National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer ID1516
Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Breast Cancer Care and Breast Cancer Now	Yes	Thank you for your comment. No action needed.
	UK Breast Cancer Group	Yes	Thank you for your comment. No action needed.
	Roche Products Limited	We recommend rewording to better reflect the anticipated marketing authorisation, see below: "To appraise the clinical and cost-effectiveness of trastuzumab emtansine within its marketing authorisation for treating human epidermal growth factor receptor 2 (HER2) positive early breast cancer in the adjuvant setting."	Thank you for your comment. The wording has been updated as suggested.
Timing Issues	Breast Cancer Care and Breast Cancer Now	No comment	-
	Association of Breast Surgery	The results of the KATHERINE trial show a significant benefit to the target population. Therefore, the magnitude of the benefit dictates that patients should have access to this therapy as soon as can be reasonably expected.	Thank you for your comment. No action needed.
	UK Breast Cancer Group	Urgent this represents a major advance in the treatment of HER-2 positive early breast cancer and would facilitate the development of de-escalation of HER-2 directed therapy trials in patients with pathological complete response	Thank you for your comment. No action needed.

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		s well as the next generation of trials in patients without pathological complete response	
	Roche Products Limited	The magnitude of benefit of trastuzumab emtansine vs. trastuzumab in the KATHERINE study, meant that an interim analysis was possible and therefore resulted in accelerated regulatory timelines. An [redacted] delay between marketing authorisation and Final appraisal document (FAD) publication (if an appraisal consultation document [ACD] is produced) is now expected. We would therefore encourage this appraisal to proceed as quickly as possible so there is no further delay to patients benefitting from the step-change improvement in outcomes that this innovative treatment offers.	Thank you for your comment. No action needed.
Additional comments on the draft remit	Roche Products Limited	None	-

Comment 2: the draft scope

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Background information	Breast Cancer Care and Breast Cancer Now	The background information should include the recent NICE recommendation regarding pertuzumab (Perjeta) which is given in combination with trastuzumab and chemotherapy. This treatment was recommended for the adjuvant treatment of HER2 positive early breast cancer in adults with lymph node-positive disease (TA509).	Thank you for your comment. TA569 (published in March 2019) was added to the background section. Please note, that TA509 was not added as this guidance is for metastatic or locally recurrent unresectable breast cancer only.
	Association of Breast Surgery	No comments to make	-
	UK Breast Cancer Group	Need to include pertuzumab as adjuvant and neo-adjuvant therapy Endocrine therapy is not relevant to this appraisal	Thank you for your comment. TA569 was added to the background section.
	Roche Products Limited	Please change 'Men are less likely to have HER-2 positive breast cancers' to 'HER2-positive' Please also include information on NICE guidance of the use of pertuzumab + trastuzumab + chemotherapy in the adjuvant treatment of HER2-positive early breast cancer – TA569.	Thank you for your comments. 'HER-2 positive' was changed to to 'HER2-positive'. TA569 was added to the background section.
The technology/ intervention	Breast Cancer Care and Breast Cancer Now	Yes – no further comments.	Thank you for your comment. No action needed.
	Association of Breast Surgery	yes	Thank you for your comment. No action

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			needed.
	UK Breast Cancer Group	Targeted intracellular delivery of a very potent chemotherapy agent	Thank you for your comment. No action needed.
	Roche Products Limited	yes	Thank you for your comment. No action needed.
Population	Breast Cancer Care and Breast Cancer Now	Yes.	Thank you for your comment. No action needed.
	Association of Breast Surgery	yes	Thank you for your comment. No action needed.
	UK Breast Cancer Group	Yes the population is appropriate. Patients without pathological complete response after standard chemotherapy trastuzumab (+/- pertuzumab) as primary medical therapy	Thank you for your comment. No action needed.
	Roche Products Limited	Please change to the following: 'Adult patients with HER2-positive early breast cancer who have residual disease, in the breast and/or lymph nodes, after neoadjuvant therapy that included a taxane (with or without anthracycline) and HER2-targeted therapy'.	Thank you for your comment. The population definition has been amended.
Comparators	Breast Cancer Care and Breast Cancer Now	Yes. It should be noted that neratinib is currently making its way through the NICE appraisal process. It is being assessed as an option for treating early hormone receptor-positive HER2-positive breast cancer after adjuvant trastuzumab.	Thank you for your comment. No action needed.
	Association of Breast Surgery	Comparators are suitably chosen.	Thank you for your comment. No action needed.
	UK Breast Cancer Group	Yes comparators are appropriate • Trastuzumab	Thank you for your comment. No action

