National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Trastuzumab emtansine for treating HER2-positive, locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Breakthrough Breast Cancer	It is often cited that there are limited treatment options for patients with metastatic/advanced breast cancer. This is certainly the case for patients with HER2 positive metastatic breast cancer as there is currently only one targeted treatment available for use on the NHS - Herceptin. Therefore, the appraisal of new drugs used to treat this type of breast cancer is essential.	Comments noted. No changes to the scope required.
	Roche Products	Yes, this topic is appropriate for appraisal	Comment noted. No changes to the scope required.
Wording	Breakthrough Breast Cancer	The wording appears appropriate	Comment noted.
	Roche Products	The draft indication specifies that patients are **unresectable**. The proposed appraisal title should therefore be amended to read “Trastuzumab emtansine for the treatment of **unresectable** locally advanced, or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane”.	Comments noted. The scope has been amended accordingly.

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Timing Issues	Breakthrough Breast Cancer	In September the manufacturer of T-DM1, Roche, announced that the drug can prolong the lives of patients with HER2 positive metastatic breast cancer by 5.8 months when compared to those being treated with lapatnib in combination with capecitabine. This finding is the latest from the Phase III EMILIA study which also demonstrated a median progression free survival enhancement of 3.2 months. Any drug that can enhance the time cancer patients are able to control their disease and stop it progressing and especially those that can prolong life should be made available to patients as quickly as possible.	Comments noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	Roche Products	Currently there are limited treatment options for people living with this type of breast cancer in the late stage of disease, particularly where traditional treatments no longer provide efficacy. We would therefore expect there to be a large clinical demand for any new treatment with proven efficacy. We would also welcome clarity around the timing of the appraisal and any subsequent changes in the process, resulting from the overlap with Value Based Pricing (VBP) being introduced on January 1st 2014.	Comments noted. The anticipated timelines are as follows: Invitation to participate will be sent to consultees and commentators on 15/10/2013. The Appraisal Committee meetings will be held in March 2014 and May 2014. Earliest anticipated date of guidance publication is August 2014.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Breakthrough Breast Cancer	The background information appears largely to be correct. However, given England and Wales incidence statistics are quoted it may be more appropriate to quote England and Wales mortality statitics instead of UK-wde. The number of female and male breast cancer deaths in 2012 in England and Wales was 10,333 (CRUK data). Additonally, your estimate of HER2 positive breast cancer accounting for 25% of all breat cancers seems quite high. The statistic Breakthrough uses in its health information is 20%.	Comments noted. The background of the scope has been updated with latest available statistics.
	Roche Products	The scope states that “In 2009 there were 43,183 diagnoses of breast cancer in England and Wales”. The true figure is 43,170*. *http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/incidence/uk-breast-cancer-incidence-statistics The EMILIA trial (NCT00829166) protocol defines the locally advanced population as those that are inoperable, unresectable and not suitable for neo-adjuvant treatment. The scope states that “HER2-positive breast cancer accounts for up to 25% of all breast cancers.” However this should be reworded to “HER2-positive breast cancer accounts for up to 25% of all metastatic breast cancers.”	Comments noted. The background of the scope has been updated with latest available statistics.
The technology/ intervention	Breakthrough Breast Cancer	The description of the technology is correct. This type of drug is called an antibody conjugate as it incorporates the HER2 targeted antibody Herceptin with the cytotoxic agent DM1 as a single therapy.	Comment noted.

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	Roche Products	The scope states that “Trastuzumab emtansine (brand name unknown, Roche Products) combines the monoclonal antibody trastuzumab with the anti-microtubule agent maytansinoid DM1”. However this is not accurate; the technology is an antibody-drug conjugate. This should be therefore be added to the text and the technology should be referred to as a monotherapy. More appropriate wording would be as follows: “Trastuzumab emtansine is an antibody-drug conjugate monotherapy.” The text states that “It has been studied in a clinical trial in comparison with lapatinib and capecitabine in people with locally advanced or metastatic HER2-positive breast cancer whose disease has progressed despite receiving prior treatment with trastuzumab and a taxane.” More appropriate wording would be to change the word “despite” to “after”.	Comments noted. The technology section of the scope has been amended accordingly.
Population	Breakthrough Breast Cancer	The population is accurate However, it is also important to note that as well as HER2 positive patients receiving Herceptin in the metastatic setting this drug is now routinely used in the adjuvant setting. Because of this there are questions around the best course of treatment for HER2 patients who have received adjuvant Herceptin and NICE Clinical Guidelines for Advanced Breast Cancer offer no advice for optimal treatment for these patients. Therefore, it would be beneficial to consider T-DM1 for use in patients who are untreated in the metastatic setting but who received adjuvant Herceptin. By not giving these patients the option to receive this drug it may deny them their only chance of receiving a targeted treatment.	Comments noted. It was agreed at the scoping workshop that the current proposed remit is broad enough to allow consideration of patients who have received trastuzumab in the adjuvant setting and are untreated in the metastatic setting.

