National Institute for Health and Care Excellence

SingleTechnology Appraisal (STA)
Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer (ID 767)
Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Roche	This topic is appropriate for a NICE appraisal	Comment noted. No action required.
Wording	Roche	The remit reflects the proposed marketing authorisation	Comment noted. No action required.
Timing Issues	Roche	Given the curative setting it is essential that timely guidance is issued	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
Additional comments on the draft remit	Roche	No comments	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Roche	No comments	Comment noted. No action required.
The technology/ intervention	Roche	The intervention is appropriate	Comment noted. No action required.
	NCRI/RCP/RCR /ACP	No response received	Response noted.
Population	Roche	The population is defined appropriately	Comment noted. For clarity, the population has been amended to 'adults with HER2-positive breast cancer which is either; • locally advanced, or • inflammatory, or • early stage (at a high-risk of recurrence)'.
Comparators	Roche	Currently, trastuzumab in combination with docetaxel and chemotherapy is the most commonly used regimen for the treatment of HER2-positive early breast cancer and therefore represents the comparator in this appraisal. It is also this regimen to which pertuzumab is expected to be added for neoadjuvant treatment of HER2-postive early breast cancer. "No neoadjuvant treatment" is not a suitable comparator as women with high	Comment noted. The scope has been updated to remove 'no neoadjuvant treatment' from the comparators.

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		risk early breast cancer, defined as per the licensed population for pertuzumab neoadjuvant therapy would be treated with anti-HER2 therapies in combination with chemotherapy, i as opposed to a surgical intervention and adjuvant treatment alone. Furthermore, adjuvant therapy would not be suitable as a direct comparator to pertuzumab neoadjuvant therapy, given the differences of these therapeutic approaches in the treatment pathway in early breast cancer.	
Outcomes	Roche	Differences in surgical outcomes are difficult to capture in clinical trials as these are normally measured as secondary objectives, and as such are not statistically powered in neoadjuvant clinical trial design. A factor in why surgical outcomes are not powered in neoadjuvant clinical trials is that patient choice in surgical intervention can confound any analysis. Pathological Complete Response (pCR) is an acceptable clinical endpoint in neoadjuvant clinical trials, associated with improved long-term survival as well as improved surgical outcomes, fewer mastectomies and enabling more conservative surgery and/or breast conservation.	Comment noted. Scoping workshop attendees agreed that pathological complete response is an appropriate outcome in neoadjuvant setting.
Economic analysis	Roche	No comment	Comment noted. No action required.
	NCRI/RCP/RCR /ACP	**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.** No.	Comment noted. No action required.
Equality and Diversity	Roche	No equality considerations have been identified	Comment noted. No action required.
Innovation	Roche	**Do you consider that the use of pertuzumab can result in any potential significant and substantial health-related benefits that are unlikely to be**	Comment noted. The

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		included in the QALY calculation? Clinical evidence from the NeoSphere and TRYPHENA trials demonstrate the benefits of dual HER2 blockade with pertuzumab and trastuzumab to achieve pCR, leading to improved clinical outcomes and significant benefit to patients with HER2-positive early breast cancer. Pertuzumab is likely to result in substantial health related benefits that are unlikely to be included in the QALY calculation. A primary benefit of improved pCR that is unlikely to be captured in the QALY estimate is increased shrinking of the tumour to facilitate surgery, therefore enabling more breast conservative surgery and/or breast conservation. As noted in the outcomes section above, differences in surgical outcomes are difficult to capture in clinical trials, and as such are not statistically powered in neoadjuvant clinical trial design. Although not captured in clinical trials, pertuzumab is anticipated to be associated with more breast conservative surgery and/or breast conservation that will have a significant benefit to women. This benefit will not be captured in the economic model and QALY estimate.	innovative nature of pertuzumab will be considered by the Committee during the course of the appraisal.
	NCRI/RCP/RCR /ACP	**Do you consider pertuzumab 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)?** Yes. Our experts believe that dual antibody therapy is potentially a significant step forward. **Do you consider that the use of pertuzumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** There is clear data indicating that pathological complete response is strongly associated with improved breast cancer outcomes. However, there is a	Comment noted. The innovative nature of pertuzumab will be considered by the Committee during the course of the appraisal.

