NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with 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 manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

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 may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

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

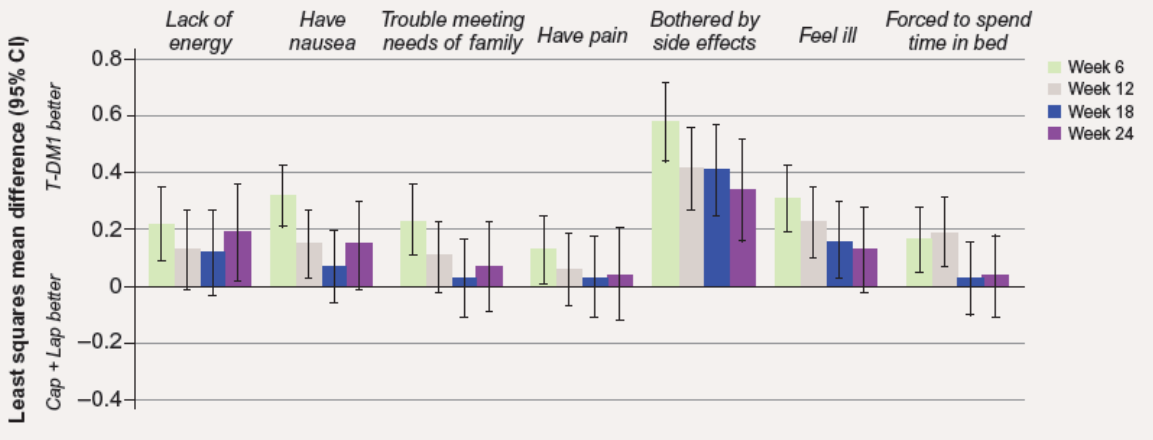
Consultee	Comment	Response
Breakthrough Breast Cancer	Breakthrough Breast Cancer is dedicated to saving lives through improving early diagnosis, developing new treatments and preventing all types of breast cancer, and we welcome the opportunity to contribute to NICE's consideration of trastuzumab emtansine through responding to this appraisal consultation document. However, Breakthrough is extremely disappointed that, despite the Committee acknowledging that trastuzumab emtansine is a novel drug which prolongs survival with less toxicity than comparator treatments, they have been unable to recommend the drug in this draft decision. This will come as a blow to the women who could benefit from more quality time with their loved ones as a result of taking the drug and leaves Breakthrough Breast Cancer deeply concerned about the future of treatment for metastatic breast cancer in England and Wales. Metastatic breast cancer is an incurable condition and treatment options are limited. The evidence considered by the committee clearly shows that trastuzumab emtansine offers women substantially prolonged survival time, with a good quality of life, and that this drug therefore represents a significant step forward in treatment. Breakthrough Breast Cancer appreciates that NICE has a difficult task when appraising drugs and that trastuzumab emtansine is simply too expensive at the current price; however we are alarmed that drugs which have been shown to be clinically effective, and improve both length and quality of life, cannot be approved for routine use in the NHS. This worrying decision highlights that, without significant changes to drug pricing and/or the system for approving drugs for use on the NHS, our persistent problem of access to treatment remains unsolved. The Department of Health's ambitious new drug pricing agreement, the Pharmaceutical Pricing Regulation Scheme (PPRS), launched this January and should have solved the apparent stalemate between the spiralling price of new cancer medicines and NICE's cost	Thank you for your comment. The Committee makes recommendations regarding the clinical and cost effectiveness of treatments for use within the NHS. Although the Committee acknowledged that trastuzumab emtansine is a novel antibody-drug conjugate and that it prolonged survival, with less toxicity than lapatinib plus capecitabine, the cost-effectiveness estimates for trastuzumab emtansine (including the patient access scheme) remained above the range that could be considered a cost effective use of NHS resources. For further details, see sections 4.16, 4.18, 4.19 and 4.20 of the FAD. It is the role of the Committee not to recommend treatments if the benefits to patients are

