NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pertuzumab in combination with trastuzumab and docetaxel for treating HER2-positive metastatic or locally recurrent unresectable breast cancer [ID523]

Committee Papers – Appraisal Committee Meeting 2 (04/09/13)

NICE National Institute for Health and Care Excellence

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SINGLE TECHNOLOGY APPRAISAL

Pertuzumab in combination with trastuzumab and docetaxel for treating HER2-positive metastatic or locally recurrent unresectable breast cancer [ID523]

Contents:

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

Janet Robertson
National Institute for Health and Care Excellence
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BY EMAIL

28 August 2013

RE: Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2-positive metastatic or locally recurrent unresectable breast cancer, which has not been previously treated, or has relapsed after adjuvant therapy.

Dear Janet,

Thank you for giving us the opportunity to comment on the above ACD. We believe this Appraisal raises a significant issue which requires special consideration by the Appraisal Committee and NICE more broadly.

In this case it is not possible to set any price at which pertuzumab is 'cost-effective'. Even if pertuzumab were provided free of charge the cost/QALY gained associated with its introduction would remain above the range considered acceptable.

Using NICE's current methods and thresholds, and the ERG's preferred assumptions, pertuzumab would not only have to be provided free of charge in order to be granted positive guidance - Roche would have to give the NHS over £100 per vial utilised[1].

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Pertuzumab provides a significant survival advantage – whilst the precise magnitude of this is uncertain, minor extrapolation of the data available indicates the median overall survival gain is likely to be at least 12 months, if not higher.

It is not reasonable to require a manufacturer to pay the NHS over £2,500 per patient in order to grant access to this medicine.

[redacted] We are extremely disappointed with this outcome.

We are committed to working with NICE and the Department of Health to find a long term solution to this problem.

Our response to the ACD is provided under the headings below. We believe the response will inform the Appraisal Committee's considerations and conclusions on:

1) The magnitude of overall survival benefit associated with pertuzumab
2) The generalisability of the CLEOPATRA trial

Due to the issue outlined above this information is unlikely to have a material impact upon the Appraisal Committee's recommendation. However, for completeness and to ensure the final decision is based on the most clinically appropriate ICER, our response is presented below.

Kind Regards

Lee Moore

Lee Moore

1. Estimate based upon base-case ICER and ERG preferred assumption of no post-progression survival gain

Has all the relevant evidence been taken to account?

No. The Appraisal Committee has not considered all evidence relevant to this decision. The primary points of contention within the ACD appear to be:

1) The magnitude of overall survival benefit associated with pertuzumab
2) The generalisability of the CLEOPATRA trial

Evidence relating to these issues is presented below.

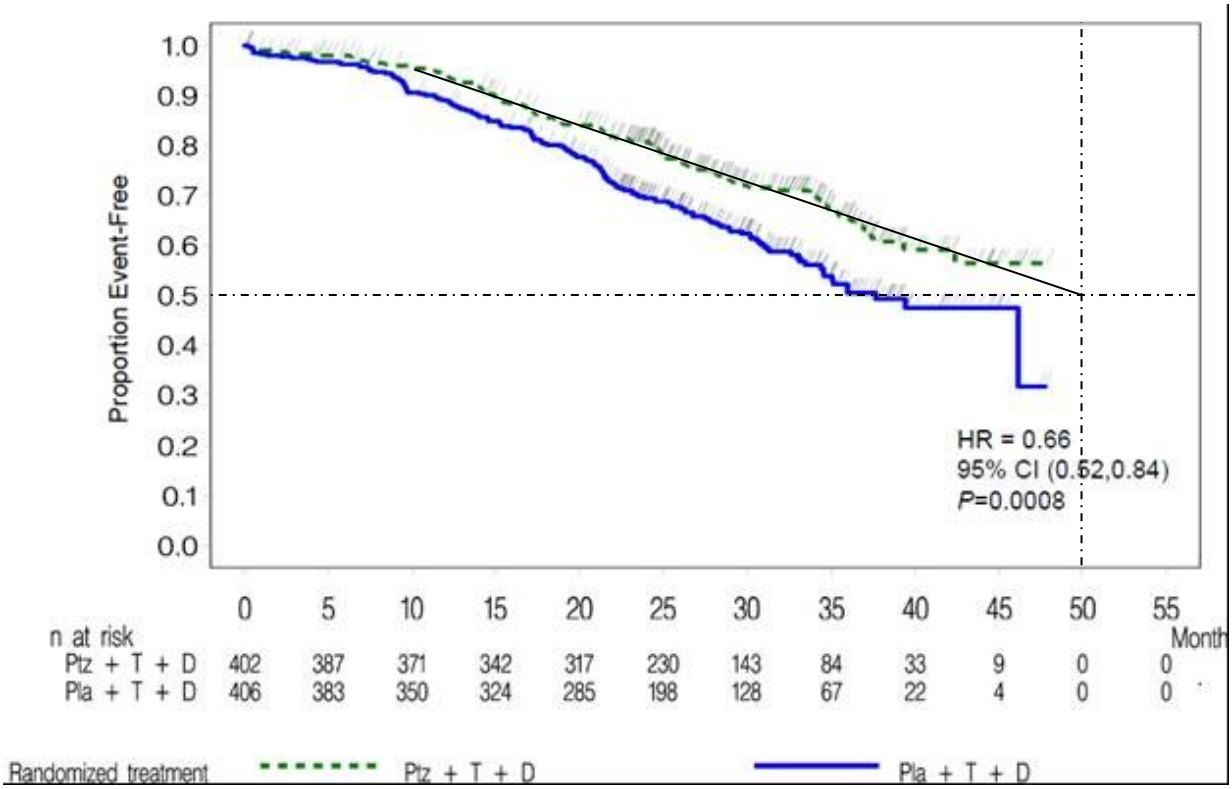
1) The magnitude of Overall Survival benefit associated with pertuzumab

Pertuzumab has been demonstrated to provide a significant increase in overall survival for women with HER2-positive mBC. However, there is currently uncertainty associated with the *precise* magnitude of survival benefit provided (a key determinant of the estimated cost-effectiveness of pertuzumab).

