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

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

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

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

5. **ERG response to the company's ACD2 response**

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

Appraisal title

Single Technology Appraisal

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

Type of stakeholder:

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

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

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

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	Roche Products Ltd.	Whilst disappointed with the decision, the Company 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. In addition, Roche has also addressed key aspects surrounding the cost-effectiveness of pertuzumab. Specifically, the assumptions surrounding trastuzumab biosimilars in the economic analysis and the use of the Committee's revised administration costs. 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 [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 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.	Comments noted (addressed separately below). Pertuzumab has now been recommended for the adjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive early stage breast cancer in adults in people with lymph-node positive disease.
2	Consultee	Roche Products Ltd.	**NICE recommendation based on a subgroup analysis is not uncommon**	Comments noted NICE often makes recommendations in a

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			The provisional recommendations are neither sound nor suitable for guidance to the NHS. The appraisal consultation document (ACD) focuses on the uncertainty in the high risk subgroups and the concern that the study was not powered to determine the treatment effects within the node-positive subgroup. However, this is inconsistent with previous appraisals where NICE have recommended a technology specifically for a subgroup (even when the study was not powered to determine the treatment effect within the subgroup). Two recent examples of this are highlighted below: ● Obinutuzumab has a broad EMA label for untreated advanced follicular lymphoma (FL) (EMC, 2018). During the appraisal for TA513, NICE subsequently recommended obinutuzumab for untreated advanced FL patients in a subgroup (patients with FLIPI scores over 2 or more) even though the key GALLIUM trial was not designed to detect a difference between FLIPI subgroups. This was revised due to a statement in section 4.4 of the SmPC which states “based on a subgroup analysis in previously untreated follicular lymphoma, the efficacy in FLIPI low risk (0-1) patients is currently inconclusive “. Overall, the committee was satisfied that the higher-risk subgroup (based on FLIPI scores) was the clinically relevant population to consider in this appraisal and subsequently made a positive recommendation based on this high risk subgroup (NICE TA513). ● Similarly, tocilizumab has a broad EMA label for patients with giant cell arteritis (GCA) (EMC, 2018). During the appraisal for TA518, NICE heard from clinical experts and patients that tocilizumab would be most valuable to people with relapsing disease. NICE subsequently recommend tocilizumab for a subgroup of patients (i.e. relapsing or refractory GCA patients only). The committee concluded that this subgroup was distinct and biologically plausible and had the highest unmet need, and subsequently made a positive recommendation based on this subgroup only (NICE TA518). Other examples in oncology which have been recommended in a subgroup are NICE TA484, TA326, TA145, TA473. When the study is positive, it is reasonable to look into the subgroups to see	subgroup for example when there is evidence of improved clinical efficacy and cost effectiveness in a particular subpopulation. Statistical tests for interaction did not indicate evidence of heterogeneity in the magnitude of treatment effect defined by lymph node status (p value of 0.17) and or hormone-receptor status (p value of 0.54) compared with the intention to treat population (0.81, 95% CI 0.66 to 1.00). The committee heard from the clinical experts, and accepted the biological plausibility, that people with lymph-node-positive disease would have more recurrences, so that even with the same relative effectiveness the numerical reduction in recurrences and absolute benefit would therefore be greater It also noted that the hazard ratio for this subgroup in the trial reached statistical significance (HR 0.77, 95% CI 0.62 to 0.96). The committee accepted that the subgroup with lymph-node-positive disease represents a population at increased risk of recurrence, and that the company’s decision to focus on people with lymph-node-positive disease is reasonable.

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			what is driving the overall treatment effect. 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) (von Minckwitz et al., 2017). In this group, the benefit of pertuzumab was clearly demonstrated by superior invasive disease-free survival (IDFS) over adjuvant trastuzumab. This is evidenced by the increased number of events, superior hazard ratio and narrower confidence intervals around the estimates. Node-positive patients are at a higher risk of relapse and therefore have a greater need for more effective treatments. We have heard through the clinical community's responses to the ACD and at both Committee meetings that the node-positive subgroup data is clinically meaningful and this is where clinical commentators would like to use adjuvant pertuzumab. This subgroup is in line with our market authorisation and has been accepted by the EMA. Whilst we agree that there is uncertainty as the study was not powered to determine the treatment effects in the subgroups of interest, this is often the case with subgroup analyses. As evidenced by the technology appraisals referenced above, a NICE recommendation based on a subgroup analysis is not uncommon. We request that the Committee consider not only the advice of the patient groups and clinical community, but also the precedent set in other appraisals, and give node-positive patients the opportunity to further reduce their risk of recurrence.	
3	Consultee	Roche Products Ltd.	**Node-negative patients are not considered high risk** **The provisional recommendations are neither sound nor suitable for guidance to the NHS. The ACD highlights the Committee's concern regarding the exclusion of node-negative patients and states that "it is unreasonable to conclude that adjuvant pertuzumab did not provide clinical benefit to these patients" based on low number of events, despite it not being in line with our EMA label.** The Company agrees that there are low numbers of events in the node-negative subgroup and it is not possible to draw any efficacy conclusions at this point in time for this subgroup. Similarly, it would be unreasonable to claim adjuvant pertuzumab benefits the node-negative subgroup. The fact that there are low numbers of events in the node-negative subgroup 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	Comments noted The committee heard from the clinical experts, and accepted the biological plausibility, that people with lymph-node-positive disease would have more recurrences, so that even with the same relative effectiveness the numerical reduction in recurrences and absolute benefit would therefore be greater It also noted that the hazard ratio for this subgroup in the trial reached statistical significance (HR 0.77, 95% CI 0.62 to 0.96). The committee accepted that the subgroup with lymph-node-positive disease represents a population at increased risk of recurrence, and that the company's decision to focus on people with lymph-node-positive disease is reasonable.The committee considered the

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			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) (von Minckwitz *et al.,* 2017). The marketing authorisation for adjuvant pertuzumab is only in the high risk population and is defined as node-positive or hormone-receptor negative based on the APHINITY trial (EMC, 2018). The node-negative subgroup is not specifically covered by this marketing authorisation and it would therefore be inappropriate to focus on this subgroup for this appraisal. The Committee's approach to subgroup selection is inconsistent with previous technology appraisals, where subgroups that are not in line with the marketing authorisation are not in scope. An example is trastuzumab for the treatment of HER2-positive metastatic gastric cancer TA208, where the Committee have noted that "there were no subgroups to be discussed, other than the licensed subgroup". Based on the current evidence, node-positive patients benefit the most from adjuvant pertuzumab. Similar to the technology appraisals referenced in comment 2, it is appropriate to focus on a high risk subgroup that is benefiting the most from the technology. We have heard from the clinical community and patients that they view the APHINITY node-positive data positively and that it makes sense to stratify patients and only offer adjuvant pertuzumab to those at highest risk of recurrence. The Company agree with the clinical community that adjuvant pertuzumab does not need to be offered to every early breast cancer patient with HER2-positive disease but should be offered to node-positive patients. Node-positive patients are at a higher risk of recurrence and are in a greater need of more effective treatments. This is the most relevant subgroup for this appraisal and we would invite the Committee to reconsider its conclusion in the ACD in this regard, reflecting the wishes of the clinical community and patients, and give these node-positive patients an opportunity to be closer to achieving their treatment goal of cure.	company proposal which only focussed on the clinical and cost effectiveness of pertuzumab in people lymph-node positive disease

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2	Consultee	Roche Products Ltd.	**<u>Unreasonable weight and focus on interaction test</u>** **Summary of the clinical effectiveness is not a reasonable interpretation of the evidence. The Committee have put an unjustifiable amount of weight on the test for heterogeneity for the selection of subgroups.** As discussed in previous Company responses throughout this appraisal, the conclusions and rationale for proposing the node-positive and hormone-receptor negative subgroups and their adoption in Health Authority labelling, are based on objective clinical rationale and supported by the results (event rates, HR and CI). These baseline factors were also in the stratification used at randomisation due to their known prognostic importance. Statistical interaction testing was performed for the primary endpoint as part of planned exploratory analyses at the time of the primary analysis, in order to understand statistical evidence of heterogeneity in the treatment effect within patient subgroups of interest. The significance levels from these exploratory tests were included in the NEJM manuscript as part of the journal's standard practice. It is acknowledged that the test results do not show strong statistical evidence of heterogeneity. However as noted in the ACD, from a statistical perspective, interaction tests are known to carry low power leading some researchers to increase the Type I error rate from 0.05 for such testing. In the case of APHINITY, low power is particularly notable for nodal status as there are a very low number of events in the node-negative subgroup and therefore the result needs to be interpreted with caution in terms of concluding homogeneity of treatment effect. Subgroup data should be appropriately interpreted with consideration of the observed data, clinical rationale and biological plausibility. The Company believes the summaries of clinical effectiveness included in the ACD around the selection of subgroups need to be re-interpreted with consideration of the multiple factors used in subgroup assessments including the totality of the observed data, clinical rationale and biological plausibility.	Comments noted (see above)

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3	Consultee	Roche Products Ltd.	**<u>OS is immature to draw solid conclusions at this point in time</u>** **Summary of the clinical effectiveness is not a reasonable interpretation of the evidence. The ACD makes claims that there are no survival benefits based on the APHINITY data. The Company believes that the data is too immature to make such claims.** In reference to no survival benefit in APHINITY, The Company request that the Committee clarifies in the ACD that as overall survival data is immature, there was no apparent difference for this outcome at this point in time. It is important to clarify in the ACD that "further OS follow up and planned statistical analyses will continue until 10 years after last patient enrolled to allow robust assessment of long-term survival effect in this population." The immature OS data at this point in time cannot be used to draw solid conclusions as there is no indication that there will not be survival benefits in the future, when more events have occurred. The expert statement from Professor Vaidya that "In the NeoSphere trial, for example, higher pathological complete response with neoadjuvant pertuzumab was not associated with improved overall survival in the long term, in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer at high risk of recurrence" is inaccurate. In the NeoSphere trial, overall survival was not a protocol-defined efficacy endpoint, therefore survival status was not systematically reported beyond disease progression, disease recurrence or withdrawal and a time-to-event analysis was not performed. Hence conclusions around association of pCR with OS cannot be drawn based on the NeoSphere data. However, there is existing evidence of the relationship between pCR and long-term outcomes. (Cortazar *et al.,* 2014; Yee *et al.,* 2017). Although highlighted in the ACD, this is not relevant to the scope of this appraisal. DFS and IDFS have been widely adopted in adjuvant studies as a surrogate for long-term outcomes, and have been accepted by both the EMA and FDA.	Comment noted The committee noted the immaturity of the overall survival data. The committee noted that invasive disease free survival has recently been adopted as a surrogate for overall survival. The committee acknowledged the difficulty of obtaining mature overall-survival data for adjuvant treatments. It concluded that in the absence of mature overall-survival data, invasive disease-free survival is the only available data for decision making. However, the extent to which invasive disease-free survival translates into long-term overall survival benefit is not known.
4	Consultee	Roche Products Ltd.	**<u>Incorporation of a more accurate biosimilar discount in the economic analysis</u>** The Company welcomes the Committee's decision to explicitly incorporate the impact of trastuzumab biosimilars on the economic analysis. At the time	Comment noted. The appropriate confidential discount for biosimilar intravenous trastuzumab which represents the current discount offered to the NHS was included in the ICER considered by the