Consultee	Comment	Response
Breakthrough Breast Cancer (cont.)	effectiveness thresholds. And we have recently heard the most decisive commitment yet that the pharmaceutical industry will honour their five year agreement to cap the NHS drugs budget. However, the rejection of trastuzumab emtansine by NICE in this draft decision clearly demonstrates that this agreement is not feeding through to ensure routine access to effective cancer drugs. Disappointing too is that NICE's proposed new 'value based assessment' looks like it will make little difference to whether breast cancer patients will be able to access drugs like trastuzumab emtansine, or any of the other innovative cancer drugs coming through the research pipeline, into the long term. Patients currently only have access through the Cancer Drugs Fund but this is both time and cash limited and a long term solution must be found. A system which allows ground-breaking new drugs to be rejected is fundamentally flawed and the UK risks falling far behind in its standards of cancer treatment if these kinds of drugs cannot be made routinely available. This Government promised to 'reform NICE and move to a system of value-based pricing so that all patients can access the drugs and treatments their doctors think they need'. Value based assessment and the PPRS, as they both currently stand, do not provide the solution that cancer patients have been promised. Breakthrough Breast Cancer understands that, under the existing system, NICE is unable to approve drugs like trastuzumab emtansine for routine use on the NHS. However, we urge NICE to do everything in its power to ensure that changes implemented to the drug approval system lead to real improvements in access to drugs for patients. If you have any questions or wish to discuss any of the aspects of this submission, please don't hesitate to contact me.	unproven, or if the treatments are not cost effective. The Committee understood that this had not been superseded by the terms of the Pharmaceutical Price Regulation Scheme, concluding that its remit and methods of appraising the clinical and cost effectiveness of technologies had not changed as a result of this scheme. For further details, see section 4.21 of the FAD.
Roche	Thank you for giving us the opportunity to comment on the above ACD. We believe this appraisal raises an important issue – an issue which must be addressed if the final recommendation is to be considered a sound and suitable basis for the issuance of guidance to the NHS. Under the terms of the Pharmaceutical Price Regulation Scheme 2014, the total spend on branded medicines in the UK is capped.	Thank you for your comment. It is the role of the Committee not to recommend treatments if the benefits to patients are

Consultee	Comment	Response
Roche (cont.)	The scheme caps the budget with annual growth limited to 0% in 2014 through to 1.9% in 2018. Forecast growth is significantly higher at 3.87% in 2014 – when the expected growth rates are compounded, by 2018 the uncapped spend on branded medicines will be 17.59% above the current level whilst the agreed spend level with the cap will be only 5.6% above the current level. This will result in an anticipated overspend above the cap in the region of £386m in 2014 rising to £1202m in 2018*. All expenditure which exceeds the cap will be rebated by industry. This agreement raises an important question. If expenditure on branded medicines remains above the agreed cap level in the scenario of a positive or negative NICE decision (as it will in the case of trastuzumab emtansine) is it reasonable for an Appraisal Committee to make a decision under the assumption that funding the medicine in question will come at an additional cost to society? In the case of this appraisal, NICE approval of trastuzumab emtansine will result in an additional cost; however this will result in an equivalent reduction in the PPRS rebate paid by industry. This issue must be considered by Committee if the decision reached is to be 'reasonable'. In addition to the above we are concerned with the Committee's conclusion that trastuzumab emtansine does not meet the "End of Life" criteria. The conclusion was reached as the survival of patients treated with lapatinib in combination with capecitabine is regarded as being above two years.	unproven, or if the treatments are not cost effective. The Committee understood that this had not been superseded by the terms of the Pharmaceutical Price Regulation Scheme, concluding that its remit and methods of appraising the clinical and cost effectiveness of technologies had not changed as a result of this scheme. For further details, see section 4.21 of the FAD.

Consultee	Comment	Response
Roche (cont.)	Lapatinib is not NICE approved and is only funded via the Cancer Drugs Fund. We believe it is unreasonable to conclude that trastuzumab emtansine does not meet the End of Life criteria due to a comparison against a medicine which is not subject to standard NHS funding. We are committed to finding a long term solution to ensure women continue to receive trastuzumab emtansine and look forward to working with NICE, NHS England and the Department of Health on this issue. **1. Has all the relevant evidence been taken into account?** No. When considering whether the 'End of Life' criteria apply to trastuzumab emtansine the Committee has not considered the median overall survival observed for patients who received lapatinib in combination with capecitabine in the EGF104009 study (Cameron 2010). In addition we believe the evidence of trastuzumab emtansine demonstrating a substantially improved tolerability profile compared to lapatinib in combination with capecitabine has been underemphasised. Details of this are identified in section 3.2 of this response. **2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**	When identifying the appropriate comparators, the Committee is guided by established practice in the NHS, irrespective of how these are funded. After discussion with clinical specialists the Committee agreed that lapatinib plus capecitabine was a clinically relevant comparator for trastuzumab emtansine. Therefore, the evaluation of expected survival with current standard of care should be based on that of patients receiving lapatinib plus capecitabine. For further details, see sections 4.3 and 4.19 of the FAD. The Committee reviewed the reported median survival times on lapatinib plus capecitabine in several trials other than EMILIA, noting that these generally fell below 24 months. Based on these data, the Committee accepted that trastuzumab emtansine fulfilled the criterion for short life expectancy. For further details, see section 4.19 of the FAD.

