National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer

Response to consultee and commentator comments on the draft remit and draft scope

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Roche Products	This topic is appropriate for a NICE appraisal.	Comment noted.
	GlaxoSmithKline	Yes it is appropriate to refer this topic to NICE for appraisal.	Comment noted.
	Lancashire & South Cumbria Cancer Network	This is appropriate as it may have an impact on the care of patients with Her 2 positive metastatic breast cancer	Comment noted.
	CSAS	This is appropriate.	Comment noted.
	Breakthrough Breast Cancer	It is appropriate for this topic to be referred to NICE	Comment noted.
Wording	Roche Products	The wording of the remit should also include the use of pertuzumab combination therapy for “previously untreated” metastatic breast cancer.	Comment noted. Scoping workshop attendees agreed that it is appropriate to amend the remit to reflect the proposed wording of marketing authorisation. The remit of the scope have been amended to “to appraise the clinical and cost-effectiveness of pertuzumab in combination with trastuzumab and docetaxel within its licensed indication for the treatment of human

Section	Consultees	Comments	Action
			epidermal growth factor receptor 2 (HER2) positive metastatic or locally recurrent unresectable breast cancer, which has not been previously treated, or has relapsed after adjuvant therapy".
	GlaxoSmithKline	No comment	Comment noted.
	Lancashire & South Cumbria Cancer Network	Yes	Comment noted. Scoping workshop attendees agreed that it is appropriate to amend the remit to reflect the proposed wording of marketing authorisation. The remit and title of the scope have been amended accordingly (see above).
	CSAS	The technology descriptions says that the treatment is for "those who have not received any prior chemotherapy for metastatic disease", whereas in the population description it says "those who have not previously received chemotherapy or HER2 directed treatment for metastatic disease"	Comment noted. Scoping workshop attendees agreed that it is appropriate to amend the remit to reflect the proposed wording of marketing authorisation. The remit and title of the scope have been amended accordingly (see above).
	Breakthrough Breast Cancer	The wording for the remit seems appropriate.	Comment noted. Scoping workshop attendees agreed that it is appropriate to amend the remit to reflect the proposed wording of marketing authorisation. The remit and title of the scope have been amended accordingly (see above).
Timing Issues	Roche Products	N/A.	Response noted
	GlaxoSmithKline	No comment	Comment noted.

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	Lancashire & South Cumbria Cancer Network	Not a high priority as the drug is not yet available	Comment noted no action required.
	CSAS	No response received	Response noted.
	Breakthrough Breast Cancer	Metastatic breast cancer is not curable so it is essential that effective treatment options, which could delay progression or improve survival, are made available to this patient group as quickly as possible.	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 Products	No response received	Response noted.
	GlaxoSmithKline	None	Comment noted.
	Lancashire & South Cumbria Cancer Network	No response received	Response noted.
	CSAS	No response received	Response noted.
	Breakthrough Breast Cancer	No response received	Response noted.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Roche Products	No comment.	Comment noted
	GlaxoSmithKline	No comment	Comment noted
	Lancashire & South Cumbria Cancer Network	No comments	Comment noted
	CSAS	This is accurate	Comment noted, no action required.

Section	Consultees	Comments	Action
	Breakthrough Breast Cancer	The background information for this submission seems to be correct.	Comment noted, no action required.
The technology/ intervention	Roche Products	In the final sentence, it should be clarified that Pertuzumab **is currently being** studied in combination with trastuzumab-emtansine compared with trastuzumab-emtansine monotherapy (without pertuzumab) **and compared to trastuzumab in combination with docetaxel** in adults with metastatic breast cancer who have not received any prior chemotherapy for their metastatic disease.	Comment noted. Following the scoping workshop reference to the MARIANNE trial has been removed from the scope as it is being used in a different indication (in combination with trastuzumab-emtansine). A more detailed description of the clinical trial evidence for pertuzumab will be included in the manufacturer's submission.
	GlaxoSmithKline	No comment	Comment noted.
	Lancashire & South Cumbria Cancer Network	Yes	Comment noted, no action required.
	CSAS	The rationale for this combination should be mentioned. As pertuzumab binds to an area of HER2 that is different from trastuzumab, the two elements may work together to potentially provide synergistic activity.	Comment noted. The scope is intended to provide a brief summary of the disease, prognosis associated with the condition, and the new technology compared with alternative treatments currently used in the NHS. A more detailed description of the technology will be included in the manufacturer's submission.
	Breakthrough Breast Cancer	The technology description seems largely to be accurate. As described in the scope pertuzumab has been studied in combination with trastuzumab and a taxane compared with trastuzumab plus a taxane alone. This is being tested in the Phase III CLEOPATRA trial.	Comment noted, no action required.

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		The other research described seems to refer to the MARIANNE trial although this could be explained a little more clearly. This is also a Phase III trial evaluating the efficacy and safety of trastuzumab emtansine (T-DM1) with pertuzumab or T-DM1 with placebo versus the combination of trastuzumab plus a taxane. This trial will enroll HER2 positive metastatic breast cancer patients who are previously untreated for their metastatic disease. (Please note your spelling error of trastuzumab emtansine.) We do question why information on the MARIANNE trial is included in this scope. The outcome of the MARIANNE trial should not impact any decision made on the assessment of pertuzumab in the indication described in this scope. Furthermore, it is difficult to see why MARIANNE alone is highlighted as there are a number of other ongoing studies into the effectiveness and safety of pertuzumab that will also not be related to this scope.	Comment noted. Following the scoping workshop reference to the MARIANNE trial has been removed from the scope as it is being used in a different indication (in combination with trastuzumab-emtansine).
Population	Roche Products	The expected licensed population is for patients with HER2-positive metastatic **or unresectable** breast cancer.	Comment noted. The population of the scope has been amended to reflect the proposed marketing authorisation (adults with HER2-positive locally recurrent, unresectable or metastatic breast cancer who have not previously received chemotherapy or HER2 directed treatment for metastatic disease or whose disease has relapsed after adjuvant therapy).
	GlaxoSmithKline	No comment	Comment noted.
	Lancashire & South	Yes	Comment noted, no action required.