This uncertainty will be reduced significantly when additional data from the CLEOPATRA study becomes available. This is due to happen once 385 women randomized to the pertuzumab arm have died (the number of events required for pre-planned analysis to occur), and is expected to be available in mid-2014. It should be noted that this data will be available 18 months later than initially planned due to the unexpectedly low rate of deaths observed for women receiving pertuzumab. The delay indicates the median survival observed in the pertuzumab arm is likely to be extremely impressive relative to the control arm of 37.6 months.

Whilst median overall survival has not yet been reached in the pertuzumab arm of CLEOPATRA, data is available up to the y-axis value just above the median. If an extremely minor, and crude, extrapolation of this data is conducted it appears clear that median survival in the pertuzumab arm is likely to be around 50 months (compared to 37.6 months in the control arm) – see Figure 1 below.

Figure 1. Minor extrapolation of CLEOPATRA indicates the median survival gain associated with pertuzumab is likely to be over 12 months – double the median PFS gain.



A gain of this magnitude is of substantial importance to women affected by breast cancer, their families and society as a whole.

When compared to a median progression free survival of 6.3 months this predicted median survival gain of over 12 months indicates that pertuzumab provides a ‘carry-over’ effect after disease progression.

The magnitude of benefit associated with pertuzumab after disease progression was a key point of discussion in the first Appraisal Committee Meeting and in the ACD. [redacted]

Given the discussion on this topic in the ACD, the following information is provided below to enable the Appraisal Committee to reconsider the plausibility that pertuzumab provides an overall survival gain longer than a progression-free survival gain:

1.1 Studies featuring HER2 targeted monoclonal antibodies consistently demonstrate OS gains larger than PFS gains

In August 2012, the NICE Decision Support Unit published a review of studies examining the relationship between progression-free survival and overall survival in advanced or metastatic cancer. This report found it was difficult to quantify the precise relationship between PFS and OS and the relationship differs depending upon the disease area and type of intervention.

The report identified a publication (Sherrill et al, 2008) which attempted to quantify the specific relationship between PFS and OS in patients with HER2-positive metastatic breast cancer. This publication included an analysis directly relevant to this appraisal – a comparison of the relationship between gains in PFS and OS in patients treated with HER2 targeted monoclonal antibodies. The report found the OS gain observed in the four studies identified is 50% higher than the gain in PFS.

Importantly this publication, and subsequent report by the DSU, **did not consider the impact of crossover** in these studies.

Two of the trials used in this analysis feature substantial cross-over upon disease progression.

More than **66% of people in Slamon** 2001 and **50% of people in Marty** 2005 crossed over to the trastuzumab containing regimen. Using overall survival data from these trials without appropriate consideration of crossover, results in misattribution of the efficacy of the intervention arms (all of which were HER2 monoclonal antibody containing regimens) to the comparator arm. As a consequence the true effectiveness and resulting relationship between PFS and OS is underestimated in the DSU reported publication.

Table 1 below demonstrates the relationship between median PFS and median OS in the Slamon and Marty studies if adjusting for crossover (albeit using crude censoring methods). When combined with the multipliers observed in the TaNDEM and Blackwell studies discussed in the previous Appraisal Committee Meeting (presented in Table 1 for completeness) it is clear that an OS gain larger than a PFS gain is typical of studies featuring HER2 targeted monoclonal antibodies.

Table 1. Studies featuring HER2 targeted monoclonal antibodies* consistently demonstrate OS gains larger than PFS gains

Trial	Interventions	Median TTP	Median OS	Diff PFS	Diff OS	Multiplier	Notes
Slamon (N Engl J Med, Vol 344, No 11, 2001)	Chemotherapy	4.6	20.3	2.8	4.8	**1.71**	2/3 of patients in the Chemo arm crossed over to receive chemo + trastuzumab
	Chemotherapy + Trastuzumab	7.4	25.1				
Marty (J Clinical Oncology, Vol 23, No 19, 2005)	Docetaxel	6.1	22.7 (16.6)	5.6	8.5 (14.6)	**1.51 (3.7)**	50% of patients in the docetaxel-alone arm crossed over to receive trastuzumab
	Docetaxel + Trastuzumab	11.7	31.2[2]				
TAnDEM - Kaufman (J Clinical Oncology, Vol 27, No 33, 2009)	Anastrozole	3.8	23.9 (17.2)	1.8	4.6 (11.3)	**2.55 (6.2)**	70% of patients in the anastrozole alone arm crossed over to receive trastuzumab
	Anastrozole + Trastuzumab	5.6	28.5 (28.5)				
Her/Lap –Blackwell (J Clinical Oncology, Vol 30, No 21, 2012)	Lapatinib	1.87	9.5	0.69	4.5	**6.49**	52 % of patients in Lapatinib mono arm crossed over to receive combination therapy.
	Lapatinib + Trastuzumab	2.56	14				

*Multiplier values refer to figures without adjustment for crossover, figures in brackets refer to values adjusted for crossover. All values are in months.

In Section 4.5 of the ACD it is stated that 'The Committee considered that it did not necessarily imply that the same effect *(the effect highlighted above)* would also be seen with the addition of pertuzumab to trastuzumab and docetaxel compared with trastuzumab and a taxane alone in metastatic disease'. Although this may be the case, the evidence available indicates that it is highly likely to occur. Even if the differential impact of pertuzumab on PFS and OS is not yet known, the fact that this has been clearly observed in multiple trastuzumab trials, and CLEOPATRA represent a trial where 50% more trastuzumab is given in the intervention arm relative to the comparator arm, there is a clear clinical basis to support this observation.

