvement in outcome, ie it was a positive trial. Due to the acknowledged small margin of significant benefit in this positive trial it is valid and certainly ethical to then use a sub-group analysis to determine a group of patients that derive the greatest proportion of this benefit.

Lymph node positivity has always been the most significant determinate of predicted outcome in early breast cancer, hence is routine use in the stratification of studies. The analysis of the lymph node positive group in the APHINTY study showed a 3.2% benefit in IDFS at 4 years with a significant odds ratio reduction and continuing separation of the curves at the 4 year analysis point indicating a progressive increase in benefit over time. A benefit of this magnitude has previously been accepted as important when considering the evolution of 3rd generation breast cancer therapies.

When this significant benefit for a population of high risk patient is considered in what is the curative setting it has to be viewed as a binary outcome for the individual patients, i.e. they either survive their cancer or succumb to the disease. The individual risk for the patient of death due to their cancer is either 0% or 100%. For this reason these smaller increments in IDFS over a population are significant and should be viewed as a marginal gain that is important to pursue as they are vital to continuing the improvements in breast cancer survival.

"

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

Name	
Role	NHS Professional
Other role	
Organisation	royal cornwall hospital
Location	England
Conflict	no
Notes	received consulting fees from Roche (but also Novartis, Pfizer, Genomic Health, Lilly, Eisai, etc)

Comments on the ACD:

"While the benefit in the overall ITT population is modest, the preplanned subgroup analysis shows the greatest benefit is seen in the high risk subgroups, especially the: N+

For the clinical community, it is particularly in the N+ subgroup where oncologists (and patients) recognise that patients are at highest risk of relapse, and would be very keen to be able to use pertuzumab. The incremental benefit of pertuzumab vs herceptin alone at 48m in iDFS is 86.7 vs 89.9% at 48 months in N+ patients; it appears that the two curves continue to diverge and the published data is still relatively immature, so this benefit is expected to grow with time. Pertuzumab is well tolerated; the added benefit does not come at the cost of additional toxicity.

A 3% increase in survival is the magnitude of benefit seen with AIs over tamoxifen; of 3rd generation vs 2nd generation chemotherapy - it is by these additional increments that we will achieve better outcomes for patients with breast cancer.

NB: I am not clear about the necessity to analyse the premenopausal women separately. This was not a preplanned study subgroup, and is a heterogenous group which may be confounded by chemotherapy induced menopause.

"

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

Name	
Role	NHS Professional
Other role	
Organisation	
Location	England
Conflict	Yes
Notes	Declaration of Interest. Advisory Board for Roche and sponsorship for meeting review at San Antonio.
Comments on the ACD:	
"As a breast cancer treating oncologist who was involved in the apphinity study, I would like to support the application for Pertuzumab for high risk i.e. Node +ve patients with HER2 +ve early stage breast cancer. This disease is an aggressive disease which presents often in younger women with young families and adjuvant and neoadjuvant anti-HER2 therapy has transformed the outcome of the disease. Whilst the overall benefit of the additional pertuzumab is relatively small compared to the step change with Trastuzumab versus no Trastuzumab, it is my belief that it will benefit the high risk patients greatly. this is a group where the risk is still high. "	