Consultee	Comment	Response
Roche (cont.)	The summaries are reasonable. **<u>3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</u>** *3.1 The Committee's conclusion on double-counting of the disutility of adverse events is incorrect* In section 4.11 the ACD states that: *'the Committee considered that applying a higher utility value for trastuzumab emtansine could result in the benefit of treatment being double-counted and overestimated, because the utility decrements for adverse events already capture part of this benefit'* This is incorrect. The utility values presented for PFS contain the disutility of adverse events. These disutilities are only applied once and so no double-counting occurs within the model. *3.2 The Committee's conclusion that there is consistent utility across all treatments is unreasonable in light of the evidence available* Trastuzumab emtansine has been demonstrated to have a substantially improved tolerability profile compared to lapatinib in combination with capecitabine. It unreasonable to ignore the impact of this upon the utility of patients and subsequently the cost-effectiveness of trastuzumab emtansine. The EMILIA study included the 'FACT-B' patient reported outcome tool. The figure below demonstrates the results of the physical well-being subscale of the FACT-B results from EMILIA.	After further discussion with the Evidence Review Group (ERG), the Committee agreed that the benefit of trastuzumab emtansine from reducing adverse events had not been double-counted in the model. For further details see section 4.11 of the FAD. The Committee was aware that EMILIA was an open-label trial, which may have introduced bias in the outcomes reported by patients, but considered the additional evidence on wellbeing and side effects submitted by the company, and concluded that a marginally higher utility value for trastuzumab emtansine in the progression-free state could be accepted. For further details see section 4.11 of the FAD.

Consultee	Comment	Response
Roche (cont.)	**Figure 3.** Mean physical well-being scores (T-DM1 vs capecitabine plus lapatinib).  Cap, capecitabine; CI, confidence interval; Lap, lapatinib; T-DM1, trastuzumab emtansine. These results demonstrate a clinically meaningful improvement in the item “Bothered by side effects” for patients in the trastuzumab emtansine arm compared with patients in the capecitabine-plus-lapatinib arm which is maintained through week 24 (Figure 3) (Welslau 2012). This result is highly supportive of the use of a higher PFS utility value for patients receiving trastuzumab emtansine (something strongly supported by our clinical experts). In addition the EMILIA study included the “Diarrhea Assessment Scale” (DAS) tool. Although similar at baseline, the number of patients reporting diarrhea symptoms increased 1.5- to 2-fold during treatment in the capecitabine-plus-lapatinib arm, whereas the number reporting diarrhea symptoms remained near baseline levels in the trastuzumab emtansine arm (Fig.	