It is important to note the publication identified by the DSU features data from two trials which included trastuzumab in both arms (as the CLEOPATRA study did).

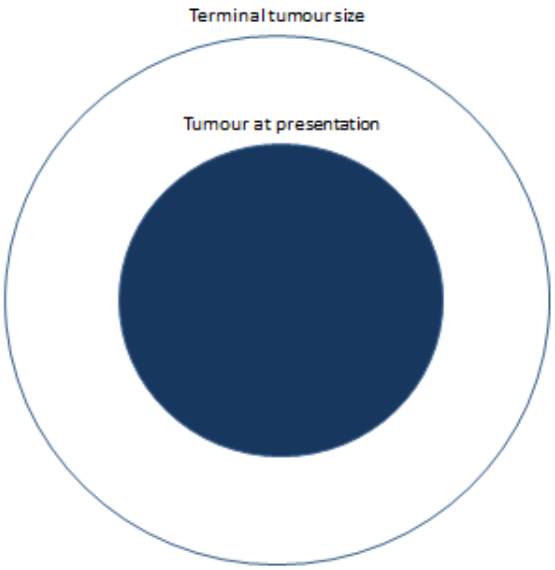
In light of this we believe it is highly likely there is an overall survival gain associated with pertuzumab that is significantly greater than the observed progression-free survival gain (especially when compared to the PFS and OS data available from CLEOPATRA).

1.2 Progression in clinical trials is assessed via the 'RECIST' criteria. This criteria defines progression relative to last observation and not baseline tumour burden. As a result patients who respond to treatment have a smaller tumour burden at the point of progression and take longer to die after progression, on average, than patients who do not respond.

In simple terms, death from metastatic disease is associated with tumour burden – when the total tumour burden reaches a critical level the patient is overwhelmed by it and dies (Figure 2). Therefore, it is reasonable to expect a tumour that is currently large to kill a patient more quickly than one that is currently small if both are progressing unchecked.

In a large randomised study like CLEOPATRA, it is further reasonable to assume that participants in both study groups had a similar average tumour burden at baseline and, if untreated, would progress to a terminal tumour bulk and die at the same rate.

Figure 2: Representation of the growth needed before a patient's tumour reaches a lethal burden



In clinical trials, tumour progression after treatment is determined by growth relative to the last assessment of disease status rather than baseline tumour bulk. Using RECIST criteria, progressive disease requires a 25% increase in tumour diameter. So, for a patient who has had a good response (high degree of tumour shrinkage) to treatment, progression will require only a small absolute increase in size on a much reduced baseline, so that immediately after progression their tumour is much smaller than it was at the start of therapy and further away from reaching a lethal tumour mass (Figures 3 and 4).

Figure 3: After a response to treatment tumour burden is lower than at presentation

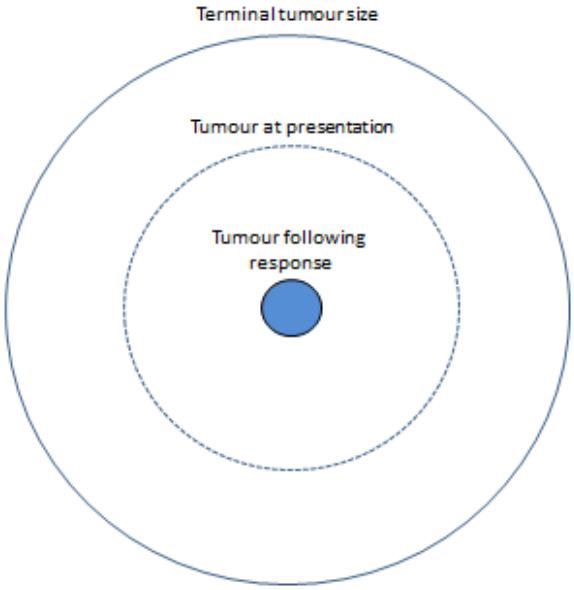
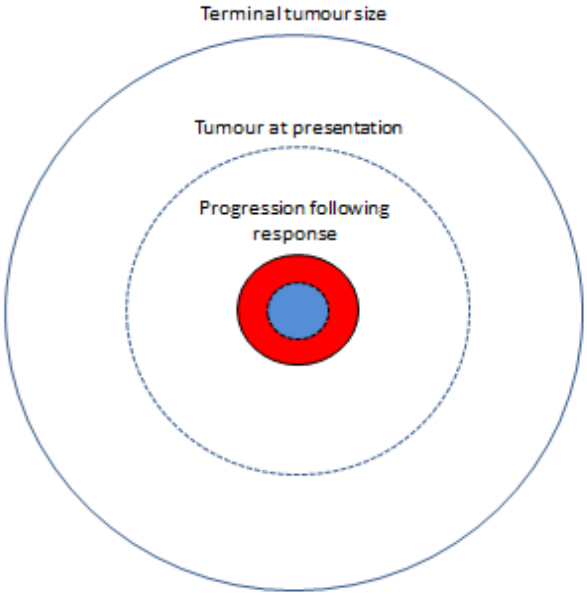


Figure 4: Immediately after progression a patient who had a good response still has a much lower tumour burden that at presentation and is further away from reaching a lethal tumour mass



By contrast, a patient experiencing only disease stabilisation will have a tumour 25% bigger than it was at the start of therapy before they are deemed to have disease progression (Figures 5 and 6). Subsequently, this patient will be closer to achieving a lethal tumour bulk than at presentation.