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

Name	
Role	NHS Professional
Other role	
Organisation	Colchester Hospital
Location	England
Conflict	No
Notes	I have received honoraria for advisory boards and lectures from the manufacturer (Roche)
Comments on the ACD:	
"The addition of Pertuzumab to Herceptin in both Metastatic and Neo-adjuvant setting have shown impressive positive results both in clinical trials as well as in routine clinical practice. The drug is endorsed by NICE for both settings. Patients with node positive Her-2 positive cancer have a 20-25% risk of systemic relapse after 3rd generation chemotherapy and adjuvant Herceptin. Most of these patients are now offered dual anti-Her2 therapy (Herceptin & Pertuzumab) in the metastatic setting till disease progression. Though the treatments are highly effective, nearly 50% patients die by 5 years. Those on treatment have to live with the burden of regular treatment visits, blood tests and clinic appointments. This also has an impact on NHS resources as many patients continue on regular treatment beyond 5 years. Treatment escalation is required for this high risk group of patients to improve survival. The Aphinity study looked at the role of Adjuvant Pertuzumab and reported positive results at ASCO 2017. There was a small but meaningful improvement in DFS with adjuvant Pertuzumab. The sub-group analysis though underpowered demonstrated the highest benefit among patients with node positive disease. The DFS improved by 1.8% at 3 years (n=2547) and 3.2% at 4 years (n=928). This is a clinically meaningful difference for the high risk patient group. We have seen similar magnitude of benefit with use of â€œAI over Tamoxifenâ€□, â€œadjuvant bisphosphonateâ€□ and â€œ3rd generation chemotherapy regime using taxane and anthracyclineâ€□. These drugs are now used in routine clinical practice across the UK. Based on the above data, clinicians would like adjuvant Pertuzumab to be made available for high risk node positive patients. "	

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

Name	[redacted]
Role	NHS Professional
Other role	
Organisation	
Location	England
Conflict	yes
Notes	I was involved with the APHINITY trial as a clinician enrolling patients and subsequently following them up
Comments on the ACD:	
As an oncologist who treats breast cancer, it is clear that some patients are still developing recurrent disease despite all current treatments available. This is particularly true of patients with breast cancer that are Her2 positive who are lymph node positive or ER negative as they are higher risk. With pertuzumab ,There is evidence of a very well tolerated treatment that reduces the risk of recurrence. With our rates of survival in the UK lagging behind that of Europe in breast cancer, we need to make the best treatments available to our payients.	

ERG views on Company's Response to ACD: updated post TC

Comment 1.
We have no comments on this point.

Comment 2. The Committee's provisional recommendations are not suitable for the NHS.
We have no comments on this point. The appraisal assessed the scope developed by NICE.

Comment 3. Nodal-positive subgroup is the most clinically relevant subgroup.
Agreed. The ERG does/did not dispute nodal status as the most important prognostic indicator for patients with eBC.
In response to "*The European Commission has now approved the use of pertuzumab in the adjuvant setting for HER2-positive early breast cancer (eBC) patients at high risk of recurrence (EMC, 2018). Within section 5.1 of the summary of product characteristics, based on APHINITY, high risk is defined as lymph node-positive or hormone receptor-negative disease. It is appropriate to focus on a high risk subgroup, defined within our label, when describing the patients who are likely to benefit the most from this treatment."*
The ERG notes that adjuvant pertuzumab was not shown to be effective in hormone receptor-negative patients (HR 0.76, 95% CI 0.56 to 1.04). We also note the rather wide confidence interval which suggests that treatment effect in this subgroup is imprecise.
In addition, our opinion, as expressed in the ERG report, is that subgroups such as tumour size and histological grade should not be disregarded.

Comment 4. Treatment effect in node-positive subgroup is consistent with other therapies that improve standard of care.
The treatments mentioned appear to have a different mechanism of action to pertuzumab (e.g., are not HER-2 receptor antagonists like Pertuzumab), so it is unclear how generalisable the points made by the company are. The comparator arms are also different types of drugs. For completeness, the ERG briefly reviewed the review article by Mobus et al 2017 paper and note:

- This article was a general review of literature, and has no methods stated (i.e., not a systematic review and analysis). It does not represent high quality evidence
- The only reference to pertuzumab is as follows "*Two phase III studies have reported positive results for new targeted drugs used in systemic adjuvant therapy to treat early HER2-positive breast cancer, i.e. there was a significant improvement in the primary study endpoint "disease-free survival" (Chan 2016, Von Minckwitz 2017)*
- All authors declare receipt of consulting fees from/or are employed by Roche.

Comment 5. Totality of the evidence indicate that pertuzumab is clinically effective in the adjuvant setting.
We have no comments on this point. It does not change the results/outcome of the trial.

