NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF RAPID RECONSIDERATION

Trastuzumab emtansine for treating HER2 positive advanced breast cancer after trastuzumab and a taxane (review of TA371) [ID1013]

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

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

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

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

4. **Member of the public response to the Appraisal Consultation Document received to NICE**

5. **ERG comments on ACD response**

6. **NICE request to company for corrected PSA**

7. **Company response to NICE request for corrected PSA** from Roche

8. **ERG critique** from SCHARR

9. **Company additional analyses** from Roche

10. **ERG response to company additional analyses** from ScHARR

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Trastuzumab emtansine for treating HER2 positive advanced breast cancer after trastuzumab and a taxane

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

Definitions:

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

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

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

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

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

Comments received from consultees

Consultee	Comment [sic]	Response
Roche	Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for trastuzumab-emtansine (hereinafter Kadcyla) for the treatment of refractory, HER2 positive breast cancer considered under the CDF rapid reconsideration process [ID1013]. Despite the disappointing ACD decision, Roche remains firmly committed to working with NICE to reach a positive outcome and as a reflection of this commitment is proposing an improvement in the Patient Access Scheme (PAS) previously offered. The benefits of Kadcyla were eloquently expressed by the clinical experts and the patients during the first Appraisal Committee Meeting (ACM) and we are confident that Kadcyla provides a valuable extension of life with a good quality of life and relatively few side effects. It can be judged cost effective when the correct comparator is considered in the end of life (EoL) setting.	Thank you for your comments. The committee considered in detail all of the comments and evidence received after consultation and the discussions are presented in sections 4.27–4.35 of the FAD. We draw your attention in particular to sections of the FAD noted below, relating to the specific issues raised.

Consultee	Comment [sic]	Response
Roche	1. Has all of the relevant evidence been taken into account? We do not feel that all the relevant evidence has been taken into account in the committee's draft recommendation in the ACD and as such we ask the committee to reconsider its decision in light of the information presented below. **Comparator** We acknowledge the argument that trastuzumab (Herceptin) in combination with capecitabine (hereinafter Her/cap) should be excluded from the analysis as it is dominated by lapatinib in combination with capecitabine (hereinafter lap/cap), or in the absence of lap/cap would be extendedly dominated by capecitabine monotherapy, and is not considered to be cost-effective. However this methodology is purely academic when lap/cap is no longer available to patients on the NHS, and we ask the committee to take a more pragmatic approach in their consideration of the most appropriate treatment option in the absence of Kadcyla, which along with NHSE (paragraph 7 of its submission) and clinical expert opinion (page 3 of the NCRI-ACP-RCP-RCR submission), we consider to be Her/cap. We are surprised to see that lapatinib remains listed as a possible treatment option if Kadcyla was not recommended. NICE began its appraisal of lapatinib [ID20] in December 2006 and after 7 appraisal committee meetings between January 2008 and February 2010 (as well as a second appeal determined in August 2010) have not published final guidance on this medicine as the STA was suspended. In addition, lapatinib was removed from the Cancer Drugs Fund (CDF) in January 2015[1]. It is well known that, without positive NICE guidance or inclusion in the new CDF, there is no routine funding mechanism for this medicine through the NHS and, as stated by NHS England during the first ACM for Kadcyla, it is unlikely that the current manufacturer of lapatinib would seek funding for it to be provided by any other means on the NHS. Concern about the use of lap/cap as a comparator was expressed by various stakeholders in their written submissions for this appraisal: NHS England stated that: 'NHS England regards the correct comparator for this NICE appraisal of trastuzumab emtansine to be trastuzumab/capecitabine as lapatinib/capecitabine is not used in the NHS in England' (paragraph 16). Breast Cancer Now stated that: 'We would like to point out that one of the comparators in the scope provided for this Technology Appraisal is lapatinib. This drug used to be available via the Cancer Drugs Fund, but had been delisted last year. It is therefore no longer available as a treatment option in England.' The NCRI-ACP-RCP-RCR submission stated that:	See section 4.31 of the FAD.

Consultee	Comment [sic]	Response
Roche	[1] We note that paragraph 4.19 states that lap/cap "is only available through the Cancer Drugs Fund". This is no longer correct and we suggest that the correct position needs to be made clear; that it is no longer available through the Cancer Drugs Fund.	Sections 4.1–4.26 reflect the committee's consideration of the evidence submitted in the original appraisal. Please see section 4.31 of the FAD for the current position.
Roche	Exclusion of vinorelbine as a comparator For the avoidance of doubt, the committee's assumption is correct that the vinorelbine and vinorelbine plus Herceptin were excluded as they were found to be dominated in the original appraisal by capecitabine and Her/cap respectively.	Please see section 4.31 of the FAD.
Roche	End of Life We are pleased that NICE agreed that Kadcyla continues to meet the EoL criteria. We understand that this is based on Lap/cap being the comparator. As stated above, we consider Her/cap is the most appropriate comparator and we ask the committee to consider this in the EoL criteria, particularly in light of the extension of life offered by Kadcyla. The model predicts that the life expectancy with Her/cap is shorter than lap/cap. As such, if lap/cap is considered to be under the EoL criteria it is logical that Her/cap should also meet the short life expectancy criterion. As stated in the submission there is limited clinical data on Her/cap combination in this setting however the key data for this combination comes from the CEREBEL study, that compared the incidence of CNS metastases in patients with HER2+ mBC receiving lap/cap or Her/cap (Pivot et al 2015). The median overall survival in the Her/cap arm was 27.3 months, however 45% of the patients in the Her/cap arm were being treated first line. Thus the survival seen is likely to be considerably higher than would be achieved in a solely 2nd line population. In addition, further evidence for the short life expectancy on Her/cap comes from the GBG26/BIG 3-05 (von Minckwitz et al 2011) which, despite comparatively small patient numbers, demonstrated that treatment with Herceptin (beyond progression from the first line) in combination with capecitabine in the second line resulted in an overall survival of 24.9 months.	Please see section 4.34 of the FAD.

Consultee	Comment [sic]	Response
Roche	Previous provision as part of the CDF While the ACD does state that this is a rapid reconsideration as part of the CDF transition process, it is important to recognise the impact of this on the supply of Kadcyla. Unlike many other NICE appraisals, Kadcyla has previously been available to patients on the NHS as a result of the CDF. Therefore, rather than this being a recommendation on whether a new treatment should be made available, a decision not to recommend Kadcyla would essentially be a recommendation to withdraw availability from patients. We note the transitional arrangements set out in chapter 6 of the CDF SOP, that "Drugs receiving negative NICE final guidance will be given two months' notice of their removal from the CDF. No new patients will be funded from this point although the CDF budget will continue to meet the drug costs of patients already receiving the drug in question." It is important to note that a decision not to recommend Kadcyla would alter the predicted course of treatment for many patients who have already been diagnosed with HER2 positive breast cancer, but have not yet been prescribed Kadcyla. While these patients would not yet have begun treatment, a decision not to recommend may profoundly impact the course of their disease and treatment, as well as their prognosis.	Please see section 4.30, 4.31 and 4.35 of the FAD.
Roche	2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? As mentioned in response to question 1 we feel that the choice of comparator does not reflect the evidence presented to the appraisal committee.	Please see section 4.31 of the FAD.

Consultee	Comment [sic]	Response
Roche	3. Are the recommendations a sound and suitable basis for guidance to the NHS? We feel that founding the cost-effectiveness argument on clinically irrelevant comparators cannot form the basis of sound and suitable guidance to the NHS, particularly when NHSE (as well as other consultees and commentators) has already expressed its disagreement with the use of lap/cap as a comparator. Disregarding expert opinion and not following NICE's own Guide to Methods would not be a sound basis on which to base publication of guidance. As stated above we are committed to working with NICE to ensure that Kadcyla remains available for patients. As such we would like to state our intention to improve the PAS by reducing the episode of care cap from 14 months to 13 months. We have informed the Patient Access Schemes Liaison Unit (PASLU) and the Department of Health (DH) of this change. The updated PAS will be reviewed by PASLU in a forthcoming meeting (23rd January). As this is an amendment to a previously approved scheme we do not expect there to be an issue in having this approved prior to the committee meeting on the 1st February.	Please see section 4.31 of the FAD.

Consultee	Comment [sic]	Response
Roche	**Calculation of treatment costs** We are happy to adjust our base case to align with the committee's preferred method of calculating treatment costs; using patient level data to calculate vial use and excluding an additional adjustment for wastage which was felt to provide a better estimate of the costs of treatment for patients in the NHS. With a 14 month EoC, using patient level data and not adjusting for wastage causes the ICER to fall from [redacted] to [redacted] vs Her/cap, from [redacted] to [redacted] vs lap/cap and from [redacted] to [redacted] versus capecitabine monotherapy. With a 13 month EoC, using patient level data and not adjusting for wastage causes the ICER to fall from [redacted] to [redacted] vs Her/cap, from [redacted] to [redacted] vs lap/cap and from [redacted] to [redacted] versus capecitabine monotherapy. As we have chosen to amend the approach used to calculate treatment costs and increase our patient access scheme to include a 13 month episode of care cap please find updated base case results and sensitivity analyses below. *Table 1-4 were presented, but not replicated here.* **Probabilistic sensitivity analysis** A 1,000 simulation probabilistic sensitivity analysis was conducted in order to evaluate the uncertainty associated with the base-case estimate. *Table 5 and Figure 1-2 were presented, but not replicated here.*	Please see section 4.33 of the FAD.

Consultee	Comment [sic]	Response
Roche	**Scenario analysis** In the base case analysis, a difference between the deterministic and probabilistic ICER is observed ([redacted] per QALY in deterministic and [redacted] per QALY in the probabilistic results). As stated in the ERG report '*within a small number of the Monte Carlo simulation runs, the estimated life years and QALYs associated with capecitabine are vastly overestimated, which leads to the expected values being overestimated'.* In addition, from the cost effectiveness scatterplot shown in Figure 2, it seems that most of the uncertainty is within the clinical efficacy parameters. This can be explained by the network meta-analysis (NMA) inputs used to determine the relative efficacy of the comparators in the model, which are characterised by large confidence intervals, as highlighted in table 6. *Table 6 was presented, but not replicated here.* For example, as shown in table 6 the upper confidence interval of the OS HR for Kadcyla vs lap/cap crosses one, implying that the efficacy between the two treatments, in terms of OS benefit, is not statistically significant. However at the time of the final analysis in the intention-to-treat (ITT) population, the median OS reached statistical significance at 29.9 months with Kadcyla versus 25.9 months with capecitabine plus lapatinib; stratified HR=0.75 (95% CI 0.64-0.88, P=0.0003). Similarly in table 6 the PFS HR for Kadcyla vs lap/cap crosses one implying the efficacy of Kadcyla vs Lap/cap is not statistically significant. However the EMILIA results show a statistically significant improvement in PFS for Kadcyla vs lap/cap; stratified HR=0.65 (96% CI 0.55-0.77, P<0.001). At the time of the final analysis in the intention-to-treat (ITT) population, the median OS was 29.9 months with Kadcyla versus 25.9 months with capecitabine plus lapatinib; stratified HR=0.75 (95% CI 0.64-0.88, P=0.0003) The ERG expressed that '*given the time and resource constraints for this work, and given the other issues with the PSA discussed above, the ERG has chosen not to amend this within the model and instead focus upon the deterministic analyses.'* Due to the inconsistency between the probabilistic and deterministic ICER of Kadcyla vs Her/cap we have run a scenario (including PSA) using inputs from the NMA which come from a smaller network with narrower CI. We note that the ERG's preference, as reflected in our base case, was to include the CEREBEL and Martin *et al* studies (full network) and utilising a random effects model to account for any between-study variability. However, if the committee wishes to consider the PSA results, the scenario provided below was generated by re-running the PSA whilst using the NMA excluding CEREBEL and Martin *et al* (small network). It is noted that the latter scenario was the base case in the original	Please see section 4.31, 4.32 and 4.35 of the FAD.

Consultee	Comment [sic]	Response
UK Breast Cancer Group (UKBCG)	On behalf of the UK Breast Cancer Group (UKBCG) we would like to respond to the NICE Appraisal Consultation Document on Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane. The UKBCG represents Clinical and Medical Oncologists throughout the UK. Trastuzumab emtansine is a novel antibody cytotoxic conjugate that delivers effective and well-tolerated treatment to patients with an aggressive form of breast cancer. There is considerable experience amongst UK oncologists with this agent as it has been widely used over the last two years via the Cancer Drugs Fund. In the key clinical trial EMILIA, trastuzamab emtansine increased progression free survival by three months and overall survival by six months compared to the combination of lapatinib and capecitabine, while also having a more favourable toxicity profile. When oncologists were asked to rank novel therapies for advanced breast cancer that were being prescribed through the Cancer Drugs Fund, trastuzumab emtansine and pertuzumab (another antibody directed at HER-2) were the clear first two choices by most oncologists. NICE did not recommend the use of trastuzumab emtansine, within its marketing authorisation,for treating HER-2 positive, unresectable locally advanced or metastatic breast cancer after trastuzumab and a taxane. We are disappointed with this recommendation as it deprives patients in the UK from receiving a well-tolerated drug that prolongs life significantly. As a result of this recommendation patients in the UK will be treated with less effective and more toxic drugs than would otherwise be possible. The poor outcomes of cancer patients in the UK compared to other European countries are well described and sadly this recommendation would continue this. As trastuzumab emtansine has been available to patients in England for some time it will not just be a case that we are not adopting a new treatment, but withdrawing an effective treatment with low toxicity. Furthermore if trastuzumab emtansine is standard of care in North America and many European countries, clinical trials exploring novel treatments for patients with relapsed HER-2 positive breast cancer require pre-treatment with this agent. As a result, patients in the UK will not be able to participate in these clinical trials.	Please see sections 4.28–4.32 of the FAD.

Consultee	Comment [sic]	Response
UK Breast Cancer Group (UKBCG)	We would also like to make a specific and important aspect of the evaluation. The comparator to trastuzumab emtansine was the combination of lapatinib and capecitabine as used in the EMILIA trial. However, as stated in the consultation document by the clinical experts consulted, this combination is hardly ever used in the UK as it is not approved by NICE. A more appropriate comparator that would be a true reflection of current UK practice would be the combination of trastuzumab and capecitabine. We would like NICE to reconsider their recommendation and to work with Roche to find a way to make trastuzumab emtansine available for patients with locally advanced or metastatic HER-2 positive breast cancer, so that they can continue to benefit from this novel well-tolerated and effective agent that helps them live longer.	Please see section 4.31 of the FAD.
Breast Cancer Now	Breast Cancer Now welcomes the opportunity to respond to the Appraisal Consultation Document (ACD) for trastuzumab emtansine (Kadcyla) for treating HER2 positive advanced breast cancer after trastuzumab (Herceptin) and a taxane, published by NICE on 29 December 2016. We would like to draw NICE‘s attention to three key points, which are set out in more detail in our answers, below, to the question posed by NICE in the ACD: • There is widespread concern from both patients and clinicians (including the UK Breast Cancer Group) about the potential withdrawal of Kadcyla, which is an effective treatment which is well tolerated by patients with fewer side effects than other treatment options. A petition launched by Breast Cancer Now calling on NICE and Roche to come together and find a solution to keep it available has been signed by nearly 105,000 people to date. • We believe that Herceptin should be the comparator used in the appraisal. Lapatinib with capecitabine – the comparator that NICE has used – is not recommended by NICE for routine use on the NHS. We believe that had Herceptin been used as the comparator this would have made a significant difference to the outcome. We will not close the current gap in cancer outcomes with other European countries if we cannot find a way to ensure that the most clinically effective medicines for breast cancer are routinely available to patients on the NHS.	Thank you for your comments. We draw your attention in particular to sections of the FAD noted below, relating to the specific issues raised.

Consultee	Comment [sic]	Response
Breast Cancer Now	Has all of the relevant evidence been taken into account? We would like the Committee to take account of the petition we have been running during the consultation on the ACD. This petition has gathered nearly 105,000 signatures in just three weeks, the highest number we have ever had for a campaign. This illustrates how important this drug is to women who are being treated with Kadcyla, and women for whom Kadcyla would be the next treatment option. The fact that Kadcyla has been available through the Cancer Drugs Fund for several years has only served to heighten the distress at its potential withdrawal, as many women were expecting, and relying on, it to be available when their current treatment stopped working, to provide quality extra time with their family, loved ones and friends. The petition was also signed by many family members, loved ones and friends of people with breast cancer. This widespread concern about the removal of Kadcyla from NHS use is important. Breast cancer is the most commonly-diagnosed cancer in the UK and a proportion of patients will be diagnosed with metastatic disease straight away. Many other patients go on to have a recurrence after initial treatment has ended. It is therefore not surprising that there is widespread concern about access to effective treatments for this disease. We would like NICE and Roche to find a way forward which would ensure that Kadcyla can remain available to all patients who will require it in the future. Alongside our petition, we also asked breast cancer patients who would be affected by NICE's final decision on Kadcyla to submit a short statement. We have received 18 statements, which we have included in appendix A of this consultation response. We have also included the response to the consultation submitted by the Younger Breast Cancer Network, which includes some additional patient statements, at appendix B (some of the patients are the same). We would like these statements to be taken into account when the final decision on Kadcyla is made. We feel that these women's personal experiences of the drug and the implications of removing access for those for whom this will be the next treatment option form a significant base of qualitative evidence for this appraisal.	Please see sections 4.30–4.32 of the FAD.

Consultee	Comment [sic]	Response
Breast Cancer Now	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? We feel that the incorrect comparator has been used to assess the clinical benefits and cost effectiveness of Kadcyla. Whilst lapatinib plus capecitabine was chosen by the Committee as the most appropriate comparator, lapatinib has not been recommended by NICE for routine use on the NHS. Whilst this drug was briefly on the old Cancer Drugs Fund, it was de-listed in March 2015. Following this delisting, no more funding was provided for this drug. This means that women cannot currently access this medicine on the NHS. Whilst Herceptin is usually given as a first line treatment to women with HER2-positive metastatic breast cancer, we understand from clinicians that Herceptin could also be given again in combination with capecitabine in a second-line setting. In our view, this would be an appropriate comparator for Kadcyla.	Please see section 4.31 of the FAD.
Breast Cancer Now	Are the recommendations sound and a suitable basis for guidance to the NHS? Kadcyla has been available in many other countries for a number of years now. Research carried out for Breast Cancer Now and Prostate Cancer UK , looked at the availability of breast cancer medicines in a number of developed countries with similar health systems to that of the UK. This research found that in France, Germany, Canada and Australia, Kadcyla has become a standard of care. We are also aware that Kadcyla is available in many other countries. It is vital that the NHS can provide clinically effective treatments to patients, which equal those available in other developed countries. We cannot close the gap in cancer outcomes with other European countries if the available treatments for cancer are not on a par with what is available in those countries.	Comment noted.
Breast Cancer Now	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Not that we are aware of.	Comment noted.

Consultee	Comment [sic]	Response
Breast Cancer Now	*Appendix A and B, including statements from individual patients are submitted, but not replicated here*.	Comment noted.

Comments received from clinical experts and patient experts

None.

Comments received from commentators

None.

Comments received from members of the public

Role*	Section	Comment [sic]	Response
[redacted]	General	Kadcyla has been proven to have a reliable and substantial increase in the life expectancy of women who are treated with the drug in comparison to lapatinib + capecitabine, which is a comparable treatment for metastatic breast cancer. Kadcyla also has a demonstrably lower toxicity than other comparable drugs which means that treatment can be provided for longer and with a much improved quality of life for the patients involved. The EMILIA study showed that patients on Kadcyla could expect to live an extra 6.3 months compared to treatment with lapatinib + capecitabine, but in some cases, the patients can expect to live for many years under the treatment. The ICER for treatment is estimated to be £166,400-£167,200 per QALY gained (excluding other mitigating factors, such as the comparatively low number of patients who need it each year). While it cannot be disputed that the treatment is expensive, I do not	Thank you for your comment. Please see sections 4.29– 4.30 and 4.35 of the FAD.

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

Role*	Section	Comment [sic]	Response
		believe that the QALY formula involved adequately reflects the true value of the treatment to patients and tremendous impact that it has on their lives. It does not appear that under the current QALY formula enough weight is given to the benefits of drugs like Kadcyla in comparison to the financial costs. Current NICE guidelines state that when appraising treatments for extending the life of a patient with a short life expectancy, further criteria can be taken into account when calculating whether a treatment is cost effective. These are: • The treatment is indicated for patients with a short life expectancy, normally less than 24 months • There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment • The treatment is licensed or otherwise indicated for small patient populations While as mitigating factors for affordability of treatment are welcome I believe that they do not adequately reflect the true benefit of treatments like Kadcyla and should be re-examined. The improved quality of life that comes from Kadcyla instead of comparative treatments ought to be considered in conjunction with these three criteria as well as within the QALY calculation. The need for this is most obvious when considering how much further a patient's life is extended. While a treatment's ability to provide the extension of life by at least an additional 3 months ought to rightly be considered a major factor when calculating cost efficiency, much greater weight ought to be lent to those treatments that provide similar extension that provide a higher standard of living. For a patient with fewer than 24 months left to live, a treatment which offers a higher standard of living ought to have the comparative quality of	

Role*	Section	Comment [sic]	Response
		life calculated. A treatment which provides a less painful, less debilitating final few months for a patient than its competitors ought to have this recognised strongly as possible. It should therefore be a very powerful mitigating factor when considering the cost of a treatment like Kadcyla. Kadcyla offers precious time to those women who need it. Time that they can spend with a decent quality of life with their families and loved ones. The low toxicity means that this is not a matter of adding a few months of bedridden agony, but of being able to spend this extra time doing what is important to them. I therefore urge you as strongly as possible to ensure that this important treatment receives NICE's backing for funding from the NHS.	
Patient	General	The decision not to fund Kadcycla is something that I need to challenge. I have been a fortunate recipient of Kadcyla. I have been on the drug for about 18months. With this treatment my secondary breast cancer in the liver is nearing remission, and I have been able to work. I run a charity that would certainly close without me. It employs 8 people and last year supported 3,500 volunteers.and contributes substantially to the London economy. Through my work I have also contributed to the work of NICE with my work on pollution and public heath. Kadcyla doesn't extend life by a mere 9months as your papers indicate. Although the work of NICE requires strong evidence RCTs . Given the number of recipients are small, such trials do not give you the full picture: your panel would benefit from gathering qualitative evidence from people such as myself , with potentially longer to live and with significantly greater quality of life than those in the RCTs. I am not on a trial and as such would be excluded from your evidence gathering, but would be very happy to give evidence to testify to the importance of this drug on my life and the economy. I would like to add to m previous comments - I don't think that the figures you used for the QALY. assessment are accurate. a) not all women with secondary breast cancer would need the drug, so the cost would not be for the whole population to use it,	Thank you for your comment. Please see sections 4.29– 4.30 and 4.35 of the FAD.