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		knowledge gap as we do not have data indicating the magnitude of neoadjuvant pertuzumab to improve long term breast cancer outcomes. It has not been possible to provide a reliable estimate for mapping an increase in pathological complete response to improvement in long term outcomes such as relapse free and overall survival for a new agent. The QUALY calculation in this instance may therefore be unreliable. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** We propose peer-reviewed published data only.	
Other considerations	Roche	No comment	Comment noted. No action required.
	NCRI/RCP/RCR /ACP	Where do you consider pertuzumab will fit into the existing NICE pathway for early and locally advanced breast cancer? 1. Neoadjuvant therapy 2. First line metastatic. Both scenarios with taxane chemotherapy and trastuzumab.	Comment noted. The NICE pathway will be reviewed following publication of the guidance.
Questions for consultation	Roche	**Who would be considered for neoadjuvant therapy in clinical practice?** NICE clinical guideline 80 recommends that systemic therapy could be offered before surgery (neoadjuvant) to people with early invasive, locally advanced or inflammatory breast cancer who are considering breast conserving surgery that is not advisable at presentation. Trastuzumab in combination with docetaxel and chemotherapy is the most commonly used regimen for the neoadjuvant treatment in HER2-positive early breast cancer. Pertuzumab is an add-on treatment and can be considered as a concomitant anti-HER2 therapy in combination with trastuzumab and docetaxel as	Comments noted. The scope has been updated to remove 'no neoadjuvant treatment' from the comparators. The description of standard neoadjuvant therapy has been incorporated in the background section.

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		neoadjuvant treatment regimen in HER2-positive early breast cancer. **Have all relevant comparators for pertuzumab been included in the scope?** "No neoadjuvant treatment" is not a suitable comparator as women with high risk early breast cancer that is defined as the licensed population for neoadjuvant therapy with pertuzumab would be treated with anti-HER2 therapies in combination with chemotherapy prior to surgery. **Are there any subgroups of people in whom pertuzumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? For example people with locally advanced or inflammatory breast cancer or those with oestrogen receptor positive tumours.** Women are tested for HER2 status at time of diagnosis. If HER2 status is positive the prognosis is poorer than for HER2 negative patients, and patients will be eligible to receive anti-HER2 targeted therapies, including trastuzumab. Data from pertuzumab neoadjuvant trials in HER2-positive early breast cancer demonstrate the addition of pertuzumab to existing trastuzumab-containing neoadjuvant regimens provides clinical benefit with no new safety concerns to women with HER2-positive early breast cancer.. Pertuzuamb is Data from NeoSphere and TRYPHAENA trials has included patients diagnosed with inflammatory breast cancer, therefore pertuzumab should be considered for this subgroup of difficult-to-treat and aggressive type of cancer.	The scoping workshop attendees agreed that If the evidence allows the subgroups indicated in the 'population' section will be considered separately. The scope has been updated.
	NCRI/RCP/RCR	**Have all relevant comparators for pertuzumab been included in the**	Comments noted. The