Comment 6. Adjuvant pertuzumab produces a clinically meaningful difference for node-positive eBC patients.
We do not object to the Committee's use of the term "marginal efficacy" to describe the efficacy of pertuzumab in the ITT population. This term was also used independently by ERGs clinical advisors for the same purposes.
Regarding ESMO-MCBS tool, the ERG notes that the ESMO-MCBS tool is an objective way to assess clinical significance of anti-cancer treatments, however using this tool, the adjuvant pertuzumab falls within Grade B (≥ 3% but < 5% improvement in survival rates and HR between 0.65 and 0.80) [Range: Grace A to C].

Comment 7. Subgroup statistical tests for interaction.
The ERG refute the following point. *"**The current summaries regarding the statistical tests of interaction are ambiguous as they could be interpreted as referring to statistical significance of treatment differences within subgroups, rather than to heterogeneity of treatment differences** (specifically "Finally the committee noted that statistical tests for interaction resulted in p values for invasive disease-free survival of less than 0.05 (p=0.17 for interaction between nodal status and invasive disease-free survival; p=0.54 for interaction between hormone receptor status) suggesting that neither nodal nor hormone receptor status were associated with a statistically significant difference in treatment effect.")."*
The ERG suggest that this comment is not ambiguous at all. The statement clearly refers to the difference in treatment effects across (not within) subgroups. The difference between node+ and node- was greater than 0.5 (p = 0.17), hence there was no variation or heterogeneity in the treatment effect of pertuzumab between node+ and node- patients. The same goes for HR status (p = 0.54)

Comment 8. Adjuvant pertuzumab is now approved for use in node-positive patients in the EU.
We have no comments on this point.

Comment 9. Updated ASCO guidelines recommend the use of adjuvant pertuzumab in node-positive patients.
We have no comments on this point. The appraisal assessed the scope developed by NICE.

Comment 10. Parameterisation of the "cure" model in the cost-effectiveness analysis.
We are content with the fact that the company has revised the specifications of their cure model as per our suggestions.

Comment 11. Proportion of metastatic and non-metastatic recurrences.

We welcome the revisions the Company has made in relation to metastatic and non-metastatic recurrence rates. ERG acknowledges that their recommendations were based on assumptions as they had no access to data, and accepts the updated information provided by the company.

Comment 12. Incorporation of trastuzumab biosimilars.
As at the time of the original submission trastuzumab biosimilars were not available in the UK, the company's base case results were calculated on the basis of no trastuzumab biosimilar treatments being available. We believe that this was the right thing to do and our base case results were also calculated on the same basis that the company adopted.
We agree that, should trastuzumab biosimilars become available, this will have a bearing on the treatment's cost-effectiveness. The company states that "trastuzumab biosimilars are now available for widespread use in the UK". We have no evidence to refute or accept this statement.
As the company acknowledges, at the time of writing, both the price and the market share of biosimilars are not definitively known. Nevertheless, the company has used comments from Professor Clark, NHSE publications, and market intelligence collected by Roche, to come up with what they consider as plausible ranges for both of these parameters (i.e. trastuzumab biosimilars will replace 90% to 100% of branded IV and trastuzumab biosimilars will be 70-80% cheaper than branded trastuzumab IV). These assumptions feed into the company's 'exploration of key areas of uncertainty'. Again, we are not aware of any evidence that one could reliably draw on to accept or reject these assertions. We have no access to Roche's market intelligence findings and we do not know how reliable they are.
It is worth noting that, in the analysis, the availability of trastuzumab biosimilars benefits significantly the pertuzumab arm (where it is assumed that 90% of patients originally treated with branded (Herceptin) intravenous treatment will be receiving the much cheaper

trastuzumab biosimilars) but leads to only a small increase in the cost of the placebo arm (as the majority of patients in this arm are assumed to receiving branded Herceptin subcutaneously and, it is assumed, they will continue receiving this treatment).
We have checked a sample of the ICER values that are based on the availability of biosimilars (provided in CE appendix, section Key Areas of Uncertainty, Tables 5-9) and these appear to be correct.