Role*	Section	Comment [sic]	Response
		b) I know several women who are working and contributing to the economy whilst taking Kadcyla - the added QALY for these women significantly outstrips the cost of the drug.	
Member of YBCN - Younger Breast Cancer Network	General	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment? The NICE Guide to the methods of technology appraisal (2013) states that: 2.23 â€¦The scope may highlight potential subgroups of the population for whom the clinical or cost effectiveness of the technology might be expected to differ from the overall population We note the remarks of the committee in the appraisal consultation document in relation to the EMILIA trial that: 4.6 â€¦ The committee appreciated that patients enrolled in clinical trials may be younger and with better performance status than those in routine clinical practice, and so might have better outcomesâ€¦ This comment suggests a general acceptance by the committee that younger age is likely to have an impact on the clinical and cost effectiveness of Kadcyla. As such, it is then inappropriate that the younger women are not considered as a potential subgroup for which separate assessment would be indicated. There is significant evidence that breast cancer in younger women (<45) is a different disease with different pathology to that in older women. Azim H & Partridge (2014) state â€œExpression of key biomarkers, including endocrine receptors, HER2 and proliferation markers, appears to be different in younger patientsâ€□. This view is corroborated by Hatem et al (2015) who conclude that tumours arising at different ages are biologically distinct. Studies by Anders et al (2011), Hatem et al (2014) and Howlader et al (2013) have all concluded that Her-2 positive breast cancer is more prevalent in women diagnosed at a younger age, with percentage ranges of 20 to 30 percent of breast cancers diagnosed at below 45 versus 16 to 23 percent in those diagnosed after 65 years of age. It is also well demonstrated that breast cancer in younger women is likely to manifest with a worse prognosis due to a higher proportion of high grade and late stage tumours, by Anders et al (2011), Lee and Han	Thank you for your comment. NICE is committed to promoting equality of opportunity and eliminating discrimination. Considering a subgroup based on age, and not on objective clinical characteristics, could potentially exclude people protected by the equality legislation who fall within the patient population for which trastuzumab emtansine is licensed. During the appraisal no evidence was submitted which suggested a differential clinical and cost effectiveness in people of different ages to support a different recommendation of trastuzumab emtansine for a particular age group. Trastuzumab emtansine has been recommended within its licensed indication which does not prevent a barrier to access for this treatment based on age.

Role*	Section	Comment [sic]	Response
		(2014), Cancello et al (2010), Copson el al (2015) POSH study, Stenger et al (2014). The difference in tumour pathology alongside the poor reported outcomes for younger patients means that many persons for whom Kadcyla is indicated will be younger than the overall profile of people with breast cancer. It also indicates that failure to consider younger persons as a distinct subgroup in assessment raises discrimination concerns which must be addressed. *References were presented but not replicated here.*	
Member of Parliament	General	Following a meeting with my constituent, [redacted], I would like to make a general comment on this consultation. Mrs Mears suffers from secondary breast cancer. While her condition is terminal, she is responding well to her existing medication and has had more than twice the expected time on this drug. When the point comes when this drug no longer has a beneficial effect, the only remaining option will be Kadcyla. Given that she has responded so well to existing treatment, and has and does lead a comparatively fit and healthy life, there is every likelihood that she will similarly respond positively to Kadcyla and enjoy a reasonable quality of life far in excess of the nine month expected benefits from the drug. This view is supported by her consultant. I would therefore like to argue that a blanket ban on the use of Kadcyla as part of the Cancer Drugs Fund would be inappropriate and potentially deprive breast cancer sufferers from a significant increase to their life expectancy. I would therefore suggest that, at the very least, Kadcyla should be available under the Cancer Drugs Fund when clinically appropriate. Moreover, by allowing patients like [redacted] to enhance their life expectancy would allow further research to be carried out on the efficacy of her existing medication. I would be happy to provide further details of my constituent's case should that be helpful. Thank you for considering these comments.	Thank you for your comment. Please see sections 4.29–4.30 of the FAD.
Patient	Section 4	The references to Lapatanib in this section suggest that it remains available as an alternative treatment (via the cancer drug fund) in some	Thank you for your comments. Please see sections 4.29–4.30 and 4.31 of the FAD.

Role*	Section	Comment [sic]	Response
		circumstances, and that lapatanib is a relevant comparator. I had understood that Lapatanib was not currently available to patients with advanced breast cancer. Although I understand that trial data is important to take in to account, the use of Lapatanib as a comparator when this is no longer available and proven to be less effective than kadcyla with significantly poorer side effects does not seem appropriate in the circumstances. During the original hearing it was implied that Lapatanib was not available because it was also too expensive and that without the comparator Kadcyla would have to be deemed too expensive also (I may have misheard this point). I don't believe Lapatanib should be used as a comparator since it is not available, but if comparisons are to be made then I feel that richer data concerning efficacy and quality of life should be sought and considered. The comment 'the committee took note of the patient expert's concern about the tolerability of treatment' implies that patient expert(s) expressed negative views about kadcyla and its tolerability and side effects. In fact the opposite view was stated, Kadcyla has been the most well tolerated of the treatments received to date and concerns about tolerability in the committee were focussed on the alternatives (such as were identified), including Lapatanib. It seems self evident that Kadcyla should be considered an end of life treatment and I support the conclusion reached by the committee in this regard. As well as considering progression-free survival and overall survival I would urge the committee to fully address the quality of life considerations and the efficacy of Kadcyla. my recollection is that the patient expert who referred to Kadcyla removing fear was focussing on the fear associated with treatment (not the fear following diagnosis). it is hard to put in to words the difference which Kadcyla has made to the quality of my life and I do not think that the approach taken by nice places sufficient emphasis on this aspect. Kadclya has enabled me to live fully again, despite (and knowing that I have) a much more limited life expectancy.	Please also note that section 4.29 has been updated according to your comment and now reads as: '*The patient experts stated that trastuzumab emtansine has removed some of the fear associated with their disease and has given them quality time with family and friends'*.
	General	I feel that NICE have made a narrow formulaic decision based on cost and	Thank you for your comment. Please see section

Role*	Section	Comment [sic]	Response
		that views and experiences of patients and clinicians were not given sufficient weight. A full economic appraisal should consider the benefits of allowing patients to live well for longer, contributing to society and supporting/spending time with friends and family. it should also look at the savings associated with fewer emergency admissions than traditional chemotherapy for example. The trial data considered is based on relatively small numbers, it is not clear to me why this information was not supplemented with real patient data. The information for the public about this decision on the NICE web site states. 'NICE looks at how well treatments work in relation to how much they cost compared with other treatments available on the NHS. NICE applies special considerations to treatments that can extend the lives of people who are nearing the end of their life. Trastuzumab emtansine does not provide enough benefit to patients to justify its high cost even when the 'special considerations' were applied, so it was not recommended.' 1) The treatment was not compared to 'other treatments available on the NHS' as the comparators were not available at the time the decision was made. 2) if the considerable benefits to patients outlined by patient experts and clinicians (and case studies which have been in the press since the draft decision was announced) are not enough to justify the high cost, then it begs the question what would be? Or perhaps it is the case that the cost would always be considered too high- in which case why appraise it. I feel strongly that other patients should not be denied the benefits of this drug which cannot be computed into simple cost and benefit calculations. it is not just a question of a relatively small amount of extra time, it is extra time after gruelling and debilitating treatment, and extra time when you feel well enough to live well. In a sense it provides a new lease on life, something which is more precious and should be more highly valued when life is shortened and when one is used to feeling so unwell. The simplistic calculations and explanations do not expose the real benefits of this drug. I urge the committee (and Roche) to reconsider.	4.35 of the FAD.

Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for trastuzumab-emtansine (hereinafter Kadcyla) for the treatment of refractory, HER2 positive breast cancer considered under the CDF rapid reconsideration process [ID1013]. Despite the disappointing ACD decision, Roche remains firmly committed to working with NICE to reach a positive outcome and as a reflection of this commitment is proposing an improvement in the Patient Access Scheme (PAS) previously offered.

The benefits of Kadcyla were eloquently expressed by the clinical experts and the patients during the first Appraisal Committee Meeting (ACM) and we are confident that Kadcyla provides a valuable extension of life with a good quality of life and relatively few side effects. It can be judged cost effective when the correct comparator is considered in the end of life (EoL) setting.

Response to ACD

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

We do not feel that all the relevant evidence has been taken into account in the committee's draft recommendation in the ACD and as such we ask the committee to reconsider its decision in light of the information presented below.

Comparator

We acknowledge the argument that trastuzumab (Herceptin) in combination with capecitabine (hereinafter Her/cap) should be excluded from the analysis as it is dominated by lapatinib in combination with capecitabine (hereinafter lap/cap), or in the absence of lap/cap would be extendedly dominated by capecitabine monotherapy, and is not considered to be cost-effective. However this methodology is purely academic when lap/cap is no longer available to patients on the NHS, and we ask the committee to take a more pragmatic approach in their consideration of the most appropriate treatment option in the absence of Kadcyla, which along with NHSE (paragraph 7 of its submission) and clinical expert opinion (page 3 of the NCRI-ACP-RCP-RCR submission), we consider to be Her/cap.

We are surprised to see that lapatinib remains listed as a possible treatment option if Kadcyla was not recommended. NICE began its appraisal of lapatinib [ID20] in December 2006 and after 7 appraisal committee meetings between January 2008 and February 2010 (as well as a second appeal determined in August 2010) have not published final guidance on this medicine as the STA was suspended. In addition, lapatinib was removed from the Cancer Drugs Fund (CDF) in

January 2015[1]. It is well known that, without positive NICE guidance or inclusion in the new CDF, there is no routine funding mechanism for this medicine through the NHS and, as stated by NHS England during the first ACM for Kadcyla, it is unlikely that the current manufacturer of lapatinib would seek funding for it to be provided by any other means on the NHS.

Concern about the use of lap/cap as a comparator was expressed by various stakeholders in their written submissions for this appraisal:

NHS England stated that:

'NHS England regards the correct comparator for this NICE appraisal of trastuzumab emtansine to be trastuzumab/capecitabine as lapatinib/capecitabine is not used in the NHS in England' (paragraph 16).

Breast Cancer Now stated that:

'We would like to point out that one of the comparators in the scope provided for this Technology Appraisal is lapatinib. This drug used to be available via the Cancer Drugs Fund, but had been delisted last year. It is therefore no longer available as a treatment option in England.'

The NCRI-ACP-RCP-RCR submission stated that:

'Most NHS patients currently do not have access to lapatinib for use in combination with capecitabine (not recommended by NICE and no longer funded by the cancer drugs fund).'

We therefore feel that the statement in the ACD that '*the committee concluded that lapatinib plus capecitabine remained relevant to its consideration of the cost effectiveness of trastuzumab emtansine and should be included in the economic analysis'* does not reflect both the evidence presented by the various stakeholders to the committee and the discussion at the appraisal committee meeting.

On 2 June 2016 NICE issued a statement as to the handling of products still on the CDF as of 1 April 2016 as a potentially valid comparator, highlighting the need to consider paragraphs 6.2.2 and 6.2.3 of the guide to the methods of technology appraisal 2013. This made clear that *"the*

[1] We note that paragraph 4.19 states that lap/cap "is only available through the Cancer Drugs Fund". This is no longer correct and we suggest that the correct position needs to be made clear; that it is no longer available through the Cancer Drugs Fund.

recommendations might be reviewed if the CDF product is no longer widely available in the NHS" and encouraged companies to specifically *"consider the implications of comparators… no longer being available in the NHS."* The NICE website states that a comparator technology is *"one that is currently used in the NHS and could be replaced by the intervention, if recommended."* This is mirrored in the ACD at paragraph 4.30, where the Committee recognises that it "*had to consider comparators in the context of what might be used if* [Kadcyla] *were not available."*

The *Guide to Methods of Technology Appraisals 2013* in sections 6.2.2 and 6.2.3 states that:

"When selecting the most appropriate comparator(s), the Committee will consider:

- *established NHS practice in England*
- *the natural history of the condition without suitable treatment*
- *existing NICE guidance*
- *cost effectiveness*
- *the licensing status of the comparator.*

"…The Committee's overall decision on whether it is a valid comparator will be guided by whether it is recommended in other extant NICE guidance, and/or whether its use is so embedded in clinical practice that its use will continue unless and until it is replaced by a new technology."

As mentioned above lapatinib is not recommended in any NICE guidance, nor is it routinely available on the NHS by any other means. Furthermore, and as the expert opinion stated above clearly highlights, lapatinib is not embedded in clinical practice. Even in the absence of Kadcyla, lapatinib would not become embedded in clinical practice.

In the ACD it states that '*if lapatinib plus capecitabine were to be excluded from the analysis, then the ICER would be calculated compared with capecitabine alone (because trastuzumab plus capecitabine was subject to extended dominance and was not cost effective)*'. Again we understand the academic argument that excludes Her/cap from the analysis, but reverting back to treatments like capecitabine monotherapy would represent a step backwards in terms of efficacy from a targeted therapy to single agent chemotherapy. Instead, we understand Her/cap would be the choice for clinicians to offer patients the best outcomes in the absence of Kadcyla[2] even though it was originally ruled out by the ERG due to extended dominance.

[2] See paragraph 4.6 of Roche's original submission and paragraph 2.4 of the appendix to Roche's original submission.

As such it is potentially perverse and contrary to NICE's own guidance to use lapatinib as the relevant comparator, and that the committee's view is that the evaluation of expected survival with current standard of care should be based on a patient receiving lap/cap.

Exclusion of vinorelbine as a comparator

For the avoidance of doubt, the committee's assumption is correct that the vinorelbine and vinorelbine plus Herceptin were excluded as they were found to be dominated in the original appraisal by capecitabine and Her/cap respectively.

End of Life

We are pleased that NICE agreed that Kadcyla continues to meet the EoL criteria. We understand that this is based on Lap/cap being the comparator. As stated above, we consider Her/cap is the most appropriate comparator and we ask the committee to consider this in the EoL criteria, particularly in light of the extension of life offered by Kadcyla.

The model predicts that the life expectancy with Her/cap is shorter than lap/cap. As such, if lap/cap is considered to be under the EoL criteria it is logical that Her/cap should also meet the short life expectancy criterion.

As stated in the submission there is limited clinical data on Her/cap combination in this setting however the key data for this combination comes from the CEREBEL study, that compared the incidence of CNS metastases in patients with HER2+ mBC receiving lap/cap or Her/cap (Pivot et al 2015). The median overall survival in the Her/cap arm was 27.3 months, however 45% of the patients in the Her/cap arm were being treated first line. Thus the survival seen is likely to be considerably higher than would be achieved in a solely 2nd line population. In addition, further evidence for the short life expectancy on Her/cap comes from the GBG26/BIG 3-05 (von Minckwitz et al 2011) which, despite comparatively small patient numbers, demonstrated that treatment with Herceptin (beyond progression from the first line) in combination with capecitabine in the second line resulted in an overall survival of 24.9 months.

Previous provision as part of the CDF

While the ACD does state that this is a rapid reconsideration as part of the CDF transition process, it is important to recognise the impact of this on the supply of Kadcyla. Unlike many other NICE appraisals, Kadcyla has previously been available to patients on the NHS as a result of the CDF. Therefore, rather than this being a recommendation on whether a new treatment

should be made available, a decision not to recommend Kadcyla would essentially be a recommendation to withdraw availability from patients.

We note the transitional arrangements set out in chapter 6 of the CDF SOP, that *"Drugs receiving negative NICE final guidance will be given two months' notice of their removal from the CDF. No new patients will be funded from this point although the CDF budget will continue to meet the drug costs of patients already receiving the drug in question."* It is important to note that a decision not to recommend Kadcyla would alter the predicted course of treatment for many patients who have already been diagnosed with HER2 positive breast cancer, but have not yet been prescribed Kadcyla. While these patients would not yet have begun treatment, a decision not to recommend may profoundly impact the course of their disease and treatment, as well as their prognosis.

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

As mentioned in response to question 1 we feel that the choice of comparator does not reflect the evidence presented to the appraisal committee.

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

We feel that founding the cost-effectiveness argument on clinically irrelevant comparators cannot form the basis of sound and suitable guidance to the NHS, particularly when NHSE (as well as other consultees and commentators) has already expressed its disagreement with the use of lap/cap as a comparator. Disregarding expert opinion and not following NICE's own Guide to Methods would not be a sound basis on which to base publication of guidance.

As stated above we are committed to working with NICE to ensure that Kadcyla remains available for patients. As such we would like to state our intention to improve the PAS by reducing the episode of care cap from 14 months to 13 months. We have informed the Patient Access Schemes Liaison Unit (PASLU) and the Department of Health (DH) of this change. The updated PAS will be reviewed by PASLU in a forthcoming meeting (23rd January). As this is an amendment to a previously approved scheme we do not expect there to be an issue in having this approved prior to the committee meeting on the 1st February.

Calculation of treatment costs

We are happy to adjust our base case to align with the committee's preferred method of calculating treatment costs; using patient level data to calculate vial use and excluding an additional adjustment for wastage which was felt to provide a better estimate of the costs of treatment for patients in the NHS.

With a 14 month EoC, using patient level data and not adjusting for wastage causes the ICER to fall from [redacted] to [redacted] vs Her/cap, from [redacted] to [redacted] vs lap/cap and from [redacted] to [redacted] versus capecitabine monotherapy.

With a 13 month EoC, using patient level data and not adjusting for wastage causes the ICER to fall from [redacted] to [redacted] vs Her/cap, from [redacted] to [redacted] vs lap/cap and from [redacted] to [redacted] versus capecitabine monotherapy.

As we have chosen to amend the approach used to calculate treatment costs and increase our patient access scheme to include a 13 month episode of care cap please find updated base case results and sensitivity analyses below.

Table 1: New base-case cost-effectiveness results using the list price

	Kadcyla	*Lap/Cap*	*Her/cap*	*Capecitabine*
Intervention cost (£)	*£88,560*	*£22,582*	*£27,235*	*£5,291*
Other costs (£)	*£9,012*	*£8,285*	*£8,024*	*£7,950*
Total costs (£)	*£97,572*	*£30,867*	*£35,259*	*£13,242*
Difference in total costs (£)	*N/A*	*£66,705*	*£62,313*	*£84,331*
LYG	*3.32*	*2.58*	*2.41*	*2.06*
LYG difference	*N/A*	*0.74*	*0.91*	*1.25*
QALYs	*2.09*	*1.56*	*1.45*	*1.20*
QALY difference	*N/A*	*0.53*	*0.63*	*0.89*
ICER (£)	*N/A*	*£125,567*	*£98,244*	*£95,279*

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 2: New base-case cost-effectiveness results using the patient access scheme

	Kadcyla	*Lap/Cap*	*Her/cap*	*Capecitabine*
Intervention cost (£)	[redacted]	*£22,582*	*£27,235*	*£5,291*
Other costs (£)	*£9,012*	*£8,285*	*£8,024*	*£7,950*
Total costs (£)	[redacted]	*£30,867*	*£35,259*	*£13,242*
Difference in total costs (£)	*N/A*	[redacted]	[redacted]	[redacted]
LYG	*3.32*	*2.58*	*2.41*	*2.06*
LYG difference	*N/A*	*0.74*	*0.91*	*1.25*
QALYs	*2.09*	*1.56*	*1.45*	*1.20*
QALY difference	*N/A*	*0.53*	*0.63*	*0.89*
ICER (£)	*N/A*	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 3: Deterministic sensitivity analysis (with PAS)

Analysis **(BC = Base case)**	**T-DM1** **Vs Her/cap (Roche analysis)**
Base case	[redacted]
Treatment dose (*BC: incl. wastage – patient level weight data)* *Incl. wastage – actual estimate* Excl. wastage – actual estimate Incl. wastage - planned Excl. wastage – planned Excl. wastage – patient level weight data	 [redacted] [redacted] [redacted] [redacted] [redacted]
PFS utility: (*BC: See Table 4*) Same values as lap/cap in all arms TH3RESA trial (0.71 Kadcyla, 0.69 comparators)	 [redacted] [redacted]
Progressed utility (*BC: 0.530*) 0.730	[redacted]
PFS extrapolation (*BC: KM until 72 weeks+gamma tail*) As original submission (KM until 72 weeks+lognormal tail) KM+Weibull tail Weibull	 [redacted] [redacted] [redacted]
OS extrapolation (*BC: Adjusting for treatment switching*) Not adjusting for treatment switching	 [redacted]
PFS & OS of Kadcyla equivalent to lap/cap after week 72 and 4 years respectively	[redacted]
NMA method (*BC: RE Full network (xo adjusted)*) FE Full network (xo adjusted) FE Small network (xo adjusted)	 [redacted] [redacted]

Table 4: Deterministic sensitivity analysis for choice of parametric function (Kadcyla vs Her/cap)

Parametric function for PFS	ICER without PAS	ICER with PAS
KM with Gamma tail (Base case)	£98,244	[redacted]
KM with log normal tail	£98,258	[redacted]
KM with log logistic tail	£95,883	[redacted]
KM with exponential tail	£94,106	[redacted]
KM with weibull tail	£86,806	[redacted]
KM with gompertz tail	£87,706	[redacted]
Gamma	£98,002	[redacted]
Log normal	£98,364	[redacted]
Log logistic	£96,182	[redacted]
Exponential	£93,440	[redacted]
Weibull	£84,344	[redacted]
Gompertz	£86,516	[redacted]

Probabilistic sensitivity analysis

A 1,000 simulation probabilistic sensitivity analysis was conducted in order to evaluate the uncertainty associated with the base-case estimate.

Table 5: PSA results using the patient access scheme

	Kadcyla	*Her/cap*	*Capecitabine*
Total costs (£)	[redacted]	*£37,778*	*£14,434*
Difference in total costs (£)	*N/A*	[redacted]	[redacted]
LYG	*3.33*	*2.62*	*2.24*
LYG difference	*N/A*	*0.72*	*1.09*
QALYs	*2.08*	*1.56*	*1.30*
QALY difference	*N/A*	*0.52*	*0.78*
ICER (£)	*N/A*	[redacted]	[redacted]

Figure 1: Cost -effectiveness acceptability curve

REDACTED

Figure 2: Cost-effectiveness plane

REDACTED

Scenario analysis

In the base case analysis, a difference between the deterministic and probabilistic ICER is observed ([redacted] per QALY in deterministic and [redacted] per QALY in the probabilistic results). As stated in the ERG report '*within a small number of the Monte Carlo simulation runs, the estimated life years and QALYs associated with capecitabine are vastly overestimated, which leads to the expected values being overestimated'.*

In addition, from the cost effectiveness scatterplot shown in Figure 2, it seems that most of the uncertainty is within the clinical efficacy parameters. This can be explained by the network meta-analysis (NMA) inputs used to determine the relative efficacy of the comparators in the model, which are characterised by large confidence intervals, as highlighted in table 6.

Table 6: Results from NMA model for OS (cross-over adjusted) and PFS (ITT)

Kadcyla vs.	OS HR	OS LCrI	OS UCrI	PFS HR	PFS LCrI	PFS UCrI
Full Network (random effects)						
Lap/cap	0.69	0.36	1.32	0.65	0.32	1.17
Cap	0.59	0.25	1.43	0.40	0.16	0.89
Her/Cap	0.70	0.29	1.72	0.67	0.27	1.45
Small Network (fixed effects)						
Lap/cap	0.69	0.57	0.84	0.65	0.55	0.77
Cap	0.55	0.41	0.74	0.36	0.25	0.51
Her/Cap	0.59	0.37	0.93	0.53	0.32	0.86

For example, as shown in table 6 the upper confidence interval of the OS HR for Kadcyla vs lap/cap crosses one, implying that the efficacy between the two treatments, in terms of OS benefit, is not statistically significant. However at the time of the final analysis in the intention-to-treat (ITT) population, the median OS reached statistical significance at 29.9 months with

Kadcyla versus 25.9 months with capecitabine plus lapatinib; stratified HR=0.75 (95% CI 0.64-0.88, P=0.0003).