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			of writing, both the price and the market share of biosimilars are not definitively known. Nevertheless, the Committee appears to have assumed a trastuzumab biosimilar market share of 100% and a discount of 55% compared to the list price of Herceptin IV. The level of biosimilar market share suggested by the Committee is aligned with comments made by Professor Clark (Consultant Medical Oncologist and current Chair of the Chemotherapy Clinical Reference Group) during the appraisal committee meetings. No plausible rationale exists for why a patient would receive Herceptin IV instead of trastuzumab biosimilar IV given that the national tender has concluded and several biosimilar trastuzumab products are readily available. The Company agrees with the Committee's proposed biosimilar market share estimate of 100% in new patients. The Committee has also assumed that trastuzumab biosimilars are available at a weighted average discount of 55% on the Herceptin IV list price. In the ACD, the Committee goes on to state that this value "had been used in the NICE Budget Impact Test analysis" – this statement is false. In the BIT analysis, the company assumed the level of discount would be 60% in 2018 before rising to 70% in 2019 and remaining constant thereafter. This assumption was subsequently agreed to be reasonable by representatives from both NHS England and NICE. Please refer to the finalised budget impact assessment published by NICE. Trastuzumab biosimilars have been available in the UK for several months. Competitive intelligence collected by the Company suggests that some manufacturers have waited until the national tender before making the final price of their products known. The Company are aware that discounts of between 50% and ~70% have been submitted as part of the tendering process. Given near identical products, logic suggests (and the CQUIN mandates) that the cheapest biologic be prescribed by physicians. Consequently, the cheaper product (~70% discount on Herceptin IV) has been acquiring market share and therefore becoming the leading trastuzumab biosimilar. The net effect of this acquisition is that the weighted average discount of trastuzumab biosimilars has risen. The discount level quoted in the ACD was presumably calculated in the days prior to the second appraisal committee meeting (19th July, 2018). This was only two weeks after the conclusion of the national tender. This is not a	committee. Following consideration of an updated model pertuzumab has now been recommended for the adjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive early stage breast cancer in adults in people with lymph-node positive disease

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			suitable length of time for the market to have fully calibrated following the results of the tender i.e.; the market dynamics described in the preceding paragraph had not yet been fully realised. Although final prices may have been known at this time, the market shares would still have been in a state of flux and not at all representative of a "steady state" or even present day. With respect to the national tender, prices submitted during this process are not necessarily the final price of a product. Following the conclusion of a tender, mechanisms are available by which a company may further lower the price of their product (until equivalent with the lowest price submitted in the tender). Therefore, the price at which the product is being offered to the hospitals may be substantially lower than the tender price. The Company suspects that the average discount in the ACD is predicated solely on the discounts submitted during the tender (Professor Clark may not be aware of all price reductions outside of the tendering process). This oversight could potentially lead to an underestimation. Market intelligence collected by the Company states that "price is not a deciding factor in this market". Given the range in submitted tender prices, this intelligence would suggest that at least one manufacturer is applying these "secondary discounts". This behaviour would further increase the weighted average discount calculated by the Committee. In summary, the Committee's assumption of a 55% discount across trastuzumab Consultee biosimilars is outdated. This average has been calculated based on potentially underestimated discount levels and immature market share data. The Company estimates that this discount will reach 60%-65% before the third committee meeting in October (three months since the previous calculation of the discount). The discount will continue to rise until the market reaches a steady state, at which point the discount is estimated to be ~70% (as per NHS England assumption during the BIT analysis). A 70% discount should be used for the purposes of decision making. This figure will most accurately reflect the state of the market upon publication of final guidance for this appraisal (January,2019).	
5	Consultee	Roche Products Ltd.	**<u>Revision of administration costs in the economic analysis</u>** In the Section 3.9 of the ACD, the Committee commented that the administration costs used in the analysis are calculated using an outdated source. The figures in the Committee's "corrected" analysis, originally	Comment noted The committee agrees that the NHS reference costs represent the cost paid by the NHS for services provided and is better aligned to the NICE reference case. The FAD has been updated

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			suggested by Professor Clark, are taken from the NHS Improvement payment-by-results (PbR) tariff (NHS Improvement, 2017). This is not the same source that was used in the company base case. In their base case, the Company used the NHS Reference Cost Schedule 2016/2017 (NHS RCS, 2016), which is the most appropriate source to use for this exercise. The Company strongly objects to the use of the PbR tariff in the updated analysis. The NHS Reference Costs is the preferred source over the PbR tariff. Reference costs report a national average unit cost to the NHS for providing defined services. Tariffs are designed as a 'transfer payment' between two different parts of the NHS (usually from a commissioner to a provider). Therefore, the NHS has neither lost nor gained any money as a result of the tariff payment (what the commissioner loses, the provider gains, resulted in a net change of zero). A tariff is designed simply to act as an incentive (or disincentive) for certain services or functions, and its value does not typically equate to the true cost of the activity that it is representing. The Reference cost therefore reflects the entire cost of administration to the NHS and not just the fee a hospital will receive from a commissioner. For the purposes of economic modelling, the entire cost of administration to the NHS should be accounted for – as per the guidance in the NICE Reference Case (NICE, 2013). In response to Professor Clark's comments, the Company has undertaken a targeted review of past NICE single technology appraisals. A total of 20 completed appraisals (see comment 10) have been incorporated as part of this review - including the 10 appraisals most recently published by NICE, 5 appraisals that have been through this Committee (A), and 5 breast cancer appraisals. In summary, none of the included appraisals used the PbR tariff to calculate administration costs in the base case economic analysis. It was found that Professor Clark had made similar comments, regarding the use of the tariff, in five of these appraisals. On all occasions, these comments were either dismissed following objection from the Company (using similar arguments as those outlined above) or ignored completely by all parties. Interestingly, this appraisal appears to be the first in which comments of this nature have been incorporated into the ACD without prior consultation from the Company. Whilst the Company acknowledges that this targeted review only takes into account a relatively small sample size, it is believed that the results seen here are reflective of decision making across all NICE	accordingly.

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			technology appraisals. The Company agrees that the NHS Reference Cost Schedule 2016/2017 could perhaps be considered outdated. As part of this response, the Company made certain that a more up-to-date version of the Reference Schedule was not available. The Company can confirm that the 2016/2017 version of the schedule is in fact the most recently published version and is therefore the best available evidence at the time of writing. Upon review of older versions of the schedule, it appears that the yearly changes to each unit cost are in fact negligible. The use of a more recent version of the schedule is unlikely to significantly impact the results of the economic analysis. A possible method of updating the analysis would be to apply an inflation factor to the costs taken from the 2016/2017 source. This would ensure that the modified costs would more accurately reflect the current price year. However, this analysis was deemed to be of limited value and therefore not undertaken by the Company as part of this response. The effect of the inflation factor would be applied across both arms of the model equally and would result in almost no impact to the overall cost-effectiveness results. Ultimately, the Company believes that the administration costs included in the base case analysis are the most appropriate for this appraisal. To use the PbR tariff would not only be incorrect from an economic modelling standpoint (prices vs. costs to the NHS), but would also be contradictory to the guidance in the NICE Reference Case. Finally, the Company's targeted review indicates that the inclusion of the PbR costs here would result in an inconsistency in decision-making that is potentially unfair and unreasonable in light of the evidence submitted.	

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6	Consultee	Roche Products Ltd.	**Pertuzumab treatment effect duration** The Company is disappointed in the Committee's decision to adopt the ERG's treatment effect assumptions. As expressed in the response to the first ACD, the Company stresses that these assumptions are highly conservative and potentially implausible. The ERG's assertion that the pertuzumab treatment effect begins to wane after only four years is not 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 1 below: **Table 1 Annualized hazard ratios in APHINITY data - Node positive population** **[not reproduced here]** The values in Table 1 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 benefit 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 1. 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 1 APHINITY KM IDFS curves – capped at 44.5 months (median FU) – node positive population** **[not reproduced here]** The company agrees 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. In conclusion, the Company maintains that the ERG's treatment effect assumptions are overly conservative and are highly unlikely to produce an efficacy pattern that is reflective of clinical practice over time.	Comment noted Although many of the ERG's preferred assumptions (including the duration of treatment benefit) were used in the company's revised model there was still uncertainty in projecting a 3% benefit in disease-free survival in the lymph node-positive group to a 0.4 quality-adjusted life year (QALY) gain. It also noted that any assessment of the acceptability of the estimated incremental cost-effectiveness ratio (ICER) should take this uncertain long-term benefit into account. The committee concluded that the long-term QALY gain is highly uncertain. The committee considered the company's final updated model. Pertuzumab has now been recommended for the adjuvant treatment of people with lymph node-positive disease.

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7	Consultee	Roche Products Ltd.	**<u>Revised cost-effectiveness analysis</u>** 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 analysis submitted during the Company's response to the first ACD: • Correction of an error associated with the trastuzumab emtansine list price and the application of the confidential discount – (~5% impact on the ICER) • Updated scenario analyses regarding the incorporation of trastuzumab biosimilars into the cost-effectiveness analysis • The Company has [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 scenarios, the resulting ICER ranges from a maximum of £29,645 down to a minimum of £9,899. As mentioned above, the Company maintains that the Committee's assumed average discount on trastuzumab biosimilars is outdated and incorrect, nevertheless, the ICER in this scenario is still under £30,000 and can therefore be 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.	Comment noted The committee considered the updated model and ICERs. It noted that the company's final model, includes only people with lymph node-positive disease, and incorporates the committee's preferred conservative estimates of how long treatment benefit with pertuzumab lasts after treatment is stopped. If the commercial discount to the price of pertuzumab, together with a weighted discount for biosimilar intravenous trastuzumab are taken into consideration, the cost-effectiveness estimate is comfortably below £20,000 per QALY gained. Therefore adjuvant pertuzumab is recommended for HER2-positive early stage breast cancer in people with lymph-node-positive disease.
27	Patient Organisation	Breast Cancer now	It is disappointing that - despite Roche adopting the majority of the ERG's recommendations in relation to cost-effectiveness modelling, and offering a further discount on the price of pertuzumab, alongside the use of information on current price and market share of trastuzumab biosimilars - NICE is still not able to recommend pertuzumab for the adjuvant treatment of early HER2 positive breast cancer.	Comment noted. Following consideration of an updated model pertuzumab has now been recommended for the adjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive early stage breast cancer in adults in people with lymph-node positive disease.