Comment 13. Overestimation of OS in the cost-effectiveness model.
Point 1: Poor fit of modelled OS data to APHINITY
ERG agree modelled OS is a poor fit, however accepted the company's explanation of using data from the ESTHER study for later line treatment use. Whilst this does not fully resolve the problem of the poor fit, it does go some way to resolving the issue. The ERG agrees that this is likely to improve generalisability of results to the UK population.
Point 2: Overestimation of modelled OS compared to other adjuvant trastuzumab trials
ERG believe it may be plausible that general OS may improve with advancements made in clinical practice, however there can be no certainty over any magnitude in the improvement, which may be negligible.
Point 3: Steep Decline in modelled OS curves not reflected in other studies.
The ERG has no further comment to make, this complaint seems vague.

Comment 14. Pertuzumab treatment effect duration.
No new information is submitted by the company and the ERG maintain the assumptions in their base case analysis. Company appears to assume (incorrectly) that the ERGs waning effect preferences were based solely on the observation of the KM curves from other trials. ERG agrees that there is large uncertainty over the specification of the treatment waning. Note that the scenarios explored by the company by changing the waning effect are combined with biosimilars.

Comment 15. Revised cost-effectiveness analysis
We welcome the company 'definitive changes' made in their analysis (i.e. adoption of ERG's specifications of the 'cure' model, revised metastatic recurrence rates and [redacted]— summarised in Table Cost-effectiveness appendix).
However, it is important to note that these specifications and the resulting ICER of £30,561 are based on the company's favourable assumptions on the duration of treatment effect and disregard the ERG's suggestions. Thus, the company's statement that, even after taking into account the ERG's overly conservative assumptions around the pertuzumab effect duration, the ICER in this scenario is still approximately £30,000 and can therefore be broadly considered as cost-effective is incorrect and misleading.
If the ERG's suggested treatment duration specifications are adopted (alongside the rest of the accepted revisions and new PAS discount), the resulting ICER is over the £30,000 per QALY gained threshold (£47.856 per QALY).

NICE National Institute for Health and Care Excellence

Clinical expert statement

Pertuzumab for the adjuvant treatment of HER2-positive breast cancer [ID1192]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Jayant S Vaidya**
2. Name of organisation	**University College London – nominated by BASO**
3. Job title or position	**Professor of Surgery and Oncology, University College London**

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

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Improve length and / or quality of life of the patient.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement in overall survival or Improvement in survival without treatment/ side effects The absolute magnitude that is considered 'important' or 'clinically significant' differs from patient to patient
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	In the last 1-2 years, many patients who are HER2 positive, whatever their other characteristics, have been perversely treated with neoadjuvant chemotherapy with dual HER2 blockade only because pertuzumab was approved and licenced to be used as neoadjuvant but not approved as

	adjuvant therapy. Oncologists, perhaps with a mistaken belief that pertuzumab must be beneficial to patients, have used the following justification ' we can only get pertuzumab 'in the patient' before surgery, therefore every patient must get neoadjuvant chemotherapy and include pertuzumab'. In this charade, they even ignored the well-known higher risk of local recurrence with neoadjuvant chemotherapy compared with adjuvant chemotherapy. Such misconception may have been prompted by a mirage of dramatically higher pathological complete response rate (pCR) with addition of pertuzumab. Unfortunately, pCR has proved to be a unreliable surrogate marker of patient benefit or cancer outcome. Improving the pCR does not always, and in case of pertuzumab did not, improve either the rate of breast conservation in the NeoSphere trial (13/56 vs 14/62, author communication) or overall survival in the Aphinity trial. Even after choosing the unconventional end point of 'invasive' disease free survival, a very small 0.9% 3-year difference was found. The relative effect was homogenous across subgroups so any differences in absolute benefit would only be because of differences in background risk.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE 2016 guidelines approved the use of pertuzumab as neoadjuvant treatment (before surgery) which may have been based on the idea that a higher pCR rate must improve patient outcomes – however, all randomised data has now confirmed that patient outcomes are not improved in a clinically meaningful way by addition of pertuzumab. A higher pCR does not always and in the case of pertuzumab did not improve either the rate of breast conservation in the NeoSphere trial (13/56 vs 14/62, author communication) or overall survival in the Aphinity trial. Even after choosing the unconventional end point of 'invasive' disease free survival, a very small 0.9% 3-year difference was found. The relative effect was homogenous across subgroups so any differences in absolute benefit would only be because of differences in background risk. Therefore the Aphinity trial unfortunately adds to the evidence that pCR should not be used as a surrogate end point.
• Is the pathway of care well defined? Does it vary or are	It is not used as adjuvant therapy in the NHS.