Figure 5: Patient with disease stabilization remains as close to a lethal tumour bulk as they were at presentation

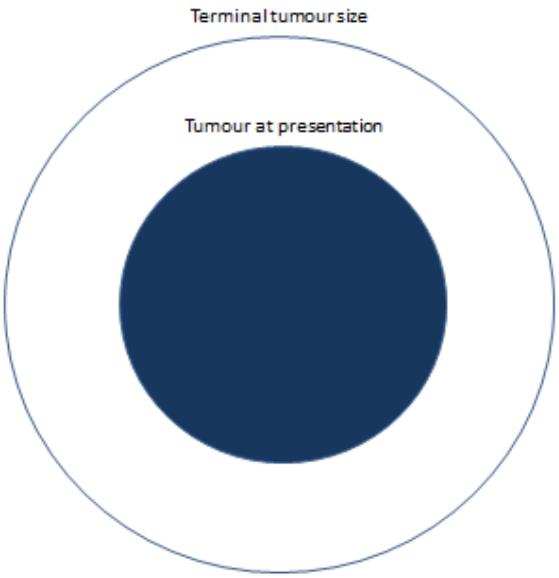
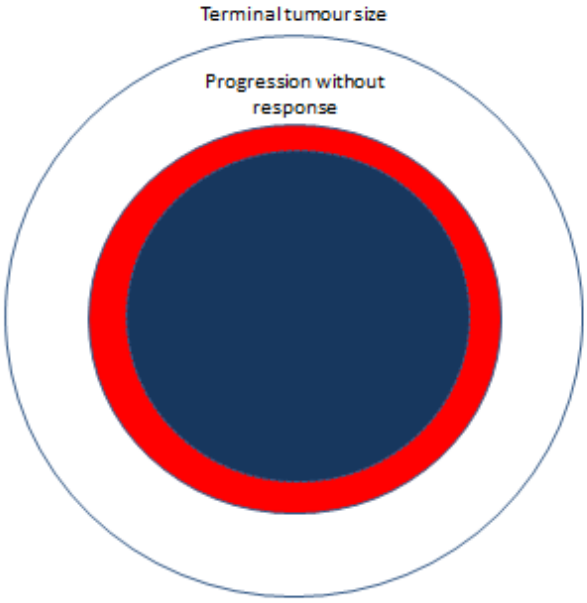


Figure 6: Patient with disease stabilization is closer to achieving a lethal tumour bulk than they were at presentation, as soon as they start to progress



Assuming that, regardless of pre-progression treatment, a patient's tumour will grow to a terminal bulk at the same rate once it is deemed to have progressed, it is clear that patients with objective responses will take longer, post-progression, to reach terminal tumour size and succumb to their

disease than those whose disease is only stabilised during treatment or progressed through therapy.

In the CLEOPATRA study the objective response rate in the pertuzumab-based group was 80.2% compared with 69.3% in the group treated with trastuzumab and docetaxel alone, a statistically significant difference of 10.8 percentage points (95% CI: 4.2,17.5; P=0.001). More patients treated with pertuzumab-based therapy, therefore, experienced tumour shrinkage that qualified as a partial response or complete response (disappearance of all signs of tumour by the imaging technique used at baseline) by RECIST criteria compared to those in the control group. In fact, in the pertuzumab-based arm 74.6% of patients achieved a partial response and 5.5% achieved a complete response compared with the trastuzumab and docetaxel group where only 65.2% achieved a partial response and 4.2% a complete response.

One would expect, therefore, the average patient treated with pertuzumab-based therapy to have a much smaller tumour bulk at the point of disease progression than the average patient treated with trastuzumab and docetaxel alone and to live longer from progression to death. For pertuzumab-based treatment patients not to live longer post-progression one would have to postulate that the drug somehow speeds up tumour growth beyond that which would have occurred had it not been given once administration is terminated. To date, no evidence for such an effect has been presented, nor has any plausible hypothesis supporting it been proposed.

In summary, because patients treated with pertuzumab-based therapy have a lower tumour burden at progression it is to be expected that they will have a longer post-progression survival with some conservation of treatment benefit post-progression.

We believe that greater magnitude of tumour shrinkage provides the rationale for expecting pertuzumab-based therapy to be associated with better post-progression survival than trastuzumab and docetaxel alone – something supported by the PFS and OS data from the CLEOPATRA study and the multiple other studies featuring HER2 targeted monoclonal antibodies.

However, there is one fundamental issue with this prediction. The post-progression survival Kaplan-Meier data from the CLEOPATRA study shows two curves that perfectly overlap. This appears counterintuitive given the actual PFS and OS data available.

1.3 The post-progression survival Kaplan Meier curves from CLEOPATRA are non-randomised, and highly immature – as a result it is not possible to draw inference about the influence of pertuzumab upon post-progression survival based upon this data

The PPS KM data from CLEOPATRA are highly immature - only 25% of people in the PTD arm and 35% of people in the TD arm have had an event in PPS health state. Based upon the data previously presented to the Appraisal Committee the immaturity of this data may not have been clearly apparent. As a result whilst the KM curves *appear* relatively complete they are based upon only upon a subset of patients within the study and should be interpreted with caution.

In addition it should be noted that patients were not randomized to the two arms of the PPS curve - due to the fact that pertuzumab influences the time of disease progression. It is highly likely that the two patient groups compared in the two arms of these curves are heterogeneous. The intervention arm is likely to feature those patients with only the highest risk disease (as they have progressed at the time of data cut-off despite being treated with pertuzumab) whilst the comparator arm contains a broader mix of patients (featuring those patients with the highest risk disease and a group with lower risk disease who may not yet have progressed on pertuzumab).

Given the immaturity of this data, the lack of randomisation and clear source of bias between the two arms we strongly question the validity of using this PPS data in economic modeling.