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	Roche Products	The population is defined as “People with advanced, or metastatic HER2-positive breast cancer whose disease has progressed after treatment with trastuzumab and a taxane”. This should include the word “unresectable”. The population should therefore be referred to as “People with unresectable advanced, or metastatic HER2-positive breast cancer whose disease has progressed after treatment with trastuzumab and a taxane	Comments noted. The definition of the population in the scope has been amended accordingly.
Comparators	NCRI/RCP/RCR /ACP/JCCO	Some experts suggest that for trastuzumab emtansine (TDM1) the real comparator is lapatinib plus capecitabine, as stated, but not really capecitabine or vinorelbine monotherapy which are also mentioned. We understand that TDM1 was compared with lapatinib & capecitabine in combination (and the former was proved to be better) in the EMILIA study which was published recently in the New England Journal of Medicine.	Comment noted. It was agreed at the scoping workshop that lapatinib in combination with capecitabine; trastuzumab in combination with capecitabine, trastuzumab in combination with vinorelbine; capecitabine monotherapy and vinorelbine monotherapy, were the most appropriate comparators.
	Roche Products	Roche market research* indicates that in 2L HER2 positive metastatic breast cancer **capecitabine in combination with lapatinib is the most dominant regimen, used in 41% of all patients.** This is followed by capecitabine in combination with trastuzumab (13%), trastuzumab alone (11%) and capecitabine alone (10%). In 3L+ HER2 positive metastatic breast cancer, **capecitabine in combination with lapatinib is the most dominant regimen, used in 27% of all patients.** This is followed by vinorelbine alone (23%), trastuzumab alone (10%) and capecitabine alone (8%). *IMS UK Metastatic Breast Cancer Enhanced Tumour Study	Comment noted. It was agreed at the scoping workshop that lapatinib in combination with capecitabine; trastuzumab in combination with capecitabine, trastuzumab in combination with vinorelbine; capecitabine monotherapy and vinorelbine monotherapy, were the most appropriate comparators.

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Outcomes	Breakthrough Breast Cancer	It may also be appropriate to consider response rate.	Comment noted. It was agreed at the scoping workshop that response rate should not be included in the scope.
Economic analysis	Breakthrough Breast Cancer	It is important that economic analysis is placed on patient quality of life since advanced/metastatic breast cancer is a life limiting condition.	Comment noted.
Equality and Diversity		No comments	N/A
Innovation	Breakthrough Breast Cancer	T-DM1 has a duel method of action. By attaching to the HER2 receptor on the surface of the cancer cell it blocks the signals that encourages the cancer to grow and spread. It then becomes internalised by the cell where it releases a cytotoxic agent which destroys the cell from the inside. This targeted approach means healthy cells are left untouched and the common side effects of chemotherapy are reduced. Therefore, the method of action and the subsequent impact on chemotherapy related side effects of this treatment can indeed be classed as innovative.	Comments noted.

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	Roche Products	While significant progress has been made in treating this condition, there remains a need to prolong remission time and improve quality of life for patients with advanced disease. T-DM1 is known as an antibody-drug conjugate or ADC, and is the first medicine of its kind for any type of solid cancer tumours. It uses a 'stable linker' to join trastuzumab and emtansine together. The stable linker binds the two agents together until T-DM1 is absorbed inside the cancer cell, where it releases the potent chemotherapy. By delivering the chemotherapy directly inside the cancer cells, T-DM1 causes fewer side effects and gives patients a much better quality of life during treatment, compared with lapatinib plus capecitabine Results from the Phase III EMILIA clinical trial, demonstrated that people with previously treated HER2-positive metastatic breast cancer (mBC) survived significantly longer (overall survival) and markedly increased the time before their disease progressed (progression free survival), when treated with trastuzumab emtansine (T-DM1) compared to the only licensed combination in second-line mBC – lapatinib and capecitabine.* *Verma, S. et al. Updated Overall Survival Results from EMILIA, a Phase 3 study of trastuzumab emtansine (T-DM1) vs. capecitabine and lapatinib in HER2-positive locally advanced or metastatic breast cancer (MBC); Abstract # LBA12. Presented at the European Society of Medical Oncology (ESMO) conference, 1 October 2012	Comments noted.
Other considerations		No Comments	N/A

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Questions for consultation	Roche Products	Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? It is important to ensure that improvements in clinical outcomes do not come at the expense of a patient's symptom burden. The EMILIA study showed that time to symptom worsening, as measured by the FACT-B TOI, was delayed in the trastuzumab emtansine arm compared with the capecitabine plus lapatinib arm (4.6 vs 7.1 months; P=0.0121). Similarly it is also important to understand the profile of adverse events from the patient's perspective since research has shown that the incidence and severity of adverse events, as reported by investigators in clinical trials, can differ from reports of adverse events provided by patients, particularly in the case of more subjective adverse events. Not only does the EMILIA study show that patients treated trastuzumab emtansine experience fewer grade ≥3 investigator reported adverse events compared with capecitabine plus lapatinib (200 (40.8%) vs 287 (57.0%) patients, respectively), but it also shows that patients in the capecitabine with lapatinib arm reported worse symptoms of diarrhoea (loose stool, frequency, urgency, with abdominal discomfort) on treatment than those on trastuzumab emtansine. Roche would also recommend patient group involvement in order to establish the full benefits from the drug. Roche believe that the results of this inventive dual mode of action from the EMILIA trial will be embraced by clinicians, patients, and their families and carers.	Comments noted.

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

Department of Health
Marie Curie Cancer Care
Medicines and Healthcare products Regulatory Agency
The Royal College of Nursing