there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Based on the current evidence, NICE should immediately reverse the approval of pertuzumab as neoadjuvant therapy in patients who have operable breast cancer. At best, it may be allowed to be used for making an operable case operable (mastectomy) – however, even for this indication, there is no randomised evidence to demonstrate that addition of pertuzumab will improve conversion to operable cancer at a rate higher than trastuzumab alone. However, until NICE reverses this decision, and if NICE gives approval to pertuzumab in the adjuvant setting it may mean that the anomalous and frankly wrong argument of using the unavailability of pertuzumab in the adjuvant setting as an excuse to give it to patients who do not benefit from it in the neoadjuvant setting cannot remain valid. The use of pertuzumab in the adjuvant setting will need to be governed by its cost effectiveness and clinical effectiveness. Unfortunately, the Aphinity trial arguably did not show clinically significant benefit to patients – There may be patients who opt to have adjuvant treatment despite the very small benefit in one outcome (but not in overall survival) and despite the additional toxicity. The question NICE needs to address is whether it is also cost effective in the adjuvant setting. However its use in the neoadjuvant setting cannot be justified any more – all scientific evidence shows that it does not add any benefit to patients when used this way – and may well do harm – because when neoadjuvant therapy is given to tumours less than 3cm, it increases the chances of having a mastectomy -and reduces the breast conservation rate. It also increases the local recurrence rates compared with adjuvant therapy.

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No
• How does healthcare resource use differ between the technology and current care?	Additional drug and its side effects need additional resource
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Mainly training and significant additional funding
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	While for some patients the small difference in one outcome may be important, I believe the vast majority would derive no clinically meaningful benefits from the addition of pertuzumab, as there is no improvement in overall survival or distant disease recurrence. The absolute benefit in terms of invasive disease free survival is very small and of borderline statistical significance – it means that if there was really no benefit, then the probability of observing the 0.9% difference seen in the trial is about 4.5%. ie one in 20 such trials would have found this difference by pure chance.
• Do you expect the technology to increase length of life more than current care?	No

• Do you expect the technology to increase health-related quality of life more than current care?	No
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Relative benefit is similar in all groups – but those with higher risk would have a higher absolute benefit but all in a few percentage points (eg at best,1-2% difference in 'invasive' disease relapse at 3 years, – none in overall survival)
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	More side effects could need more supportive care

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It should not be used in neoadjuvant setting unless the cancer is not operable – as improvement in breast conservation was not seen in the randomised NeoSphere trial. Even in this situation, there is no evidence that it will improve operability.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	It is indeed innovative and logically might have been great. Unfortunately the randomised data does not show a meaningful patient benefit.

• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	No -
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Yes – mainly diarrhoea and cardiac -
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	yes
• If not, how could the results be extrapolated to the UK setting?	n/a
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival – measured – and not found to be improved.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Invasive disease free survival was the surrogate end point used – it does not seem to adequately predict long term clinical benefit in terms of overall survival. I have not been able to find any evidence that addition of pertuzumab improves quality of life. Also distant disease free survival was not improved.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	https://www.bmj.com/content/360/bmj.j5913
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA107]?	The Tailor-X trial (NEJM 2018) found that for many patients who are ER positive may not need chemotherapy at all further emphasising that such patients should not get it before their surgery is done.