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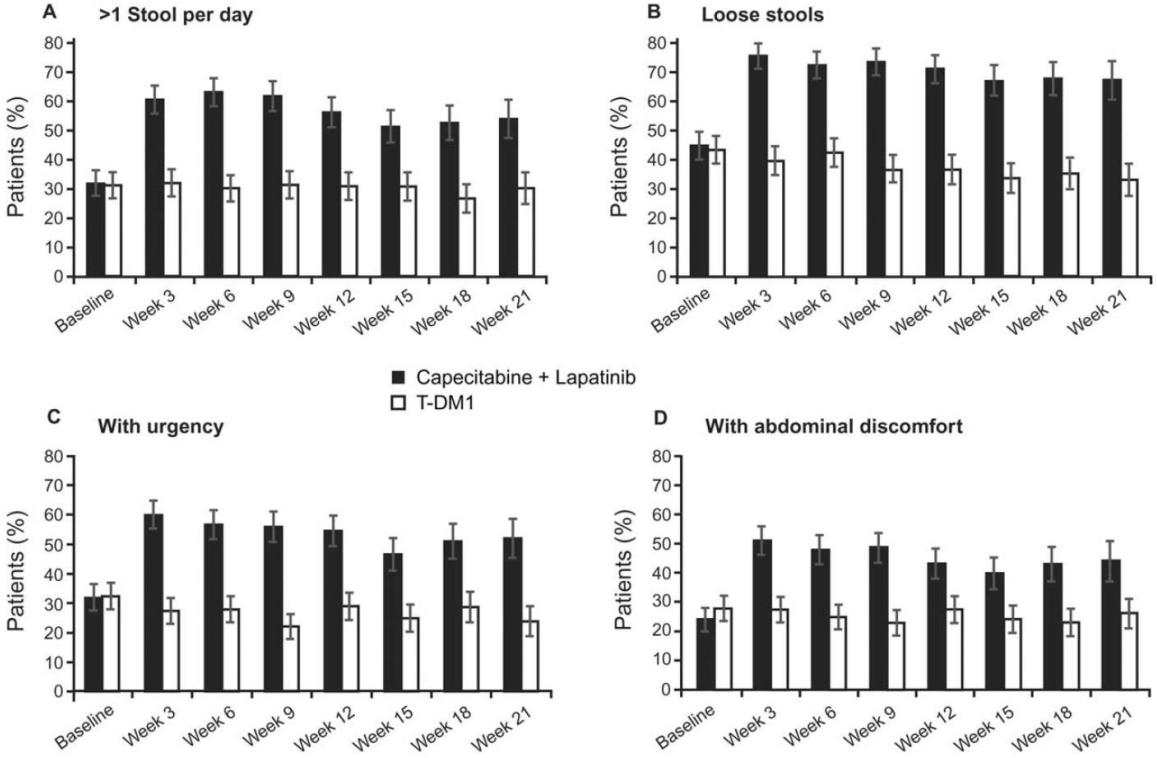
Roche (cont.)	4). At cycle 2, more patients in the capecitabine-plus-lapatinib arm versus the trastuzumab emtansine arm had more than 1 stool per day (60.5% versus 31.7%), had unformed stools (75.1% versus 39.5%), developed urgency (60.2% versus 27.5%), and had abdominal discomfort (51.0% versus 27.3%) (Welslau 2013).  **Figure 4.** Diarrhea Assessment Scale results are shown. Error bars indicate 95% confidence intervals. Abbreviation: T-DM1, trastuzumab emtansine. The combination of the EMILIA FACT-B data, the DAS data and the reduced number of symptomatic adverse events experienced with trastuzumab emtansine strongly support the	

Consultee	Comment	Response
Roche (cont.)	use of a higher utility value for trastuzumab emtansine compared to lapatinib in combination with capecitabine. *3.3 It is unreasonable for the Committee to fail to consider the impact of the PPRS medicines cap upon this Appraisal* In the context of a capped medicines budget it is unreasonable to continue to operate as if the medicines budget is not capped. This argument is detailed further in the cover letter for this response. *3.4 It is unreasonable to conclude that trastuzumab emtansine does not meet the 'End of Life' criteria due to the estimated survival of patients treated with a medicine only available via the Cancer Drugs Fund* In Section 4.18 of the ACD the Committee concluded that patients treated with lapatinib are likely to live beyond 2 years. On the basis of this it was determined that trastuzumab emtansine did not meet the 'End of Life' criteria. We believe this conclusion is fundamentally unreasonable. Lapatinib is only available via the Cancer Drugs Fund (CDF) and is not NICE approved. We do not believe it is reasonable to consider a medicine funded via the CDF as a comparator for the evaluation of whether or not 'End of Life' is met. If lapatinib plus capecitabine is considered to be an appropriate comparator for determining whether trastuzumab emtansine meets the end of life criteria then it appears unreasonable to not consider the totality of evidence available on the expected survival with this regimen. It should be noted that in the final survival analysis of lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer (Cameron D. *et al.* 2010) the median overall survival for the combination arm was 75 weeks. [*References were provided but are not reproduced here*.]	Comment noted. Comment noted. When identifying the appropriate comparators, the Committee is guided by established practice in the NHS, irrespective of how these are funded. After discussion with clinical specialists the Committee agreed that lapatinib plus capecitabine was a clinically relevant comparator for trastuzumab emtansine. Therefore, the evaluation of expected survival with current standard of care should be based on that of patients receiving lapatinib plus capecitabine. The Committee reviewed evidence of the reported survival times from several trials other than EMILIA which suggested that life expectancy on lapatinib plus capecitabine generally fell below 24 months. Based on