2 The generalisability of the CLEOPATRA trial

As detailed in our submission, the proportion of the CLEOPATRA study population that had received prior (neo) adjuvant trastuzumab treatment was lower than could be expected compared with the current standard of care in England and Wales. Of the recruited population, 10.1% (41 people) in the trastuzumab and docetaxel group and 11.7% (47 people) in the pertuzumab-based group had received prior trastuzumab in the (neo) adjuvant setting. Most of these 88 individuals came from the EU or North America. This prior usage of trastuzumab reflects the timing of trial recruitment and global nature of the study: the lack of availability of trastuzumab in some regions of the world during the recruitment period (2008-2010); the licensing of trastuzumab for adjuvant use in the EU in mid-2006 and the requirement for a disease free interval of at least 12 months from completion of adjuvant treatment to study entry would have resulted in relatively few eligible patients who had received prior trastuzumab.

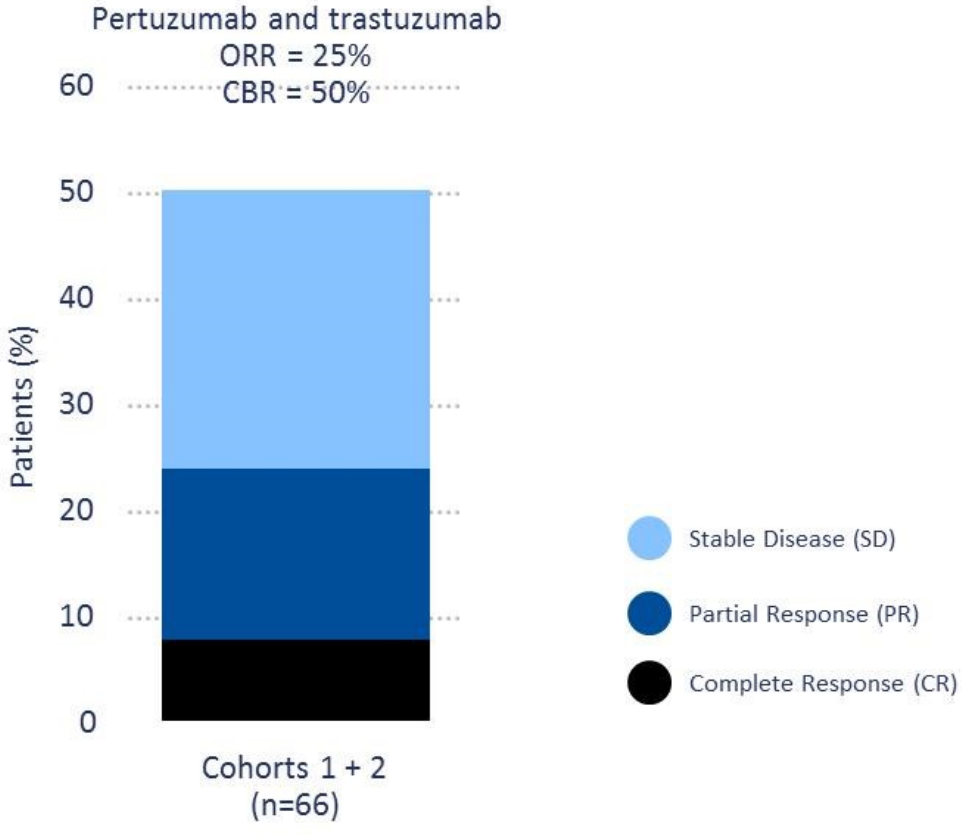
The benefit of pertuzumab-based treatment for this sub-group of participants was investigated in an exploratory *post-hoc* analysis, which showed remarkably similar point estimates for

progression-free survival for people who received prior trastuzumab, HR 0.62 (95% CI: 0.35; 1.07) compared with the overall participant population, HR 0.62 (96% CI: 0.51; 0.75). This was supported by the overall survival results with the prior trastuzumab subgroup, HR 0.68 (96% CI: 0.3; 1.55) comparable with the study population, HR 0.66 (95% CI: 0.52; 0.84).

Moreover, the supporting study BO17929 demonstrated the activity of pertuzumab in people pre-treated with trastuzumab, albeit in the metastatic setting (Baselga et al 2010, Cortes et al 2012). This study was a phase II single-arm study of the safety and efficacy of pertuzumab and trastuzumab in HER2-positive participants with metastatic breast cancer who had received up to three previous chemotherapy lines in the metastatic setting and who had experienced disease progression on trastuzumab-based therapy as the last treatment prior to study entry.

Two initial cohorts (a total of 66 patients) who had experienced disease progression whilst receiving trastuzumab were continued on trastuzumab with the addition of pertuzumab. In these two cohorts combined, 24% of patients responded to therapy (12 [18%] with partial response and 4 [6%] with complete response). A further 17 individuals (26%) experienced stable disease lasting at least 6 months or 8 cycles (Figure 7).

Figure 7: Response rates in cohorts 1 and 2 of study BO17929



ORR - overall response rate; CBR - clinical benefit rate

Despite the advanced disease setting for this study, these results demonstrate an impressive clinical benefit rate of 50% for people receiving pertuzumab and trastuzumab together after just having progressed on trastuzumab-based treatment.

In summary, the benefit of pertuzumab-based treatment for people previously treated with trastuzumab is supported by the *post-hoc* analysis from the CLEOPATRA study showing comparable efficacy, for both progression-free survival and overall survival, between the sub-group of participants pre-treated with trastuzumab and the overall study population. Further reassurance is provided by the BO17929 study that documented the activity of pertuzumab and trastuzumab in people pre-treated with trastuzumab in the metastatic setting.

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

The summaries of clinical and cost effectiveness should be updated to reflect the information highlighted above.