22. How do data on real-world experience compare with the trial data?	In the real world, pertuzumab is being given to patients with small tumours just because they are HER2 positive – as neoadjuvant therapy (only because it cannot be given as an adjuvant drug) – yet it does not have any benefit to patients in any way.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
23b. Consider whether these issues are different from issues with current care and why.	no
Topic-specific questions	
24. a) Is there any enthusiasm in the clinical community for adding pertuzumab to standard adjuvant	a) There was enthusiasm but it has been reduced due to recent data which showed how the earlier enthusiasm was logical but misguided and erroneously based on surrogate end point of pathological complete response rate

treatment with trastuzumab and chemotherapy? b) The primary outcome in the APHINITY trial was 'Invasive Disease-Free Survival (IDFS) excluding primary non-breast cancer events' (not the standard STEEP definition of IDFS which includes primary non-breast cancer events). Is there any reason for not using the standard STEEP definition of IDFS and what is the impact of this? c) The company would like the committee to consider node positive (base case) and hormone receptor negative subgroups. Are these clinically relevant? Are there any other subgroups that have a similar	b) I cannot understand why such narrow end point was used – the end point that should be used is overall survival – which was indeed analysed (page 31 of appendix) and they found no difference - . c) The result was homogenous across all subgroups – these subgroups (mainly node positive) may have higher background risk and therefore a higher absolute benefit – but even that is less than 2% at 3 years. d) it is not relevant – neoadjuvant therapy per se has little real patient benefit – and NICE's guideline on neoadjuvant therapy should now be reversed and not allow that addition of pertuzumab because it does not have any meaningful patient benefit.

risk profile which would also be appropriate to consider? d) In clinical practice what proportion of people will have had neoadjuvant therapy (biologic or chemotherapy). As the APHINITY trial did not include people who had prior neoadjuvant therapy how generalizable are the results of the trial?	

Key messages

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

- Unfortunately, pertuzumab (in adjuvant or neoadjuvant setting) does not improve overall survival or quality of life of patients
- In the adjuvant setting, it may improve a narrow measure of invasive disease free survival by 0.9 – 1.9% - but does not reduce distant recurrence rate. Most patients may not consider this as a meaningful difference
- The use of pertuzumab in adjuvant setting needs to be decided based on increased toxicity, increased cost and very small (if any) patient benefit. If on longer follow up, a survival benefit or a QOL improvement is shown then NICE could recommend it then.
- The use of pertuzumab in the neoadjuvant setting which was based on a surrogate end point of pCR rate, should now be completely stopped as it does not improve breast conservation, nor does it improve survival.
- Surrogate end point of pathological response rate in neoadjuvant setting should not be used to approve new drugs.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Pertuzumab for the adjuvant treatment of HER2-positive breast cancer [ID1192]

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

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

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Andrew M. Wardley**

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

after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment of early breast cancer is cure.
	HER-2 positive breast cancer is considered to be one of the most aggressive types of breast cancer. HER-2 protein over-expression or gene Amplification is a significant predictor of both overall survival and time to relapse in patients with breast cancer. Trastuzumab revolutionised the outlook for HER-2 positive breast cancer. Other anti-HER-2 therapies have added to the benefit of trastuzumab. For early breast cancer there is a huge variation across the UK with respect to primary medical therapy versus surgery for HER-2 positive breast cancer despite the evidence that early commencement of anti-HER-2 directed therapy improves survival in the metastatic and EARLY breast cancer settings. NICE approved primary medical therapy with pertuzumab and trastuzumab in 2016
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In the adjuvant setting improvement in invasive DISEASE FREE SURVIVAL is most likely to lead to an improvement in overall survival as it is invasive (especially metastatic breast cancer) than leads to breast cancer mortality.
9. In your view, is there an unmet need for patients and healthcare professionals in this	Yes although pertuzumab is available as primary medical therapy there is variable uptake of this across the country, partly related to the relative under provision of non-surgical oncology supporting breast cancer multi-disciplinary team meetings and also the time to available pathology results