Similarly in table 6 the PFS HR for Kadcyla vs lap/cap crosses one implying the efficacy of Kadcyla vs Lap/cap is not statistically significant. However the EMILIA results show a statistically significant improvement in PFS for Kadcyla vs lap/cap; stratified HR=0.65 (96% CI 0.55-0.77, P<0.001).

At the time of the final analysis in the intention-to-treat (ITT) population, the median OS was 29.9 months with Kadcyla versus 25.9 months with capecitabine plus lapatinib; stratified HR=0.75 (95% CI 0.64-0.88, P=0.0003)

The ERG expressed that '*given the time and resource constraints for this work, and given the other issues with the PSA discussed above, the ERG has chosen not to amend this within the model and instead focus upon the deterministic analyses.'*

Due to the inconsistency between the probabilistic and deterministic ICER of Kadcyla vs Her/cap we have run a scenario (including PSA) using inputs from the NMA which come from a smaller network with narrower CI.

We note that the ERG's preference, as reflected in our base case, was to include the CEREBEL and Martin *et al* studies (full network) and utilising a random effects model to account for any between-study variability. However, if the committee wishes to consider the PSA results, the scenario provided below was generated by re-running the PSA whilst using the NMA excluding CEREBEL and Martin *et al* (small network). It is noted that the latter scenario was the base case in the original submission. The two studies were excluded due to the increased heterogeneity in the network based on the patient population, prior treatment status and lack of detailed information on the study population's baseline characteristics.

Table 7: Results using a fixed effects model from a small network (cross over adjusted)

	Deterministic Results			***Probabilistic Results***		
	Kadcyla	***Her/cap***	***Capecitabine***	***Kadcyla***	***Her/cap***	***Capecitabine***
Total costs (£)	[redacted]	*£29,384*	*£12,607*	[redacted]	*£31,041*	*£13,412*
Difference in total costs (£)	*N/A*	[redacted]	[redacted]	*N/A*	[redacted]	[redacted]
LYG	*3.32*	*2.06*	*1.94*	*3.34*	*2.12*	*1.97*

LYG difference	*N/A*	*1.26*	*1.38*	*N/A*	*1.20*	*1.35*
QALYs	*2.09*	*1.23*	*1.13*	*2.09*	*1.27*	*1.51*
QALY difference	*N/A*	*0.86*	*0.96*	*N/A*	*0.82*	*0.94*
ICER (£)	*N/A*	[redacted]	[redacted]	*N/A*	[redacted]	[redacted]

As shown in table 7 the results for the deterministic and probabilistic results are similar in the scenario as the confidence intervals generated from the NMA are of a more plausible range. In addition the ICER for Kadcyla versus Her/cap falls from [redacted] to [redacted] per QALY.

References

Pivot et al. *CEREBEL (EGF111438): A Phase III, Randomized, Open-Label Study of Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer*. J Clin Oncol 2015 May 10;33(14):1564-73.

von Minckwitz et al 2011. *Trastuzumab beyond progression: overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer.* Eur J Cancer 2011 Oct; 47(15):2273-81

Jenna Dilkes
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20 January 2017

Dear Ms Dilkes,

Re: Response to Appraisal Consultation Document on trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane

Breast Cancer Now welcomes the opportunity to respond to the Appraisal Consultation Document (ACD) for trastuzumab emtansine (Kadcyla) for treating HER2 positive advanced breast cancer after trastuzumab (Herceptin) and a taxane, published by NICE on 29 December 2016.

We would like to draw NICE's attention to three key points, which are set out in more detail in our answers, below, to the question posed by NICE in the ACD:

- There is widespread concern from both patients and clinicians (including the UK Breast Cancer Group) about the potential withdrawal of Kadcyla, which is an effective treatment that is well tolerated by patients with fewer side effects than other treatment options. A petition launched by Breast Cancer Now calling on NICE and Roche to come together and find a solution to keep it available has been signed by nearly 105,000 people to date.
- We believe that Herceptin should be the comparator used in the appraisal. Lapatinib with capecitabine – the comparator that NICE has used – is not recommended by NICE for routine use on the NHS. We believe that had Herceptin been used as the comparator this would have made a significant difference to the outcome.
- We will not close the current gap in cancer outcomes with other European countries if we cannot find a way to ensure that the most clinically effective medicines for breast cancer are routinely available to patients on the NHS.

<u>Has all of the relevant evidence been taken into account?</u>

We would like the Committee to take account of the petition we have been running during the consultation on the ACD. This petition has gathered nearly 105,000 signatures in just three weeks, the highest number we have ever had for a campaign. This illustrates how important this drug is to women who are being treated with Kadcyla, and women for whom Kadcyla would be the next treatment option.

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The fact that Kadcyla has been available through the Cancer Drugs Fund for several years has only served to heighten the distress at its potential withdrawal, as many women were expecting, and relying on, it to be available when their current treatment stopped working, to provide quality extra time with their family, loved ones and friends. The petition was also signed by many family members, loved ones and friends of people with breast cancer. This widespread concern about the removal of Kadcyla from NHS use is important.

Breast cancer is the most commonly-diagnosed cancer in the UK and a proportion of patients will be diagnosed with metastatic disease straight away. Many other patients go on to have a recurrence after initial treatment has ended. It is therefore not surprising that there is widespread concern about access to effective treatments for this disease. We would like NICE and Roche to find a way forward which would ensure that Kadcyla can remain available to all patients who will require it in the future.

Alongside our petition, we also asked breast cancer patients who would be affected by NICE's final decision on Kadcyla to submit a short statement. We have received 18 statements, which we have included in appendix A of this consultation response. We have also included the response to the consultation submitted by the Younger Breast Cancer Network, which includes some additional patient statements, at appendix B (some of the patients are the same). We would like these statements to be taken into account when the final decision on Kadcyla is made. We feel that these women's personal experiences of the drug and the implications of removing access for those for whom this will be the next treatment option form a significant base of qualitative evidence for this appraisal.

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

We feel that the incorrect comparator has been used to assess the clinical benefits and cost effectiveness of Kadcyla. Whilst lapatinib plus capecitabine was chosen by the Committee as the most appropriate comparator, lapatinib has not been recommended by NICE for routine use on the NHS. Whilst this drug was briefly on the old Cancer Drugs Fund, it was de-listed in March 2015.[1] Following this delisting, no more funding was provided for this drug. This means that women cannot currently access this medicine on the NHS.

Whilst Herceptin is usually given as a first line treatment to women with HER2-positive metastatic breast cancer, we understand from clinicians that Herceptin could also be given again in combination with capecitabine in a second-line setting. In our view, this would be an appropriate comparator for Kadcyla.

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

Kadcyla has been available in many other countries for a number of years now. Research carried out for Breast Cancer Now and Prostate Cancer UK[2], looked at the availability of breast cancer medicines in a number of developed countries with similar health systems to that of the UK. This research found that in France, Germany, Canada and Australia, Kadcyla has become a standard of care. We are also aware that Kadcyla is available in many other countries. It is vital that the NHS can provide clinically effective treatments to patients, which

[1] HL3340 Parliamentary written question answered by Lord Prior on 19 November 2015.
[2] International comparisons of Health Technology Assessment, Breast Cancer Now and Prostate Cancer UK, July 2016.

equal those available in other developed countries. We cannot close the gap in cancer outcomes with other European countries if the available treatments for cancer are not on a par with what is available in those countries.

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

Not that we are aware of.

Yours sincerely,

[redacted]

[redacted]

Breast Cancer Now

APPENDIX A

What does Kadcyla mean to you?

On 29 December 2016, NICE announced that Kadcyla would not be recommended for use on the NHS, in a draft decision on the drug. This is because NICE did not think that Kadcyla was good value for money. Kadcyla was also compared to the drug lapatanib, which is not routinely available to patients on the NHS, which we believe has also contributed to the negative decision on the drug.

However, the decision is not final and we now have until 20 January to submit a response to NICE as Breast Cancer Now. We are therefore looking for patients who are either taking Kadcyla at the moment or where it will be their next drug to help us make a compelling argument about why this drug is so important and should stay available to NHS patients.

If you would like to help, please tell us about your experience of Kadcyla and/or what the drug means to you in a short statement and email it to [redacted] by **Tuesday 17 January 2017**. We will then include your statements in our submission to try to change NICE's decision on Kadcyla.

Name: Patient from London	**Age:** 34

Statement:

At the age of 32 my life was shattered. I was told I had not only breast cancer, but it was very very aggressive and had also metastasised to my lungs. I was going to die - and likely before I turned 35. My cancer is ER+, PR+ and HER2+. My tumour grew from nowhere and was 10cm when I was diagnosed 3 weeks after finding the lump.

I was immediately started on palliative chemotherapy. This was docetaxel, perjeta and herceptin. After 3 rounds my lump had reduced by over half. After 6 rounds, my CT scan was clear (NED). Perjeta is on the CDF and is said to add months on to a life. My scans are currently STILL clear and now we are 2 years on.

I'm saying this as kadcyla is my next drug after herceptin and perjeta stop working for me. Kadcyla is a drug that is said to have a similar outcome to perjeta and this drug has not only kept me stable but kept me CLEAR of cancer for 2 years. This means that kadcyla could work just as well for me or even better. But I'll never know if I'm not given a chance. A chance of life and a chance to make it closer to 40.

It's sad I have to beg to live to the age of 40 but sadly that's what I'm having to do. Without this drug it's unlikely I will.

What does Kadcyla mean to you?

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Name: [redacted]	**Age: 30**

Statement:

My mets are in lymph nodes in my neck, down my windpipe to lung. Started Kadcyla in March 2013 at [redacted]. I can't rave about Kadcyla enough. I've done loads while I've been on it! I was told I was incurable at the age of 27 and started Kadcyla then – I've been on it nearly three years now. I decided to start making memories instead of feeling sorry for myself. First thing I did was learn to drive so I could continue working as my employer was moving to the other side of the city. I passed my test and got my car. I've discovered a love of camping and go a few times a year, I love it in France. Been to Italy, seen the northern lights in Iceland and experienced the blue lagoon, and here I am in Australia at the moment. I went to the Barrier Reef yesterday and was snorkeling in the sea. Seen the opera house and seen Sydney skyline from Taronga zoo while looking at giraffes... I plan to do so much more (when I can afford it) I could go on forever. It's just made me look at life differently, sad I have to get cancer to see it but being on Kadcyla means I can enjoy what I have got left. My wish is that everyone can get it who needs it and be able to make the memories I've been able to make with my family.

What does Kadcyla mean to you?

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Name: [redacted]	**Age: 35**

Statement:

I had been on Kadcyla for 2 and a half years. Campaigned on BBC breakfast couch with NICE and Breast Cancer Now. Their arguments were it wasn't worth the price tag of £80k per year to extend ladies lives by 6 months....My argument was 'who has the right to put a price on my life' to my 4 children. I am priceless. I had an amazing quality of life on Kadcyla with minimal side effects (again priceless!!).

After being told she was out of treatment options on the NHS in January 2016, [redacted] is now funding private treatment at [redacted].

What does Kadcyla mean to you?

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Name: [redacted]	**Age: 38**

Statement:

I was diagnosed November 2011 with SBC to the other breast and skin. I'm under [redacted] hospital. Was put on Kadcyla (Marianne trial phase3 with Kadcyla-TDM1 as it was called with Pertuzumab). I've since been unblinded and did receive both drugs together. I was on it from Nov 2011-Feb 2014. Slight progression in my lymph node under left arm so had to cease the trial under trial rules. These are my SBC lines I've had since 2011.
1st line = kadcyla with Pertuzumab. Full response.
2nd line=Herceptin with anastrozole (even though my cancer changed status to hormone negative)... this did not work and after 2 months my cancer progressed to the skin and lungs.
3rd line Cape/lapatinib funded on the CDF and it was funded as I had herceptin previously which was a criteria to get funding. I had a full response until progression.
My cancer progressed again in July 2016 to the left breast so I had a mastectomy and radiotherapy. My latest CT in Dec was clear. Currently I'm off all drugs due to low platelets but if platelets recover will have lapatinib at half dose until progression.
Next line? Might be eligible for the SOPHIA trial which is the experimental drug Margetuximab with chemo or herceptin and chemo or will self fund herceptin to have with lapatinib then after this herceptin with vinorelbine. No further funded her2 drugs available.
I'm lucky that I have fully responded to two her2 lines of treatment which have given me over 5 years.

What does Kadcyla mean to you?

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If you would like to help, please tell us about your experience of Kadcyla and/or what the drug means to you in a short statement and email it to [redacted] by **Tuesday 17 January 2017**. We will then include your statements in our submission to try to change NICE's decision on Kadcyla.

Name: [redacted]	**Age: 35**

Statement:

I was diagnosed with breast cancer and liver mets in a double whammy on my sons 3rd birthday in November 2011. In Jan 2013 I started Kadcyla or TDM-1 as it was known then. I had Kadcyla for 2 years on a clinical trial. I came off it in February 2015 whilst I underwent some separate investigations. What was supposed to be a temporary decision has turned into something more permanent as I've been progression free from liver mets for almost two years without any treatment. I haven't been on any treatment since February 2015. Kadcyla is my wonder drug!

What does Kadcyla mean to you?

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Name: [redacted]	**Age: 43**

Statement:

I was 29 when I was diagnosed with primary breast cancer and 31 when I was diagnosed with secondaries. In January 2012 I had already had 7 years of continuous chemotherapy regimes. Completely desperate, as cancer was travelling fairly rapidly across my skin, I was accepted on the clinical trial for Kadcyla at [redacted]. At that point I only had one other treatment option which was Eribulin (Halaven) which was not available on the NHS. So not really an option for me.

Kadcyla did literally save my life. I arrived at the clinic very unwell and wearing dressings and a tubi grip (with arm holes cut out of it) on the top half of my body as the cancer on my skin was weeping so badly and skin had started to rot and smell really bad. I had mets in my lymph nodes around the neck/collar bone, along my abdomen and chest wall. I could see the skin mets starting to disappear after 2 cycles of Kadcyla. I was on it for 2 years and 10 months (Jan 2012 – October 2014). I had to come off it because my liver needed a bit of a rest. Kadcyla was still working as far as the cancer was concerned. I was told that there was no reason (apart from cost) that I couldn't revisit Kadcyla once my liver had recovered. My quality of life improved massively, very rapidly. My skin mets started to disappear after the 2nd cycle. The main side effect that I experienced were periods of tiredness. But in between these periods I was able to live a fairly full life. Whilst on Kadcyla, I enjoyed holiday to places including India and USA, played an active role in my 9 year old daughter's (now 14) life and just as importantly it gave me hope. And rightfully so, because after Kadcyla in December 2014 I enrolled on the Shionogi Phase 1 trial for a drug that wasn't available in 2012. I have been on this drug and Herceptin for the past 2 years and touch wood, I am doing well. The extending life by 6 months statistic is complete rubbish. I may not be on Kadcyla now, but without it, I would not be here now. So 5 years on from starting Kadcyla, I am feeling very alive and am a very big part of my teenage daughter's life and if I need them, I have more options available to me to extend my life by many more years.

What does Kadcyla mean to you?

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Name: [redacted]	**Age: 33 years**

Statement:

This decision is unfair and unjust - When I got diagnosed with Stage 4 breast cancer, I got told I had years to live as there were third-line treatments available (firstly, Herceptin, then Kadcyla, then Tykeb). This knowledge alone helped me come to terms with my diagnosis. You can imagine the upset when I heard you were removing Tykerb from the NHS. So I'd only have 2 chances, I thought. Now, again you are talking about removing a life-saving drug that could give young women like me years of life left with their families. You are only giving us one drug when there are three available. That is extremely cruel. I am a working mother, working for the Government Digital Service, contributing to the economy and paying my taxes, receiving no benefits from the state. How is this fair?

This decision ignores differences in breast cancer responses (from diff types of breast cancer) - In this decision, the different breast cancers Kadcyla treats are being ignored. Kadcyla works on HER2+ breast cancers, so women who are HER2+ with no other factors like hormone involvement tend to do best. They tend to live YEARS. Women who are HER2+ and hormone positive don't respond as well to the drug and tend to live months. This brings down the statistics. Research here: http://www.hematologyandoncology.net/index.php/archives/july-2016/long-term-outcomes-of-neoadjuvant-treatment-of-her2-positive-breast-cancer/ In the conclusion, it states: "Neoadjuvant studies using chemotherapy plus HER2-targeted therapy consistently demonstrate higher pCR rates in the HR– subgroup than in the HR+ subgroup."

This decision is based on inaccurate facts

I keep hearing Kadcyla only gives 6-9 months of life but the cost of the drug is £90,000. The cost of the drug is only £90,000 if it's used for 14 months. So if you are going to argue Kadcyla only gives 6 months, at least use the right price tag (£38,000). And on that note, chemotherapy costs not that much less if used for 6 months. But then chemo seldom keeps people alive for 6 months does it?

What does Kadcyla mean to you?

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If you would like to help, please tell us about your experience of Kadcyla and/or what the drug means to you in a short statement and email it to [redacted] by **Tuesday 17 January 2017**. We will then include your statements in our submission to try to change NICE's decision on Kadcyla. Please let us know if you wish to remain anonymous.

Name: [redacted]	**Age:** 56

Statement:

Kadcyla means I get to live! I have incurable breast cancer which as you can imagine is an awful thing to hear. Kadcyla has given me hope and life, my cancer is getting better. My children get to keep me, their Mum for much longer. Since this statement about withdrawing it I have cried every day as I know my life is shortened but I am LIVING it but there are some people whose life will end. PLEASE DO NOT WITHDRAW CADCYLA.

Love [redacted] lady trying to enjoy something in every bonus day.

What does Kadcyla mean to you?

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Name: [redacted]	**Age: 44**

Statement:

I am being treated at St Barts in London. I was diagnosed with inflammatory breast cancer in October 2012. Had the full Fect, mastectomy, axilla clearance, 25 rads followed by the Herceptin 2013. I started February 2014 Kadcyla for mets to liver, bones and lung and later brain mets. Have been on Kadcyla ever since and it has stabilised my aggressive inflammatory breast cancer. I have sung from the roof tops about this drug and how it should be accessed by all. I can't return to be near my family in Scotland as would not be able to get the drug. I am struggling now with platelets due to long term use on the drug so we are on a reduced dose and moved to 4 week cycles to try to eek it out for as long as possible. I have had two cyber knife blasts, the first being over 2 years ago. I am currently recovering from brain surgery as original met developed a liquid cyst around it but hoping to go back onto Kadcyla when platelets recover.

I have achieved things I never thought would have been possible on a chemo drug due to its targeted nature. Travelled, climbed mountains, completed a 42 mile bike challenge and most importantly played an active role as a mum to my two energetic boys and that is priceless. I am grateful for this drug ever day there is no price that can be put on a drug that has given me not just extra time but quality extra time.

What does Kadcyla mean to you?

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Name: [redacted]	**Age: 59**

Statement:

I have terminal HER2 + breast cancer, with secondaries in liver, bones, lungs and lymph nodes. Diagnosed last May, when it had already spread. I was told I could reasonably expect 2 good years of life initially on Herceptin/Pertuzamab and then Kadcyla. Initially I had to have chemotherapy as well, and this has compromised my life for the past 8 months. So my expectation was to have at least another 16 months of quality life, but without Kadcyla this time will probably be halved.

It seems very unfair that Kadcyla has been available up to now, and will be available again when it is off patent, but for those of us who will need it in the meantime it will not be available.

I understand the cost of developing new drugs, and also the budget constraints of the NHS, but a system which sees effective ground breaking drugs being developed and then not available to the people who need them is a broken system. Surely some imagination can be applied to find a way around the usual price modelling of Roche and the cost/benefit analysis of NICE. Maybe Roche could have a longer patent period, or funding could separate the marginal cost of supplying the drug from the historic development costs?

Kadcyla is available in other countries – even Greece! The NHS is severely under funded, yet the figures are not being publicised. We pay only about 6% of GDP on healthcare – less than any other European country apart from Ireland and Luxembourg. We need to fund the NHS more effectively and stop wasting money, such as the £10bn wasted on the NHS IT system before it was abandoned.

My family are devastated by the news of NICE's draft decision. My birthday is tomorrow – maybe my last if Kadcyla is withdrawn as there seems to be no alternative. The substantial additional period of lifetime that we thought Kadcyla would give us together would mean everything to us.

What does Kadcyla mean to you?

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Name: [redacted]	**Age: 56**

Statement:

Kadcyla has been very important for me to live whilst I undergoing treatment for advanced breast cancer – the tumour in my liver was deemed to be unresectable.

Although I coped and kept going with surgery, chemo and radiotherapy, it was grim. I worked a bit, but regular chemotherapy is not a doddle. Exhaustion and hair loss is just the least of it. Putting on a brave face and wearing a wig just a surface issue, getting up vomiting and going to work to deal with the VAT is about the hardest thing I have ever done. It wasn't simply because I don't have enough sick pay at work to cover my mortgage, I actually like work – work allows me to make my contribution, and I think that's pretty near the most important thing, making my life make a difference. And Kadcyla means that my life isn't over, it really gives me hope.

There is a big hole where my 45mm tumour used to be in my liver, and scar tissue and other bits, but I am cancer free without having to take another year off my life. My work is precious; I have kept the business going. Eight people are employed, because I could keep going, and Kadcyla made it possible for me.

I know that we need to control costs in our NHS, but we need to invest in cancer treatment too – with about half of us getting cancer, more of us are learning to live with the Big C than ever before, we need innovation in our drugs and that's what we need to invest in.

The Cancer Drugs Fund enabled me to get this innovative drug on the NHS, it doesn't have the same guidelines and strict 'proven' criteria that NICE require, but they didn't seem to be able to collect as much evidence as was needed for this drug. Maybe we need a Cancer Drugs Fund mark 2. I have been kicked off two trials already, because my cancer was just too plain aggressive, so I don't feel good at all about the idea of hoping that a new trial will come along.

Hi

My name is [redacted] and I am 48 years old, the mother of a 19 year old son, and a 14 year old daughter.

I was diagnosed with primary breast cancer in October 2013, and before treatment could start, following a variety of scans, was diagnosed with secondaries in my right hip and sternum. I underwent an 18 week cycle of docetaxol along with herceptin and pertuzamab, and continued with the herceptin/pertuzamab combo as maintenance. These kept me stable until around May 2016 when the cancer spread slightly within my hip.

By September 2016, it was clear that the combo had ceased to work as scans showed it had spread to my spine and lungs. At this stage I had a difficult decision to make. I could either go onto Kadcyla, or take part in phase 1 trials of SYD985. With the understanding that Kadcyla would probably still be available should the trial fail to work further down the line, I opted to go on the trial drug.

To hear last week that Kadcyla might not be available after the trial, was devastating to me, as it is still my next available option. I'm not ready to die and give up on my children. Kadcyla has been proven to extend life in ladies such as myself and I am worth the £90,000 the drug costs. Every woman or man who needs Kadcyla is worth the cost. The Government MUST come to some sort of realisation that it's own citizens are needlessly having premature deaths. Never mind about saving lives of people in Africa, it's time that the Government looks closer to home.

People like me need Kadcyla. We need more time with our families. We didn't choose to have cancer, it's not our faults so why should we miss out on the drugs that can help to extend our lives?

Thank you, and I hope this helps.