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

Recent studies indicate that society has a preference for QALYs gained in people with a high burden of illness (such as women with metastatic breast cancer). We do not believe this preference is appropriately considered within the current Technology Appraisal process. As a result we question whether the current Technology Appraisal process is capable of issuing sound and suitable guidance to the NHS – guidance that does not appropriately reflect the views of society cannot be regarded as sound and suitable.

Furthermore, using NICE's current methods and thresholds, and the ERG's preferred assumptions, pertuzumab would not only have to be provided free of charge in order to be granted positive guidance - Roche would have to give the NHS over £100 per vial utilised.

Pertuzumab provides a significant survival advantage – whilst the precise magnitude of this is uncertain, minor extrapolation of the data available indicates the median overall survival gain is likely to be at least 12 months, if not higher.

It is not reasonable to require a manufacturer to pay the NHS over £2,500 per patient in order to grant access to this medicine. As a result we do not believe the provisional recommendations are a reasonable basis for the issuance of guidance to the NHS.

4. Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?

None that we are aware of.

References

Baselga J et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. J Clin Oncol 2010; 28(7):1138-1144.

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BREAKTHROUGH BREAST CANCER

Bijal Joshi
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9th August 2013

Dear Mrs Joshi,

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer

Breakthrough Breast Cancer is dedicated to saving lives through improving early diagnosis, developing new treatments and preventing all types of breast cancer. Breakthrough welcomes the opportunity to contribute to NICE's consideration of pertuzumab both through providing input from the patient perspective at the NICE committee meetings and responding to this appraisal consultation document. However, we are very disappointed that, despite hearing about the benefit which this drug can provide for patients, NICE has been unable to recommend pertuzumab in its draft decision.

This decision will come as a blow to the women who could benefit from more quality time with their loved ones as a result of taking the drug. Treatment options for women with locally recurrent or metastatic breast cancer are limited. Evidence shows pertuzumab offers more time with a good quality of life and is therefore hugely significant for women with this type of disease.

Has all of the relevant evidence been taken into account?

The committee considered clinical evidence from the CLEOPATRA trial, comparing pertuzumab plus trastuzumab and docetaxel with trastuzumab and docetaxel alone. The primary end point in this trial was progression-free survival (PFS) and results showed that the addition of pertuzumab to the treatment regime resulted in PFS being extended by over 6 months. Trial data also showed that a greater percentage of patients had an objective response in the pertuzumab arm (80% vs. 69%). From the patient perspective, these data represent a huge gain. During the time in which the disease is stable, patients are able to get on with their daily lives and spend good quality time with their loved ones before their disease progresses and their symptoms become worse. We know from our work with patients that those with metastatic breast cancer greatly value treatments which help them control their disease for longer, and allow them to maintain a good quality of life.

'Simply put, length of life is only worth having if there is quality of life as well.'
Breakthrough Supporter, in response to a survey about metastatic breast cancer

The committee also considered data from the trial relating to overall survival (OS). Breakthrough Breast Cancer acknowledges that mature data on the magnitude of the gain in OS is not yet available. However, we believe the committee has not adequately considered the reason why this data is not available; treatment with pertuzumab has been so successful that median OS had yet to be reached in this arm at the latest data cut off in May 2012. Nonetheless, data from the May 2012 interim analysis demonstrates a statistically significant benefit in OS for patients in the pertuzumab arm compared with the control arm. Breakthrough Breast Cancer feels that the committee failed to acknowledge this and focussed only on the exact magnitude of the potential gain in OS. This was particularly apparent in the press statement issued by NICE which stated that the evidence was 'not robust enough' to be able to judge the gain in OS. We disagree and feel that the evidence robustly demonstrates a significant gain in OS. A gain in OS cannot be accurately calculated at this time because treatment with pertuzumab has had such a substantial benefit that not enough people have died in this arm of the trial yet. This in no way indicates a lack of 'robustness' in the data from the CLEOPATRA trial. Breakthrough Breast Cancer is also concerned about what this focus on the extent of the gain in OS, means for appraisal of drugs for metastatic breast cancer in the future if NICE is unwilling to approve drugs without final OS data.

Furthermore, this approach underestimates the importance of PFS for patients. These patients know that they have a terminal diagnosis. What they are looking for are treatments which can delay progression and allow them to continue to live full lives for as long as possible with as few symptoms and side effects as possible. They are looking for treatments which will allow them to make the most of the time they have left.

'When people know they have a terminal diagnosis every extra day is so important. This has to be balanced by the impact on their quality of life. If the drug causes too many side effects the additional time gained may not be the quality time they need.'
Breakthrough Supporter, in response to a survey about metastatic breast cancer

What is remarkable is that treatment with pertuzumab significantly increases PFS and OS with no significant additional side effects, allowing patients to do just that. We urge the committee not to underestimate the huge advance in treatment that pertuzumab represents for patients with HER2+ metastatic disease.

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

We are aware that the committee has expressed concerns about the applicability and generalisability of the CLEOPATRA trial data to UK clinical practice. It was deemed that there were considerable differences between the CLEOPATRA trial population and people currently receiving treatment for HER2+ metastatic breast cancer in the NHS. This was because only 11% of the population in the CLEOPATRA trial had received previous treatment with trastuzumab in the adjuvant setting, compared to the approximately 90% of patients with HER2+ who would receive trastuzumab to treat their early breast cancer in the NHS. However, we feel that this is an indirect and misleading comparison.

Although around 90% of patients receive trastuzumab to treat early HER2+ breast cancer, these will not all be the same population of patients who would receive treatment with pertuzumab for metastatic disease. We have spoken to three breast cancer oncologists who believe that around 25-50% of patients eligible for pertuzumab treatment for metastatic disease would not have received prior trastuzumab treatment for early breast cancer. This group would be made up mostly of patients whose disease is diagnosed only once it has already become metastatic and who therefore would not have had any prior treatment for breast cancer, but also by some patients who have relapsed but who were not treated with trastuzumab in the adjuvant setting because their primary breast cancer occurred prior to the introduction of trastuzumab to treat the disease in its early stages.