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28	Patient Organisation	Breast Cancer now	We would reiterate that 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. Any improvement in outcomes is welcomed by patients and their loved ones. The risk of breast cancer recurring or spreading to other parts of the body, where it becomes incurable, can be a source 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.	Comment noted. The committee acknowledged the difficulty of obtaining mature overall-survival data for adjuvant treatments. It concluded that in the absence of mature overall-survival data, invasive disease-free survival is the only available data for decision making. However, the extent to which invasive disease-free survival translates into long-term overall survival benefit is not known.
29	Patient Organisation	Breast Cancer now	We note the Committee's comments in section 3.3 and 3.8 on the reliability of early markers such as invasive disease free survival (IDFS) as surrogates for longer term outcomes such as overall survival and the impact that this may have on decision making. We understand that the immaturity of overall survival data is an issue in many technology appraisals for cancer medicines, and urge NICE to ensure that a consistent approach is taken to decision making across technology appraisals when using surrogates such as IDFS and progression free survival.	Comment noted (please see the response above)
30	Patient Organisation	Breast Cancer now	We would also reiterate that, 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 in 2019. This may help provide greater certainty for the Committee in relation to data on IDFS and OS. We would urge Roche, NICE and NHS England to work together to see if the cost-effectiveness of adjuvant pertuzumab could be improved to the extent that it could be recommended for use on the CDF.	Comment noted. Following consideration of an updated model pertuzumab has now been recommended for the adjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive early stage breast cancer in adults in people with lymph-node positive disease.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
31	Professional organisation	UK Breast Cancer Group (UKBCG)	• The ACD comments on expert consultation with reference to pCR in NeoSphere not translating to overall survival. Neosphere was not powered to show any difference in progression free, event free or overall survival. Progression-free survival and disease-free survival at 5-year follow-up in the NeoSphere trial show large and overlapping confidence intervals, but support the primary endpoint (pathological complete response) and suggest that neoadjuvant pertuzumab is beneficial when combined with trastuzumab and docetaxel. Additionally, they suggest that total pathological complete response could be an early indicator of long-term outcome in early-stage HER2-positive breast cancer. Per patient pathological complete response (pCR) is an accepted surrogate for long-term outcomes (Cortazaar et al., 2014, Yee et al., 2017)	Comment noted. The committee considered the usefulness of invasive disease free survival as a surrogate marker for overall survival. It acknowledged the difficulty of obtaining mature overall-survival data for adjuvant treatments. It concluded that in the absence of mature overall-survival data, invasive disease-free survival is the only available data for decision making. However, the extent to which invasive disease-free survival translates into long-term overall survival benefit is not known.
32	Professional organisation	UK Breast Cancer Group (UKBCG	• Section 3.5 is somewhat contradictory in that the committee agreed that it is biologically plausible that patients would be at high risk of recurrence if there were lymph node involvement (which is an indicator of disease spread) or if the tumour were hormone receptor-negative (because these patients cannot have endocrine treatment). The committee was concerned that APHINITY was not powered to determine treatment effects within the subgroups of interest. It recognised that the separation of the curves for each treatment arm shown in the Kaplan– Meier plots appeared greater in these subgroups compared with the intention-to-treat population, and this was reflected in the improved hazard ratios for these populations (lymph-node positive 0.77, 95% confidence interval [CI] 0.62 to 0.96; hormone-receptor negative 0.76, 95% CI 0.56 to 1.04) compared with the intention-to-treat population. However, the absolute difference in event rates across the treatment arms of all the node-status and hormone-receptor status subgroups is small (range 0.5% to 3.2). ○ The hazard ratio is the important factor in determining effect of treatment. The hazard ratio for IDFS for node positive group is 0.62-0.96 which is consistent with what would be expected in a population of patients with micro-metastatic disease rather than a population that includes a large proportion of patients with no micro-metastatic breast cancer	Comment noted. The committee heard from the clinical experts, and accepted the biological plausibility, that people with lymph-node-positive disease would have more recurrences, so that even with the same relative effectiveness the numerical reduction in recurrences and absolute benefit would therefore be greater. It also noted that the hazard ratio for this subgroup in the trial reached statistical significance (HR 0.77, 95% CI 0.62 to 0.96). The committee accepted that the subgroup with lymph-node-positive disease represents a population at increased risk of recurrence, and that the company's decision to focus on people with lymph-node-positive disease is reasonable.

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33	Professional organisation	UK Breast Cancer Group (UKBCG	• The committees conclusion that, “there is considerable uncertainty in the results for the node-negative subgroup, and it is not reasonable to conclude that pertuzumab did not provide clinical benefit these patients although patients with lymph node positive or hormone receptor-negative disease would benefit most from pertuzumab as adjuvant therapy in absolute terms, there is no evidence that the relative treatment effect differs between these subgroups” is not consistent with clinical reality in that by definition patients with lymph node positive breast cancer have cancer that has demonstrated metastatic potential and are therefore much more likely to have distant metastatic breast cancer. The rationale for adjuvant systemic anti-cancer therapy is to eradicate such metastatic breast cancer before it becomes established and incurable. Therefore, there is a clear biological explanation why there would be a greater treatment effect in patients with lymph node positive breast cancer than those with lymph node negative breast cancer.	Comment noted. People with node-negative disease are not included in the ‘high risk’ population of the marketing authorisation. The committee considered the company proposal which only focussed on the clinical and cost effectiveness of pertuzumab in people lymph-node positive disease. Pertuzumab has now been recommended for treating people with lymph node-positive disease.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
34	Professional organisation	UK Breast Cancer Group (UKBCG	We believe it is important for the committee to understand the following: • NICE are being inconsistent with their approach to subgroups. NICE recommendation based on a subgroup analysis is not uncommon. There are examples where NICE have recommended a technology for use in a subgroup when the study was not statistically powered to detect a treatment effect in that subgroup. ○ *NICE recommendation of nivolumab in previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer was based on PDL-1+ subgroup [TA484]* ○ *NICE recommendation of cetuximab in recurrent or metastatic squamous cell cancer of the head and neck was based on a subgroup that started in oral cavity [TA473]* ○ *NICE recommendation of cetuximab in locally advanced squamous cell cancer of the head and neck was based on a subgroup with Karnofsky performance-status score of 90% or greater [TA145]* ○ *NICE recommendation of cetuximab in previously untreated metastatic colorectal cancer was based on a post-hoc subgroup analyses in RAS wild type subgroup [TA439]* ○ *NICE recommendation of imatinib for adjuvant treatment of KIT (CD117)-positive gastrointestinal stromal tumours in a high risk subgroup defined by the Miettinen criteria [TA326]*	NICE often makes recommendations in a subgroup for example when there is evidence of improved clinical efficacy and cost effectiveness in a particular subpopulation. The committee heard from the clinical experts, and accepted the biological plausibility, that people with lymph-node-positive disease would have more recurrences, so that even with the same relative effectiveness the numerical reduction in recurrences and absolute benefit would therefore be greater It also noted that the hazard ratio for this subgroup in the trial reached statistical significance (HR 0.77, 95% CI 0.62 to 0.96). The committee accepted that the subgroup with lymph-node-positive disease represents a population at increased risk of recurrence, and that the company's decision to focus on people with lymph-node-positive disease is reasonable.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
35	Professional Organisation	UK Breast Cancer Group (UKBCG	• The improvement in outcomes in the node-positive patients represents a clinically meaningful benefit in the curative setting and adjuvant pertuzumab should be available as an option on the NHS for node-positive patients.	Comment noted . The committee heard from the clinical experts, and accepted the biological plausibility, that people with lymph-node-positive disease would have more recurrences, so that even with the same relative effectiveness the numerical reduction in recurrences and absolute benefit would therefore be greater It also noted that the hazard ratio for this subgroup in the trial reached statistical significance (HR 0.77, 95% CI 0.62 to 0.96). The committee accepted that the subgroup with lymph-node-positive disease represents a population at increased risk of recurrence, and that the company's decision to focus on people with lymph-node-positive disease is reasonable. Adjuvant pertuzumab has now been recommended for treating people with lymph node-positive disease.
36	Web comment	NHS Professional	Comments relating to NICE 2nd ACD for adjuvant Perjeta ®(pertuzumab) for patients with HER2+ early breast cancer at high risk of recurrence. I would like to raise the attention of the committee to 2 areas of concern I have regarding the latest assessment of Adjuvant Perjeta. The first Area of concern is the approach towards the use of the data from the APHINITY Trial as the basis of not supporting the application. This was a positive trial all be it a small impact in the ITT group. When considering the use of a therapy with a small impact over a whole trial population it is entirely valid to begin to look at the sub-groups that may well be deriving this benefit. We understand that patients with node positive disease have the highest risk of local and distant failure and this trial demonstrated in a sub group analysis that these are indeed the patients most likely to be deriving the benefit. This benefit is the basis of the adjuvant licencing of Perjeta hence it is entirely in keeping to consider the therapy in line with its approved licencing. There are a number of examples of NICE therapy approvals based on sub-groups not statistically powered to detect an effect such as the approval of Imatinib for KIT positive GIST. The definitive value of any cancer treatment has to be based upon overall survival (OS.) What we know about the modern management of breast cancer is that advances in primary oncological treatments are reducing the OS events in all modern trials. This in turn has	Comment noted NICE often makes recommendations in a subgroup for example when there is evidence of improved clinical efficacy and cost effectiveness in a particular subpopulation. . The committee heard from the clinical experts, and accepted the biological plausibility, that people with lymph-node-positive disease would have more recurrences, so that even with the same relative effectiveness the numerical reduction in recurrences and absolute benefit would therefore be greater It also noted that the hazard ratio for this subgroup in the trial reached statistical significance (HR 0.77, 95% CI 0.62 to 0.96). The committee accepted that the subgroup with lymph-node-positive disease represents a population at increased risk of recurrence, and that the company's decision to focus on people with lymph-node-positive disease is reasonable. Adjuvant pertuzumab has now been recommended for treating people with lymph

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			pushed back the length of time that trials have to be followed up to demonstrate OS benefit. The data in the APHINITY trial is too immature to derive the conclusion that there is no OS benefit. In this setting the surrogate of IDFS show be adopted and the improvement if outcome for this measure in the node positive group is clinically significant and represents a tangible benefit for these patients. The second area of concern is the expert opinion given to the committee by Professor Viadya. I would like to highlight the fact that his opinion regarding the neo-adjuvant therapy approach to the management of breast cancer is completely out of step and contradicts the vast majority of surgeons and oncologists with experience in managing this disease. This has been highlighted by the responses to his recent BMJ article on this subject which was thoroughly refuted by expert groups from across the UK, Europe and the USA. (see responses to https://doi.org/10.1136/bmj.j5913) His point of view was also challenged and dismissed at the session â€œNeoadjuvant chemotherapy: Addressing the mythsâ€ at the ABS conference in June 2018 (https://video.associationofbreastsurgery.org.uk/webcast2018birmingham/Session16/1100Untch/index.html) I would suggest that his opinion on this subject is at best regarded as a personal opinion not representative of the wider breast cancer expert community.	node-positive disease. The committee considered the usefulness of invasive disease free survival as a surrogate marker for overall survival. The committee noted that invasive disease free survival has recently been adopted as a surrogate for overall survival. The committee acknowledged the difficulty of obtaining mature overall-survival data for adjuvant treatments. It concluded that in the absence of mature overall-survival data, invasive disease-free survival is the only available data for decision making. However, the extent to which invasive disease-free survival translates into long-term overall survival benefit is not known.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
37	Web comment	NHS professional	People with HER2 +ve breast cancer, now enjoy significantly better outcomes as a consequence of the development of highly effective targeted therapy. Indeed, those with HER2-positive disease have a better outcome that those with other types of breast cancer. As the outlook for these people improves, it is axiomatic that further improvements in outcome will be increasingly difficult to demonstrate. Nevertheless, the APHINITY data, clearly demonstrate clinically relevant improvements in longer-term outcomes for those patients with higher-risk HER2 positive breast cancer as defined by conventional prognostic criteria such as node-status and hormone-receptor status. As a result of the statistical analysis plan for the study, these positive results have emerged relatively early in the follow-up of people with early-stage disease and as with other interventions using systemic therapy in the adjuvant setting, it is highly likely that these improvements will be seen to be more substantial with time. The use of pertuzumab in the adjuvant setting is another important and relevant step in the treatment of this type of breast cancer and in my view, to ignore these benefits would do a disservice to people with early-stage, HER2-positive disease whose chances of remaining disease-free are enhanced by this novel, targeted therapy.	Comments noted. Adjuvant pertuzumab has now been recommended for treating people with lymph node-positive disease.
38	Web comment	NHS Professional	Breast cancer in many patients has metastasised by the time of diagnosis so the only way to improve the outcome of these patients is to give effective systemic therapy. It is important biologically to stop cancers proliferating. One consequence of proliferation is the development of new clones. A characteristic feature of a cancer cell is the failure to copy DNA without developing more mutations and deletions. So cancer therapy is essentially targeted at stopping proliferation and stopping the development of new generations of cancer cells with more mutations some of which render the cancer resistant to a particular therapy. The fundamental lesson we have learnt in cancer is to give the most effective therapies up front as once resistant clones develop then cure is very unlikely. Once a therapy has been identified to be effective then the only way that that therapy will improve outcome is for it to be used at diagnosis and the idea of limiting a drugs to the metastatic setting once a drug has been shown to improve cancer outcomes makes no biological sense. Pertuzumab has been shown to be effective at eliminating cancers in the neoadjuvant setting. Consistent with this finding pertuzumab in the adjuvant setting also improves outcomes. The data supporting these statements have been very extensively documented above by many others.	Comments noted. Adjuvant pertuzumab has now been recommended for treating people with lymph node-positive disease.