[redacted]

My name is [redacted] and I am 44 years old.
I have two children aged 12 and 9. I am also being treated for inflammatory breast cancer, which is particularly aggressive.
There is a 40pc chance that my treatment will not work and, once spread, my cancer will be terminal.
Kadcyla to me, means hope and survival. It means that if I need it and I can have it, I might get to see my daughter go to secondary school, maybe university, maybe married and with child.
Please don't take this away from me.
Yours faithfully
[redacted]

Dear [redacted]

I have only just seen your e-mail about the Nice refusal to fund Kadcyla. I realise that you asked for reponses by yesterday so I hope that I am not too late. I went onto a drug trial programme for Kadcyla in April 2013, after having been treated with Cyclophosphamide and Epirubicin, then Taxotare, Herception and finally capecitabin/lapatinib. Despite all of these my breast cancer returned again in my neck and then my shoulder. I had several tumours across my left shoulder, one being 51/2 cm long. This made doing many things uncomfortable encluding walking any distance as the pain in my shoulder was so severe. I had to give up my job as a school dinner lady because I could not stand for any period of time. After 2 sessions of Kadcyla the tumours had shrunk considerably and within 6 months had completely gone. I have very few side effects except I am more tired than I used to be (this may also be because I am now in my mid 50s). I feel that I have got my life back. I am able to go on holiday, go shopping, go to the gym and do the things that I used to do.

The original Kamilla trial has now ended but I am still receiving Kadcyla every 3 weeks and am on a new trial to examine the long term side effects of it's use. Although my treatment is funded by Roche I feel very strongly that all women who could benefit from this drug should have access to it through the NHS, and so have the chance of survival that I have been given.

Yours sincerely

[redacted]

Name: [redacted] Age: 69

I am writing this on Ward [redacted] while my daughter [redacted] is having treatment with Kadcyla.

[redacted] is 35 and has two children aged 10 and 8. In the summer of 2012 she suffered pain in the left breast and went to her GP, saying she was worried she might have breast cancer. The young doctor, following NICE guidelines, told her that it could not be cancer because "breast cancer does not present with pain".

Consequently there was an eight-month delay, which we will always regard as fateful. She was finally referred by another doctor who by now could feel a lump (though she still said the guidelines were against referral). As soon as staff at the Breast Clinic at Birmingham Women's Hospital examined [redacted] they - in her words - "were running around like headless chickens".

There was a large tumour in the breast and another under her arm, and a scan indicated cancer in the liver and lungs. A doctor told her: "We are not going to lie to you: we are very worried."

So much so, in fact, that her consultant decided to start treatment straight away with docetaxel rather than a milder drug, as would have been normal.

Fortunately, [redacted] response was dramatic. After a mastectomy it was found that there was no cancer left in the breast. The doctor who gave her the results told her the response to chemotherapy was a good indicator for prognosis, and that her prognosis was "very good".

But after only a few months of being treated with Herceptin alone, scans revealed that the cancer in the lungs was growing. So at the beginning of 2015 [redacted] began treatment with Kadcyla. Since then her cancer has remained stable and the fact that Kadcyla is highly targeted means that the side effects are much milder than with docetaxel.

The actual treatment takes 30 minutes once every three weeks, and apart from a couple of days of extreme tiredness [redacted] is able to lead a normal and active life between treatments. She goes hill walking and in the summer went for a 14-mile bicycle ride with her children. You have to remember that when she was first diagnosed it seemed unlikely she would live long enough to see either of her children learn to ride.

I feel that Kadcyla has been poorly reported and that the quality, as well as the extension, of life it delivers has been little understood. For our family it has delivered huge benefits: not least for my grandchildren who have had their mother to help them through years of rapid growth and development. They are very different people now from the six and four year-olds they were when [redacted] was diagnosed.

Cancer puts huge stress not just on the individual patient but on a wide circle of family and friends: parents, partners, sisters and brothers, aunts and uncles. In a sense, we are all on Kadcyla.

Awaiting the results of the latest scan is always stressful. Fortunately we had good news this week and can relax for another three months. To people with an objective, value-for-money perspective that might sound pathetic, but this time is indescribably precious to us.

Yesterday, in the Brexit euphoria following the prime minister's speech, I heard it claimed that we have the strongest economy in Europe. In that case, why do we value women's lives less than our neighbours in France and Germany? The thought that other women who find themselves in the same situation as our daughter will not be able to enjoy the same quality of treatment in the future makes me feel physically sick.

Please, reverse this decision, as the editorial in *The Lancet* urges, and resume efforts to make this wonderful drug generally available.

*The names have been changed to protect patient confidentiality.

What does Kadcyla mean to you?

On 29 December 2016, NICE announced that Kadcyla would not be recommended for use on the NHS, in a draft decision on the drug. This is because NICE did not think that Kadcyla was good value for money. Kadcyla was also compared to the drug lapatanib, which is not routinely available to patients on the NHS, which we believe has also contributed to the negative decision on the drug.

However, the decision is not final and we now have until 20 January to submit a response to NICE as Breast Cancer Now. We are therefore looking for patients who are either taking Kadcyla at the moment or where it will be their next drug to help us make a compelling argument about why this drug is so important and should stay available to NHS patients.

If you would like to help, please tell us about your experience of Kadcyla and/or what the drug means to you in a short statement and email it to Francesca.demunnich@breastcancernow.org **by Tuesday 17 January 2017.** We will then include your statements in our submission to try to change NICE's decision on Kadcyla. Please let us know if you wish to remain anonymous.

Name: [redacted]	**Age:** 42

Statement:

Hello. I'm [redacted], 42 years old, diagnosed with stage iv, HER2+ breast cancer 5 years and 3.5 months ago.

I am currently on Herceptin but am counting on Kadcyla when the cancer becomes resistant to Herceptin. I am in contact with [redacted] who, when all other options had run out, tried Kadcyla under compassionate use. For the last 4 years, she has had NED (No Evidence of Disease)!!! I know the drug doesn't work for everyone, but I want to be given that chance to try it! Who knows...I too can become NED and get another chance of life...how can another human being deny me that?

Although my children are now 12 and 9, there are milestones that I want to be here to attend...

What does Kadcyla mean to you?

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If you would like to help, please tell us about your experience of Kadcyla and/or what the drug means to you in a short statement and email it to [redacted] by **Tuesday 17 January 2017**. We will then include your statements in our submission to try to change NICE's decision on Kadcyla.

Name: [redacted]	**Age: 39**

Statement:

I feel so strongly about this drug it has been amazing for me. I've had secondaries for 11.5 years and been on Kadcyla for 6 yrs and 8 months. I have had side effects and had to have reduced dose and treatment moved to every 4 weeks. Tumours on my liver took about 18 months to disappear off my scans so now I'm NED. I've been well enough to travel to Australia for 4 weeks, New York for my daughters 21st (which I never dared hope I would see). Basically I've seen my children develop into young adults and they were 7 and 4 when I was diagnosed originally at 27. So for me and lots of others it's been a life saver and a blessing to my whole family.

Hello [redacted]

Apologies for the late email.

I've been on Kadcyla since the end of 2016 and although I am tired any pain I had in my liver and bones has gone.

I live as normal as life as possible. I go to work, I pay taxes, I socialise and everything else. I am NOT lying on my death bed waiting for the grim reaper.

With kind regards

[redacted]

APPENDIX B

Younger Breast Cancer Network

Response to NICE appraisal consultation document: Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane

Contact details: [redacted]

Introduction – The Younger Breast Cancer Network

The Younger Breast Cancer Network ("YBCN") is an online voluntary peer support organisation founded in the last five years, already with more than 2,500 female members from across the UK. All YBCN members have had a diagnosis of primary or secondary breast cancer at age 45 or under. YBCN members' individual experiences, taken in combination, provide a compelling insight into the treatment of breast cancer and its effects. A significant proportion of YBCN members with secondary breast cancer have a diagnosis of HER2+ metastatic breast cancer. Some currently receive Kadcyla, and their input enables us as a group to build a composite picture of their experience and the side effects of this treatment, while others are at earlier stages of progression.

Response to consultation questions:

Has all of the relevant evidence been taken into account?

We consider that the evidence presented as relating to current clinical practice has been incorrectly interpreted (section 4.3).

The original selection of lapatinib plus capecitabine as a relevant comparator was based on being reflective of current clinical practice. However, lapatinib plus capecitabine was removed from the cancer drugs fund in January 2015, lapatanib as a standalone treatment having previously been rejected by NICE in 2010. People with secondary breast cancer are no longer able to access treatment with lapatinib as it becomes indicated. As such it does not represent the current standard of clinical practice. Lapatinib plus capecitabine is a flawed comparator, resulting in failure of the evidential standard required for an accurate assessment.

YBCN considers that the estimated life extension does not accurately reflect the benefit of Kadcyla to patients, as demonstrated by the experience of members of our group. The reduced side effect profile compared to the remaining chemotherapeutic agents has not been appropriately taken into account. The consistent finding of YBCN members is that the side effects of Kadcyla enable them to lead full lives without the debilitation of serious side effects. This would not be the case with remaining treatment options. To be quite clear, your provisional rejection of Kadcyla not only presents our members with the prospect of dying sooner, but also of unnecessary suffering during their remaining life.

Section 4.18 and 4.19 discuss the supplementary advice criterion for short life expectancy and the need to be guided by established practice in the NHS regardless of funding. As clarified above the issue of funding of the comparator is no longer applicable, as the comparator itself is no longer available.

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

As discussed in the response to the previous question, the assessments of clinical and cost effectiveness do not reasonably interpret the available evidence, due to lack of patient access to the key comparator in the EMILIA trial, lapatinib plus capecitabine. Assumptions have been made to fit the available evidence to the standard of comparison required, undermining reasonable interpretation of the evidence.

Further, we have concerns that the cost effectiveness summaries do not take into account the side effect profile of Kadcyla compared with the remaining treatments which would be available to patients on the NHS following its removal from access. Chemotherapy agents present significant incremental costs associated with debilitating side effects including neutropenia.

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

Based on the points raised above we do not believe there is sufficient evidence comparing the improved life expectancy of Kadcyla versus the treatments available to our members in the NHS setting to correctly determine cost-benefit to patients.

In light of this, Kadcyla should be made available until a stronger evidence base is identified to determine the true increase in life expectancy and difference in side effect profile with Kadcyla. It would equally be unethical to subject some women with secondary breast cancer to an alternative regimen far below modern day international standards of care purely for the purposes of creating comparator data. Consequently, assessment would necessarily have to be based on historical data relating to the proposed reduced standards of care rather than estimating against an unsuitable comparator in order to produce a legitimate cost-benefit analysis.

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

The NICE Guide to the methods of technology appraisal (2013) states that:

> *2.23 ...The scope may highlight potential subgroups of the population for whom the clinical or cost effectiveness of the technology might be expected to differ from the overall population*

We note the remarks of the committee in the appraisal consultation document in relation to the EMILIA trial that:

4.6 ... The committee appreciated that patients enrolled in clinical trials may be younger and with better performance status than those in routine clinical practice, and so might have better outcomes...

This comment suggests a general acceptance by the committee that younger age is likely to have an impact on the clinical and cost effectiveness of Kadcyla. As such, it is then inappropriate that the younger women are not considered as a potential subgroup for which separate assessment would be indicated.

There is significant evidence that breast cancer in younger women (<45) is a different disease with different pathology to that in older women.

Azim H & Partridge[1] (2014) state "Expression of key biomarkers, including endocrine receptors, HER2 and proliferation markers, appears to be different in younger patients". This view is corroborated by Hatem et al[2] (2015) who conclude that tumours arising at different ages are biologically distinct.

Studies by Anders et al (2011), Hatem et al (2014) and Howlader et al (2013)[3] have all concluded that Her-2 positive breast cancer is more prevalent in women diagnosed at a younger age, with percentage ranges of 20 to 30 percent of breast cancers diagnosed at below 45 versus 16 to 23 percent in those diagnosed after 65 years of age.

It is also well demonstrated that breast cancer in younger women is likely to manifest with a worse prognosis due to a higher proportion of high grade and late stage tumours, by Anders et al (2011)[4], Lee and Han (2014)[5], Cancello et al (2010)[6], Copson el al (2015) POSH study[7], Stenger et al (2014)[8].

The difference in tumour pathology alongside the poor reported outcomes for younger patients means that many persons for whom Kadcyla is indicated will be younger than the overall profile of people with breast cancer. It also indicates that

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[1] Azim HA Jr, Partridge AH. Biology of breast cancer in young women. Breast Cancer Res. 2014 Aug 27;16(4):427

[2] Hatem A. Azim, Jr, Bastien Nguyen, Sylvain Brohée, Gabriele Zoppoli, and Christos Sotiriou Genomic aberrations in young and elderly breast cancer patients BMC Med. 2015; 13: 266.

[3] Nadia Howlader, Sean F. Altekruse, Christopher I. Li, Vivien W. Chen, Christina A. Clarke, Lynn A. G. Ries, Kathleen A. Cronin US Incidence of Breast Cancer Subtypes Defined by Joint Hormone Receptor and HER2 Status Oxford JournalsMedicine & Health JNCI: Jnl of National Cancer Institute Volume 106, Issue 510.1093/jnci/dju055

[4] Carey K. Anders, Cheng Fan, Joel S. Parker, and Lisa A. Carey Breast Carcinomas Arising at a Young Age: Unique Biology or a Surrogate for Aggressive Intrinsic Subtypes? JOURNAL OF CLINICAL ONCOLOGY CORRESPONDENCE Jan 2011

[5] Han-Byoel Lee and Wonshik Han Unique Features of Young Age Breast Cancer and Its Management J Breast Cancer. 2014 Dec; 17(4): 301–307.

[6] Cancello G, Maisonneuve P, Rotmensz N, Viale G, Mastropasqua MG, Pruneri G, Veronesi P, Torrisi R, Montagna E, Luini A, Intra M, Gentilini O, Ghisini R, Goldhirsch A, Colleoni M. Prognosis and adjuvant treatment effects in selected breast cancer subtypes of very young women (<35 years) with operable breast cancer. Ann Oncol. 2010 Oct;21(10):1974-81

[7] Copson E, Eccles B, Maishman T, Gerty S, Stanton L, Cutress RI, Altman DG, Durcan L, Simmonds P, Lawrence G, Jones L, Bliss J, Eccles D; POSH Study Steering Group. Prospective observational study of breast cancer treatment outcomes for UK women aged 18-40 years at diagnosis: the POSH study.

[8] Stenger M Incidence of Breast Cancer According to Joint Hormone Receptor and HER2 Status Differs According to Race/Ethnicity and Other Factors http://www.ascopost.com/News/16208 2014

failure to consider younger persons as a distinct subgroup in assessment raises discrimination concerns which must be addressed.
As an addendum to YBCN's consultation response, we also attached eight individual YBCN member statements below which comprise a significant snapshot of how the withdrawal of this drug will impact our members.

[redacted]-I've only been on Kadcyla for just over a year and haven't done anything spectacular except work part time as a TA for Children with additional needs, exercise 4 times a week, run a home, with help from my husband and continue to raise 3 growing up children, oh and keep my lung mets stable! Will that do?

[redacted]- I was diagnosed Nov 2011 with SBC to the other breast and skin. I'm under [redacted] hospital. Was put on kadcyla (Marianne trial phase3 with Kadcyla-TDM1 as it was called with Pertuzumab. I've since been unblinded and did receive both drugs together. I was on it from Nov 2011-Feb 2014. Slight progression in my lymph node under left arm so had to cease the trial under trial rules. These are my SBC lines I've had since 2011.
1st line = kadcyla with Pertuzumab. Full response.
2nd line=Herceptin with anastrozole (even though my cancer changed status to hormone negative)... this did not work and after 2 months my cancer progressed to the skin and lungs.
3rd line Cape/lapatinib funded on the CDF and it was funded as I had herceptin previously which was a criteria to get funding. I had a full response until progression. My cancer progressed again in July 2016 to the left breast so I had a mastectomy and radiotherapy. My latest CT in Dec was clear. Currently I'm off all drugs due to low platelets but if platelets recover will have lapatinib at half dose until progression. Next line? Might be eligible for the SOPHIA trial which is the experimental drug Margetuximab with chemo or herceptin and chemo or will self fund herceptin to have with lapatinib then after this herceptin with vinorelbine. No further funded her2 drugs available.
I'm lucky that I have fully responded to two her2 lines of treatment which have given me over 5 years

[redacted]- I have been on Kadcyla for 2 and a half years. Campaigned on BBC breakfast couch with NICE and Breast Cancer Now. Their arguments were it wasn't worth the price tag of £80k per year to extend ladies lives by 6 months....My argument was 'who has the right to put a price on my life' to my 4 children I am priceless. I had an amazing quality of life on Kadcyla with minimal side effects (again priceless!!) And They are completely out of date with their average on extending life's by six months.... Both Julie and I have/ had been on it for over 2 years....Good luck xx

[redacted]– I am being treated at [redacted] I was diagnosed with inflammatory breast cancer in Oct 2012. Had the full FEC-T, mastectomy,

axillary node clearance, 25 rads followed by herceptin in 2013. I started February 2014 kadcyla for mets to liver, bones and lung and later brain mets. Have been on kadcyla ever since and it has stabilised my aggressive inflammatory breast cancer. I have sung from the roof tops about this drug and how it should be accessed by all. I can't return to be near my family in Scotland as would not be able to get the drug. I am struggling now with platelets due to long term use on the drug so we are on a reduced dose and moved to 4 week cycles to try to eek it out for as long as possible. I have had two cyber knife blasts, the first being over 2 years ago. I am currently recovering from brain surgery as original met developed a liquid cyst around it but hoping to go back onto kadcyla when platelets recover.
I have achieved things I never thought would have been possible on a chemo drug due to its targeted nature. Travelled, climbed mountains, completed a 42 mile bike challenge and most importantly played an active role as a mum to my two energetic boys and that as [redacted] says is priceless. I am grateful for this drug ever day there is no price that can be put on a drug that has given me not just extra time but quality extra time..

[redacted] - my mets are in lymph nodes in my neck, down my windpipe to lung. Started kadcyla in March 2013 at [redacted]. I can't rave about Kadcyla enough. I've done loads while I've been in it! I was told I was incurable at the age of 27 and started kadcyla then – I've been on it nearly three years now. And decided to start making memories instead of feeling sorry for myself. First thing I did was learn to drive so I could continue working as my employer was moving to the other side of the city. I passed my test and got my car :-) I've discovered a love of camping and go a few times a year love it in france. Been to Italy seen the northern lights in Iceland and experienced the blue lagoon, and here I am in australia at the moment I went to the barrier reef yesterday and was snorkeling in the sea. Seen the opera house and seen sydney skyline from Taronga zoo while looking at giraffes... I plan to do so much more (when I can afford it :-)) I could go on forever. It's just made me look at life differently sad I have to get cancer to see it but being on Kadcyla means I can enjoy what I have got left. My wish is that everyone can get it who needs it and be able to make the memories I've been able to make with my family.

[redacted] - I've had secondaries for 11.5 yrs and been on Kadcyla for 6 yrs and 8 months. I have had side effects and had to have reduced dose and treatment moved to every 4 wks. Tumours on my liver took about 18 months to disappear of my scans so now I'm NED. I've been well enough to travel to Australia for 4 wks, New York for my daughters 21st (which I never dared hope I would see). Basically I've seen my children develop into young adults and they were 7 and 4 when I was diagnosed originally at 27. So for me and lots of others it's been a life saver and a blessing to my whole family.

[redacted] In Jan 2012 I had already had 7 years of continuous chemotherapy regimes. Completely desperate, as cancer was travelling fairly rapidly across my

skin, I was accepted on the clinical trial for Kadcyla at t[redacted]. At that point I only had one other treatment option which was Eribulin (Halaven) which was not available on the NHS. So not really an option for me.
Kadcyla did literally save my life. I arrived at the clinic very unwell and wearing dressings and a tubi grip (with arm holes cut out of it) on the top half of my body as the cancer on my skin was weeping so badly and skin had started to rot and smell really bad. I had mets in my lymph nodes around the neck/collar bone, along my abdomen and chest wall. I could see the skin mets starting to disappear after 2 cycles of Kadcyla. I was on it for 2 years and 10 months (Jan 2012 – October 2014). I had to come off it because my liver needed a bit of a rest. Kadcyla was still working as far as the cancer was concerned. I was told that there was no reason (apart from cost) that I couldn't revisit Kadcyla once my liver had recovered. My quality of life improved massively, very rapidly. My skin mets started to disappear after the 2nd cycle. The main side effect that I experienced were periods of tiredness. But in between these periods I was able to live a fairly full life. Whilst on Kadcyla, I enjoyed holiday to places including India and USA, played an active role in my 9 year old daughter's (now 14) life and just as importantly it gave me hope. And rightfully so, because after Kadcyla in December 2014 I enrolled on the Shionogi Phase 1 trial for a drug that wasn't available in 2012. I have been on this drug and Herceptin for the past 2 years and touch wood, I am doing well. The extending life by 6 months statistic is complete rubbish. I may not be on Kadcyla now, but without it, I would not be here now. So 5 years on from starting Kadcyla, I am feeling very alive and am a very big part of my teenage daughter's life and if I need them, I have more options available to me to extend my life by many more years.

[redacted]- Hello. I'm also on Kadcyla. Have been on it since April this year to help stabilise my lung mets. So far, so good. Minimal se's, just get quite tired but it I'm carrying on looking after a 13 and 18 yr old on my own plus have returned to work full time. I'm off to discuss Kadcyla at a NICE committee at the end of November so will be making a note of these incredible success stories. Xx

breast cancer now

For immediate release: Tuesday 24th January 2017

Campaigners deliver 115,000 signatures urging NICE and Roche to save breast cancer drug Kadcyla on the NHS – as the clock ticks

Seven campaigners living with incurable secondary breast cancer today joined Breast Cancer Now in delivering the charity's petition to the National Institute for Health and Care Excellence (NICE) and Roche Pharmaceuticals, demanding the two parties reach an urgent deal to ensure breast cancer drug **Kadcyla** remains available in England on the NHS.

More than **115,000 people** across the country signed the petition urging NICE and Roche to return to the negotiating table to find an agreement that would see NICE's provisional rejection of Kadcyla – announced to patients on 29th December 2016 – overturned.

Today's hand-in brought both sides together to hear from a remarkable group of campaigners living with advanced cancer – three of whom have had Kadcyla with tremendous results and four for whom Kadcyla would be their next treatment option and who stand to miss out if NICE's decision is not reversed – about what Kadcyla means to NHS patients, as the clock ticks down on the final decision.

The consultation period on the draft decision closed on Friday (20 January 2017) and the NICE committee will now meet again next week – on **Wednesday 1st February 2017** – to make a final decision on whether Kadcyla will be made routinely available on the NHS.

Kadcyla (trastuzumab emtansine) is currently being funded for patients through the Cancer Drugs Fund (CDF), but unless this draft recommendation is reversed ahead of its final consultation, this drug would now not be available to new patients in England – despite currently being available in this and many other European countries.

Kadcyla is a unique and effective combination drug for incurable secondary breast cancer that is HER2-positive, and is used as a 'second-line' treatment when a patient's disease has progressed on other treatments. It specifically targets the cancerous cells leaving healthy cells relatively untouched, meaning that the side effects normally associated with chemotherapy treatment are reduced.

According to NICE's recent draft assessment, Kadcyla offers on average an extra 9 months of additional and good quality life – with minimal side effects – **compared to existing treatments**, with many women even living on it for many years.

Having been available via the CDF since 2014, there are many women living with incurable breast cancer who have for some time been relying on the promise of Kadcyla as their next and possibly final treatment option to significantly extend their lives. More than 1,200 women living with secondary breast cancer each year in England would be eligible to take the drug, which is available in 18 other countries.