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		Pertuzumab in combination with trastuzumab and chemotherapy as adjuvant therapy for patients with evidence of lymph node involvement (the residual breast cancer maybe in the breast or lymph node. For pertuzumab funding in NHSE evidence of prior involvement of lymph node qualifies for funding)	needed.
	Roche Products Limited	Please remove "(subject to NICE guidance"). Guidance for TA569 (Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer) has now been published.	Thank you for your comment. This has been removed.
Outcomes	Breast Cancer Care and Breast Cancer Now	Yes.	Thank you for your comment. No action needed.
	Association of Breast Surgery	It is not clear how "response rate" will be measured	Thank you for your comment. Response rate has been removed from the list of outcomes.
	UK Breast Cancer Group	yes	Thank you for your comment. No action needed.
	Roche Products Limited	The outcome measures to be considered include: • Invasive disease-free survival (IDFS) • IDFS with second non-breast primary cancers included • Disease-free survival (DFS) • Overall survival (OS) • Distant recurrence-free interval • Cardiac & overall safety • Health-related quality of life (HRQoL)	Thank you for your comment. No action needed.
Economic analysis	Breast Cancer Care and Breast Cancer Now	N/A	-
	Association of	No comments	-

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	Breast Surgery		
	UK Breast Cancer Group	Appropriate	Thank you for your comment. No action needed.
	Roche Products Limited	No comment	-
Equality and Diversity	Breast Cancer Care and Breast Cancer Now	The scope does not appear to promote discrimination.	Thank you for your comment. No action needed.
	Association of Breast Surgery	n/a	-
	UK Breast Cancer Group	Response directed therapy would require that the ability to deliver primary medical therapy with HER-2 directed therapies be uniformly accessible to patients across UK	Thank you for your comment. This relates to implementation. It is not a guidance related issue.. No action needed.
	Roche Products Limited	No comment	-
Other considerations	Breast Cancer Care and Breast Cancer Now	The majority of patients in the trial for this treatment had received trastuzumab alone as the neoadjuvant HER2 therapy, with a smaller group of people having received trastuzumab plus pertuzumab. It will be important to understand during the appraisal how this reflects current practice in England. Pertuzumab in combination with trastuzumab and chemotherapy is recommended as an option for the neoadjuvant treatment of adults with HER2 positive early or locally advanced breast cancer who are at high risk of recurrence (TA424).	Thank you for your comment. The following subgroups were added to the scope: If evidence allows, the following subgroups will be considered separately: • prior

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			neoadjuvant therapy including trastuzumab, and • prior neoadjuvant therapy including pertuzumab with trastuzumab and chemotherapy.
	UK Breast Cancer Group	As above *[Response directed therapy would require that the ability to deliver primary medical therapy with HER-2 directed therapies be uniformly accessible to patients across UK] comment added for clarity*	Thank you for your comment. This relates to implementation. It is not a guidance related issue. No action needed.
	Roche Products Limited	No comment	-
Innovation	Breast Cancer Care and Breast Cancer Now	It is significant that in the trial invasive disease-free survival was higher in the trastuzumab emtansine group than the trastuzumab group. Women with early HER2 positive breast cancer (with residual disease following neoadjuvant treatment) who received adjuvant trastuzumab emtansine had improved invasive disease free survival by 11% at 3 years, when compared to those that had trastuzumab.	Thank you for your comment. No action needed.
	Association of Breast Surgery	Yes, as suggested by the results of the randomised controlled KATHERINE study	Thank you for your comment. No action needed.
	UK Breast Cancer Group	Yes highly innovative and represents a step change in treatment for HER2 positive early breast cancer There is a need to consider how this will affect the pathway for HER-2	Thank you for your comments. No action needed.