Furthermore, for those patients who would have previously received trastuzumab in the adjuvant setting, the additional analysis requested at the time of licensing by the Committee for Medicinal Products for Human Use (CHMP) indicated that the results were consistent with those for the general trial population, and this was accepted by the CHMP. Whilst we appreciate that this group was small compared to the whole trial population, there was no indication from the data that pertuzumab would be less effective in this group of patients. In addition, we draw the committee's attention to the fact that trastuzumab is prescribed for patients with HER2+ metastatic disease regardless of whether they have received it in the adjuvant setting, and it continues to be effective in these patients. This supports a role for HER2 targeted therapies in patients previously treated with trastuzumab.

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

Breakthrough Breast Cancer appreciates that NICE has a difficult task when appraising drugs and that pertuzumab is simply too expensive at the current price; however the committee has acknowledged that this drug is innovative and that these kinds of treatments are important to patients who could benefit.

We are deeply concerned that such a drug, which has been demonstrated to be clinically effective, has not been approved in this draft decision. We acknowledge that the NHS has finite resources and that difficult decisions must sometimes be made. However, the system in its current form simply does not work for patients with metastatic breast cancer. We feel that a system which allows ground-breaking

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new drugs to be rejected is fundamentally flawed; the UK risks falling far behind in its standards of cancer treatment if these kinds of drugs cannot be made routinely available.

General comments

Breakthrough Breast Cancer feels that this draft decision is part of a wider problem around access to drugs; this is the second extremely promising breast cancer drug to be rejected by NICE in a month. We are also concerned about the outcome for other drugs that are coming up for approval in the near future which also show a lot of promise. The rejection of two exciting new drugs in quick succession indicates that the future may be bleak for advances in the treatment of metastatic breast cancer in the UK unless changes to the system are implemented. We know that the Government is currently looking at the way that drugs are priced and we urge the Government, the pharmaceutical industry, and NICE to work together to make sure that the changes implemented result in drugs like pertuzumab being made routinely available on the NHS.

If you have any questions or wish to discuss any of the aspects of this submission, please don't hesitate to contact me.

Kind regards,

Senior Policy Officer

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Patron HRH The Prince of Wales

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

Role	Public
Location	England
Conflict	no
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	This is not discriminatory on the grounds of gender, disabililty etc. However it does penalise those who are receiving their diagnosis late. The access to the treatment is not equitable.
Section 2 (The technology)	A Social Return on Investment exercise with the patients that are benefiting from the treatment and their families may demonstrate the real value for money of the treatment. I would suggest that negotiating with drug manufacturers and working with cancer charities to lobby for fairer pricing should be prioritised. If Pertusumab is not made available on the nhs for new patients it is only those that can afford private treatment that will be able to access it. Again this in inequitable. I would suggest that the continuation of this treatment would prove better value for money that continuing the contracts of overpaid senior managers in the health sector.
Section 3 (The manufacturer's submission)	I would suggest a Â trial is needed over a more prolonged period to establish stronger data.
Section 5 (Implementation)	It seems that the treatment would benefit from a UK based trial that reflects current clinical practice to establish a better indication of the effects that it is likely to have on patients treated within the UK. The views of the patients should be given greater weight than the trial results. The above text seems to indicate that it would be beneficial to receive further information from the manufacturer about post-progression survival in the trial, and modelling in which PFS and post-progression survival were estimated separately before any assumptions are made about its cost effectiveness and any decisions are made.

Role	Public
Location	Other
Conflict	no
Notes	I have a relative who is currently taking pertuzumab
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Pertuzumab in combination with trastuzumab and docetaxel should be recommended for treating people with human epidermal growth factor receptor 2 (HER2)-positive metastatic or locally recurrent unresectable breast cancer. People currently taking this drug should be allowed to continue to do so on their clinicians advice.
Section 2 (The technology)	No comments on the technology.
Section 3	The combination of pertuzumab plus trastuzumab plus

(The manufacturer's submission)	docetaxel, as compared with placebo plus trastuzumab plus docetaxel, when used as first-line treatment for HER2-positive metastatic breast cancer, significantly prolonged progression-free survival, with no increase in cardiac toxic effects. This treatment should therefore be available for women with HER2-positive metastatic breast cancer.
Section 4 (Consideration of the evidence)	Are there specific groups of people for whom the technology is particularly cost effective? Yes. The fact that that pertuzumab plus trastuzumab and docetaxel offered a benefit in progression-free survival (PFS) and overall survival should mean this drug is funded despite the cost for women who need it. You can not put a cost on people's lives, if this extends the lives of women with advanced breast cancer then it should be approved for use.
Section 5 (Implementation)	No comments
Section 6 (Proposed recommendations for further research)	No comments
Section 7 (Related NICE guidance)	Review should be as soon as possible.

Role	Public
Location	England
Conflict	no
Comments on individual sections of the ACD:	
Section 4 (Consideration of the evidence)	I am concerned that the way of assessing cost effectiveness doesn't take account of the bigger picture. Patients receiving this treatment are facing, in many cases, a greatly shortened life expectancy and will not have the benefit of the many years of NHS care that people with a 'normal' life span will enjoy. This means that the money spent now for a vitally important extra 6 months could well be no different to, or in fact much less, the care that we all might expect from the NHS across our life time. Especially since there are many younger people with breast cancer, whilst it is often older people who are going to receive more NHS care/treatment. 6 months extra time doesn't sound a lot, but as an addition to 12 months it is a huge improvement. I am very concerned that this isn't considered 'cost effective'. Why is the only choice between spending Â£30,000 or nothing (no access to pertuzumab)? Would it not be possible to investigate some compromise on this scenario, with patients paying some costs on a means tested basis?