The petition was formally handed in this afternoon to **Meindert Boysen** (Programme Director at NICE) and **Richard Erwin** (UK General Manager at Roche) at Breast Cancer Now's office in Aldgate, calling on both parties to find a compromise ahead of the upcoming final NICE committee meeting.

Handing the petition over to NICE and Roche alongside the charity's [redacted] were campaigners and secondary breast cancer patients [redacted] – all of whom have very bravely shared their personal stories publicly this month to rally support and plead with NICE and Roche to reconsider.

[redacted] **at Breast Cancer Now, said:**

"This is the very last chance for Kadcyla in England. If a deal is not reached this week, more than a thousand women with incurable breast cancer each year will be cruelly denied significant extra time with their families.

"We have been overwhelmed by the support from the public in a very short time and are truly grateful that over 115,000 people have taken this stand for women with incurable breast cancer."

"Patients desperately need this crucial option and many clinicians desperately want to prescribe it. There are very few treatment options for secondary breast cancer patients as it is and we cannot let a drug as good as Kadcyla pass England by.

"Both sides must now take responsibility before it is too late. With the final committee meeting on Kadcyla next week, Roche must lower the price even further and NICE must reconsider the inappropriate comparator drug they have used to evaluate Kadcyla's cost-effectiveness."

[redacted] **43 from Reading, took Kadcyla for three years having been one of the first patients in England to be given the drug on a clinical trial in 2012:**

"I truly believe that Kadcyla is the reason my daughter still has a mother.

"I have been living with advanced breast cancer for twelve years now. Not only did this drug give me hope at a time when I was absolutely desperate almost five years ago, it has enabled me to go on to new options that have become available since then.

"For me and many other women with secondary breast cancer, this is the closest thing we have to 'a cure' right now. I just want other women to have the chances that I have had."

[redacted] **from Croydon, was 37 when she was diagnosed with both primary and secondary cancer 18 months ago – her son** [redacted] **was just four months old. When her current treatment becomes ineffective, Kadcyla would be her next viable treatment option:**

"This drug could give me more time – and more quality time – to see my son grow up and go to school. If Kadcyla were to be taken off the NHS for good, my hopes and expectations would be absolutely shattered.

"I've a rough timescale laid out in my head of what treatments I could have and how much time I might have to live – and I've been banking on this time. These planned years have become so precious, and I'd be devastated to have them taken away."

[redacted] **49 from Aylesbury, is living with secondary breast cancer and has been on Kadcyla for 20 months to date:**

"Kadcyla has had the most amazing impact on my life. I'm living with secondary breast cancer and thanks to this drug, I have a 'normal' life back. I feel incredibly lucky to be able to have had this lifeline and I desperately want it for other women in the future."

ENDS

For more information, please contact [redacted]

Photo caption:

Notes to Editors

About Breast Cancer Now:

- Breast Cancer Now is the UK's largest breast cancer charity.
- Breast Cancer Now's ambition is that by 2050 everyone who develops breast cancer will live. The charity is determined to stop women dying from the disease, working in a new, collaborative way and bringing together all those affected by the disease to fund research, share knowledge and find answers.
- Breast Cancer Now's world-class research is focused entirely on breast cancer. The charity supports nearly 400 of the world's brightest researchers at more than 30 locations across the UK and Ireland. Together, they're working to discover how to prevent breast cancer, how to detect it earlier and how to treat it effectively at every stage so we can stop the disease taking lives.
- Breast cancer is still the most common cancer in the UK. Nearly 700,000 people living in the UK have experienced a diagnosis and one in eight women will face it in their lifetime. This year alone, more than 50,000 women will be told they have the disease.
- The UK still has one of the lowest breast cancer survival rates in Western Europe and this year alone around 11,500 women and 80 men will lose their lives. It's time to act.
- Breast Cancer Now launched in June 2015, created by the merger of leading research charities Breast Cancer Campaign and Breakthrough Breast Cancer.
- For more information on Breast Cancer Now's work, visit breastcancernow.org or follow us on Twitter or on Facebook.

20 January 2017

jenna.dilkes@Nice.org.uk

Dear Jenna

On behalf of the UK Breast Cancer Group (UKBCG) we would like to respond to the NICE Appraisal Consultation Document on Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane. The UKBCG represents Clinical and Medical Oncologists throughout the UK.

Trastuzumab emtansine is a novel antibody cytotoxic conjugate that delivers effective and well-tolerated treatment to patients with an aggressive form of breast cancer. There is considerable experience amongst UK oncologists with this agent as it has been widely used over the last two years via the Cancer Drugs Fund. In the key clinical trial EMILIA, trastuzamab emtansine increased progression free survival by three months and overall survival by six months compared to the combination of lapatinib and capecitabine, while also having a more favourable toxicity profile. When oncologists were asked to rank novel therapies for advanced breast cancer that were being prescribed through the Cancer Drugs Fund, trastuzumab emtansine and pertuzumab (another antibody directed at HER-2) were the clear first two choices by most oncologists.

NICE did not recommend the use of trastuzumab emtansine, within its marketing authorisation,for treating HER-2 positive, unresectable locally advanced or metastatic breast cancer after trastuzumab and a taxane. We are disappointed with this recommendation as it deprives patients in the UK from receiving a well-tolerated drug that prolongs life significantly. As a result of this recommendation patients in the UK will be treated with less effective and more toxic drugs than would otherwise be possible. The poor outcomes of cancer patients in the UK compared to other European countries are well described and sadly this recommendation would continue this.

As trastuzumab emtansine has been available to patients in England for some time it will not just be a case that we are not adopting a new treatment, but withdrawing an effective treatment with low toxicity. Furthermore if trastuzumab emtansine is standard of care in North America and many European countries, clinical trials exploring novel treatments for patients with relapsed HER-2 positive breast cancer require pre-treatment with this agent. As a result, patients in the UK will not be able to participate in these clinical trials.

We would also like to make a specific and important aspect of the evaluation. The comparator to trastuzumab emtansine was the combination of lapatinib and capecitabine as used in the EMILIA trial. However, as stated in the consultation document by the clinical experts consulted, this combination is hardly ever used in the UK as it is not approved by NICE. A more appropriate comparator that would be a true reflection of current UK practice would be the combination of trastuzumab and capecitabine.

We would like NICE to reconsider their recommendation and to work with Roche to find a way to make trastuzumab emtansine available for patients with locally advanced or metastatic HER-2 positive breast cancer, so that they can continue to benefit from this novel well-tolerated and effective agent that helps them live longer.

On behalf of the UKBCG

UKBCG Steering Committee: Chairs: [redacted]

Secretariat/Correspondence Address: [redacted]

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

Name	[redacted]
Role	Patient
Location	England
Conflict	No
Comments on the ACD:	

The decision not to fund Kadcycla is something that I need to challenge.

I have been a fortunate recipient of Kadcyla. I have been on the drug for about 18months. With this treatment my secondary breast cancer in the liver is nearing remission, and I have been able to work. I run a charity that would certainly close without me. It employs 8 people and last year supported 3,500 volunteers.and contributes substantially to the London economy. Through my work I have also contributed to the work of NICE with my work on pollution and public heath.

Kadcyla doesn't extend life by a mere 9months as your papers indicate.

Although the work of NICE requires strong evidence RCTs . Given the number of recipients are small, such trials do not give you the full picture: your panel would benefit from gathering qualitative evidence from people such as myself , with potentially longer to live and with significantly greater quality of life than those in the RCTs.

I am not on a trial and as such would be excluded from your evidence gathering, but would be very happy to give evidence to testify to the importance of this drug on my life and the economy.

I would like to add to m previous comments - I don't think that the figures you used for the QALY. assessment are accurate.

a) not all women with secondary breast cancer would need the drug, so the cost would not be for the whole population to use it,

b) I know several women who are working and contributing to the economy whilst taking Kadcyla - the added QALY for these women significantly outstrips the cost of the drug.

Name	[redacted]
Role	[redacted]
Organisation	[redacted]
Location	England
Conflict	No
Comments on the ACD:	

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

The NICE Guide to the methods of technology appraisal (2013) states that:

2.23 â€¦The scope may highlight potential subgroups of the population for whom the clinical or cost effectiveness of the technology might be expected to differ from the overall population

We note the remarks of the committee in the appraisal consultation document in relation to the EMILIA trial that:

4.6 â€¦ The committee appreciated that patients enrolled in clinical trials may be younger and with better performance status than those in routine clinical practice, and so might have better outcomesâ€¦

This comment suggests a general acceptance by the committee that younger age is likely to have an impact on the clinical and cost effectiveness of Kadcyla. As such, it is then inappropriate that the

younger women are not considered as a potential subgroup for which separate assessment would be indicated.

There is significant evidence that breast cancer in younger women (<45) is a different disease with different pathology to that in older women.

Azim H & Partridge (2014) state â€œExpression of key biomarkers, including endocrine receptors, HER2 and proliferation markers, appears to be different in younger patientsâ€ . This view is corroborated by Hatem et al (2015) who conclude that tumours arising at different ages are biologically distinct.

Studies by Anders et al (2011), Hatem et al (2014) and Howlader et al (2013) have all concluded that Her-2 positive breast cancer is more prevalent in women diagnosed at a younger age, with percentage ranges of 20 to 30 percent of breast cancers diagnosed at below 45 versus 16 to 23 percent in those diagnosed after 65 years of age.

It is also well demonstrated that breast cancer in younger women is likely to manifest with a worse prognosis due to a higher proportion of high grade and late stage tumours, by Anders et al (2011), Lee and Han (2014), Cancello et al (2010), Copson el al (2015) POSH study, Stenger et al (2014).

The difference in tumour pathology alongside the poor reported outcomes for younger patients means that many persons for whom Kadcyla is indicated will be younger than the overall profile of people with breast cancer. It also indicates that failure to consider younger persons as a distinct subgroup in assessment raises discrimination concerns which must be addressed.

Azim HA Jr,Â Partridge AH. Biology of breast cancer in young women. Breast Cancer Res. 2014 Aug 27;16(4):427

Hatem A. Azim, Jr, Bastien Nguyen,Â Sylvain BrohÃ©e,Â Gabriele Zoppoli,Â andÂ Christos Sotiriou Genomic aberrations in young and elderly breast cancer patients BMC Med. 2015; 13: 266.

NadiaÂ Howlader, Sean F.Â Altekruse, Christopher I.Â Li, Vivien W.Â Chen, Christina A.Â Clarke, Lynn A.Â G.Â Ries, Kathleen A.Â Cronin US Incidence of Breast Cancer Subtypes Defined by Joint Hormone Receptor and HER2 Status Oxford JournalsMedicine & Health JNCI: Jnl of National Cancer Institute Volume 106, Issue 510.1093/jnci/dju055

Carey K. Anders, Cheng Fan, Joel S. Parker, and Lisa A. Carey Breast Carcinomas Arising at a Young Age: Unique Biology or a Surrogate for Aggressive Intrinsic Subtypes? JOURNAL OF CLINICAL ONCOLOGY CORRESPONDENCE Jan 2011

Han-Byoel Lee andÂ Wonshik Han Unique Features of Young Age Breast Cancer and Its Management J Breast Cancer. 2014 Dec; 17(4): 301â€“307.

Cancello G,Â Maisonneuve P,Â Rotmensz N,Â Viale G,Â Mastropasqua MG,Â Pruneri G,Â Veronesi P,Â Torrisi R,Â Montagna E,Â Luini A,Â Intra M,Â Gentilini O,Â Ghisini R,Â Goldhirsch A,Â Colleoni M. Prognosis and adjuvant treatment effects in selected breast cancer subtypes of very young women (<35 years) with operable breast cancer. Ann Oncol.Â 2010 Oct;21(10):1974-81

Copson E,Â Eccles B,Â Maishman T,Â Gerty S,Â Stanton L,Â Cutress RI,Â Altman DG,Â Durcan L,Â Simmonds P,Â Lawrence G,Â Jones L,Â Bliss J,Â Eccles D;Â POSH Study Steering Group. Prospective observational study of breast cancer treatment outcomes for UK women aged 18-40 years at diagnosis: the POSH study.

Stenger M Incidence of Breast Cancer According to Joint Hormone Receptor and HER2 Status Differs According to Race/Ethnicity and Other Factors http://www.ascopost.com/News/16208 2014

Name	[redacted]
Role	[redacted]

Organisation	[redacted]
Location	England
Conflict	No
Comments on the ACD:	

Following a meeting with my constituent, [redacted]
, I would like to make a general comment on this consultation.

[redacted]suffers from secondary breast cancer. While her condition is terminal, she is responding well to her existing medication and has had more than twice the expected time on this drug. When the point comes when this drug no longer has a beneficial effect, the only remaining option will be Kadcyla.

Given that she has responded so well to existing treatment, and has and does lead a comparatively fit and healthy life, there is every likelihood that she will similarly respond positively to Kadcyla and enjoy a reasonable quality of life far in excess of the nine month expected benefits from the drug. This view is supported by her consultant.

I would therefore like to argue that a blanket ban on the use of Kadcyla as part of the Cancer Drugs Fund would be inappropriate and potentially deprive breast cancer sufferers from a significant increase to their life expectancy.

I would therefore suggest that, at the very least, Kadcyla should be available under the Cancer Drugs Fund when clinically appropriate.

Moreover, by allowing patients like [redacted]to enhance their life expectancy would allow further research to be carried out on the efficacy of her existing medication.

I would be happy to provide further details of my constituent's case should that be helpful.

Thank you for considering these comments.

Name	[redacted]
Role	Patient
Location	England
Conflict	No
Comments on individual sections of the ACD:	
Section 4 (Consideration of the evidence)	The references to Lapatanib in this section suggest that it remains available as an alternative treatment (via the cancer drug fund) in some circumstances, and that lapatanib is a relevant comparator. I had understood that Lapatanib was not currently available to patients with advanced breast cancer. Although I understand that trial data is important to take in to account, the use of Lapatanib as a comparator when this is no longer available and proven to be less effective than kadcyla with significantly poorer side effects does not seem appropriate in the circumstances. During the original hearing it was implied that Lapatanib was not available because it was also too expensive and that without the comparator Kadcyla would have to be deemed too expensive also (I may have misheard this point). I don't believe Lapatanib should be used as a comparator since it is not available, but if comparisons are to be made then I feel that richer data concerning efficacy and quality of life should be sought and considered. The comment 'the committee took note of the patient expert's concern about the tolerability of treatment' implies that patient expert(s) expressed negative views about kadcyla and its tolerability and side effects. In fact the opposite view was stated, Kadcyla has been the most well tolerated of the treatments received to date and concerns about tolerability in the committee were focussed on the alternatives (such as were identified), including Lapatanib.

	It seems self evident that Kadcyla should be considered an end of life treatment and I support the conclusion reached by the committee in this regard. As well as considering progression-free survival and overall survival I would urge the committee to fully address the quality of life considerations and the efficacy of Kadcyla. my recollection is that the patient expert who referred to Kadcyla removing fear was focussing on the fear associated with treatment (not the fear following diagnosis). it is hard to put in to words the difference which Kadcyla has made to the quality of my life and I do not think that the approach taken by nice places sufficient emphasis on this aspect. Kadclya has enabled me to live fully again, despite (and knowing that I have) a much more limited life expectancy.
General comments	I feel that NICE have made a narrow formulaic decision based on cost and that views and experiences of patients and clinicians were not given sufficient weight. A full economic appraisal should consider the benefits of allowing patients to live well for longer, contributing to society and supporting/spending time with friends and family. it should also look at the savings associated with fewer emergency admissions than traditional chemotherapy for example. The trial data considered is based on relatively small numbers, it is not clear to me why this information was not supplemented with real patient data. The information for the public about this decision on the NICE web site states. 'NICE looks at how well treatments work in relation to how much they cost compared with other treatments available on the NHS. NICE applies special considerations to treatments that can extend the lives of people who are nearing the end of their life. Trastuzumab emtansine does not provide enough benefit to patients to justify its high cost even when the 'special considerations' were applied, so it was not recommended.' 1) The treatment was not compared to 'other treatments available on the NHS' as the comparators were not available at the time the decision was made. 2) if the considerable benefits to patients outlined by patient experts and clinicians (and case studies which have been in the press since the draft decision was announced) are not enough to justify the high cost, then it begs the question what would be? Or perhaps it is the case that the cost would always be considered too high- in which case why appraise it. I feel strongly that other patients should not be denied the benefits of this drug which cannot be computed into simple cost and benefit calculations. it is not just a question of a relatively small amount of extra time, it is extra time after gruelling and debilitating treatment, and extra time when you feel well enough to live well. In a sense it provides a new lease on life, something which is more precious and should be more highly valued when life is shortened and when one is used to feeling so unwell. The simplistic calculations and explanations do not expose the real benefits of this drug. I urge the committee (and Roche) to reconsider.

Kadcyla has been proven to have a reliable and substantial increase in the life expectancy of women who are treated with the drug in comparison to lapatinib + capecitabine, which is a comparable treatment for metastatic breast cancer. Kadcyla also has a demonstrably lower toxicity than other comparable drugs which means that treatment can be provided for longer and with a much improved quality of life for the patients involved.

The EMILIA study showed that patients on Kadcyla could expect to live an extra 6.3 months compared to treatment with lapatinib + capecitabine, but in some cases, the patients can expect to live for many years under the treatment.

The ICER for treatment is estimated to be £166,400-£167,200 per QALY gained (excluding other mitigating factors, such as the comparatively low number of patients who need it each year).

While it cannot be disputed that the treatment is expensive, I do not believe that the QALY formula involved adequately reflects the true value of the treatment to patients and tremendous impact that it has on their lives.

It does not appear that under the current QALY formula enough weight is given to the benefits of drugs like Kadcyla in comparison to the financial costs. Current NICE guidelines state that when appraising treatments for extending the life of a patient with a short life expectancy, further criteria can be taken into account when calculating whether a treatment is cost effective. These are:

- *The treatment is indicated for patients with a short life expectancy, normally less than 24 months*
- *There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment*
- *The treatment is licensed or otherwise indicated for small patient populations*

While as mitigating factors for affordability of treatment are welcome I believe that they do not adequately reflect the true benefit of treatments like Kadcyla and should be re-examined.

The improved quality of life that comes from Kadcyla instead of comparative treatments ought to be considered in conjunction with these three criteria as well as within the QALY calculation.

The need for this is most obvious when considering how much further a patient's life is extended. While a treatment's ability to provide the extension of life by at least an additional 3 months ought to rightly be considered a major factor when calculating cost efficiency, much greater weight ought to be lent to those treatments that provide similar extension that provide a higher standard of living.

For a patient with fewer than 24 months left to live, a treatment which offers a higher standard of living ought to have the comparative quality of life calculated. A treatment which provides a less painful, less debilitating final few months for a patient than its competitors ought to have this recognised strongly as possible. It should therefore be a very powerful mitigating factor when considering the cost of a treatment like Kadcyla.

Kadcyla offers precious time to those women who need it. Time that they can spend with a decent quality of life with their families and loved ones. The low toxicity means that this is not a matter of adding a few months of bedridden agony, but of being able to spend this extra time doing what is important to them.

I therefore urge you as strongly as possible to ensure that this important treatment receives NICE's backing for funding from the NHS.

The new PAS has been incorporated into the company's model appropriately. The error highlighted by the ERG around the calculation of post-progression treatment costs has not been corrected or commented upon by the company. This does not, however, have a substantial impact upon the model results. Excluding this small error, all analyses presented on pages 6-8 are correct in terms of a marginal analysis.

Full incremental analyses are not presented by the company. These have been calculated below using the company's model. In all analyses below, (a) the new PAS is included, and (b) the patient-level data for patient weight is used to calculate the planned dosage of T-DM1.

Table 1: Full incremental analysis including lapatinib as a comparator (deterministic)

Technologies	Totals			Incrementals			
	Costs (£)	LYs	QALYs	Costs (£)	LYG	QALYs	ICER (Cost per QALY gained)
Capecitabine	£13,242	2.06	1.20	-	-	-	-
Trastuzumab and capecitabine	£32,259	2.41	1.45	-	-	-	Dominated by lap/cap
Lapatinib and capecitabine	£30,867	2.58	1.56	£17,625	0.52	0.36	£48,958
T-DM1	[redacted]	3.32	2.09	[redacted]	0.74	0.53	[redacted]

Table 2: Full incremental analysis without lapatinib as a comparator (deterministic)

Technologies	Totals			Incrementals			
	Costs (£)	LYs	QALYs	Costs (£)	LYG	QALYs	ICER (Cost per QALY gained)
Capecitabine	£13,242	2.06	1.20				
Trastuzumab and capecitabine	£32,259	2.41	1.45	-	-	-	[redacted]
T-DM1	[redacted]	3.32	2.09	[redacted]	1.26	0.89	[redacted]

These can be recalculated using the ERG model which corrects the error mentioned above if required; however the results would not change substantially.

As noted by the company in their response, the deterministic results are notably different to the probabilistic results. Since probabilistic results account for any non-linearity, it is these results which should normally be considered (if they are correct) rather than the deterministic results. In this case, however, the increase in the probabilistic ICER is likely due to error in the PSA model parameterisation rather than due to non-linearity.

Steps for correcting the model for trastuzumab emtansine (using the latest available version of the model received on 24/01/2017 from Roche):

1. Using the network meta-analysis results that uses the
    - full network of the studies, which includes the CEREBEL and Martin et al. studies
    - and a random effects model.

2. Correct the PSA model parameterisation by making the following corrections to the model (as described in section 3.10 of the ERG report):
    - Use CODA samples for all comparators i.e. use the hazard ratio estimated from the crossover analysis within the network meta-analysis in order to generate CODA samples for all comparators
    - In the model, use the samples row by row (corresponding to the Markov chain Monte Carlo iteration) rather than sampling the draws from the Markov chain
    - incorporate uncertainty around the treatment duration and PFS Kaplan-Meier survivor functions
    - justify or amend the characterisation of uncertainty around the adverse events proportions
    - correct the two cell referencing errors within the 'simulation' model
    - check for any other errors in the PSA implementation, in particular check why within a small number of the Monte Carlo simulation runs, the estimated life years and QALYs associated with capecitabine are vastly overestimated, which leads to the expected values being overestimated.

3. The company should also correct the error in the calculation of the average cost of post-progression treatment

Cost effectiveness analyses with updated probabilistic sensitivity analyses for Kadcyla (ID1013)

As requested, please find below an update to the probabilistic sensitivity analysis (PSA) for Kadcyla against comparators.

In the base case the network meta-analysis incorporates the full network of studies (including CEREBEL and Martin et al) and uses the random effects model.

We have addressed the following areas which were highlighted as part of the ERG's review:

- The ERG's preference is to use a look-up table of samples from the posterior distribution, referred to as the Convergence Diagnostic and Output Analysis (CODA), which preserves the underlying joint distribution of treatment effects. This has now been reflected in the model in the "ITC" tab.

- Currently it is not possible to incorporate uncertainty around the treatment duration or the PFS Kaplan Meier (KM) curve in use. In order to incorporate uncertainty around the treatment duration the method of extrapolation has been changed from using KM data followed by a gamma tail to using a gamma function to model the entire treatment duration. In the base case, PFS was modelled using KM data followed by a gamma function, this has been changed to a log-normal for the entire time horizon. The Gamma function for treatment duration and log-normal function for PFS were chosen as they represent the best statistical fit.