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39			My role as I see it is to defend the position that one can rely on evidence from neoadjuvant trials and that improvements in outcomes in the neoadjuvant setting can be used to reliably identify drugs that will improve patients outcomes in the adjuvant setting. It is also illogical to believe that a drug is effective in the neoadjuvant setting but should not also be available in the adjuvant setting. Pertuzumab in addition to trastuzumab clearly improves the rate of complete pathological responses (cPR) in the neoadjuvant setting (see data from NeoSphere and Tryphaena studies). The Aphinity study in the adjuvant setting included many lower risk patients but clearly shows that the results seen in the neoadjuvant setting do translate in to better outcomes. The absolute improvements with the addition of pertuzumab are commensurate with that expected given the low risk of the overall population of many of the patients included in the study. The risk profile of the patients in the neoadjuvant setting was much higher so the absolute benefits are greater. In aphinity the improvement in outcome was seen to be greater in the node positive population.	Comments noted. Adjuvant pertuzumab has now been recommended for treating people with lymph node-positive disease.
40			In locally advanced breast cancer neoadjuvant systemic therapy is now standard care and has revolutionised the outcome of many patients particularly those with inflammatory breast cancer. Following the studies that have shown that neoadjuvant chemotherapy (NACT) +/- trastuzumab and pertuzumab produces high rates of complete pathological response (pCR), its use has been increasing and guidelines for patient selection and its use are now in place. The increasing rates of pCR has also allowed increasing numbers of women to preserve their breast and have less extensive breast and axillary surgery. This in itself is associated with significant cost savings as there is no need for breast reconstruction (Sang et al 2014).	Comments noted. Adjuvant pertuzumab has now been recommended for treating people with lymph node-positive disease.
41			There are two major concerns raised by Vaidya in his evidence as a BASO advisor that I would like to address. Specifically Vaidya advises first that pCR after NACT +/- trastuzumab and pertuzumab does not translate into better outcomes 1. Does pathological complete response (pCR) related to improved survival? Prospective randomized trials have shown that those patients who had a pCR after neoadjuvant chemotherapy have much better long term outcomes than patients with residual disease (Fisher et al, 1997). Following the first generation of NACT trials, studies that included the monoclonal antibodies trastuzumab and pertuzumab that target HER2 showed a dramatic increase	Comments noted The committee considered the usefulness of invasive disease free survival as a surrogate marker for overall survival. It acknowledged the difficulty of obtaining mature overall-survival data for adjuvant treatments. It concluded that in the absence of mature overall-survival data, invasive disease-free survival is the only available data for decision making. However, the extent to which invasive disease-free survival translates into long-term overall survival benefit is not known.

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			in the pCR rate from less than 20 % to about 40-45% with trastuzumab alone and over 60% with the trastuzumab and pertuzumab and this improvement in pCR rate does translate to a significant increase in disease free and overall survival, demonstrating that pCR is an excellent surrogate marker for long term outcome in this patient group (Earl et al 2015, Gianni et al 2014, Schneeweiss et al 2013, 2018, Untch et al 2011). The largest worldwide meta-analysis of prospective randomized trials with NACT showed an excellent correlation of pCR with disease free and overall survival particularly in patients who had triple negative or HER2-positive tumours (Cortazar et al 2014). The St. Gallen Consensus Meeting panelists 2017 voted with a large majority in favour NACT with the addition of anti-HER2 therapies as the preferred option for patients with HER2 positive early breast cancer and for NACT in patients with triple negative tumors (Curigliano et al 2017). NACT has the potential to improve outcomes of breast cancer patients by using pCR as a surrogate marker for DFS and OS (Schneeweiss et al 2017, Untch et al 2016). Information on response to chemotherapy from NACT trials has triggered a new generation of postneoadjuvant trials: the first one is coming from Japan showed a survival benefit in those patients who had NACT and had residual disease in the breast and/or in the ipsilateral axillary lymph nodes and received additional Capecitabine chemotherapy after NACT (Masuda et al 2017). This has also led to a strong recommendation by more than 90% of the International St. Gallen Committee members for postneoadjuvant Capecitabine in patients who have triple negative breast cancer and have a residual disease of greater than 1 cm or positive nodes after NACT (Curigliano et al 2017). The newest generation of postneoadjuvant trials includes the KATHERINE study of patients with HER2-positive tumors and residual tumour in the breast and or in the lymph nodes after optimal NACT including anti-HER2 therapy with patients being randomized to standard anti-HER2 postoperative treatment versus treatment against HER2 with the antibody conjugate TDM1. This study will be presented in San Antonio in December 2018. This and other trials have been possible only by identifying patients with disease resistant to standard current treatment regimens. The view that neoadjuvant treatment has not contributed to our understanding and improved outcomes is clearly incorrect and the view that NACT +/-	

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			trastuzumab + pertuzumab should be abandoned as suggested by Vaidya in the BMJ recently is very clearly not evidence based and clearly is against international opinion.	

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 07/09/2018

	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 Ltd.**
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] *Health economist at Roche Products Ltd.*

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 07/09/2018

Comment number	Comments
1	Whilst disappointed with the decision, the Company 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. In addition, Roche has also addressed key aspects surrounding the cost-effectiveness of pertuzumab. Specifically, the assumptions surrounding trastuzumab biosimilars in the economic analysis and the use of the Committee's revised administration costs. 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 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	**NICE recommendation based on a subgroup analysis is not uncommon** **The provisional recommendations are neither sound nor suitable for guidance to the NHS. The appraisal consultation document (ACD) focuses on the uncertainty in the high risk subgroups and the concern that the study was not powered to determine the treatment effects within the node-positive subgroup. However, this is inconsistent with previous appraisals where NICE have recommended a technology specifically for a subgroup (even when the study was not powered to determine the treatment effect within the subgroup).** Two recent examples of this are highlighted below: ● Obinutuzumab has a broad EMA label for untreated advanced follicular lymphoma (FL) (EMC, 2018). During the appraisal for TA513, NICE subsequently recommended obinutuzumab for untreated advanced FL patients in a subgroup (patients with FLIPI scores over 2 or more) even though the key GALLIUM trial was not designed to detect a difference between FLIPI subgroups. This was revised due to a statement in section 4.4 of the SmPC which states "based on a subgroup analysis in previously untreated follicular lymphoma, the efficacy in FLIPI low risk (0-1) patients is currently inconclusive ". Overall, the committee was satisfied that the higher-risk subgroup (based on FLIPI scores) was the clinically relevant population to consider in this appraisal and subsequently made a positive recommendation based on this high risk subgroup (NICE TA513). ● Similarly, tocilizumab has a broad EMA label for patients with giant cell arteritis (GCA) (EMC,

	2018). During the appraisal for TA518, NICE heard from clinical experts and patients that tocilizumab would be most valuable to people with relapsing disease. NICE subsequently recommend tocilizumab for a subgroup of patients (i.e. relapsing or refractory GCA patients only). The committee concluded that this subgroup was distinct and biologically plausible and had the highest unmet need, and subsequently made a positive recommendation based on this subgroup only (NICE TA518). Other examples in oncology which have been recommended in a subgroup are NICE TA484, TA326, TA145, TA473. When the study is positive, it is reasonable to look into the subgroups to see what is driving the overall treatment effect. 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) (von Minckwitz *et al.,* 2017). In this group, the benefit of pertuzumab was clearly demonstrated by superior invasive disease-free survival (IDFS) over adjuvant trastuzumab. This is evidenced by the increased number of events, superior hazard ratio and narrower confidence intervals around the estimates. Node-positive patients are at a higher risk of relapse and therefore have a greater need for more effective treatments. We have heard through the clinical community's responses to the ACD and at both Committee meetings that the node-positive subgroup data is clinically meaningful and this is where clinical commentators would like to use adjuvant pertuzumab. This subgroup is in line with our market authorisation and has been accepted by the EMA. Whilst we agree that there is uncertainty as the study was not powered to determine the treatment effects in the subgroups of interest, this is often the case with subgroup analyses. As evidenced by the technology appraisals referenced above, a NICE recommendation based on a subgroup analysis is not uncommon. We request that the Committee consider not only the advice of the patient groups and clinical community, but also the precedent set in other appraisals, and give node-positive patients the opportunity to further reduce their risk of recurrence.
3	**Node-negative patients are not considered high risk** **The provisional recommendations are neither sound nor suitable for guidance to the NHS. The ACD highlights the Committee's concern regarding the exclusion of node-negative patients and states that "it is unreasonable to conclude that adjuvant pertuzumab did not provide clinical benefit to these patients" based on low number of events, despite it not being in line with our EMA label.** The Company agrees that there are low numbers of events in the node-negative subgroup and it is not possible to draw any efficacy conclusions at this point in time for this subgroup. Similarly, it would be unreasonable to claim adjuvant pertuzumab benefits the node-negative subgroup. The fact that there are low numbers of events in the node-negative subgroup 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) (von Minckwitz *et al.,* 2017). The marketing authorisation for adjuvant pertuzumab is only in the high risk population and is defined as node-positive or hormone-receptor negative based on the APHINITY trial (EMC, 2018). The node-negative subgroup is not specifically covered by this marketing authorisation and it would therefore be inappropriate to focus on this subgroup for this appraisal. The Committee's approach to subgroup selection is inconsistent with previous technology appraisals, where subgroups that are not in line with the marketing authorisation are not in scope. An example is trastuzumab for the treatment of HER2-positive metastatic gastric cancer TA208, where the Committee have noted that "there were no subgroups to be discussed, other than the licensed subgroup". Based on the current evidence, node-positive patients benefit the most from adjuvant pertuzumab.

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 07/09/2018

	Similar to the technology appraisals referenced in comment 2, it is appropriate to focus on a high risk subgroup that is benefiting the most from the technology. We have heard from the clinical community and patients that they view the APHINITY node-positive data positively and that it makes sense to stratify patients and only offer adjuvant pertuzumab to those at highest risk of recurrence. The Company agree with the clinical community that adjuvant pertuzumab does not need to be offered to every early breast cancer patient with HER2-positive disease but should be offered to node-positive patients. Node-positive patients are at a higher risk of recurrence and are in a greater need of more effective treatments. This is the most relevant subgroup for this appraisal and we would invite the Committee to reconsider its conclusion in the ACD in this regard, reflecting the wishes of the clinical community and patients, and give these node-positive patients an opportunity to be closer to achieving their treatment goal of cure.
4	**Unreasonable weight and focus on interaction test** **Summary of the clinical effectiveness is not a reasonable interpretation of the evidence. The Committee have put an unjustifiable amount of weight on the test for heterogeneity for the selection of subgroups.** As discussed in previous Company responses throughout this appraisal, the conclusions and rationale for proposing the node-positive and hormone-receptor negative subgroups and their adoption in Health Authority labelling, are based on objective clinical rationale and supported by the results (event rates, HR and CI). These baseline factors were also in the stratification used at randomisation due to their known prognostic importance. Statistical interaction testing was performed for the primary endpoint as part of planned exploratory analyses at the time of the primary analysis, in order to understand statistical evidence of heterogeneity in the treatment effect within patient subgroups of interest. The significance levels from these exploratory tests were included in the NEJM manuscript as part of the journal's standard practice. It is acknowledged that the test results do not show strong statistical evidence of heterogeneity. However as noted in the ACD, from a statistical perspective, interaction tests are known to carry low power leading some researchers to increase the Type I error rate from 0.05 for such testing. In the case of APHINITY, low power is particularly notable for nodal status as there are a very low number of events in the node-negative subgroup and therefore the result needs to be interpreted with caution in terms of concluding homogeneity of treatment effect. Subgroup data should be appropriately interpreted with consideration of the observed data, clinical rationale and biological plausibility. The Company believes the summaries of clinical effectiveness included in the ACD around the selection of subgroups need to be re-interpreted with consideration of the multiple factors used in subgroup assessments including the totality of the observed data, clinical rationale and biological plausibility.
5	**OS is immature to draw solid conclusions at this point in time** **Summary of the clinical effectiveness is not a reasonable interpretation of the evidence. The ACD makes claims that there are no survival benefits based on the APHINITY data. The Company believes that the data is too immature to make such claims.** In reference to no survival benefit in APHINITY, The Company request that the Committee clarifies in the ACD that as overall survival data is immature, there was no apparent difference for this outcome at this point in time**.** It is important to clarify in the ACD that "further OS follow up and planned statistical analyses will continue until 10 years after last patient enrolled to allow robust assessment of long-term survival effect in this population." The immature OS data at this point in time cannot be used to draw