condition?	
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Adjuvant treatment is usually anthracycline based chemotherapy followed by trastuzumab in combination with taxane followed by trastuzumab alone or in combination with endocrine therapy, if appropriate, or taxane based chemotherapy in combination with trastuzumab from the outset. Treatment choice is often based on patient factors and also some cancer related factors (stage). There may still be some use of sequential trastuzumab after chemotherapy which is probably not optimal. The Persephone trial showed evolution of practice in the UK to incorporate more concurrent treatment with taxane chemotherapy. The disadvantage of the adjuvant approach is that there is no response data and treatment is essentially one size fits all. Also there are data that delayed commencement of appropriate systemic anti-cancer therapy has a deleterious effect on survival. Primary medical therapy in the HER2 arena is usually anthracycline → taxane + trastuzumab or Docetaxel Carboplatin Trastuzumab. With the European license for Pertuzumab some sites are offering Pertuzumab as top up. Primary medical therapy has the advantage of understanding the response of the cancer to the treatment. The pathological complete response is high. Pathological complete response is associated with a very strong correlation with overall survival in HER2 positive breast cancer (Cortazar et al).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ASCO and ESMO guidelines
• Is the pathway of care well defined? Does it vary or are there differences of opinion	There is variable uptake of primary medical therapy with pertuzumab as per the NICE guidance The majority of patients probably still receive trastuzumab in the adjuvant setting

between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Patients with higher risk HER-2 positive early breast cancer (N+ and/or ER –ve) would receive pertuzumab in combination with trastuzumab Currently pertuzumab requires administration of trastuzumab intravenously Most adjuvant trastuzumab is currently administered subcutaneously
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The uptake of the technology is likely to be high
• How does healthcare resource use differ between the technology and current care?	Currently pertuzumab requires administration of trastuzumab intravenously Most adjuvant trastuzumab is currently administered subcutaneously
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In systemic anti-cancer therapy services (usually secondary and some tertiary care)
• What investment is	The services already exist (capacity is an issue for iv therapy)

needed to introduce the technology? (For example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes improved likelihood of cure
• Do you expect the technology to increase length of life more than current care?	Yes improvement in invasive disease free survival is likely to result in improved breast cancer specific survival and overall survival
• Do you expect the technology to increase health-related quality of life more than current care?	Yes improved invasive disease free survival will reduce the number of patients having ongoing treatment for metastatic breast cancer
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate)	The relative effectiveness is likely to be greater in patients with ER negative and node positive breast cancer because of the different biology of these HER-2 positive breast cancers compared to ER + ve and node negative.

than the general population?	
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The clinical service is already well established there will be longer treatment times and more requirement for intravenous systemic anti-cancer therapy services
15. Will any rules (informal or formal) be used to start or stop treatment with the technology?	Stopping rules will be the same as those in routine use for adjuvant trastuzumab

Do these include any additional testing?	
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes depending on the modelling and the price
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes Improved Invasive disease free survival will mean less patients requiring treatment for metastatic breast cancer. In HER-2 positive breast cancer this involves many years of iv therapy with trastuzumab and pertuzumab followed by TDM-1 and subsequent chemotherapy
• Is the technology a 'step-change' in the	In first line metastatic breast cancer and primary medical therapy the addition of pertuzumab to

management of the condition?	trastuzumab certainly represented a step change The population in the APHINITY trial included some patients with lower risk hence the overall benefit was less than that seen in the former two settings. In the appropriate population use of pertuzumab in the adjuvant setting is likely to be a step change
• Does the use of the technology address any particular unmet need of the patient population?	Yes in the population destined to have recurrence with standard therapy
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Diarrhoea is the main additional side-effect of pertuzumab. It is usually mild to moderate and relatively easy to control. It rarely leads to discontinuation.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Improvement in invasive disease free survival was the primary endpoint
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	It is likely that improvement in overall survival will emerge with loner follow-up
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No the treatment is well established in clinical practice and no new advers events are apparent in clinical practice
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new	Technology appraisal guidance [TA424]

evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA107]?	PERSEPHONE Trial presented at ASCO 2018
22. How do data on real-world experience compare with the trial data?	Not aware of any relevant real world data on adjuvant pertuzumab
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not that I am aware of
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	