- The ERG commented that "*AE proportions were associated with some uncertainty, although based upon review of the model this appears to be arbitrary".* The standard errors for the proportion of adverse events for Kadcyla and lapatinib in combination with capecitabine are taken from the pivotal trial. The standard errors for the other comparator arms (Her/cap and Capecitabine monotherapy) are estimated by calculating a weighted average of three trials (CEREBEL, GBG and Cameron). As such standard errors could not be calculated for these comparator arms and a value of 10% was chosen for the standard error. Given the AE cost has insignificant effect on the overall cost of a treatment, the selection of the variation around those costs is also minimal upon the PSA.

- Two cell referencing errors were noted by the ERG within the 'simulation' sheet in the model. Errors have been found in cells 'BN9' and 'BQ9' and these have been corrected.

The results for the updated PSA are shown in table 1.

Table 1: Deterministic and probabilistic sensitivity analyses for Kadcyla vs Lap/cap, Her/cap and capecitabine monotherapy

	Deterministic Results				*Probabilistic Results*			
	Kadcyla	*Lap/cap*	*Her/cap*	*Capecitabine*	*Kadcyla*	*Lap/cap*	*Her/cap*	*Capecitabine*
Total costs	[redacted]	*£31,56*	*£37,07*	*£13,432*	[redacted]	*£32,45*	*£40,36*	*£14,740*

(£)		*3*	*8*			*7*	*1*	
Difference in total costs (£)	*N/A*	[redacted]	[redacted]	[redacted]	*N/A*	[redacted]	[redacted]	[redacted]
LYG	*3.32*	*2.58*	*2.41*	*2.06*	*3.33*	*2.59*	*2.52*	*2.13*
LYG difference	*N/A*	*0.74*	*0.91*	*1.25*	*N/A*	*0.74*	*0.81*	*1.20*
QALYs	*2.08*	*1.57*	*1.45*	*1.20*	*2.07*	*1.57*	*1.53*	*1.25*
QALY difference	*N/A*	*0.51*	*0.62*	*0.87*	*N/A*	*0.51*	*0.55*	*0.83*
ICER (£)	*N/A*	[redacted]	[redacted]	[redacted]	*N/A*	[redacted]	[redacted]	[redacted]
Difference between deterministic and Probabilistic	-	-	-	-	-	[redacted]	[redacted]	[redacted]
Results include the PAS [redacted]								

Please note that Lapatinib in combination with capecitabine (lap/cap) has been included in the updated analyses for completeness; however as stated previously in our submission (and echoed by other commentators and consultees during the appraisal) we do not consider this to a relevant comparator.

Following the amendments to the PSA, the deterministic and probabilistic results are more comparable. The reason the PSA results remain slightly above the deterministic results is most likely due to the large confidence interval associated with the network meta-analysis.

The deterministic results are higher than previously present [redacted] This is a result of changing the method of extrapolation for treatment duration and PFS to allow uncertainty to be factored into the PSA. As the ERG accepted the method of survival modelling in the base case of our submission and given that the time to event data for the treatment duration and PFS are relatively mature, we consider it most appropriate to use the KM curves rather than the parametric function for the entirety of the extrapolation. As such the [redacted] presented to the committee on the 1st February provides the most accurate point estimate for the deterministic results.

The ERG note that within a small number of the Monte Carlo simulation runs, the estimated life years and QALYs associated with capecitabine are vastly overestimated, which leads to the expected values being overestimated. We have explored the reasons for this and believe it is a result of the large confidence intervals generated by the meta-analysis when using the full network with random effects.

When the small network is used with fixed effects the QALYS associated with capecitabine compared to Kadcyla are no longer vastly overestimated. This is because of the 95% CI around

the HRs against the indirect comparators, as explained at the ACD response. The hazard ratios are shown in table 2.

Table 2: Results from NMA model for OS (cross-over adjusted) and PFS (ITT)

Kadcyla vs.	OS HR	OS LCrI	OS UCrI	PFS HR	PFS LCrI	PFS UCrI
Full Network (random effects)						
Lap/cap	0.69	0.36	1.32	0.65	0.32	1.17
Cap	0.59	0.25	1.43	0.40	0.16	0.89
Her/Cap	0.70	0.29	1.72	0.67	0.27	1.45
Small Network (fixed effects)						
Lap/cap	0.69	0.57	0.84	0.65	0.55	0.77
Cap	0.55	0.41	0.74	0.36	0.25	0.51
Her/Cap	0.59	0.37	0.93	0.53	0.32	0.86

Table 3 shows the reduction in the confidence intervals when the small network is used versus the large network. Therefore we believe this is an artefact of the data rather than an error in the implementation of the PSA.

Table 3: Results for Life years and QALYS with runs of PSA for full and small network

	Full network (Random effects)				*Small Network (Fixed effects) -Probabilistic*				*Small Network (Fixed effects)-Deterministic*			
	Kadcyla	***Lap/cap***	***Her/cap***	***Capecitabine***	***Kadcyla***	***Lap/cap***	***Her/cap***	***Capecitabine***	***Kadcyla***	***Lap/cap***	***Her/cap***	***Capecitabine***
Life years	3.33 (3.07; 3.62)	2.59 (2.31; 2.91	2.52 (0.92-4.88)	2.13 (0.80-4.01)	3.32 (3.06; 3.59)	2.60 (2.30; 2.88)	2.12 (1.31; 3.18)	1.97 (1.47; 2.59)	3.32	2.58	2.06	1.94
Incr life years	N/A	0.74 (0.36; 1.08)	0.81 (-1.53; 2.41)	1.98 (-0.80; 2.53)	N/A	0.73 (0.37; 1.06)	1.20 (0.22; 1.99)	1.36 (0.78; 1.83)	N/A	0.74	1.26	1.38
QALYS	2.07 (1.36; 2.76)	1.57 (1.01; 2.13)	1.51 (0.53; 2.93)	1.25 (0.46; 2.55)	2.04 (1.27; 2.70)	1.55 (0.93; 2.09)	1.25 (0.62; 2.04)	1.12 (0.61; 1.70)	2.08	1.57	1.23	1.13
Incr QALYS	N/A	0.51 (0.28; 0.79)	0.55 (-0.65; 1.51)	0.83 (-0.28; 1.59)	N/A	0.50 (0.28; 0.75)	0.80 (0.22; 1.40)	0.92 (0.54; 1.3)	N/A	0.51	0.85	0.95
ICER	N/A	[redacted]	[redacted]	[redacted]	N/A	[redacted]	[redacted]	[redacted]	N/A	[redacted]	[redacted]	[redacted]
Difference between deterministic and probabilistic ICERs with small network and fixed effects										[redacted]	[redacted]	[redacted]
Point estimates are shown with 95% lower and upper confidence intervals shown in parenthesis. Results include the PAS [redacted]												

For each of the suggestions made by the ERG regarding improving the PSA, this document sets out how the company have addressed the issue and the ERG's feedback on this.

Steps for correcting the model for trastuzumab emtansine (using the latest available version of the model received on 24/01/2017 from Roche):

1. Using the network meta-analysis results that uses the
    - full network of the studies, which includes the CEREBEL and Martin et al. studies
    - and a random effects model.

This has been done within the base case presented. However, the results presented by the company are not fully incremental. If the company believes some of the comparators should not be included, it would be most useful if they could present the fully incremental results with all comparators included, in addition to an analysis excluding comparators.

2. Correct the PSA model parameterisation by making the following corrections to the model (as described in section 3.10 of the ERG report):

    - Use CODA samples for all comparators i.e. use the hazard ratio estimated from the crossover analysis within the network meta-analysis in order to generate CODA samples for all comparators.

This has not been done within the model or discussed within the response. The ERG cannot see a reason why the company has been unable to undertake this analysis.

    - In the model, use the samples row by row (corresponding to the Markov chain Monte Carlo iteration) rather than sampling the draws from the Markov chain

This has been done correctly for the hazard ratios for TDM1 versus capecitabine and TDM1 versus trastuzumab plus capecitabine i.e. for the comparators where the CODA samples are used (see point above).

    - incorporate uncertainty around the treatment duration and PFS Kaplan-Meier survivor functions

This has not been done. The company have instead used a parametric distribution for the entire curves. For the treatment duration, this remains a gamma distribution. For the PFS curve, this has been changed from a gamma distribution to a lognormal distribution, since this represents the best statistical fit. This results in a slightly higher ICER for TDM1, irrespective of the comparator. The company state that they still believe that using the Kaplan-Meier curves directly is most appropriate. The ERG would accept this if the company could incorporate uncertainty around the Kaplan-Meier curves. It is unclear to the ERG why the company cannot incorporate uncertainty around the Kaplan-Meier curves.

    - justify or amend the characterisation of uncertainty around the adverse events proportions

The company have stated that the selection of the variation around those costs is minimal upon the PSA. The ERG agrees that any amendment to the standard errors is likely to have a minimal impact upon the PSA.

- correct the two cell referencing errors within the 'simulation' model

This has been done.

- check for any other errors in the PSA implementation, in particular check why within a small number of the Monte Carlo simulation runs, the estimated life years and QALYs associated with capecitabine are vastly overestimated, which leads to the expected values being overestimated.

The company believe this is a result of the large confidence intervals generated by the meta-analysis when using the full network with random effects. The ERG can confirm that it is a small number of the CODA samples generated for the hazard ratios which are causing these long survival estimates. For example, some of the hazard ratios generated are greater than 10 for capecitabine and trastuzumab plus capecitabine compared with TDM1. The ERG does not have access to the meta-analysis model to confirm the issue but suspects that it is a consequence of the inappropriate implementation of the random effects analysis. Prior distributions for variance parameters in random effects models with only a few studies are not non-informative; prior distributions should not be used unthinkingly and the company should incorporate weakly informative prior information to exclude implausible values.

3. The company should also correct the error in the calculation of the average cost of post-progression treatment

This has not been done in the model or discussed within the response. The ERG cannot see a reason why the company have not resolved this.

Cost effectiveness analyses with updated probabilistic sensitivity analyses for Kadcyla (ID1013)

As requested, on the 9th of March, please find below further updates to the cost effectiveness analyses for Kadcyla against comparators.

The following updates were made to the model to incorporate the ERG's comments and preferred assumptions:

1. NMA
    - Based on the comments provided by the ERG around the NMA, specifically the comment that "*Prior distributions for variance parameters in random effects models with only a few studies are not non informative; prior distributions should not be used unthinkingly and the company should incorporate weakly informative prior information to exclude implausible values.*", Roche has re-run the NMA using weakly informative prior information as suggested by the ERG.
    - The between study standard deviation was taken from the following publication: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3396310/pdf/dys041.pdf
        - Overall survival: Table 4: pharmacological vs. pharmacological: All-cause mortality: Log-normal (-4.27,1.48^2)
        - PFS: Table 4: pharmacological vs. pharmacological: semi objective: Log-normal (-3.23,1.88^2)
    - The NMA uses the full network of the studies (which includes the CEREBEL and Martin et al. studies) and a random effects (RE) model
    - Results of the updated NMA are shown in Table 1. As shown, the mean HR has remained consistent with previous analyses (Table 2); however the confidence intervals have narrowed.
    - The code used for the NMA is provided below in Appendix 1.

2. Incorporation of the NMA in the model
    - The HRs estimated by the updated NMA using the RE model full network with cross-over adjustment (as presented in Table 1) were used in the model for all comparators, i.e. vs. lap/cap, vs. tras/cap and vs. cap
    - The CODA samples for all comparators as generated by the updated NMA were used for the PSA results vs. lap/cap, vs. tras/cap and vs. cap.
3. Uncertainty around the KM
    - Uncertainty was incorporated for the PFS and TTD KM curves
    - A beta distribution was used, please see KM PFS and KM TTD sheets

4. Post-progression costs
    - The post-progression costs applied in the model are calculated based on the following assumptions (as in the re-submission):
        - 36% of patients would receive a post-progression therapy (irrespective of which treatment arm patients are assigned to)
        - 50% of those would get Vinorelbine for 9.5 weeks and the rest 50% would get capecitabine for 9.5 weeks
        - The calculated overall costs per patient in progression is therefore at £593 (irrespective of treatment arm)
        - This cost is then applied to the discounted proportion of new patients entering progression state at each model cycle for the different comparators
    - Sensitivity analyses on this value showed that is not a key driver in the model and hence we have not focussed additional attention on this point.

5. Results representation
    - A fully incremental analysis is presented in Table 3. This has been presented on request of the ERG; however, we would like to reaffirm our position (as stated in the original submission and in response to the ACD) that we do not believe that lap/cap should be considered as a comparator due to the non-availability of lapatinib within the NHS. Pairwise results are presented in Table 5.

Table 1: Hazard ratios used in the economic model: RE full network model with cross-over adjustment (informative priors)

PFS	**HR**	**2.5%**	**97.5%**
T-DM1 vs. LapCap	0.65	0.46	0.91
T-DM1 vs. Cap	0.40	0.24	0.64
T-DM1 vs. TrastCap	0.67	0.41	1.07
OS			
T-DM1 vs. LapCap	0.69	0.56	0.86
T-DM1 vs. Cap	0.58	0.42	0.80
T-DM1 vs. TrastCap	0.70	0.47	1.03

Table 2: Previously reported hazard ratios used in the economic model: RE full network model with cross-over adjustment (non-informative priors)

PFS	**HR**	**2.5%**	**97.5%**
T-DM1 vs. LapCap	0.65	0.32	1.17
T-DM1 vs. Cap	0.40	0.16	0.89
T-DM1 vs. TrastCap	0.67	0.27	1.45
OS			
T-DM1 vs. LapCap	0.69	0.36	1.32
T-DM1 vs. Cap	0.59	0.25	1.43
T-DM1 vs. TrastCap	0.70	0.29	1.72

Results

Table 3: Deterministic and probabilistic incremental analyses for Kadcyla vs. all comparators

Deterministic results							
Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc.LYG	Inc.QALYs	ICER (£)
Capecitabine	£13,369	2.03	1.18				
Lap/Cap	£30,409	2.40	1.45	£17,040	0.37	0.27	£63,273
Her/cap	£36,983	2.40	1.45	£6,574	0.01	0.00	Her/cap is dominated by Lap/cap
Kadcyla	[redacted]	3.32	2.09	[redacted]	1.29	0.90	[redacted]
Probabilistic results							
Capecitabine	£14,147	2.06	1.20				
Lap/Cap	£31,007	2.43	1.46	£16,861	0.37	0.27	£62,926
Her/cap	£38,424	2.45	1.47	£7,417	0.02	0.01	£1,209,319
Kadcyla	[redacted]	3.33	2.08	[redacted]	1.27	0.89	[redacted]
Results include the PAS [redacted]							

Table 4: Deterministic and probabilistic sensitivity analyses for Kadcyla vs all comparators

	Deterministic Results				Probabilistic Results			
	Kadcyla	Lap/Cap	Her/cap	Cap	Kadcyla	Lap/Cap	Her/cap	Capecitabine
Total costs (£)	[redacted]	£30,409	£36,983	£13,369	[redacted]	£31,007	£38,424	£14,147
Difference in total costs (£)	N/A	[redacted]	[redacted]	[redacted]	N/A	[redacted]	[redacted]	[redacted]
LYG	3.32	2.40	2.40	2.03	3.33	2.43	2.45	2.06
LYG difference	N/A	0.92	0.91	1.29	N/A	0.896	0.879	1.266
QALYs	2.09	1.45	1.45	1.18	2.083	1.465	1.471	1.197
QALY difference	N/A	0.63	0.64	0.90	N/A	0.618	0.612	0.886
ICER (£)	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference between deterministic and Probabilistic	-		-	-	-	-£1,342	-£420	-£852
Results include the PAS [redacted]								

Appendix 1

WINBUGS Code

```
# Kadcyla EMILIA - 6 studies - Random effects - half informative prior for b/w
study variance
# Stratified HR were used
# ONLY TWO ARMS STUDIES ALLOWED

model {
# LOOP THROUGH STUDIES
for(i in 1:ns) {
# Normal likelihood
   y[i,2] ~ dnorm(delta[i,2],prec[i,2])
# Deviance contribution for trial i
   resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
# Treatment effect is zero for control arm
   delta[i,1] <- 0
# LOOP THROUGH ARMS
   for (k in 2:na[i]) {
# Calculate variances
      var[i,k] <- pow(se[i,k],2)
# Set precisions
      prec[i,k] <- 1/var[i,k]
# Trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],tau)
# Mean of random effects distributions
      md[i,k] <-  d[t[i,k]] - d[t[i,1]]
    }
 }
# Total Residual Deviance
totresdev <- sum(resdev[])
# Treatment effect is zero for reference treatment
d[1]<-0
# Vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
# Vague prior for between-trial SD
# sd ~ dunif(0,2)
# Half-informative prior for between-trial SD
# sd ~ dnorm                    (0,prec2)I(0,)
# prec2<-pow(0.32,-2)
# PFS: Log normal prior for between-trial SD (Turner et al., 2012 - Table 4)
sd ~ dlnorm(-3.23,prec3)
prec3<-pow(1.88,-2)
# OS: Log normal prior for between-trial SD (Turner et al., 2012 - Table 4)
```

```
# sd ~ dlnorm(-4.27,prec3)
# prec3<-pow(1.48,-2)
# between-trial precision = (1/between-trial variance)
tau <- pow(sd,-2)

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
HR[c,k] <- exp(d[k] - d[c])
lnHR[c,k] <- (d[k]-d[c])
}
}
# ranking on relative scale
for (k in 1:nt) {
# assumes events are “good”
# rk[k] <- nt+1-rank(d[],k)
# assumes events are “bad”
rk[k] <- rank(d[],k)
# calculate probability that treat k is best
best[k] <- equals(rk[k],1)
# calculates probability that treat k is h-th best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) }
}
}
```

Data

```
# ns= number of studies
# nt=number of treatments

list(ns=5, nt=5)
```

t[,1]	t[,2]	y[,2]	se[,2]	na[]
1	2	-0.431	0.087	2
2	3	-0.598	0.157	2
4	3	-0.393	0.178	2
5	2	0.174	0.15	2
2	4	0.122	0.145	2

```
END
```

Initial Values

```
#chain 1
list(d=c(NA,0,0,0,0),
delta = structure(.Data = c(
        NA,-0.4938823680111212,
                                    NA,-0.220354268595284,
```

```
                                        NA,-0.08475345772168494,
                                        NA,0.463835272895844,
                                        NA,-0.1310726778258793),
.Dim = c(5,2)),sd=1)
#chain 2
list(d=c(NA,-1,-3,-1,1),
delta = structure(.Data = c(
        NA,-6.875326288330025,
                                        NA,-3.618512084108584,
                                        NA,-4.261936051121992,
                                        NA,-2.369065621971651,
                                        NA,-3.33115832917117),
.Dim = c(5,2)),sd=4)
```

T-DM1 for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane: A Cancer Drugs Fund review:

ERG response to the company's additional analyses April 2017

Aim of this document

This document sets out the second set of changes made by the company to improve their probabilistic sensitivity analyses (PSA) (copied from the company's document), and the ERG's feedback on these changes in blue text following each.

1. NMA
    - Based on the comments provided by the ERG around the NMA, specifically the comment that "*Prior distributions for variance parameters in random effects models with only a few studies are not non informative; prior distributions should not be used unthinkingly and the company should incorporate weakly informative prior information to exclude implausible values.*", Roche has re-run the NMA using weakly informative prior information as suggested by the ERG.
    - The between study standard deviation was taken from the following publication: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3396310/pdf/dys041.pdf
        - Overall survival: Table 4: pharmacological vs. pharmacological: All-cause mortality: Log-normal (-4.27,1.48^2)

- PFS: Table 4: pharmacological vs. pharmacological: semi objective: Log-normal (-3.23,1.88^2)

- The NMA uses the full network of the studies (which includes the CEREBEL and Martin et al. studies) and a random effects (RE) model
- Results of the updated NMA are shown in Table 1. As shown, the mean HR has remained consistent with previous analyses (Table 2); however the confidence intervals have narrowed.
- The code used for the NMA is provided below in Appendix 1.

Table 1: Hazard ratios used in the economic model: RE full network model with cross-over adjustment (informative priors)

PFS	**HR**	**2.5%**	**97.5%**
T-DM1 vs. LapCap	0.65	0.46	0.91
T-DM1 vs. Cap	0.40	0.24	0.64
T-DM1 vs. TrastCap	0.67	0.41	1.07
OS			
T-DM1 vs. LapCap	0.69	0.56	0.86
T-DM1 vs. Cap	0.58	0.42	0.80
T-DM1 vs. TrastCap	0.70	0.47	1.03

Table 2: Previously reported hazard ratios used in the economic model: RE full network model with cross-over adjustment (non-informative priors)

PFS	**HR**	**2.5%**	**97.5%**
T-DM1 vs. LapCap	0.65	0.32	1.17
T-DM1 vs. Cap	0.40	0.16	0.89
T-DM1 vs. TrastCap	0.67	0.27	1.45
OS			
T-DM1 vs. LapCap	0.69	0.36	1.32
T-DM1 vs. Cap	0.59	0.25	1.43
T-DM1 vs. TrastCap	0.70	0.29	1.72

The company have attempted to improve upon the previous analysis by using informative prior information. However, they did not present any information on model checking, including assessing convergence of the Markov chains to their stationary distributions, the extent to which the Markov chains were mixing across their posterior distributions and the plausibility of the samples drawn from the posterior distribution. The ERG re-ran the code provided by the company (Appendix 1) to assess the plausibility of their analyses, detailed results of which are shown in Appendix 2. This checking showed that the posterior distributions are highly skew and extreme values remain which are unlikely to be clinically plausible.

Therefore, the ERG has explored alternative priors for the NMA for both progression-free survival (PFS) and overall survival (OS) because it was the only way to determine the impact of more plausible prior distributions upon the health economic model results. These analyses are described in Appendix 3. The health economic model results using the ERG's analyses are shown in Table 5 on page 8 of this document.

2. Incorporation of the NMA in the model
    - The HRs estimated by the updated NMA using the RE model full network with cross-over adjustment (as presented in Table 1) were used in the model for all comparators, i.e. vs. lap/cap, vs. tras/cap and vs. cap
    - The CODA samples for all comparators as generated by the updated NMA were used for the PSA results vs. lap/cap, vs. tras/cap and vs. cap.

Subject to the response to point 1, the ERG believes that this has been undertaken correctly within the economic model.

3. Uncertainty around the KM
    - Uncertainty was incorporated for the PFS and TTD KM curves
    - A beta distribution was used, please see KM PFS and KM TTD sheets

The ERG believes that this has been undertaken correctly within the economic model.

4. Post-progression costs
    - The post-progression costs applied in the model are calculated based on the following assumptions (as in the re-submission):
        - 36% of patients would receive a post-progression therapy (irrespective of which treatment arm patients are assigned to)
        - 50% of those would get Vinorelbine for 9.5 weeks and the rest 50% would get capecitabine for 9.5 weeks
        - The calculated overall costs per patient in progression is therefore at £593 (irrespective of treatment arm)
        - This cost is then applied to the discounted proportion of new patients entering progression state at each model cycle for the different comparators
    - Sensitivity analyses on this value showed that is not a key driver in the model and hence we have not focussed additional attention on this point.

Whilst the ERG agrees that this is not a key driver of the model results, the company have had a number of opportunities to resolve this so that the model does not lack external validity. These assumptions have changed for no apparent reason from the original submission so that substantially less post-progression therapy is assumed to be provided. Within the original submission, it is stated that "Given that 52% are on third line treatment within EMILIA, these patients are assumed to have no further treatment once they progress. However for those patients who are on second line or first line treatment, their post-progression costs are captured within the model in line with CG81. For second line patients it is assumed that 50% would receive capecitabine third line and 50% would receive vinorelbine. For first line patients it is assumed that all would receive capecitabine and vinorelbine as second and third line treatments (in either order). The model applies the cost of second and third line treatments to the progressed health state for 4.3 months (19 weeks)."