	solid conclusions as there is no indication that there will not be survival benefits in the future, when more events have occurred. The expert statement from Professor Vaidya that "In the NeoSphere trial, for example, higher pathological complete response with neoadjuvant pertuzumab was not associated with improved overall survival in the long term, in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer at high risk of recurrence" is inaccurate. In the NeoSphere trial, overall survival was not a protocol-defined efficacy endpoint, therefore survival status was not systematically reported beyond disease progression, disease recurrence or withdrawal and a time-to-event analysis was not performed. Hence conclusions around association of pCR with OS cannot be drawn based on the NeoSphere data. However, there is existing evidence of the relationship between pCR and long-term outcomes. (Cortazar *et al.,* 2014; Yee *et al.,* 2017). Although highlighted in the ACD, this is not relevant to the scope of this appraisal. DFS and IDFS have been widely adopted in adjuvant studies as a surrogate for long-term outcomes, and have been accepted by both the EMA and FDA.
6	**Incorporation of a more accurate biosimilar discount in the economic analysis** The Company welcomes the Committee's decision to explicitly incorporate the impact of trastuzumab biosimilars on the economic analysis. At the time of writing, both the price and the market share of biosimilars are not definitively known. Nevertheless, the Committee appears to have assumed a trastuzumab biosimilar market share of 100% and a discount of 55% compared to the list price of Herceptin IV. The level of biosimilar market share suggested by the Committee is aligned with comments made by Professor Clark (Consultant Medical Oncologist and current Chair of the Chemotherapy Clinical Reference Group) during the appraisal committee meetings. No plausible rationale exists for why a patient would receive Herceptin IV instead of trastuzumab biosimilar IV given that the national tender has concluded and several biosimilar trastuzumab products are readily available. The Company agrees with the Committee's proposed biosimilar market share estimate of 100% in new patients. The Committee has also assumed that trastuzumab biosimilars are available at a weighted average discount of 55% on the Herceptin IV list price. In the ACD, the Committee goes on to state that this value "had been used in the NICE Budget Impact Test analysis" – this statement is false. In the BIT analysis, the company assumed the level of discount would be 60% in 2018 before rising to 70% in 2019 and remaining constant thereafter. This assumption was subsequently agreed to be reasonable by representatives from both NHS England and NICE. Please refer to the finalised budget impact assessment published by NICE. Trastuzumab biosimilars have been available in the UK for several months. Competitive intelligence collected by the Company suggests that some manufacturers have waited until the national tender before making the final price of their products known. The Company are aware that discounts of between 50% and ~70% have been submitted as part of the tendering process. Given near identical products, logic suggests (and the CQUIN mandates) that the cheapest biologic be prescribed by physicians. Consequently, the cheaper product (~70% discount on Herceptin IV) has been acquiring market share and therefore becoming the leading trastuzumab biosimilar. The net effect of this acquisition is that the weighted average discount of trastuzumab biosimilars has risen. The discount level quoted in the ACD was presumably calculated in the days prior to the second appraisal committee meeting (19th July, 2018). This was only two weeks after the conclusion of the national tender. This is not a suitable length of time for the market to have fully calibrated following the results of the tender i.e.; the market dynamics described in the preceding paragraph had not yet been fully realised. Although final prices may have been known at this time, the market shares would still have been in a state of flux and not at all representative of a "steady state" or even present day.

	With respect to the national tender, prices submitted during this process are not necessarily the final price of a product. Following the conclusion of a tender, mechanisms are available by which a company may further lower the price of their product (until equivalent with the lowest price submitted in the tender). Therefore, the price at which the product is being offered to the hospitals may be substantially lower than the tender price. The Company suspects that the average discount in the ACD is predicated solely on the discounts submitted during the tender (Professor Clark may not be aware of all price reductions outside of the tendering process). This oversight could potentially lead to an underestimation. Market intelligence collected by the Company states that "price is not a deciding factor in this market". Given the range in submitted tender prices, this intelligence would suggest that at least one manufacturer is applying these "secondary discounts". This behaviour would further increase the weighted average discount calculated by the Committee. In summary, the Committee's assumption of a 55% discount across trastuzumab biosimilars is outdated. This average has been calculated based on potentially underestimated discount levels and immature market share data. The Company estimates that this discount will reach 60%-65% before the third committee meeting in October (three months since the previous calculation of the discount). The discount will continue to rise until the market reaches a steady state, at which point the discount is estimated to be ~70% (as per NHS England assumption during the BIT analysis). A 70% discount should be used for the purposes of decision making. This figure will most accurately reflect the state of the market upon publication of final guidance for this appraisal (January,2019).
7	**Revision of administration costs in the economic analysis** In the Section 3.9 of the ACD, the Committee commented that the administration costs used in the analysis are calculated using an outdated source. The figures in the Committee's "corrected" analysis, originally suggested by Professor Clark, are taken from the NHS Improvement payment-by-results (PbR) tariff (NHS Improvement, 2017). This is not the same source that was used in the company base case. In their base case, the Company used the NHS Reference Cost Schedule 2016/2017 (NHS RCS, 2016), which is the most appropriate source to use for this exercise. The Company strongly objects to the use of the PbR tariff in the updated analysis. The NHS Reference Costs is the preferred source over the PbR tariff. Reference costs report a national average unit cost to the NHS for providing defined services. Tariffs are designed as a 'transfer payment' between two different parts of the NHS (usually from a commissioner to a provider). Therefore, the NHS has neither lost nor gained any money as a result of the tariff payment (what the commissioner loses, the provider gains, resulted in a net change of zero). A tariff is designed simply to act as an incentive (or disincentive) for certain services or functions, and its value does not typically equate to the true cost of the activity that it is representing. The Reference cost therefore reflects the entire cost of administration to the NHS and not just the fee a hospital will receive from a commissioner. For the purposes of economic modelling, the entire cost of administration to the NHS should be accounted for – as per the guidance in the NICE Reference Case (NICE, 2013). In response to Professor Clark's comments, the Company has undertaken a targeted review of past NICE single technology appraisals. A total of 20 completed appraisals (see comment 10) have been incorporated as part of this review - including the 10 appraisals most recently published by NICE, 5 appraisals that have been through this Committee (A), and 5 breast cancer appraisals. In summary, none of the included appraisals used the PbR tariff to calculate administration costs in the base case economic analysis. It was found that Professor Clark had made similar comments, regarding the use of the tariff, in five of these appraisals. On all occasions, these comments were either dismissed following objection from the Company (using similar arguments as those outlined above) or ignored completely by all parties. Interestingly, this appraisal appears to be the first in which comments of this nature have been incorporated into the ACD without prior consultation from the Company. Whilst the Company acknowledges that this targeted review only takes into account a relatively small sample size, it is believed that the results seen here are reflective of decision making across all NICE technology appraisals.

	The Company agrees that the NHS Reference Cost Schedule 2016/2017 could perhaps be considered outdated. As part of this response, the Company made certain that a more up-to-date version of the Reference Schedule was not available. The Company can confirm that the 2016/2017 version of the schedule is in fact the most recently published version and is therefore the best available evidence at the time of writing. Upon review of older versions of the schedule, it appears that the yearly changes to each unit cost are in fact negligible. The use of a more recent version of the schedule is unlikely to significantly impact the results of the economic analysis. A possible method of updating the analysis would be to apply an inflation factor to the costs taken from the 2016/2017 source. This would ensure that the modified costs would more accurately reflect the current price year. However, this analysis was deemed to be of limited value and therefore not undertaken by the Company as part of this response. The effect of the inflation factor would be applied across both arms of the model equally and would result in almost no impact to the overall cost-effectiveness results. Ultimately, the Company believes that the administration costs included in the base case analysis are the most appropriate for this appraisal. To use the PbR tariff would not only be incorrect from an economic modelling standpoint (prices vs. costs to the NHS), but would also be contradictory to the guidance in the NICE Reference Case. Finally, the Company's targeted review indicates that the inclusion of the PbR costs here would result in an inconsistency in decision-making that is potentially unfair and unreasonable in light of the evidence submitted.
8	**Pertuzumab treatment effect duration** The Company is disappointed in the Committee's decision to adopt the ERG's treatment effect assumptions. As expressed in the response to the first ACD, the Company stresses that these assumptions are highly conservative and potentially implausible. The ERG's assertion that the pertuzumab treatment effect begins to wane after only four years is not 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 1 below: **Table 1 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 1 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 benefit 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 1. 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.