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		positive early breast cancer The uptake of neoadjuvant pertuzumab has been variable across UK Response directed therapy would require that the ability to deliver primary medical therapy with HER-2 directed therapies be uniformly accessible to patients across UK NCRI BCSG has recently conducted a survey on HER2 directed therapy which maybe useful	
	Roche Products Limited	Yes. Trastuzumab emtansine is an antibody drug conjugate that consists of: • Trastuzumab as the monoclonal antibody to target HER2 receptors • DM1 as the potent cytotoxic agent • A stable linker which binds trastuzumab to DM1 and is broken down within HER2-overexpressing tumour cells to release DM1 With this innovative mechanism of action, trastuzumab emtansine is designed to maximise targeted delivery of a cytotoxic agent to HER2-positive tumour cells whilst minimising systemic exposure and cytotoxic effects on normal tissue. In the KATHERINE trial, at the interim analysis, invasive disease or death had occurred in 91 patients in the T-DM1 group (12.2%) and 165 patients in the trastuzumab group (22.2%). Invasive disease-free survival was significantly higher in the T-DM1 group than in the trastuzumab group (hazard ratio for invasive disease or death, 0.50; 95% confidence interval, 0.39 to 0.64; P<0.001); thus the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant trastuzumab emtansine than with trastuzumab alone. Through its unique mechanism of action, trastuzumab emtansine has previously represented a step change in the treatment of HER2-postive breast cancer in the metastatic setting. , Patients with HER2-positive early breast cancer who have residual disease following optimal neoadjuvant treatment have a very poor prognosis. , , Trastuzumab emtansine again	Thank you for your comments. No action needed.

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		represents a step change in the management of these very high risk patients, and represents the first robust breast cancer example of adapting treatment based on tumour response in the neoadjuvant setting – the ultimate goal of that treatment approach. Early treatment of breast cancer has a curative intent and, where successful, is likely to allow patients to return to their normal lives. Increasing the number of women who achieve a clinical cure/long-term remission, as achieved with the treatment of trastuzumab emtansine in this setting, is likely to result in wider societal benefits that are not captured by the QALY and NHS & PSS cost perspective. An example of these wider benefits is illustrated by the potential gains in productivity. Many of the women in this patient population are below the UK retirement age. Achieving a long-term remission in this setting is likely to result in many women returning to work which will subsequently lead to a positive impact on productivity and the UK economy as a whole. Additionally, long term remission will also lead to benefits relating to carers. Many women with metastatic disease may require part/full-time care - often given by family members. The prevention of recurrences, and therefore metastatic disease, will result in substantial gains in both carer productivity (they are free to return to the labour market) and health-related quality of life. Evidence of a “step-change” can be seen in the recent read-out of the KATHERINE trial. In the KATHERINE trial, at the interim analysis, invasive disease or death had occurred in 91 patients in the T-DM1 group (12.2%) and 165 patients in the trastuzumab group (22.2%). The estimated percentage of patients who were free of invasive disease at 3 years was 88.3% in the T-DM1 group and 77.0% in the trastuzumab group. Invasive disease-free survival was significantly higher in the T-DM1 group than in the trastuzumab group (hazard ratio for invasive disease or death, 0.50; 95% confidence interval, 0.39 to 0.64; P<0.001). These data are extremely compelling and can be regarded as practice changing.2	

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		It is difficult to quantify the exact impact of the wider (indirect) costs and benefits not captured in the QALY calculation. As part of this appraisal, Roche is conducting systematic literature reviews into costs and quality of life in early breast cancer. Data sources evaluating productivity and carer quality of life captured in these reviews will be discussed in detail in the Company submission dossier. If no suitable data is captured, these benefits may not be quantified in the cost-effectiveness model. It is important to note here that the omission of these factors, from the economic analysis, will result in an underestimation of the incremental health benefits associated with trastuzumab emtansine treatment in this setting.	
Questions for consultation	UK Breast Cancer Group	Trastuzumab in lymph node negative and trastuzumab pertuzumab in lymph node positive would be appropriate comparators TDM-1 (trastuzumab-emtansine) would be considered for patients without pathological complete response whether they received pertuzumab or not in combination with trastuzumab based primary medical therapy TDM-1 (trastuzumab-emtansine) is likekly to be equally effective clinically in all populations but more likely to be cost-effective when the comparator is pertuzumab and trastuzumab It would fit in the pathway in accordance with the application ie in patients for whom primary medical therapy has not resulted in a pathological complete response The issue of the increasing number of systemic anti-cancer therapy treatments in breast cancer (increase of 584% in Greater Manchester over 5 years, with similar increases over previous quinquennials) without increase in workforce presents an issue that needs consideration. Likewise the variability	Thank you for your comment. No action needed.