24. a) Is there any enthusiasm in the clinical community for adding pertuzumab to standard adjuvant treatment with trastuzumab and chemotherapy? b) The primary outcome in the APHINITY trial was 'Invasive Disease-Free Survival (IDFS) excluding primary non-breast cancer events' (not the standard STEEP definition of IDFS which includes primary non-breast cancer events). Is there any reason for not using the standard STEEP definition of IDFS and what is the impact of this?	A) Yes b) IDFS: as per STEEP definition includes second primary non-BC tumours it is unlikely tt this would be affected by pertuzumab. The hazard ratio for this was 0.82 (0.68-.099) which is very similar to the iDFS used c) Node positivity represents the single most important prognostic factor. It represents evolution of the cancer to have metastatic potential. ER-ve breast cancer have a more aggressive biology than ER+ve breast cancer. They are also more likely to be sensitive to HER-2 directed antibody therapy. Tumour size is also an important prognostic factor. d) upto 25% in some units

c) The company would like the committee to consider node positive (base case) and hormone receptor negative subgroups. Are these clinically relevant? Are there any other subgroups that have a similar risk profile which would also be appropriate to consider? d) In clinical practice what proportion of people will have had neoadjuvant therapy (biologic or chemotherapy). As the APHINITY trial did not include people who had prior neoadjuvant therapy how generalizable are the results of the trial?	

Key messages

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

- A significant proportion of patients with HER-2 positive breast cancer still relapse in spite of adjuvant trastuzumab. (~30% in patients with node positive breast cancer)
- Pertuzumab in the early breast cancer setting is likely to greatly improve this
- The Persephone trial shows that in some patients 12 months of trastuzumab is not necessary
- Better understanding of which patients require less and which patients require more treatment is required (I am conflicted as I am helping to develop a trial in this setting in the early breast cancer sub-group of the NCRI CSG.
- An agreement on the appropriate pricing of this technology to enable access would be welcomed by patients and clinicians

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

ERG addendum – Adjuvant pertuzumab ID1192 (July 2018)

Biosimilar preparations of intravenous trastuzumab became available during the course of this appraisal. The Cancer Drugs Fund clinical lead advised on the current commercial in confidence price and market share of intravenous trastuzumab which the committee considered to be most appropriate for decision making.

The Cancer Drugs Fund clinical lead also noted that the company had not used the correct administration costs for pertuzumab and trastuzumab for the remaining treatment time after chemotherapy has been completed. The NHS England chemotherapy delivery tariff in 2017/18 for subcutaneous trastuzumab (tariff SB12Z) should be £150 per cycle not £260 per cycle. The tariff for pertuzumab and trastuzumab (tariff SB13Z) should be £301 not £310.

The committee considered the potential impact of these changes on the ICER. It also requested that the ERG provide the ICERs which incorporate the corrected administration costs and current confidential price and market share of intravenous trastuzumab.

Cost effectiveness estimates for patients with lymph node-positive disease

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£ per QALY gained)
Company's original base case					
HC	[redacted]	[redacted]	[redacted]	[redacted]	£33,857
PHC	[redacted]	[redacted]			
ERG's original base case					
HC	[redacted]	[redacted]	[redacted]	[redacted]	£60,679
PHC	[redacted]	[redacted]			
Revised company estimates taking into account an updated commercial access agreement					
HC	[redacted]	[redacted]	[redacted]	[redacted]	£30,561
PHC	[redacted]	[redacted]			
Revised ERG estimates taking into account an updated commercial access agreement					
HC	[redacted]	[redacted]	[redacted]	[redacted]	£47,856
PHC	[redacted]	[redacted]			
Revised company estimates taking account of cost correction*					
HC	[redacted]	[redacted]	[redacted]	[redacted]	£33,700
PHC	[redacted]	[redacted]			
Revised ERG estimates taking account of cost correction*					
HC	[redacted]	[redacted]	[redacted]	[redacted]	£52,136
PHC	[redacted]	[redacted]			
Revised company estimates taking account of cost correction and biosimilar price as follows: [redacted]					
HC	[redacted]	[redacted]	[redacted]	[redacted]	£24,985
PHC	[redacted]	[redacted]			
Revised ERG estimates taking account of cost correction and biosimilar price as follows: [redacted]					
HC	[redacted]	[redacted]	[redacted]	[redacted]	£39,939
PHC	[redacted]	[redacted]			