With these original assumptions, the ERG had initially highlighted that post-progression costs may be underestimated "…because there is a lack of external validity associated with patients remaining in the progressed disease state for an average of 1.2 – 2.5 years (depending upon treatment within the PFS state) whilst only receiving active treatment for a maximum of 38

weeks." This lack of external validity is increased if only 36% of patients are assumed to receive active treatment, and this being for a maximum of 9.5 weeks.

The ERG calculates that the average per patient cost of post progression treatment using the original assumptions would be £1,977. Either the assumptions have changed for clinical reasons, or the calculation of costs within the current model is estimated incorrectly. The ERG believes that this large discrepancy in costs should have been resolved by the company, even if it only affects the ICER marginally. The ERG use this corrected cost within their analyses to recalculate the ICERs below.

5. Results representation
    - A fully incremental analysis is presented in Table 3. This has been presented on request of the ERG; however, we would like to reaffirm our position (as stated in the original submission and in response to the ACD) that we do not believe that lap/cap should be considered as a comparator due to the non-availability of lapatinib within the NHS. Pairwise results are presented in Table 4.

Table 3: Deterministic and probabilistic incremental analyses for Kadcyla vs. all comparators (company results)

Deterministic results							
Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc.LYG	Inc.QALYs	ICER (£)
Capecitabine	£13,369	2.03	1.18				
Lap/Cap	£30,409	2.40	1.45	£17,040	0.37	0.27	£63,273
Her/cap	£36,983	2.40	1.45	£6,574	0.01	0.00	Her/cap is dominated by Lap/cap
Kadcyla	[redacted]	3.32	2.09	[redacted]	1.29	0.90	[redacted] (vs. cap)
Probabilistic results							
Capecitabine	£14,147	2.06	1.20				
Lap/Cap	£31,007	2.43	1.46	£16,861	0.37	0.27	£62,926
Her/cap	£38,424	2.45	1.47	£7,417	0.02	0.01	£1,209,319
Kadcyla	[redacted]	3.33	2.08	[redacted]	1.27	0.89	[redacted] (vs. cap)
Results include the PAS ([redacted])							

Table 4: Deterministic and probabilistic sensitivity analyses for Kadcyla vs all comparators (company results)

	Deterministic Results				Probabilistic Results			
	Kadcyla	Lap/Cap	Her/cap	Cap	Kadcyla	Lap/Cap	Her/cap	Capecitabine
Total costs (£)	[redacted]	£30,409	£36,983	£13,369	[redacted]	£31,007	£38,424	£14,147
Difference in total costs (£)	N/A	[redacted]	[redacted]	[redacted]	N/A	[redacted]	[redacted]	[redacted]
LYG	3.32	2.40	2.40	2.03	3.33	2.43	2.45	2.06
LYG difference	N/A	0.92	0.91	1.29	N/A	0.896	0.879	1.266
QALYs	2.09	1.45	1.45	1.18	2.083	1.465	1.471	1.197
QALY difference	N/A	0.63	0.64	0.90	N/A	0.618	0.612	0.886
ICER (£)	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference between deterministic and Probabilistic	-		-	-	-	-£1,342	-£420	-£852
Results include the PAS ([redacted])								

The deterministic results within Table 3 differ from those originally presented by the company. The ERG believes that this can be explained by the company's use of the informative priors within the NMA and that to calculate PFS and OS for lapatinib plus capecitabine, within the original model the SAS regression output was used directly, whilst within the model dated 16/03/2017, the hazard ratios from the NMA were used instead. The ERG agrees that using the output from the NMA (subject to the issues highlighted within point 1) is appropriate for both the deterministic and probabilistic analyses. Using the hazard ratios from the NMA leads to a slightly lower PFS and a substantially lower OS for the patients receiving lapatinib and capecitabine than previously predicted (for the deterministic results predicted PFS life years change from 0.83 to 0.8, whilst progressed life years change from 1.76 to 1.59). The total QALYs for lapatinib in combination with capecitabine change from 1.56 to 1.45 (deterministic) and from 1.57 to 1.47 (probabilistic). There is a minimal impact upon costs because the biggest change is in the post progression state, where limited costs are incurred (see point 4 for discussion of this cost). Because of this change (and the fact that the costs and QALYs for all other comparators remain approximately the same), lapatinib in combination with capecitabine is now extendedly dominated, both within the deterministic analyses and the PSA (not highlighted by the company in Table 3 above). Given this, the ICERs that the company present for T-DM1 in Table 3 are correctly compared with capecitabine.

Health economic model results from the ERG re-analysis

Incorporating the CODA samples from the preferred ERG PFS Sensitivity Analysis 4 and the OS Sensitivity Analysis (see Appendix 3 for details) within the economic model and rerunning the model over 1,000 iterations, produces the PSA results shown within Table 5.

Table 5: ERG PSA model results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc.LYG	Inc.QALYs	ICER (£)
capecitabine	£15,619	2.09	1.21				
lapatinib/ capecitabine	£32,360	2.44	1.465	£16,741	0.35	0.26	Extendedly dominated
trastuzumab/ capecitabine	£39,639	2.45	1.467	£7,279	0.01	0.002	Extendedly dominated
T-DM1	[redacted]	3.32	2.08	[redacted]	1.24	0.87	[redacted] (vs. cap)
Results include the PAS ([redacted])							

These are similar to the PSA results produced by the company, shown in Table 3 on page 6. Thus, the choice of prior distribution did not substantially affect the expected values. However, it should be noted that the uncertainty around these expected values would also differ between the ERG results and the company results given the updated priors for the NMA.

Implications for decision making

The main difference between the previous submission by the company and the new analyses is that lapatinib in combination with capecitabine is extendedly dominated by capecitabine and T-DM1 in both the deterministic and probabilistic analyses.

Thus, under the new analyses, if capecitabine is considered to be a comparator, then the probabilistic ICER for T-DM1 is estimated to be [redacted] by the ERG and [redacted] by the company, compared with capecitabine. Both lapatinib in combination with capecitabine and trastuzumab in combination with capecitabine would be extendedly dominated by capecitabine and T-DM1.

If capecitabine is not considered to be a comparator, then the ERG probabilistic ICER for T-DM1 is estimated to be [redacted] per QALY gained compared with lapatinib in combination with capecitabine (the company estimate [redacted]). Trastuzumab in combination with capecitabine would be extendedly dominated by lapatinib in combination with capecitabine and T-DM1.

If both capecitabine and laptinib in combination with capecitabine are not considered to be comparators, then the ERG probabilistic ICER for T-DM1 is estimated to be [redacted] per QALY gained compared with trastuzumab in combination with capecitabine (company estimate [redacted]). In this case, T-DM1 is being compared against a non-cost-effective option (if all licensed treatments are considered); however the use of trastuzumab is not being assessed within this STA. The impact of the choice of comparator upon the model results is tabulated in Table 6 below.

Table 6: Impact of choice of comparator on the cost per QALY gained

Included comparators	Deterministic ICER used in previous committee meeting from company	Latest deterministic ICER from company	Latest probabilistic ICER from company	Probabilistic ICER from ERG using alternative priors for NMA parameters	Notes
If capecitabine is a comparator	[redacted] vs lap/cap, which has ICER of £48,958 vs capecitabine OR [redacted] vs capecitabine if lap/cap is not considered to be a comparator	[redacted] vs cap	[redacted] vs cap	[redacted] vs cap	Except in first column, lap/cap and trast/cap are extendedly dominated by cap and T-DM1
If capecitabine is not a comparator, but lap/cap is a comparator	[redacted] vs lap/cap	[redacted] vs lap/cap	[redacted] vs lap/cap	[redacted] vs lap/cap	Trast/cap is extendedly dominated by lap/cap and T-DM1
If both capecitabine and lap/cap are not comparators	[redacted] vs trast/cap	[redacted] vs trast/cap	[redacted] vs trast/cap	[redacted] vs trast/cap	Trast/cap is not estimated to be good value for money compared with existing treatments, but trast/ cap is not being assessed in this STA

Appendix 1 (from company submission)

WINBUGS Code

```
# Kadcyla EMILIA - 6 studies - Random effects - half informative prior
for b/w study variance
# Stratified HR were used
# ONLY TWO ARMS STUDIES ALLOWED

model {
# LOOP THROUGH STUDIES
for(i in 1:ns) {
# Normal likelihood
   y[i,2] ~ dnorm(delta[i,2],prec[i,2])
# Deviance contribution for trial i
   resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
# Treatment effect is zero for control arm
   delta[i,1] <- 0
# LOOP THROUGH ARMS
   for (k in 2:na[i]) {
# Calculate variances
      var[i,k] <- pow(se[i,k],2)
# Set precisions
      prec[i,k] <- 1/var[i,k]
# Trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],tau)
# Mean of random effects distributions
      md[i,k] <-  d[t[i,k]] - d[t[i,1]]
     }
  }
# Total Residual Deviance
totresdev <- sum(resdev[])
# Treatment effect is zero for reference treatment
```

```
d[1]<-0
# Vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
# Vague prior for between-trial SD
# sd ~ dunif(0,2)
# Half-informative prior for between-trial SD
# sd ~ dnorm                (0,prec2)I(0,)
# prec2<-pow(0.32,-2)
# PFS: Log normal prior for between-trial SD (Turner et al., 2012 -
Table 4)
sd ~ dlnorm(-3.23,prec3)
prec3<-pow(1.88,-2)
# OS: Log normal prior for between-trial SD (Turner et al., 2012 -
Table 4)
# sd ~ dlnorm(-4.27,prec3)
# prec3<-pow(1.48,-2)
# between-trial precision = (1/between-trial variance)
tau <- pow(sd,-2)

# pairwise ORs and LORs for all possible pair-wise comparisons, if
nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
HR[c,k] <- exp(d[k] - d[c])
lnHR[c,k] <- (d[k]-d[c])
}
}
# ranking on relative scale
for (k in 1:nt) {
# assumes events are “good”
# rk[k] <- nt+1-rank(d[],k)
# assumes events are “bad”
rk[k] <- rank(d[],k)
```

```
# calculate probability that treat k is best
best[k] <- equals(rk[k],1)
# calculates probability that treat k is h-th best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) }
}
}
```

Data

```
# ns= number of studies
# nt=number of treatments

list(ns=5, nt=5)
```

t[,1]	t[,2]	y[,2]	se[,2]	na[]
1	2	-0.431	0.087	2
2	3	-0.598	0.157	2
4	3	-0.393	0.178	2
5	2	0.174	0.15	2
2	4	0.122	0.145	2

END

Initial Values

```
#chain 1
list(d=c(NA,0,0,0,0),
delta = structure(.Data = c(
        NA,-0.4938823680111212,
                                NA,-0.220354268595284,
                                NA,-0.08475345772168494,
                                NA,0.463835272895844,
                                NA,-0.1310726778258793),
.Dim = c(5,2)),sd=1)
#chain 2
list(d=c(NA,-1,-3,-1,1),
delta = structure(.Data = c(
```

```
NA,-6.875326288330025,
                                    NA,-3.618512084108584,
                                    NA,-4.261936051121992,
                                    NA,-2.369065621971651,
                                    NA,-3.33115832917117),
.Dim = c(5,2)),sd=4)
```

Appendix 2: Network meta-analysis model checking for PFS

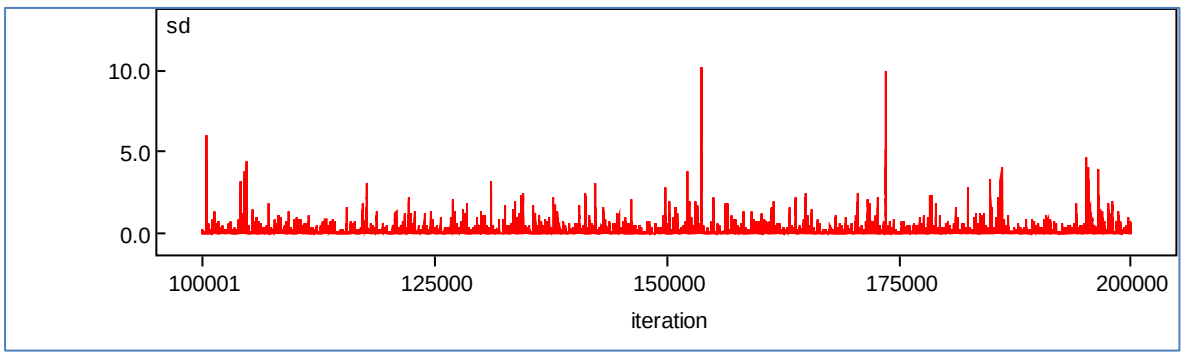
We re-ran the code provided by the company using a burn-in of 100,000 iterations and by drawing 100,000 samples from the posterior distributions to estimate parameters (Table A). The posterior means for HR[1,3], HR[1,5], HR[2,5], HR[3,4], HR[3,5] and HR[4,5] were all higher than the 97.5 percentile of their posterior distributions, which indicates that their posterior distributions are highly skew.

Table A: Reproducing company's results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
HR[1,2]	0.679	1.241	0.008	0.4501	0.6512	0.9193	100001	100000
HR[1,3]	0.9535	119.7	0.4094	0.2386	0.3995	0.6468	100001	100000
HR[1,4]	0.9597	55.29	0.2082	0.3986	0.6751	1.074	100001	100000
HR[1,5]	3.623	857.3	2.714	0.3125	0.549	0.9288	100001	100000
HR[2,3]	0.7295	20.99	0.06748	0.4279	0.6118	0.8727	100001	100000
HR[2,4]	1.269	51.3	0.1641	0.7246	1.036	1.438	100001	100000
HR[2,5]	103.4	32250.0	101.7	0.5514	0.8436	1.296	100001	100000
HR[3,4]	11.87	3174.0	10.07	1.143	1.695	2.432	100001	100000
HR[3,5]	609.8	191500.0	604.1	0.798	1.375	2.435	100001	100000
HR[4,5]	1.556E+6	4.706E+8	1.484E+6	0.472	0.8161	1.432	100001	100000
sd	0.09904	0.2218	0.003942	0.001057	0.03422	0.5761	100001	100000

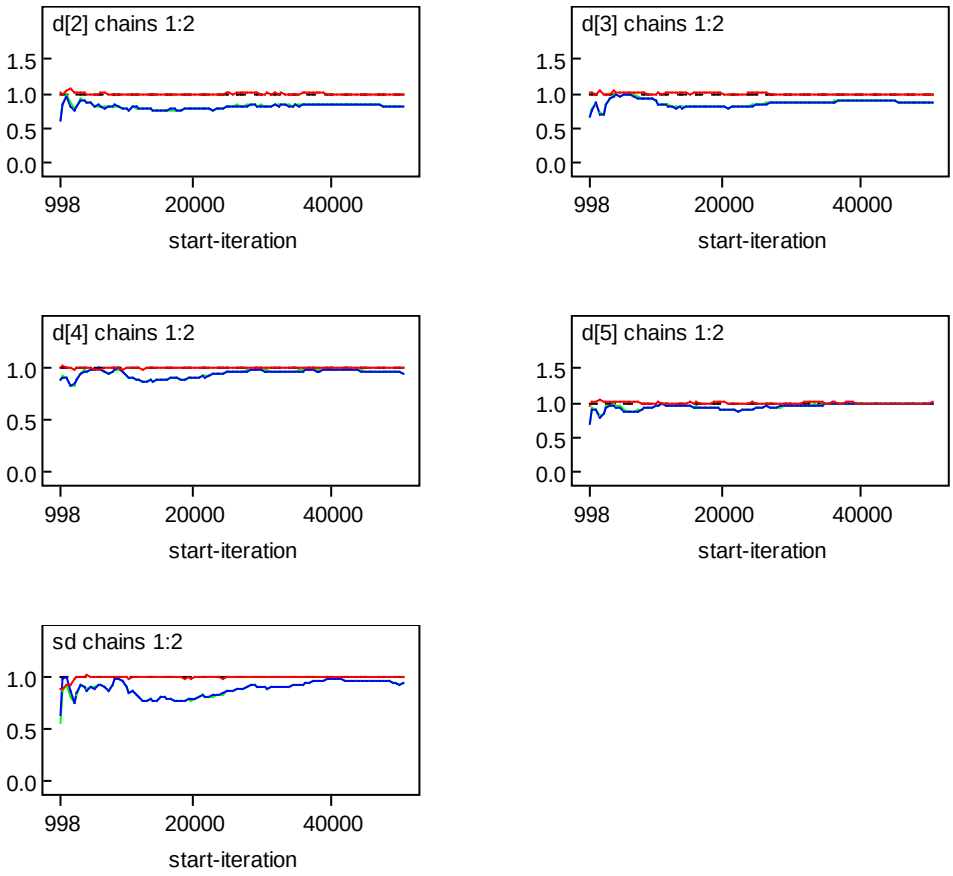
The history plot of the between-study standard deviation indicates that values in excess of 5 and many in excess of 1 are plausible values in spite of the weakly informative prior distribution specified by the company (Figure A); values in excess of 1 are indicative of extreme heterogeneity. It is these large values that are leading to the highly skew posterior distributions for the hazard ratios.

Figure A: History plot: Company's submission



There was a suggestion that the two chains defined by the two sets of initial values specified by the company converged to their stationary distributions after at least 50,000 iterations (Figure B). The ERG has reproduced the answers using a burn-in of 100,000 iterations.

Figure B: Assessing convergence: Company's submission



There was some suggestion that the Markov chain for the between-study standard deviation was not mixing well across its posterior distribution (Figure C). We will thin the chain by retaining every tenth sample. (The poor mixing probably indicates that the posterior distribution for the between-study standard deviation is highly skew with a heavy tail.)

Figure C: Assessing autocorrelation: Company's submission

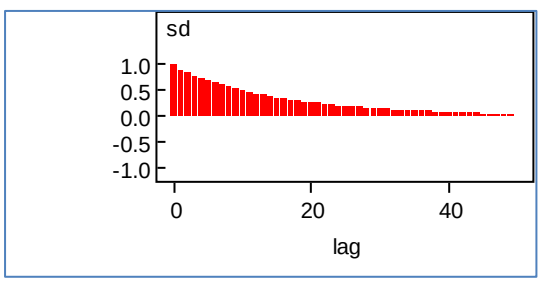
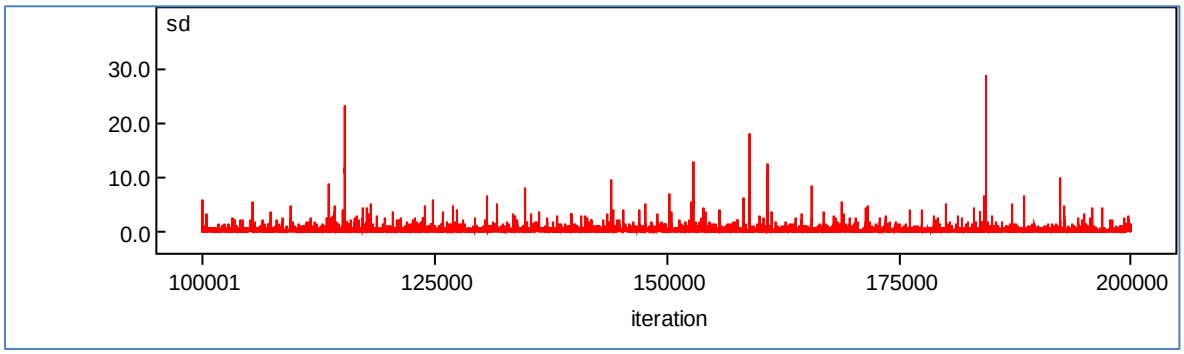


Table B presents results based on a burn-in of 100,000 iterations, thinning the chain by retaining every tenth sample and drawing 100,000 samples with which to estimate parameters. Inferences based on this model are highly unstable, and even more extreme than generated by the company, most likely because of even more extreme values for the between-study standard deviation being drawn than in the reproduction of the company's analysis (Figure D).

Table B: Reproducing company's results

node	Mean	sd	MC error	2.5%	median	97.5%	start	sample
HR[1,2]	13530.0	4.188E+6	13250.0	0.4589	0.6503	0.9248	100001	100000
HR[1,3]	333.1	68700.0	236.0	0.2437	0.3976	0.6466	100001	100000
HR[1,4]	33590.0	7.564E+6	33110.0	0.4075	0.6712	1.084	100001	100000
HR[1,5]	9.949E+11	3.144E+14	9.95E+11	0.318	0.5469	0.9347	100001	100000
HR[2,3]	8.969	2235.0	7.046	0.429	0.6101	0.8705	100001	100000
HR[2,4]	364.9	114800.0	363.3	0.7244	1.031	1.446	100001	100000
HR[2,5]	1.703E+9	5.385E+11	1.699E+9	0.5535	0.8415	1.282	100001	100000
HR[3,4]	547.0	1.64E+5	517.3	1.16	1.688	2.422	100001	100000
HR[3,5]	5.921E+11	1.872E+14	5.906E+11	0.7959	1.379	2.384	100001	100000
HR[4,5]	2.952E+19	9.334E+21	2.944E+19	0.4756	0.8161	1.427	100001	100000
best[1]	0.00401	0.0632	2.274E-4	0.0	0.0	0.0	100001	100000
best[2]	0.00253	0.05024	1.609E-4	0.0	0.0	0.0	100001	100000
best[3]	0.8962	0.305	0.001804	0.0	1.0	1.0	100001	100000
best[4]	0.00626	0.07887	2.932E-4	0.0	0.0	0.0	100001	100000
best[5]	0.09101	0.2876	0.001692	0.0	0.0	1.0	100001	100000
d[2]	-0.4291	0.2849	0.001284	-0.7789	-0.4303	-0.07818	100001	100000
d[3]	-0.9233	0.3872	0.001843	-1.412	-0.9222	-0.4361	100001	100000
d[4]	-0.4008	0.4033	0.001963	-0.8977	-0.3988	0.08079	100001	100000
d[5]	-0.6008	0.4533	0.002174	-1.146	-0.6035	-0.06757	100001	100000
rk[1]	4.917	0.4259	0.002041	4.0	5.0	5.0	100001	100000
rk[2]	3.254	0.6361	0.003982	2.0	3.0	4.0	100001	100000
rk[3]	1.126	0.4173	0.002191	1.0	1.0	2.0	100001	100000
rk[4]	3.422	0.7945	0.005315	2.0	4.0	5.0	100001	100000
rk[5]	2.281	0.8144	0.005107	1.0	2.0	4.0	100001	100000
sd	0.09956	0.2912	0.001748	9.452E-4	0.03254	0.5746	100001	100000

Figure D: Assessing autocorrelation[1]



[1] Burn-in 100,000; thinning the chain by retaining every 10th sample; parameters estimated based on 100,000 samples

The percentiles in Table B are similar to the company's results (company's response; Table 1). What the company referred to as the mean HRs are the medians of the posterior distributions. Although the medians are typically used as a measure of centrality in skew distributions, the whole posterior distributions will be influential when using them to characterise uncertainty about inputs in the economic model and estimate mean benefit.

We therefore recommend that these results are treated with caution unless the company believes that the posterior distributions are plausible.