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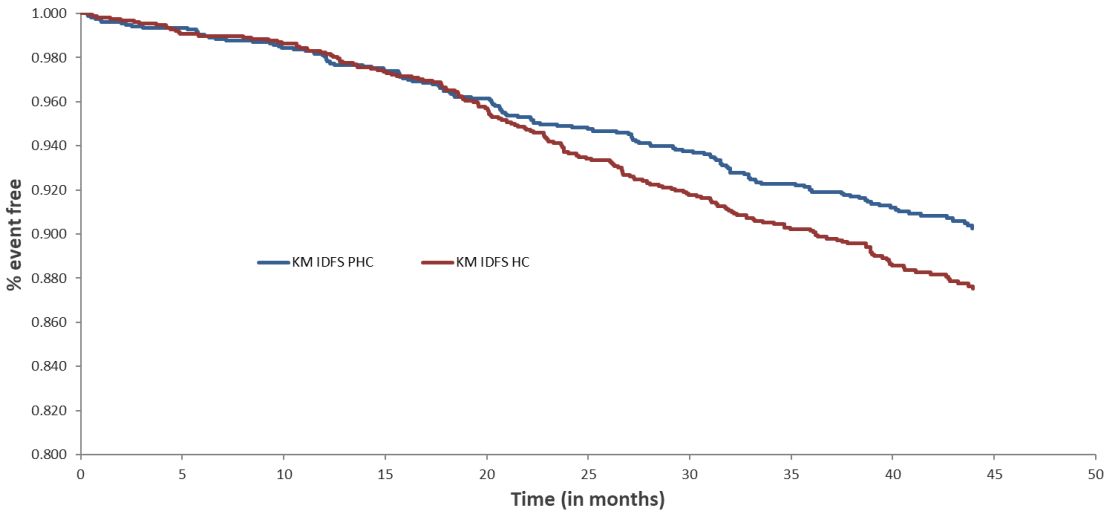
	Figure 1 APHINITY KM IDFS curves – capped at 44.5 months (median FU) – node positive population  The company agrees that this aspect of the analysis is highly uncertain. The currently available evidence does not definitively point to a specific duration of effect. Revised cost-effectiveness results, across a range of treatment effect duration scenarios, have therefore been provided as part of this response – see supplementary appendix. In conclusion, the Company maintains that the ERG's treatment effect assumptions are overly conservative and are highly unlikely to produce an efficacy pattern that is reflective of clinical practice over time.
9	**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 analysis submitted during the Company's response to the first ACD: • Correction of an error associated with the trastuzumab emtansine list price and the application of the confidential discount – (~5% impact on the ICER) • Updated scenario analyses regarding the incorporation of trastuzumab biosimilars into the cost-effectiveness analysis • The Company has [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 scenarios, the resulting ICER ranges from a maximum of £29,645 down to a minimum of £9,899. As mentioned above, the Company maintains that the Committee's assumed average discount on trastuzumab biosimilars is outdated and incorrect, nevertheless, the ICER in this scenario is still under £30,000 and can therefore be 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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10	**Bibliography** Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164-72. Electronic Medicines Compedium (EMC). Gavyvaro Summary of Product Characteristics. Available on: https://www.medicines.org.uk/emc/product/3279/smpc (accessed: August 2018) Electronic Medicines Compedium (EMC). Perjeta Summary of Product Characteristics. Available on: https://www.medicines.org.uk/emc/product/2993/smpc (accessed: August 2018) Electronic Medicines Compedium (EMC). RoActemra Summary of Product Characteristics. Available on: https://www.medicines.org.uk/emc/product/5357/smpc (accessed: August 2018) National Institute for Health and Care Excellence - Guide to the methods of technology appraisal 2013 –Available at: https://www.nice.org.uk/process/pmg9/chapter/foreword National Institute for Health and Care Excellence. Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck technology appraisal [TA145]. Available on: https://www.nice.org.uk/guidance/ta145 (accessed: August 2018) National Institute for Health and Care Excellence. Cetuximab for the treatment of recurrent or metastatic squamous cell cancer of the head and neck technology appraisal [TA473]. Available on: https://www.nice.org.uk/guidance/ta473 (accessed: August 2018) National Institute for Health and Care Excellence. Imatinib for the adjuvant treatment of gastrointestinal stromal tumours technology appraisal [TA326]. Available on: https://www.nice.org.uk/guidance/ta326 (accessed: August 2018) National Institute for Health and Care Excellence. Nivolumab for previously treated non-squamous non-small-cell lung cancer technology appraisal guidance [TA484]. Available on: https://www.nice.org.uk/guidance/ta484 (accessed: August 2018) National Institute for Health and Care Excellence. Obinutuzumab for untreated advanced follicular lymphoma technology appraisal guidance [TA513]. Available on: https://www.nice.org.uk/guidance/ta513 (accessed: August 2018) National Institute for Health and Care Excellence. Tocilizumab for treating giant cell arteritis technology appraisal guidance [TA518]. Available on: https://www.nice.org.uk/guidance/ta518 (accessed: August 2018) National Institute for Health and Care Excellence. Trastuzumab for the treatment of HER2-positive metastatic gastric cancer [TA208]. Available on: https://www.nice.org.uk/guidance/ta208 (accessed: August 2018) NHS Improvement - National tariff payment system 2017/18 and 2018/19 – 2018 Available at: https://improvement.nhs.uk/resources/national-tariff-1719/#h2-tariff-documents NHS Reference costs schedule – 2017 Available at: https://improvement.nhs.uk/resources/reference-costs/ 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. Yee D, DeMichele A, Isaacs C, et al. Pathological complete response predicts event-free and distant disease-free survival in the I-SPY2 TRIAL. Presented at SABCS 2017, San Antonio, U.S.A.

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	Appraisals included in Company's targeted review (as described in Comment 7): *10 most appraisals most recently published by NICE* TA 534, TA 536, TA 537, TA 538, TA 528, TA 529, TA 530, TA 531, TA 532, TA 533 *5 breast cancer appraisals* TA 509, TA 515, TA 503, TA 496, TA 458 *5 most recent appraisals reviewed by Committee A* TA 517, TA 502, TA 495, TA 491, TA 479

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 following the first and second appraisal committee meetings. 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]	[redacted]	[redacted]	[redacted]	£34,087
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	[redacted]			

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]	[redacted]	[redacted]	[redacted]	£60,679
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	[redacted]			

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 5.

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
Corrections			
Markov trace	Incorrect formula	N/A	Corrected formula
"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]

Abbreviations: P, Pertuzumab; TE, Trastuzumab emtansine.

Table 4 Changes made to company base case following second appraisal committee meeting

Parameter	Values in company's original submission	ERG's preferred value	Value used in company's revised estimates
Corrections			
List price of TE (100mg vial)	£959.99	N/A	£1,641.01
List price of TE (160mg vial)	£1,535.93	N/A	£2,625.62
Confidential PAS discounts			
Discount on [redacted]	[redacted]	N/A	[redacted]

Abbreviations: P, Pertuzumab; TE, Trastuzumab emtansine.

Table 5 Effect of changes outlined in Table 3 and Table 4 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]	[redacted]	[redacted]	[redacted]	£34,087
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	[redacted]			
Revised estimates (incorporating changes highlighted in part a)					
HC (trastuzumab + chemotherapy)	[redacted]	[redacted]	[redacted]	[redacted]	£25,516
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	[redacted]			

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**
  - Discount vs. Herceptin IV = 55%-75%
- **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 6 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 (%)										
		55%	57%	59%	61%	63%	65%	67%	69%	71%	73%	75%
Trastuzumab biosimilar market share (%)	**100%**	£29,645	£28,675	£27,704	£26,734	£25,763	£24,793	£23,822	£22,852	£21,881	£20,911	£19,941

Table 7 Treatment effect – Runs for 5 years before waning and ceasing completely at 8 years

		Trastuzumab biosimilar discount compared to branded trastuzumab list price (%)										
		55%	57%	59%	61%	63%	65%	67%	69%	71%	73%	75%
Trastuzumab biosimilar market share (%)	**100%**	£22,950	£22,126	£21,303	£20,479	£19,655	£18,831	£18,007	£17,183	£16,360	£15,536	£14,712

Table 8 Treatment effect – Runs for 7 years ceases completely at 7 years – Neoadjuvant pertuzumab appraisal

		Trastuzumab biosimilar discount compared to branded trastuzumab list price (%)										
		55%	57%	59%	61%	63%	65%	67%	69%	71%	73%	75%
Trastuzumab biosimilar market share (%)	**100%**	£20,427	£19,658	£18,890	£18,121	£17,352	£16,584	£15,815	£15,046	£14,278	£13,509	£12,740

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

		Trastuzumab biosimilar discount compared to branded trastuzumab list price (%)										
		55%	57%	59%	61%	63%	65%	67%	69%	71%	73%	75%
Trastuzumab biosimilar market share (%)	**100%**	£19,055	£18,316	£17,576	£16,837	£16,097	£15,358	£14,618	£13,879	£13,139	£12,400	£11,660

Table 10 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 (%)										
		55%	57%	59%	61%	63%	65%	67%	69%	71%	73%	75%
Trastuzumab biosimilar market share (%)	**100%**	£16,814	£16,123	£15,431	£14,740	£14,048	£13,356	£12,665	£11,973	£11,282	£10,590	£9,899

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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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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 - despite Roche adopting the majority of the ERG's recommendations in relation to cost-effectiveness modelling, and offering a further discount on the price of pertuzumab, alongside the use of information on current price and market share of trastuzumab biosimilars - NICE is still not able to recommend pertuzumab for the adjuvant treatment of early HER2 positive breast cancer.
2	We would reiterate that 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. Any improvement in outcomes is welcomed by patients and their loved ones. The risk of breast cancer recurring or spreading to other parts of the body, where it becomes incurable, can be a source 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.
3	We note the Committee's comments in section 3.3 and 3.8 on the reliability of early markers such as invasive disease free survival (IDFS) as surrogates for longer term outcomes such as overall survival and the impact that this may have on decision making. We understand that the immaturity of overall survival data is an issue in many technology appraisals for cancer medicines, and urge NICE to ensure that a consistent approach is taken to decision making across technology appraisals when using surrogates such as IDFS and progression free survival.
4	We would also reiterate that, 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 in 2019. This may help provide greater certainty for the Committee in relation to data on IDFS and OS. We would urge Roche, NICE and NHS England to work together to see if the cost-effectiveness of adjuvant pertuzumab could be improved to the extent that it could be recommended for use on the CDF.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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- 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.

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- 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.

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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:	UKBCG
Comment number	**Comments**

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	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	• The ACD comments on expert consultation with reference to pCR in NeoSphere not translating to overall survival. Neosphere was not powered to show any difference in progression free, event free or overall survival. Progression-free survival and disease-free survival at 5-year follow-up in the NeoSphere trial show large and overlapping confidence intervals, but support the primary endpoint (pathological complete response) and suggest that neoadjuvant pertuzumab is beneficial when combined with trastuzumab and docetaxel. Additionally, they suggest that total pathological complete response could be an early indicator of long-term outcome in early-stage HER2-positive breast cancer. Per patient pathological complete response (pCR) is an accepted surrogate for long-term outcomes (Cortazaar et al., 2014, Yee et al., 2017)
2	• Section 3.5 is somewhat contradictory in that the committee agreed that it is biologically plausible that patients would be at high risk of recurrence if there were lymph node involvement (which is an indicator of disease spread) or if the tumour were hormone receptor-negative (because these patients cannot have endocrine treatment). The committee was concerned that APHINITY was not powered to determine treatment effects within the subgroups of interest. It recognised that the separation of the curves for each treatment arm shown in the Kaplan– Meier plots appeared greater in these subgroups compared with the intention-to-treat population, and this was reflected in the improved hazard ratios for these populations (lymph-node positive 0.77, 95% confidence interval [CI] 0.62 to 0.96; hormone-receptor negative 0.76, 95% CI 0.56 to 1.04) compared with the intention-to-treat population. However, the absolute difference in event rates across the treatment arms of all the node-status and hormone-receptor status subgroups is small (range 0.5% to 3.2). ○ The hazard ratio is the important factor in determining effect of treatment. The hazard ratio for IDFS for node positive group is 0.62-0.96 which is consistent with what would be expected in a population of patients with micro-metastatic disease rather than a population that includes a large proportion of patients with no micro-metastatic breast cancer
3	• The committees conclusion that, “there is considerable uncertainty in the results for the node-negative subgroup, and it is not reasonable to conclude that pertuzumab did not provide clinical benefit these patients although patients with lymph node positive or hormone receptor-negative disease would benefit most from

	pertuzumab as adjuvant therapy in absolute terms, there is no evidence that the relative treatment effect differs between these subgroups" is not consistent with clinical reality in that by definition patients with lymph node positive breast cancer have cancer that has demonstrated metastatic potential and are therefore much more likely to have distant metastatic breast cancer. The rationale for adjuvant systemic anti-cancer therapy is to eradicate such metastatic breast cancer before it becomes established and incurable. Therefore, there is a clear biological explanation why there would be a greater treatment effect in patients with lymph node positive breast cancer than those with lymph node negative breast cancer.
4	We believe it is important for the committee to understand the following: • NICE are being inconsistent with their approach to subgroups. NICE recommendation based on a subgroup analysis is not uncommon. There are examples where NICE have recommended a technology for use in a subgroup when the study was not statistically powered to detect a treatment effect in that subgroup. ○ *NICE recommendation of nivolumab in previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer was based on PDL-1+ subgroup [TA484]* ○ *NICE recommendation of cetuximab in recurrent or metastatic squamous cell cancer of the head and neck was based on a subgroup that started in oral cavity [TA473]* ○ *NICE recommendation of cetuximab in locally advanced squamous cell cancer of the head and neck was based on a subgroup with Karnofsky performance-status score of 90% or greater [TA145]* ○ *NICE recommendation of cetuximab in previously untreated metastatic colorectal cancer was based on a post-hoc subgroup analyses in RAS wild type subgroup [TA439]* ○ *NICE recommendation of imatinib for adjuvant treatment of KIT (CD117)-positive gastrointestinal stromal tumours in a high risk subgroup defined by the Miettinen criteria [TA326]*
5	• The improvement in outcomes in the node-positive patients represents a clinically meaningful benefit in the curative setting and adjuvant pertuzumab should be available as an option on the NHS for node-positive patients.