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	/ACP	**scope?** Yes. **Which neoadjuvant treatments are considered to be established clinical practice in the NHS for people with HER2-positive, locally advanced, inflammatory, or early stage breast cancer?** There is ample clinical evidence for effectiveness of multiple trastusumab containing regimens a model with a single regimen backbone while simple may not be the most representative The most commonly used regimen is 5-Flourouracil Epirubicin Cyclophosphamide followed by Docetaxel (FEC-T 6-8 cycles)with trastusumab given with the docetaxel. With the emerging data demonstrating safety with anthracyclines and traztsumab in the neoadjuvant setting the sequence may be reversed (T-FEC) with concurrent trastuzumab given across all 6 cycles. This regimen is used because the Neotango study demonstrated an advantage to taxane up front compared to taxane after anthracycline. As this data was derived from HER-2 negative and HER-2 positive patients in the absence of trastusumab it is unclear if this increases the neoadjuvant efficacy in HER-2 positive disease but it is cost neutral as less adjuvant trastuzumab is given in the post-operative setting. . **Who would be considered for neoadjuvant therapy in clinical practice?** Our experts believe that any patient with early breast cancer with HER2 positive breast cancer where the clinician wishes to consider neoadjuvant therapy, probably excluding 1cm or less with no confirmed positive axillary nodes, should be considered. **Are there any subgroups of people in whom pertuzumab is expected to**	scope has been updated to remove 'no neoadjuvant treatment' from the comparators. The description of standard neoadjuvant therapy has been has been incorporated in the background section. The scoping workshop attendees agreed that people with Pam 50 HER-2 enriched phenotype are not routinely identified in clinical practice. They also heard from clinical experts that people with oestrogen/progesterone receptor negative breast cancer constitute a very small proportion of people with HER2 positive breast cancer and therefore should not be examined separately. The scoping workshop attendees agreed that if

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		be more clinically effective and cost effective or other groups that should be examined separately? (For example people with locally advanced or inflammatory breast cancer or those with oestrogen receptor positive tumours). 1. Locally advanced 2. oestrogen/progesterone receptor negative. In addition patients with the Pam 50 HER-2 enriched phenotype on molecular profiling which includes some ER positive disease appear to have very high pathological complete response rates. (this test is not routinely available in the NHS and is probably currently impractical as a selection tool)	the evidence allows the subgroups indicated in the 'population' section could be considered separately. The scope has been updated.
Additional comments on the draft scope	Roche	No comments	Comment noted. No action required.

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

Allergan
Department of Health
Royal College of Nursing

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (MTA) (STA)

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Breast cancer campaign	NICE Secretariat		Removed	This organisation's has merged with Breast Care Campaign and has been removed from the list of consultees and commentators under 'patient group'

2.	Breast Cancer Now	NICE Secretariat		Added	This organisation has an area of directly related to this appraisal topic and meets the selection criteria to participate in this appraisal. Breast Cancer Now has been added to the matrix of consultees and commentators under 'patient groups'.
3.	Tenovus Cancer Care	NICE Secretariat		Amended	Tenovus Cancer Care (formerly known as Tenovus) has been amended on the matrix of consultees and commentators under 'patient group'.
4.	Haven	NICE Secretariat		Removed	This organisation does not have an area of interest directly related to the appraisal topic Haven has been removed from the matrix of consultees and commentators under 'patient' groups'.

5.	Accord Healthcare (Docetaxel)	NICE Secretariat		Removed	This organisation is not a comparator company for the appraisal topic Accord Healthcare (Docetaxel) been removed from the matrix of consultees and commentators under 'comparator company.
6.	Actavis UK (Docetaxel)	NICE Secretariat		Removed	This organisation is not a comparator company for the appraisal topic **Actavis UK** (Docetaxel) been removed from the matrix of consultees and commentators under 'comparator company.

7.	Hospira UK (Docetaxel)	NICE Secretariat		Removed	This organisation is not a comparator company for the appraisal topic **Hospira UK** (Docetaxel) been removed from the matrix of consultees and commentators under 'comparator company.
8.	Medac GmbH (Docetaxel)	NICE Secretariat		Removed	This organisation is not a comparator company for the appraisal topic **Medac GmbH** (Docetaxel) been removed from the matrix of consultees and commentators under 'comparator company.

9.	Roche (Trastuzumab)	NICE Secretariat		Removed	This organisation is not a comparator company for the appraisal topic Roche (Trastuzumab) been removed from the matrix of consultees and commentators under 'comparator company.
10.	Sanofi (Docetaxel)	NICE Secretariat		Removed	This organisation is not a comparator company for the appraisal topic Sanofi (Docetaxel) been removed from the matrix of consultees and commentators under 'comparator company.

11.	Teva UK (Docetaxel)	NICE Secretariat		Removed	This organisation is not a comparator company for the appraisal topic Teva UK (Docetaxel) been removed from the matrix of consultees and commentators under 'comparator company.