Role	Public
Location	England
Conflict	no
Comments on individual sections of the ACD:	
Section 2 (The technology)	It could be as life changing as Herceptin and therefore should be used to prolong life.
Section 4	It would appear to have been successful in the trials completed,

(Consideration of the evidence)	although is expensive. Could the drug company be allowed to recoup their cost over a longer period before generic drugs are allowed, therefore reducing the cost per dose. It is a vital step forward and if we are to beat cancer new drugs, showing such good trial results, must be approved.

Role	Public
Location	England
Conflict	no
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	if the treatment is working under no circumstances should it be stopped.
Section 2 (The technology)	the cost should be immaterial-especially considering the vast amounts that are wasted in the NHS
Section 3 (The manufacturer's submission)	If I had cancer I would try anything and everything to prolong life or hopefully effect a cure
Section 4 (Consideration of the evidence)	The effective use of NHS resources is to cure illness or alleviate symptoms.

Role	Patient
Location	England
Conflict	no
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	This time of hormone sensitive cancer is well known to be sensitive to this drug. What about all the ladies who have a late diagnosis. Are they to be denied a chance to receive this drug when it could actually make a dramatic difference?
Section 2 (The technology)	The cost of a life...

Role	Public
Location	England
Conflict	no
Comments on individual sections of the ACD:	
Section 4 (Consideration of the evidence)	I realise that the cost effectiveness of pertuzumab has come in to question but surely this drug is not used long term as it is administered to terminally ill patients to extend their life. Â The NHS spends considerable money related to smoking and obesity. Just because a disease cannot be cured then it doesn't mean patients should not receive treatments as they cost a lot. If a small percentage of patients benefitted from the use of pertuzumab then I feel it is 'cost' effective.

Role	Public
Other role	Also breast cancer sufferer
Location	England
Conflict	no

Comments on individual sections of the ACD:	
Section 4 (Consideration of the evidence)	Pertuumab has show signification positive results extending life. The decision is based on cost. This makes the NHS a second rate health system. The general public do not want a second rate heath system.

ERG erratum

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer: A Single Technology Appraisal

This report was commissioned by the NIHR HTA Programme as project number 11/139/01

Erratum completed 20 August 2013

CONTAINS COMMERCIAL IN CONFIDENCE DATA (CIC)

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

ERG ESTIMATION OF CHEMOTHERAPY ADMINISTRATION COSTS IN ROCHE PERTUZUMAB ECONOMIC MODEL

Please note that the calculations used in the ERG report have been reviewed and some errors detected. The following figures have been calculated after correction of these errors, and the impact of these changes incorporated in a revised version of Table 36 from the ERG report. This amendment has a minor effect on estimated ICERs.

Basis of estimation:

1) Pharmacy dispensing costs apply to each active element of the regimen of approximately £9 per item.

2) NHS Reference Costs 2011/12 used for administration of chemotherapy, using weighted average of all modes of treatment (Day case, out-patient and other).

3) In the first cycle of treatment pertuzumab is delivered separately on day 1 and trastuzumab/docetaxel on day 2. In subsequent cycles, all components are delivered on day 1.

4) Administration of all cycles after the first are coded as "subsequent elements of a chemotherapy cycle (SB15Z)."

Trastuzumab and docetaxel

Cycle 1:

SB13Z (More complex chemotherapy at first attendance)

Mode	Volume	Average cost
Day case	*89,159*	*£248.29*
Outpatient	*13,298*	*£245.04*
Other	*8,194*	*£268.52*
Weighted average	110,651	£249.40
Dispensing	2 items	£18.00
Total		**£267.40**

Subsequent cycles:

SB15Z

Mode	Volume	Average cost
Day case	*133,610*	*£238.89*
Outpatient	*31,739*	*£210.57*
Other	*14,734*	*£275.60*
Weighted average	180,074	£236.90
Dispensing	2 items	£18.00
Total		**£254.90**

Pertuzumab and trastuzumab and docetaxel

Cycle 1, Day 1: Pertuzumab only

SB12Z (Simple parenteral chemotherapy at first attendance)

Mode	Volume	Average cost
Day case	*165,110*	*£203.16*
Outpatient	*26,571*	*£197.06*
Other	*17.042*	*£171.86*
Weighted average	208,718	£199.83
Dispensing	1 item	£9.00
Total		**£208.83**

Cycle 1, Day 2: Trastuzumab & docetaxel only

SB15Z Subsequent elements of chemotherapy cycle £254.90 (see above)

Cycle 1 Total cost of administration = £208.83 + £254.90 = **£463.73**

Subsequent cycles (all given on day 1):

SB15Z

Mode	Volume	Average cost
Day case	*133,610*	*£238.89*
Outpatient	*31,739*	*£210.57*
Other	*14,734*	*£275.60*
Weighted average	180,074	£236.90
Dispensing	3 items	£27.00
Total		**£263.90**

Corrected ERG Report Table 36:

Revised cost and outcome effects of ERG model amendments relative to the manufacturer's original base case analysis

Adjustment	Trastuzumab + docetaxel				Pertuzumab + trastuzumab + docetaxel				Incremental				
	Therapy cost	Other costs	Survival (months)[a]	QALYs	Therapy cost	Other costs	Survival (months)[a]	QALYs	Survival (months)[a]	Cost	QALYs	ICER (£/QALY)	ICER change
Original Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG utility values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	+£767
ERG drug prices	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	+£780
ERG chemo admin costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	+£787
Munich survival estimates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised base case including all amendments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£243,642**	[redacted]

ICER=incremental cost-effectiveness ratio; QALY=quality adjusted life year
a survival is undiscounted, all other figures are discounted