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

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	References Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164-72. Yee D, DeMichele A, Isaacs C, et al. Pathological complete response predicts event-free and distant disease-free survival in the I-SPY2 TRIAL. Presented at San Antonio Breast Cancer Symposium 2017, U.S.A. NICE TA484: https://www.nice.org.uk/guidance/ta484/chapter/1-Recommendations NICE TA473: https://www.nice.org.uk/guidance/ta473/chapter/1-Recommendations NICE TA145: https://www.nice.org.uk/guidance/ta145 NICE TA439: https://www.nice.org.uk/guidance/ta439/history NICE TA326: https://www.nice.org.uk/guidance/ta326
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Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The

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

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comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Comments on the ACD received from experts through the NICE website

Name	Alistair Ring
Role	NHS Professional
Other role	Consultant in Medical Oncology
Organisation	
Location	England
Conflict	No
Notes	I have received honoraria from Roche for advisory boards and lectures.

Comments on the ACD:

1) Node positive subgroup.

As stated at a previous committee meeting, I feel that looking at the node positive subgroup is entirely appropriate in the context of early breast cancer. It is well-recognised as a valid prognostic marker, indicative of higher rates of relapse. Absence of benefit in a node negative population is almost certainly due to lack of events, reflecting better prognosis, not true lack of efficacy of the agent. Nonetheless reasonable to exclude this node negative group as lower risk therefore less benefit regardless, and less unmet need.

2) IDFS

IDFS is a well-established endpoint in EBC studies, where long term impact on OS may be many years in maturing.

3) Neoadjuvant setting and pCR.

I am not sure the discussions around pathCR and neoadjuvant therapy are particularly relevant to the discussion of adjuvant pertuzumab. They relate to a study not-powered to detect an impact on survival endpoints. The focus should be on the APHINITY data.

Comments on the ACD received from the public through the NICE website

Name	[redacted]
Role	NHS Professional
Other role	Consultant breast surgeon
Organisation	
Location	England
Conflict	No
Notes	I have previously received an honorarium from Roche

Comments on the ACD:

Comments relating to NICE 2nd ACD for adjuvant PerjetaÂ®(pertuzumab) for patients with HER2+ early breast cancer at high risk of recurrence.

I would like to raise the attention of the committee to 2 areas of concern I have regarding the latest assessment of Adjuvant Perjeta. The first Area of concern is the approach towards the use of the data from the APHINITY Trial as the basis of not supporting the application. This was a positive trial all be it a small impact in the ITT group. When considering the use of a therapy with a small impact over a whole trial population it is entirely valid to begin to look at the sub-groups that may well be deriving this benefit. We understand that patients with node positive disease have the highest risk of local and distant failure and this trial demonstrated in a sub group analysis that these are indeed the patients most likely to be deriving the benefit. This benefit is the basis of the adjuvant licencing of Perjeta hence it is entirely in keeping to consider the therapy in line with its approved licencing. There are a number of examples of NICE therapy approvals based on sub-groups not statistically powered to detect an effect such as the approval of Imatinib for KIT positive GIST. The definitive value of any cancer treatment has to be based upon overall survival (OS.) What we know about the modern management of breast cancer is that advances in primary oncological treatments are reducing the OS events in all modern trials. This in turn has pushed back the length of time that trials have to be followed up to demonstrate OS benefit. The data in the APHINITY trial is too immature to derive the conclusion that there is no OS benefit. In this setting the surrogate of IDFS show be adopted and the improvement if outcome for this measure in the node positive group is clinically significant and represents a tangible benefit for these patients.

The second area of concern is the expert opinion given to the committee by Professor Viadya. I would like to highlight the fact that his opinion regarding the neo-adjuvant therapy approach to the management of breast cancer is completely out of step and contradicts the vast majority of surgeons and oncologists with experience in managing this disease. This has been highlighted by the responses to his recent BMJ article on this subject which was thoroughly refuted by expert groups from across the UK, Europe and the USA. (see responses to https://doi.org/10.1136/bmj.j5913) His point of view was also challenged and dismissed at the session â€œNeoadjuvant chemotherapy: Addressing the mythsâ€ at the ABS conference in June 2018 (https://video.associationofbreastsurgery.org.uk/webcast2018birmingham/Session16/1100Untch/index.html) I would suggest that his opinion on this subject is at best regarded as a personal opinion not representative of the wider breast cancer expert community.

Name	[redacted]
Role	NHS Professional
Other role	Professor of Surgery and Consultant Surgeon
Organisation	Association of Breast Surgery
Location	Scotland
Conflict	No
Notes	n/a

Comments on the ACD:

1.

Breast cancer in many patients has metastasised by the time of diagnosis so the only way to improve the outcome of these patients is to give effective systemic therapy. It is important biologically to stop cancers proliferating. One consequence of proliferation is the development of new clones. A characteristic feature of a cancer cell is the failure to copy DNA without developing more mutations and deletions. So cancer therapy is essentially targeted at stopping proliferation and stopping the development of new generations of cancer cells with more mutations some of which render the cancer resistant to a particular therapy. The fundamental lesson we have learnt in cancer is to give the most effective therapies up front as once resistant clones develop then cure is very unlikely. Once a therapy has been identified to be effective then the only way that that therapy will improve outcome is for it to be used at diagnosis and the idea of limiting a drugs to the metastatic setting once a drug has been shown to improve cancer outcomes makes no biological sense. Pertuzumab has been shown to be effective at eliminating cancers in the neoadjuvant setting. Consistent with this finding pertuzumab in the adjuvant setting also improves outcomes. The data supporting these statements have been very extensively documented above by many others.

2.

My role as I see it is to defend the position that one can rely on evidence from neoadjuvant trials and that improvements in outcomes in the neoadjuvant setting can be used to reliably identify drugs that will improve patients outcomes in the adjuvant setting. It is also illogical to believe that a drug is effective in the neoadjuvant setting but should not also be available in the adjuvant setting. Pertuzumab in addition to trastuzumab clearly improves the rate of complete pathological responses (cPR) in the neoadjuvant setting (see data from NeoSphere and Tryphaena studies). The Aphinity study in the adjuvant setting included many lower risk patients but clearly shows that the results seen in the neoadjuvant setting do translate in to better outcomes. The absolute improvements with the addition of pertuzumab are commensurate with that expected given the low risk of the overall population of many of the patients included in the study. The risk profile of the patients in the neoadjuvant setting was much higher so the absolute benefits are greater. In aphinity the improvement in outcome was seen to be greater in the node positive population.

3.

In locally advanced breast cancer neoadjuvant systemic therapy is now standard care and has revolutionised the outcome of many patients particularly those with inflammatory breast cancer. Following the studies that have shown that neoadjuvant chemotherapy (NACT) +/- trastuzumab and pertuzumab produces high rates of complete pathological response (pCR), its use has been increasing and guidelines for patient selection and its use are now in place. The increasing rates of pCR has also allowed increasing numbers of women to preserve their breast and have less extensive breast and axillary surgery. This in itself is associated with significant cost savings as there is no need for breast reconstruction (Sang et al 2014).

4.

There are two major concerns raised by Vaidya in his evidence as a BASO advisor that I would like to address. Specifically Vaidya advises first that pCR after NACT +/- trastuzumab and pertuzumab does not translate into better outcomes

1. Does pathological complete response (pCR) related to improved survival?

Prospective randomized trials have shown that those patients who had a pCR after neoadjuvant chemotherapy have much better long term outcomes than patients with residual disease (Fisher et al, 1997). Following the first generation of NACT trials, studies that included the monoclonal antibodies trastuzumab and pertuzumab that target HER2 showed a dramatic increase in the pCR rate from less than 20 % to about 40-45% with trastuzumab alone and over 60% with the trastuzumab and pertuzumab and this improvement in pCR rate does translate to a significant increase in disease free and overall survival, demonstrating that pCR is an excellent surrogate marker for long term outcome in this patient group (Earl et al 2015, Gianni et al 2014, Schneeweiss et al 2013, 2018, Untch et al 2011). The largest worldwide meta-analysis of prospective randomized trials with NACT showed an excellent correlation of pCR with disease free and overall survival particularly in patients who had triple negative or HER2-positive tumours (Cortazar et al 2014). The St. Gallen Consensus Meeting panelists 2017 voted with a large majority in favour NACT with the addition of anti-HER2 therapies as the preferred option for patients with HER2 positive early breast cancer and for NACT in patients with triple negative tumors (Curigliano et al 2017). NACT has the potential to improve outcomes of breast cancer patients by using pCR as a surrogate marker for DFS and OS (Schneeweiss et al 2017, Untch et al 2016).

Information on response to chemotherapy from NACT trials has triggered a new generation of postneoadjuvant trials: the first one is coming from Japan showed a survival benefit in those patients who had NACT and had residual disease in the breast and/or in the ipsilateral axillary lymph nodes and received additional Capecitabine chemotherapy after NACT (Masuda et al 2017). This has also led to a strong recommendation by more than 90% of the International St. Gallen Committee members for postneoadjuvant Capecitabine in patients who have triple negative breast cancer and have a residual disease of greater than 1 cm or positive nodes after NACT (Curigliano et al 2017).

The newest generation of postneoadjuvant trials includes the KATHERINE study of patients with HER2-positive tumors and residual tumour in the breast and or in the lymph nodes after optimal NACT including anti-HER2 therapy with patients being randomized to standard anti-HER2 postoperative treatment versus treatment against HER2 with the antibody conjugate TDM1. This study will be presented in San Antonio in December 2018.

This and other trials have been possible only by identifying patients with disease resistant to standard current treatment regimens. The view that neoadjuvant treatment has not contributed to our understanding and improved outcomes is clearly incorrect and the view that NACT +/- trastuzumab + pertuzumab should be abandoned as suggested by Vaidya in the BMJ recently is very clearly not evidence based and clearly is against international opinion.

5.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted a meta-analysis of the early trials comparing adjuvant vs neoadjuvant chemotherapy (EBCTCG Lancet 2017). They did report that there was an increase in local recurrence rate (LRR) at 10 years of 17.9% in the NAC group vs 13.2% in the adjuvant group, although there was importantly no difference in overall survival between groups. There are a number of issues with the early trials included in this analysis:

1. In the two trials the majority of patients after NACT had no surgery. In these 2 trials there was a much higher LRR at 10 years in the NACT group (33.7%) compared with the adjuvant group (20.4%). This compares with the groups who had surgery 15.1% after NACT vs 11.9% following adjuvant chemotherapy. A difference of 13.3% without surgery and only 3.2% with surgery.

2. There was no marking of the tumour prior to surgery in any of these trials so in patients who had a clinical response after NACT the surgeon was uncertain where in the breast the tumour was and may have missed residual invasive cancer after NACT. This was clearly not an issue in the adjuvant group

3. Trial entry was from 1983 to 2002 with most patients being enrolled between 1983 and 1989. During this period there were high rates of in-breast tumour recurrence (IBTR) in published series of patients treated by breast conserving surgery (BCS) and in meta analyses of trials comparing mastectomy with BCS, there was a significantly higher rates of local recurrence with BCS compared with mastectomy (ECBCTG 2005). Local Recurrence rates in 2018 are dramatically less than they were from 1983-200 and there is no longer an excess of local recurrences after BCS than after mastectomy. Since 1983 the 10 year rate of IBTR after BCS in Edinburgh has fallen from 12.4% to 2.3%, an absolute reduction of 10.1% and a relative reduction of 82%.