Appendix 3: Re-analysis of the PFS and OS data using alternative prior distributions

This Appendix presents a re-analysis by the ERG of the PFS and OS (adjusted for treatment switching) data using alternative prior distributions.

In general, we expect heterogeneity between studies such that the actual treatment effect depends on study characteristics. Assuming that the quality of the studies is acceptably high then any differences in study-specific treatment effect will be a consequence of patient characteristics that are treatment effect modifiers.

Whether to analyse the data using a fixed effect or random effects meta-analysis depends on the objective. The company originally performed a fixed effect meta-analysis which (assuming heterogeneity rather than a common treatment effect) answers the question, "Did the treatment(s) have an effect in the observed studies?". In general, the question of interest is, "What is the expected treatment effect in a future study (or when the treatment is given to future patients)?". This can be answered using a random effects meta-analysis. However, when there are only a few studies it is necessary to incorporate external evidence about the magnitude of the between-study standard deviation. Given that the aim of the analysis is to generate probability distributions for inputs in the economic model, we use a Bayesian approach and incorporate prior information about the between-study standard deviation.

The company subsequently performed random effect meta-analyses using conventional reference prior distributions and a prior distribution for the between-study standard deviation appealing to Turner et al (2012):

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3396310/pdf/dys041.pdf.

Prior distributions for variance parameters are not non-informative and it is unlikely that a reference prior distribution for the between-study standard deviation represents reasonable prior beliefs. Turner et al (2012) provides predictive distributions for the between-study standard deviation for a future meta-analysis of a semi-objective outcome measure (i.e. PFS) and all-cause mortality (i.e. OS) comparing pharmacological agents, which the company used in their analyses.

A proper Bayesian analysis would involve a discussion on potential treatment effect modifiers and the range of treatment effects that might be anticipated in patients with different patient characteristics. In the absence of a discussion on potential treatment effect

modifiers, we assessed the plausibility of the results generated by the company and present results of analyses using different assumptions as sensitivity analyses.

Progression-free Survival

The company's most recent random effects meta-analyses used a prior distribution for the between-study standard deviation, SD, such that:

$$\text{PFS: } SD \sim LN(-3.23, 1.88^2).$$

It is good practice to check that the prior distribution represents reasonable prior beliefs. When there are only a few studies there will be very little Bayesian updating from the prior distribution for the between-study standard deviation to its posterior distribution. This prior distribution has median 0.039 (95% CrI: 0.001, 1.558) and gives probabilities 0.025, 0.018, 0.005 and 0.00007 that the true value for the between-study standard deviation is greater than 1.558, 2, 5 and 50, respectively. These values may be completely plausible, although it should be noted that values greater than 1 are indicative of extreme heterogeneity.

Sensitivity Analysis 1 (i.e. the company's most recent analysis but with prior distributions for the log hazard ratios such that $d \sim N(0,1000)$ and allowing for burn-in and autocorrelation) estimates the posterior distribution for the between-study standard deviation with median 0.034 (95% CrI: 0.001, 0.556) and gives probabilities 0.025, 0.002, 0.0002 and 0 that the true value for the between-study standard deviation is greater than 0.556, 2, 5 and 50 i.e. still non-negligible probability of extreme heterogeneity. The posterior distributions for the hazard ratios are highly skew with several mean values greater than the 97.5-percentile. We suggest that these results are unlikely to be plausible for the random effects means.

PFS Sensitivity Analysis 1[1]

node	mean	Sd	MC error	2.5%	Median	97.5%	start	sample
HR[1,2]	1.098	144.0	0.3278	0.4589	0.6504	0.9198	100001	250000
HR[1,3]	32980.0	1.643E+7	32860.0	0.2442	0.3967	0.6493	100001	250000
HR[1,4]	7.431E+9	3.715E+12	7.431E+9	0.4097	0.67	1.075	100001	250000
HR[1,5]	1496.0	727600.0	1455.0	0.3199	0.5473	0.9302	100001	250000
HR[2,3]	95.46	44130.0	88.25	0.4315	0.61	0.8684	100001	250000
HR[2,4]	2.382E+8	9.254E+10	1.85E+8	0.7286	1.03	1.447	100001	250000
HR[2,5]	2.71	780.2	1.56	0.5549	0.8409	1.271	100001	250000
HR[3,4]	3.715E+9	1.858E+12	3.715E+9	1.168	1.689	2.399	100001	250000
HR[3,5]	19270.0	9.631E+6	19260.0	0.7983	1.378	2.364	100001	250000
HR[4,5]	3891.0	1.944E+6	3888.0	0.48	0.8163	1.4	100001	250000

d[2]	-0.4309	0.2556	7.207E-4	-0.779	-0.4302	-0.08359	100001	250000
d[3]	-0.9237	0.353	0.001117	-1.41	-0.9245	-0.4318	100001	250000
d[4]	-0.4016	0.3492	0.001093	-0.8924	-0.4005	0.07263	100001	250000
d[5]	-0.6048	0.3722	0.001076	-1.14	-0.6027	-0.07231	100001	250000
p2	0.001816	0.04258	1.131E-4	0.0	0.0	0.0	100001	250000
p5	1.88E-4	0.01371	3.116E-5	0.0	0.0	0.0	100001	250000
p50	0.0	0.0	2.0E-13	0.0	0.0	0.0	100001	250000
Sd	0.09648	0.2246	8.507E-4	9.32E-4	0.0335	0.5561	100001	250000

[1] $d \sim N(0,1000)$; $SD \sim LN(-3.23, 1.88^2)$

Sensitivity Analysis 2 (i.e. with prior distributions for the log hazard ratios and between-study standard deviation such that $d \sim N(0,1000)$ and $SD \sim LN(-3.23, 1.62^2)$, repectively, and allowing for burn-in and autocorrelation) indicates that the posterior distributions for the hazard ratios are highly skew with several mean values greater than the 97.5-percentile. We suggest that these results are unlikely to be plausible for the random effects means.

PFS Sensitivity Analysis 2[1]

node	**mean**	**Sd**	**MC error**	**2.5%**	**Median**	**97.5%**	**start**	**Sample**
HR[1,2]	0.7744	34.62	0.06985	0.4766	0.6501	0.8845	100001	250000
HR[1,3]	35.45	16430.0	32.85	0.2538	0.3967	0.6231	100001	250000
HR[1,4]	2.955	1022.0	2.044	0.4292	0.6703	1.033	100001	250000
HR[1,5]	3.667	1208.0	2.415	0.333	0.5467	0.8978	100001	250000
HR[2,3]	4.296	1687.0	3.374	0.4395	0.6108	0.8486	100001	250000
HR[2,4]	1.263	104.5	0.2091	0.7456	1.031	1.414	100001	250000
HR[2,5]	0.8849	4.982	0.01005	0.5682	0.8409	1.24	100001	250000
HR[3,4]	1.728	1.118	0.002516	1.194	1.687	2.37	100001	250000
HR[3,5]	15.6	7048.0	14.1	0.8224	1.378	2.285	100001	250000
HR[4,5]	50.08	24580.0	49.17	0.4941	0.8157	1.356	100001	250000
d[2]	-0.4308	0.1983	5.655E-4	-0.741	-0.4307	-0.1227	100001	250000
d[3]	-0.9237	0.2788	9.748E-4	-1.371	-0.9246	-0.4731	100001	250000
d[4]	-0.4009	0.2753	8.907E-4	-0.8458	-0.4001	0.03233	100001	250000
d[5]	-0.6048	0.3045	0.00101	-1.1	-0.6039	-0.1078	100001	250000
p2	7.6E-4	0.02756	6.354E-5	0.0	0.0	0.0	100001	250000
p5	3.2E-5	0.005657	1.123E-5	0.0	0.0	0.0	100001	250000
p50	0.0	0.0	2.0E-13	0.0	0.0	0.0	100001	250000
Sd	0.08489	0.1618	5.931E-4	0.001577	0.03521	0.459	100001	250000

[1] $d \sim N(0,1000)$; $SD \sim LN(-3.23, 1.62^2)$

Sensitivity Analysis 3 (i.e. with prior distributions for the log hazard ratios and between-study standard deviation such that $d \sim N(0,1000)$ and $SD \sim LN(-3.23, 1.48^2)$, repectively, and allowing for burn-in and autocorrelation) indicates that the posterior distributions for the

hazard ratios are highly skew with several mean values greater than the 97.5-percentile. We suggest that these results are unlikely to be plausible for the random effects means.

PFS Sensitivity Analysis 3[1]

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
HR[1,2]	0.6679	1.602	0.003224	0.484	0.6501	0.8735	100001	250000
HR[1,3]	0.8751	225.5	0.451	0.2577	0.397	0.6112	100001	250000
HR[1,4]	0.7092	3.995	0.007966	0.4347	0.6704	1.018	100001	250000
HR[1,5]	30.82	15110.0	30.22	0.3391	0.5467	0.8818	100001	250000
HR[2,3]	0.6339	3.759	0.007549	0.4433	0.6108	0.8407	100001	250000
HR[2,4]	1.049	0.5925	0.001269	0.7489	1.031	1.402	100001	250000
HR[2,5]	1.244	186.7	0.3734	0.5761	0.84	1.227	100001	250000
HR[3,4]	1.729	4.446	0.00917	1.201	1.689	2.351	100001	250000
HR[3,5]	1.587	52.04	0.104	0.8381	1.376	2.258	100001	250000
HR[4,5]	8302.0	4.151E+6	8301.0	0.5031	0.8147	1.341	100001	250000
d[2]	-0.4306	0.1817	5.497E-4	-0.7257	-0.4306	-0.1353	100001	250000
d[3]	-0.9236	0.2602	9.127E-4	-1.356	-0.9239	-0.4923	100001	250000
d[4]	-0.401	0.2558	8.78E-4	-0.8332	-0.3999	0.01826	100001	250000
d[5]	-0.6042	0.2832	8.915E-4	-1.081	-0.6039	-0.1258	100001	250000
p2	4.48E-4	0.02116	4.753E-5	0.0	0.0	0.0	100001	250000
p5	8.0E-6	0.002828	5.651E-6	0.0	0.0	0.0	100001	250000
p50	0.0	0.0	2.0E-13	0.0	0.0	0.0	100001	250000
sd	0.0804	0.1405	5.115E-4	0.002121	0.03672	0.4133	100001	250000

[1] $d \sim N(0,1000)$; $SD \sim LN(-3.23, 1.48^2)$

Sensitivity Analysis 4 was performed with prior distributions for the log hazard ratios and between-study standard deviation such that $d \sim N(0,1000)$ and $SD \sim LN(-3.23, 1.35^2)$, repectively. The prior distribution for the between-study standard deviation has median 0.039 (95% CrI: 0.003, 0.555) and gives probabilities 0.025, 0.002, 0.0002 and 0 that the true value for the between-study standard deviation is greater than 0.555, 2, 5 and 50, respectively i.e. non-negligible probability that the true value could be greater than 2. After allowing for burn-in and autocorrelation, the posterior distribution for the between-study standard deviation has median 0.038 (95% CrI: 0.003, 0.368) and gives probabilities 0.025, 0.0002, 0 and 0 that the true value for the between-study standard deviation is greater than 0.555, 2, 5 and 50, respectively. The mean hazard ratios are all less than the 95-percentiles of their posterior distributions. Although the prior distribution that we have used for the between-study standard deviation is somewhat arbitrary, in the absence of any further empirical evidence or expert beliefs, we suggest that these generate more plausible results

than those produced by the company. We have therefore employed these values within the economic model.

PFS Sensitivity Analysis 4[1]

Node	mean	Sd	MC error	2.5%	median	97.5%	start	sample
HR[1,2]	0.6617	1.09	0.002206	0.4925	0.6498	0.859	100001	250000
HR[1,3]	0.4149	2.342	0.004691	0.2622	0.3968	0.6022	100001	250000
HR[1,4]	0.6923	0.6491	0.00141	0.4432	0.6704	1.003	100001	250000
HR[1,5]	0.57	0.6834	0.001416	0.3446	0.5465	0.8637	100001	250000
HR[2,3]	0.6207	0.1941	5.024E-4	0.4471	0.6109	0.8348	100001	250000
HR[2,4]	1.046	0.4481	9.538E-4	0.7589	1.031	1.388	100001	250000
HR[2,5]	0.859	0.3009	7.43E-4	0.5809	0.8407	1.213	100001	250000
HR[3,4]	1.72	2.687	0.005413	1.216	1.687	2.325	100001	250000
HR[3,5]	1.445	5.354	0.01066	0.8465	1.376	2.229	100001	250000
HR[4,5]	0.879	11.43	0.02286	0.5078	0.8154	1.318	100001	250000
d[2]	-0.431	0.1637	5.149E-4	-0.7082	-0.4311	-0.152	100001	250000
d[3]	-0.9237	0.2364	8.415E-4	-1.339	-0.9242	-0.5072	100001	250000
d[4]	-0.4013	0.2355	8.119E-4	-0.8136	-0.3998	0.00342	100001	250000
d[5]	-0.6049	0.2622	8.47E-4	-1.065	-0.6043	-0.1466	100001	250000
p2	2.0E-4	0.01414	3.228E-5	0.0	0.0	0.0	100001	250000
p5	0.0	0.0	2.0E-13	0.0	0.0	0.0	100001	250000
p50	0.0	0.0	2.0E-13	0.0	0.0	0.0	100001	250000
Sd	0.07495	0.1171	4.002E-4	0.002781	0.03773	0.3675	100001	250000

[1] $d \sim N(0,1000)$; $SD \sim LN(-3.23, 1.35^2)$

Overall Survival

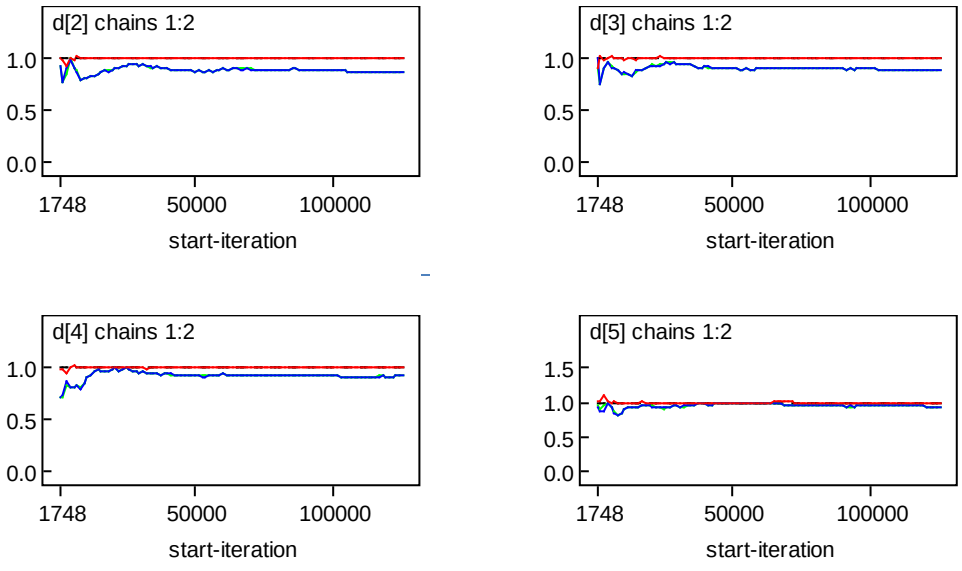
The company's most recent random effects meta-analyses used a prior distribution for the between-study standard deviation, SD, such that:

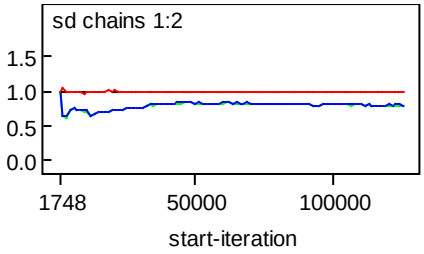
$$\text{OS: } SD \sim LN(-4.27, 1.48^2).$$

It is good practice to check that the prior distribution represents reasonable prior beliefs. When there are only a few studies there will be very little Bayesian updating from the prior distribution for the between-study standard deviation to its posterior distribution. This prior distribution has median 0.014 (95% CrI: 0.001, 0.252) and gives probabilities 0.025, 0.0004, 0.0005 and 0 that the true value for the between-study standard deviation is greater than 0.252, 2, 5 and 50, respectively. These values may be completely plausible, although it should be noted that the distribution is generally indicative of mild heterogeneity with small prior probability of extreme heterogeneity.

After changing the company's prior distributions for the log hazard ratios for the treatment effects from $N(0,10{,}000)$ to $N(0,1000)$, we assessed convergence and autocorrelation.

Using the Brooks-Gelman-Rubin statistic, convergence occurs after between 50,000 and 100,000 iterations; we will use a burn-in of 100,000 iterations.





We inspected the extent to which the Markov chains are were mixing across their posterior distributions using autocorrelation. There was a strong suggestion that the chains were not mixing well across their posterior distributions. We will thin the chains by retaining every 10th sample from the posterior distributions.

We will draw 250,000 samples with which to estimate parameters. The posterior distribution for the between-study standard deviation has median 0.014 (95% CrI: 0.001, 0.200) and gives probabilities 0.025, 0.00006, 0.000004 and 0 that the true value for the between-study standard deviation is greater than 0.200, 2, 5 and 50. However, the posterior standard deviation of the hazard ratios for the comparisons of trastuzumab/Capecitabine (Treatment 4) and Niratinib (Treatment 5) versus T-DM1 (Treatment 1) are 46.51 and 13.68, respectively, which indicates that their posterior distributions include extreme values. There are no direct estimates of these treatment effects so that the sample estimates of effects that contribute to their indirect estimates are very uncertain. Consequently, the prior distributions for the log hazard ratios are likely to be influential.

node	Mean	Sd	MC error	2.5%	median	97.5%	start	sample
HR[1,2]	0.6996	0.4244	0.001048	0.549	0.6927	0.8737	100001	250000
HR[1,3]	0.5897	0.1798	7.895E-4	0.4215	0.579	0.8021	100001	250000
HR[1,4]	0.8025	46.51	0.09311	0.4654	0.6919	1.032	100001	250000
HR[1,5]	0.6025	13.68	0.02747	0.3443	0.5557	0.8977	100001	250000
HR[2,3]	0.8432	0.1238	5.748E-4	0.6701	0.8359	1.05	100001	250000
HR[2,4]	1.017	1.758	0.003693	0.7247	0.9998	1.382	100001	250000
HR[2,5]	0.892	26.74	0.05356	0.5277	0.8024	1.216	100001	250000
HR[3,4]	1.213	1.449	0.003118	0.877	1.195	1.623	100001	250000
HR[3,5]	1.082	39.62	0.07929	0.5955	0.9588	1.537	100001	250000
HR[4,5]	1.193	170.1	0.3404	0.4725	0.8021	1.356	100001	250000
d[2]	-0.3669	0.1295	8.502E-4	-0.5997	-0.3672	-0.135	100001	250000

d[3]	-0.545	0.1775	0.001153	-0.8639	-0.5464	-0.2205	100001	250000
d[4]	-0.3674	0.2142	0.001561	-0.7649	-0.3684	0.0311	100001	250000
d[5]	-0.5879	0.2518	0.001771	-1.066	-0.5875	-0.1079	100001	250000
p2	6.4E-5	0.008	1.941E-5	0.0	0.0	0.0	100001	250000
p5	4.0E-6	0.002	4.0E-6	0.0	0.0	0.0	100001	250000
p50	0.0	0.0	2.0E-13	0.0	0.0	0.0	100001	250000
sd	0.03477	0.07096	2.608E-4	7.619E-4	0.01359	0.1996	100001	250000

We conducted a sensitivity analysis by replacing prior distribution for the log hazard ratios such that $d \sim N(0, 100)$. As expected, this had the effect of eliminating extreme values for the log hazard ratios and reducing the large posterior standard deviations. The median estimates of treatment effects and the 2.5 and 97.5 percentile of the posterior distributions, although the mean estimate of the effect of trastuzumab/capecitabine versus T-DM1 had changed from 0.80 to 0.71 as a consequence of eliminating the extreme values. The ERG has employed these values within the economic model.

node	**mean**	**sd**	**MC error**	**2.5%**	**median**	**97.5%**	**start**	**sample**
HR[1,2]	0.6989	0.1679	6.389E-4	0.55	0.6929	0.8744	100001	250000
HR[1,3]	0.5904	0.4309	0.001094	0.4211	0.5786	0.8051	100001	250000
HR[1,4]	0.7105	0.4175	0.001347	0.4682	0.6922	1.034	100001	250000
HR[1,5]	0.5739	0.7162	0.001721	0.345	0.5545	0.8916	100001	250000
HR[2,3]	0.8431	0.1094	5.359E-4	0.6706	0.8361	1.051	100001	250000
HR[2,4]	1.015	0.177	0.001188	0.7266	1.001	1.382	100001	250000
HR[2,5]	0.8187	0.2091	0.001221	0.5273	0.7997	1.211	100001	250000
HR[3,4]	1.212	0.1985	0.001287	0.8775	1.197	1.629	100001	250000
HR[3,5]	0.9855	0.2869	0.001592	0.5932	0.9566	1.53	100001	250000
HR[4,5]	0.8338	2.162	0.004586	0.4704	0.7986	1.347	100001	250000
d[2]	-0.3672	0.1277	8.053E-4	-0.5978	-0.3669	-0.1342	100001	250000
d[3]	-0.5452	0.1761	0.001128	-0.8648	-0.5472	-0.2168	100001	250000
d[4]	-0.366	0.2101	0.001526	-0.7588	-0.3679	0.03336	100001	250000
d[5]	-0.5906	0.2492	0.001722	-1.064	-0.5897	-0.1148	100001	250000
p2	2.8E-5	0.005291	1.052E-5	0.0	0.0	0.0	100001	250000
p5	0.0	0.0	2.0E-13	0.0	0.0	0.0	100001	250000
p50	0.0	0.0	2.0E-13	0.0	0.0	0.0	100001	250000
sd	0.03471	0.06749	2.398E-4	7.642E-4	0.01368	0.2	100001	250000

Discussion

There are a number of limitations to note for the additional statistical analysis undertaken by the ERG.

We have not assessed the goodness-of-fit of the models to the observed data.

We have not assessed inconsistency between the direct estimates of treatment effect and the indirect estimates, which is particularly important in the case of overall survival. There is one closed loop of three two-arm studies comparing capecitabine with lapatinibatinib/capecitabine, capecitabine with trastuzumab/capecitabine and trastuzumab/capecitabine with lapatinib/capecitabine. The comparison of capecitabine with lapatinib/capecitabine was adjusted for treatment switching, whereas the comparisons of capecitabine with trastuzumab/capecitabine and trastuzumab/capecitabine with lapatinib/capecitabine were not adjusted for treatment switching. The indirect and direct estimates may be inconsistent. In addition, the comparison of lapatinib/capecitabine with T-DM1 was adjusted for treatment switching. T-DM1 is the reference treatment in the analysis so that all estimates of treatment effect except for that of lapatinib/capecitabine with T-DM1 will comprise a mixture of adjusted and unadjusted estimates.

We have not assessed the relevance of using hazard ratios to estimate treatment effect and their impact of the predicted long-term overall and progression-free survival.

When making decisions, it should also be noted that when heterogeneity is expected, the mean of a random effects distribution does not relate to any specific patient population and inferences should be based on the predictive distribution for the treatment effect(s) in a new study. On the log hazard ratio scale the treatment effect(s) will be centred on the same value but the uncertainty will be greater; on the hazard ratio scale the means of the predictive distributions will be greater than the random effects means.