Consultee	Comment	Response
		the reported median survival on lapatinib plus capecitabine in those trials, the Committee accepted that trastuzumab emtansine fulfilled the criterion for short life expectancy. For further details, see section 4.3 and 4.19 of the FAD.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Breakthrough Breast Cancer	Thank you for forwarding the above document to me. I apologise for replying so late. I have read through the document thoroughly, but slowly. I am of course, not qualified to answer any of the above questions. However, I would like to comment by reiterating what I said at the meeting. People with advanced cancer, have a different concept of time to a non cancer sufferer. To the experts, three months or six month is a short time. To advanced cancer patients, it is a long time. The few extra months brings hope. Everyone wants those few extra months. There is always the possibility that the 'extra months' will turn out to be much longer. The problem as always, is cost, I do understand this. The meeting was both interesting and enlightening. May I thank you all most sincerely, for making me feel so comfortable and involved in it.	Thank you for your comment and for sharing your views at the Committee meeting. The Committee acknowledged that patients and their families often highly value what may seem to others even relatively short extensions to life, as long as the person's quality of life is maintained. It also recognised that trastuzumab emtansine would be welcomed by patients and their families. However, given the price and estimated cost-effectiveness of trastuzumab emtansine, the Committee was unable to recommend trastuzumab emtansine for routine use in the NHS. For further details, see section 4.1 of the FAD.

Comments received from commentators

Commentator	Comment	Response
GSK	• **GSK Response** No comments • <u>Error/Inconsistency</u> In section 7.4.9 page 203 of the manufacturer's submission it states: *"The response rates for trastuzumab and capecitabine and capecitabine monotherapy are estimated indirectly versus trastuzumab emtansine through using the response rates from the EGF100151 and GBG26 trials respectively."* Section 3.28, page 20 of the ACD states. *"For trastuzumab emtansine and lapatinib plus capecitabine, the manufacturer obtained response rates from EMILIA, estimating utility values of 0.78 and 0.74 respectively. Similarly, it estimated a utility value of 0.72 for capecitabine based on response rates from GBG26 and a utility value of 0.73 for trastuzumab plus capecitabine based on response rates from EGF100151."* The EGF100151 trial compared lapatinib plus capecitabine with capecitabine monotherapy and the GBG26 trial compared trastuzumab plus capecitabine with capecitabine monotherapy. It therefore seems likely that the ACD is incorrect and that the utility value for capecitabine was based on response rates from the EGF100151 trial and the utility values for trastuzumab plus capecitabine are based on the response rates from the GBG26 trial.	Thank for your comment. This error has been corrected in the FAD (section 3.28).

Summary of comments received from members of the public

Theme	Response
Medicines that could extend lives should be recommended even if they are expensive	It is the role of the Committee not to recommend treatments if the treatments are not cost effective. The cost-effectiveness estimates for trastuzumab emtansine (including the patient access scheme) remained well above the range that could be considered a cost effective use of NHS resources. For further details, see sections 4.16, 4.18, 4.19 and 4.20 of the FAD.
Trastuzumab emtansine has wider societal benefit that should be taken into account	The Committee appreciated that metastatic breast cancer is a debilitating condition that can affect women of all ages and leads to premature death. However, given the price and estimated cost-effectiveness of trastuzumab emtansine, the Committee was unable to recommend trastuzumab emtansine for routine use in the NHS. For further details, see section 4.1 of the FAD.
Trastuzumab emtansine can extend lives by more than 6 months	In Single Technology Appraisals, the key evidence on clinical effectiveness is provided by the company. In the most relevant trial for trastuzumab emtansine, EMILIA, trastuzumab emtansine increased median overall survival by 5.8 months. For further details, see sections 3.7 and 4.4 of the FAD.
Trastuzumab emtansine is too expensive	The Committee concluded that the most plausible cost-effectiveness estimate for trastuzumab emtansine (including the patient access scheme) was above the range of estimates that would normally be considered a cost effective use of NHS resources. The Committee noted that the patient access scheme did not reduce the ICER to a level close to one that could be accepted as a cost effective use of NHS resources. For further details, see sections 4.15 and 4.16 of the FAD.