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		of patient access to services where primary medical therapy is routine practice.	
	Roche Products Limited	1) Have all relevant comparators for trastuzumab emtansine been included in the scope? • Which treatments are considered to be established clinical practice in the NHS for HER2-positive breast cancer in the adjuvant setting? At the time of writing, trastuzumab is established clinical practice in the adjuvant treatment of HER2-positive early breast cancer patients (irrespective of nodal status). Given the recent positive NICE recommendation, at the time of submission it is anticipated that pertuzumab + trastuzumab + chemotherapy will be the standard of care in the adjuvant treatment of HER2-positive, early breast cancer in patients with node-positive disease.1 • Would pertuzumab in combination with trastuzumab and chemotherapy (subject to positive guidance) be the only relevant comparator for people with lymph-node-positive disease? Yes, though as previously stated, please remove “subject to positive guidance”. The guidance for this appraisal has now been published.1 2) Pertuzumab in combination with trastuzumab and chemotherapy is recommended as an option for the neoadjuvant treatment of adults with HER2-positive, locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence neoadjuvant therapy (TA424). • Would a treatment with trastuzumab emtansine in the adjuvant setting be considered following a prior neoadjuvant treatment recommended in TA424? Or would trastuzumab emtansine be used only after prior neoadjuvant treatment without pertuzumab?	Thank you for your comments. No action needed.

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		Patients who have been treated neoadjuvantly with pertuzumab + trastuzumab should be considered suitable for treatment with trastuzumab emtansine in the adjuvant setting. Reflective of the standard of care when the KATHERINE study was recruiting, the majority of patients in the KATHERINE trial were treated neoadjuvantly with chemotherapy and trastuzumab only. However, there was also a sizable proportion of patients in each arm who received trastuzumab plus additional HER2-directed agent(s). Around 18% of patients (trastuzumab arm: 139/734 = 18.71% / trastuzumab emtansine arm: 133/743 = 17.90%) received pertuzumab + trastuzumab in the neoadjuvant setting (i.e. TA424) of the trial.2, Efficacy results in patients who were pre-treated with pertuzumab and those patients who were pre-treated with trastuzumab only are displayed in Table 1. *[Table 1 is not included here. Please see the Roche consultation comments for more details.]* Despite the low number of events, the results seen in this analysis show that the treatment effect of trastuzumab emtansine is broadly consistent, regardless of whether or not a patient had pertuzumab in the neoadjuvant setting. There is no biological/clinical rationale why the addition of pertuzumab to the neoadjuvant treatment regimen would impact on the efficacy of trastuzumab emtansine in the adjuvant setting. Pertuzumab + trastuzumab is the current standard of care in the neoadjuvant setting, with approximately 85% market share. Given the unprecedented results of the KATHERINE trial, excluding patients pre-treated with pertuzumab (i.e. the majority of UK eligible patients) from this appraisal could have considerable equality, and importantly, ethical implications: If treating physicians were limited in their ability to access trastuzumab emtansine in the adjuvant setting, it could create a perverse incentive to treat using	

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		trastuzumab monotherapy in the neoadjuvant setting, resulting in HER2-positive breast cancer patients being treated in a sub-optimal manner, creating poorer overall outcomes for patients. 3) Are the outcomes listed appropriate? Please see the “Outcomes” section above. 4) Are there any subgroups of people in whom trastuzumab emtansine is expected to be more clinically effective and cost effective or other groups that should be examined separately? None. 5) Where do you consider trastuzumab emtansine will fit into the existing NICE pathway, Early and locally advanced breast cancer? Within the early and locally advanced breast cancer pathway, trastuzumab emtansine should be an adjuvant treatment option for HER2-positive patients who received neoadjuvant therapy and are determined to have remaining residual disease 6) NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatments will be licenced;	

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		• could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. No comment. 7) Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. No comment. 8) Do you consider trastuzumab emtansine to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Please see the "Innovation" section above. 9) Do you consider that the use of trastuzumab emtansine can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please see the "Innovation" section above. 10) Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits	

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		Please see the “Innovation” section above. 11) To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. None. 12) NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. The STA process is appropriate for appraising this topic 13) NICE has published an addendum to its guide to the methods of technology appraisal, which states the methods to be used where a cost comparison case is made. • Would it be appropriate to use the cost comparison methodology for this topic? Cost comparison methodology is not applicable in this appraisal.	
Additional comments on the draft scope	Breast Cancer Care and Breast Cancer Now	Under “related NICE recommendations and NICE pathways” – the following guidance is included: NICE diagnostic guidance 10 – gene expression profiling. However, this guidance has been replaced by Tumour profiling Diagnostics guidance [DG34]. This is not relevant for this group of patients as tumour profiling is for a group of patients who are hormone receptor positive, HER2 negative.	Thank you for your comment, the guidance was removed.

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	UK Breast Cancer Group	This represents the biggest advance in treatment of HER-2 positive early breast cancer since the introduction of trastuzumab	Thank you for your comment. No action needed.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Amgen.