6.

4. In the NACT group in the EBCTG analysis there were 1.32 times more patients in the NACT group who had BCS. Patients in the NACT group with low ER tumours had a significantly excess of BCS. Patients at young age and those with ER negative tumours are significantly more likely to be BRCA1 and BRCA2 gene mutation carriers (Nillson et al 2014). Such patients are at significantly greater risk of IBTR than non-gene carriers. Patients in the adjuvant arm who were mutation carriers were more likely to have had a mastectomy and so would not have been at the risk of developing IBTR. In the NACT group such women who often respond well to NACT and so would have had BCS and thus would be at increasing risk of second cancers in the conserved breast.

5. LRR was defined by ECTCG as in-breast tumour recurrence, chest wall recurrence, axillary and supraclavicular fossa recurrence. NACT sterilises axillary nodes in up to 40% of patients (Boughey 2013). Node status influences the extent of any local radiotherapy after surgery. There is likely to have been differences in the use of radiotherapy to regional nodes between the NACT and adjuvant chemotherapy arms and this will have influenced LRR. No details of radiotherapy given were available to the EBCTCG and this is a weakness of the study.

6. The complete clinical response rate in the EBTCG analysis was 28% but the pCR rate was much lower and varied from 5.9 to 18% with a median of <10%. This is much lower than

the modern rates of pCR. In Gepartrio young women with triple negative cancers had a 57% rate of pCR (Huober et al 2010). In Tryphaena 12 weeks of chemotherapy and anti HER2 blockade with trastuzumab and pertuzumab resulted in an overall pCR rate of well over 50% with some groups having rate of pCR rate of over 80% (Schneeweiss et al 2014, 2018). There was no analysis of outcome versus pathological complete response rates in the EBCTCG. Rates of LRR in patients obtaining a pCR are exceeding low and in Tryphaena the Hazard ratio of events in the pCR vs non pCR group was 0.27 (Schneeweiss et al 2018). This shows the benefit of the neoadjuvant approach and completely justifies the licence for the use of neoadjuvant pertuzumab and shows that there is indeed a correlation between pCR and outcome completely contrary to the views expressed by Vaidya.

7. There was inconsistent in the use of endocrine therapy in the studies included in the EBCTG analysis. In the National Surgical Breast and Bowel Project (NSABPB) 18 study no tamoxifen was given in women under 50 and yet women under 50 had an IBTR after BCS of 13.1% compared to the 5.2% in patients over 50 who received tamoxifen (Mamounas et al 2007, 2012, 2017). IBTR is reduced by over 50% with tamoxifen alone and by almost 75% when tamoxifen is combined with extended therapy. In NSABP B27 tamoxifen was given to younger women and there was no excess of IBTR in the NACT group (Mamounas et al 2012).

8. The chemotherapy regimens used in most of the studies included in the EBCTCG analysis are no longer in clinical use. Systemic therapy has a major role in preventing LRR. The NSABP B27 study was not included in the EBTCG analysis and looked at the addition of docetaxel to anthracyclines given as pre-operative chemotherapy (Mamounas et al 2007, 2012). In this study there was a significant reduction in the 10 year LRR in patients who received docetaxel in addition to anthracyclines before surgery (8.5% p=0.02 versus the anthracycline arm alone). The importance of systemic therapies in reducing LR is also evident for the work of Kies et al 2012 where the addition of trastuzumab given as adjuvant reduced IBTR from 7% to 1% at three years to 1% at three years.

7.

More effective NACT regimens have gradually increased the rate of pCR and allowed increasing numbers of women to have BCS. A recent systemic review of meta-analysis of oncological outcomes in patients having a pCR after NACT showed a highly significant reduction in local relapse free survival with a risk ratio of 0.59 (95% CI 0.38-0.92) p=0.02 (Li et al 2017). This is clear current evidence that pCR is an important endpoint and Can be relied on to predict patient outcomes (Yee et al 2017).

More recent studies have now shown better survival outcomes for BCS than mastectomy so there should no longer be the concern that NACT increases the rate BCS, because BCS followed by whole breast radiotherapy may have better outcomes than mastectomy (Johns et al 2017). A recent meta-analysis of a comparison of BCS and mastectomy in patients locally advanced breast cancer who have good responses to NACT showed a lower distant recurrence rate, in women having BCS compared with those having mastectomy, OR 0.51 95% CI 0.42-0.63 p<0.01 (Sun et al 2018). There were also improvements for the BCS group in disease free survival OR 2.35 (95% CI 1.84-3.01) p<0.01 and overall survival OR 2.12 (95% CI 1.51-2.98 p<0.01). There was also a non-significant lower rate of local recurrence than in patients having BCS, OR 0.83 (95% CI 0.6-1.15).

8.

Better NACT and dual HER2 regimens with pertuzumab and trastuzumab have resulted in dramatic improvements in pathological complete response rates with neoadjuvant chemotherapy. This is now being translated into lower rates of local recurrence. Early studies included in the EBCTCG analysis are no longer relevant to current practice. The view that we should return to surgery and adjuvant chemotherapy as advised by Vaidya and colleagues is not well supported by evidence (Dixon et al 2018, Macpherson et al 2018).

In summary in relation to the neoadjuvant use of pertuzumab the view by Vaidya that NICE should reconsider its use of pertuzumab in the neoadjuvant setting is not based on the current evidence of patients managed in 2018. It ignores the majority of the literature. There is absolutely no need for NICE to reconsider neoadjuvant use of pertuzumab. There is in contrast new and increasing evidence of the value of pCR as a predictor of outcome. This is the basis of many trials worldwide. The evidence is such that given the effectiveness of pertuzumab in the neoadjuvant setting and the fact that metastatic breast cancer cannot be cured, pertuzumab should now be available in the adjuvant setting particularly in women at higher risk of metastatic disease such as those women with involved nodes.

9.

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Name	[redacted]
Role	NHS Professional
Other role	Consultant Medical Oncologist
Organisation	
Location	England
Conflict	No
Notes	I have received honoraria for advisory boards, from companies including Roche, Genentech, Easai, Genomic Health, Elli-Lilly

Comments on the ACD:

People with HER2 +ve breast cancer, now enjoy significantly better outcomes as a consequence of the development of highly effective targeted therapy. Indeed, those with HER2-positive disease have a better outcome that those with other types of breast cancer. As the outlook for these people improves, it is axiomatic that further improvements in outcome will be increasingly difficult to demonstrate. Nevertheless, the APHINITY data, clearly demonstrate clinically relevant improvements in longer-term outcomes for those patients with higher-risk HER2 positive breast cancer as defined by conventional prognostic criteria such as node-status and hormone-receptor status. As a result of the statistical analysis plan for the study, these positive results have emerged relatively early in the follow-up of people with early-stage disease and as with other interventions using systemic therapy in the adjuvant setting, it is highly likely that these improvements will be seen to be more substantial with time.

The use of pertuzumab in the adjuvant setting is another important and relevant step in the treatment of this type of breast cancer and in my view, to ignore these benefits would do a disservice to people with early-stage, HER2-positive disease whose chances of remaining disease-free are enhanced by this novel, targeted therapy.

ERG comments on Company's response following ACD 2

Comment 1. Summary of Company's response to ACD 2.

The ERG has no comments on the Company's summary of responses to ACD 2.

Comment 2. NICE recommendation based on a subgroup analysis is not uncommon.

The ERG agrees that NICE recommendations have, when deemed necessary, been made on the basis of subgroup analyses. The ERG's comments are guided by the belief that any recommendations for particular subgroups ought to be underpinned by robust and consistent evidence, supported by clinical and biological plausibility. This evidence should be presented for each clearly defined subgroup of interest, which should in turn be clearly emphasised as key subgroups from the trial inception. In this appraisal, the ERG believes that the company's decision to focus on the node-positive subgroup was not clearly emphasised from the beginning of APHINITY. In our opinion, the company has not presented strong evidence supporting the biological plausibility of a greater effect in the node-positive population compared to the other high-risk subgroups.

Comment 3. Node-negative patients are not considered high risk

The ERG notes that in the von Minckwitz (2017) paper, the node-negative patients in APHINITY are referred to as "high-risk node-negative HER2-positive" patients. It is worth noting that the node negative patients in APHINITY have other high risk features (tumour size >1cm, or tumour size between 0.5 and 1cm with either histological grade 3, HR negative or aged under 35). Similarly, hormone-receptor negative patients are routinely referred to as "high-risk" (including the pertuzumab EMA label and the original company submission), showing inconsistency in the definition of the high-risk population.

Comment 4. Unreasonable weight and focus on interaction test

The ERG believes that appropriate consideration of the interaction test has been presented in ACD2. The ERG are unclear about exactly how the ACD should have interpreted "the totality of the observed data, clinical rationale and biological plausibility" as suggested by the company.

Comment 5. OS is immature to draw solid conclusions at this point in time

The ERG believe the comments on OS by the Committee in ACD2 are appropriate, as they acknowledge immaturity of data, and only make inference in reference to observed period. For example: "*the impact of pertuzumab on overall survival is unknown because data for this outcome are immature."*

Comment 6. Incorporation of a more accurate biosimilar discount in the economic analysis

As stated in ACDs 1 and 2, neither the price nor the market share of biosimilars are definitively known. In the ERG's opinion, it is plausible that the market share of biosimilar trastuzumab is 100% (the Committee and Roche agree on this value). The ERG has no intelligence on manufacturers' level of discount on Herceptin IV, thus we are unable to comment on the accuracy of the discount level put forward by the Company (~70% by the anticipated time of final guidance publication in January 2019). We have checked the ICER values produced on the basis of the Company's amendments following the second appraisal committee meeting (detailed in Table 4 of the submitted CE appendix) and different discount levels of biosimilar trastuzumab (reported in Tables 6-10). These appear to be correct.

Comment 7. Revision of administration costs in the economic analysis.

The ERG considers the NHS Reference Cost Schedule to be a preferable source of unit cost values for chemotherapy administration. The ERG confirms that the version of the NHS Reference Costs Schedule (2016/17) used in the Company's base case analysis and the Company's amendments following the appraisal committee meetings is the latest available version (as of 1st October 2018).

Comment 8. Pertuzumab treatment effect duration

The ERG's position on this point has been made known in the past. Briefly, the ERG agree that it is ultimately unclear what the duration of treatment effect is. We would like to reiterate that under the ERG's assumptions the survival curves widen until 78 months (6.5 years). It is only when the effect is fully waned (i.e., 8 years), that the hazard and transition probability for the two arms are equal, meaning some benefit of pertuzumab is maintained up until this point. Under company assumptions, curves are furthest apart at 109 months (9 years), with some treatment effect maintained until 10 years. Whilst the hazard ratios for each year of follow-up presented by the company demonstrate an increasing benefit of pertuzumab, the company do not present confidence intervals around these estimates, and the ERG are concerned that these estimates may contain considerable uncertainty.

Comment 9. Revised cost-effectiveness analysis

The ERG has assessed the revised cost-effectiveness results provided by the Company in their CE appendix. We can confirm that the ICER values reported in the appendix (Tables 6 – 10) reflect the amendments summarised under Comment 9 in the Company's response (main body). These include an appropriately corrected value for the list price of trastuzumab emtansine, incorporation of trastuzumab biosimilars (market share: 100%, discount over Herceptin IV ranging from 55% to 75%) and the [redacted] Depending on the exact assumptions

made about the incremental treatment effect duration of pertuzumab (including the Company's base case and the ERG's preferred assumptions), the resulting ICER ranges from £9,899 (based on the Company's assumptions about incremental treatment effect and a trastuzumab biosimilar discount of 75%) to £29,645 (based on the ERG's preferred assumption about incremental treatment effect and a trastuzumab biosimilar discount of 55%).