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	Cumbria Cancer Network		
	CSAS	Does 'adults' mean that men as well as women are within scope? Is the appraisal for treatment in pre-, peri- and post-menopausal women?	Comment noted. Attendees at the scoping workshop heard from the clinical specialist that breast cancer in men is very rare and diagnosis and treatment of breast cancer are all very similar to women with breast cancer. However, the pivotal trial did not include men in the treatment arm. Attendees also heard that because of its mechanism of action (which is independent of hormone receptors) pertuzumab is not expected to have different effectiveness in pre, peri or post menopausal women.
	Breakthrough Breast Cancer	The population appears to be accurate.	Comment noted.
Comparators	Roche Products	Trastuzumab in combination with docetaxel is the most common regimen used for previously untreated metastatic breast cancer (43%) and therefore represents the key comparator. Trastuzumab in combination with paclitaxel is the second most popular regimen with an uptake of approximately 8%. Lapatinib in combination with paclitaxel is not licenced for 1st line HER2+ mBC and it is thus not regularly utilised. Therefore, lapatinib should not be a comparator in this appraisal unless a licence is received prior to the commencement of a pertuzumab appraisal.	Comment noted. Scoping workshop attendees agreed that as the manufacturer of lapatinib has withdrawn its application for marketing authorisation in this indication lapatinib in combination with paclitaxel has been removed as a comparator.
	GlaxoSmithKline	Trastuzumab in combination with docetaxel or paclitaxel are appropriate comparators. Lapatinib in combination	Comment noted. Scoping workshop attendees agreed that as the

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		with paclitaxel is awaiting European Marketing Authorisation and as such the appropriateness of this intervention as a comparator is dependent on anticipated future, rather than current, NHS use. Lapatinib in combination with paclitaxel is the subject of a proposed NICE Technology Appraisal.	manufacturer of lapatinib has withdrawn its application for marketing authorisation in this indication lapatinib in combination with paclitaxel has been removed as a comparator.
	Lancashire & South Cumbria Cancer Network	I am not aware of lapatinib in combination with paclitaxel being widely used. Trastuzumab in combination with a taxane is considered the standard.	Comment noted. Scoping workshop attendees agreed that it is appropriate to remove lapatinib in combination with paclitaxel as a comparator.
	CSAS	These are appropriate.	Comment noted. Scoping workshop attendees agreed that it is appropriate to remove lapatinib in combination with paclitaxel as a comparator
	Breakthrough Breast Cancer	Trastuzumab in combination with a taxane is accurate to be listed as a comparator. Lapatinib in combination with paclitaxel has been trialled as a first line treatment for metastatic breast cancer and was found to improve clinical outcomes for HER2 positive patients. In this respect it is appropriate to include it as a comparator. However, it should be noted that this treatment combination is not a standard one on the NHS.	Comment noted. Scoping workshop attendees agreed that it is appropriate to remove lapatinib in combination with paclitaxel as a comparator
Outcomes	Roche Products	No comment.	Comment noted.
	GlaxoSmithKline	No comment	Comment noted.
	Lancashire & South Cumbria Cancer Network	Yes	Comment noted, no action required.

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	CSAS	Overall survival is the most appropriate outcome of importance to patients for this technology. The formal assessment of quality of life is also important if consideration is being given to progression-free survival.	Comment noted, no action required.
	Breakthrough Breast Cancer	These outcome measures will capture the most important benefits and harms of the technology. It should be noted for patients with metastatic disease quality of life is very important and should not be underestimated. Metastatic breast cancer is a life-limiting disease so access to treatments that give a chance of an increased length of survival and improved quality of life (for example so patients can spend more quality time with their friends and families) is very important.	Comment noted, no action required.
Economic analysis	Roche Products	No comment.	Comment noted.
	GlaxoSmithKline	No comment	Comment noted.
	Lancashire & South Cumbria Cancer Network	No comment	Comment noted.
	CSAS	No response received	Response noted.
	Breakthrough Breast Cancer	No comment	Comment noted.
Equality and Diversity	Roche Products	No comment.	Comment noted.
	GlaxoSmithKline	No comment	Comment noted.
	Lancashire & South Cumbria Cancer Network	No issues	Comment noted, no action required.
	CSAS	No response received	Response noted.

Section	Consultees	Comments	Action
	Breakthrough Breast Cancer	The remit and scope appear not to promote discrimination.	Comment noted, no action required.
Innovation	Roche Products	Pertuzumab represents a step change in the management of HER2 positive breast cancer. Similar to the introduction of trastuzumab, the pertuzumab and trastuzumab combination with docetaxel (pertuzumab group) regimen extends progression-free survival (PFS) by a median of 6.1 months (12.4 months vs 18.5 months, HR 0.62, p<0.001) compared to trastuzumab plus docetaxel alone (control group). These results whilst immature, also demonstrated a strong trend towards overall survival in favour of the pertuzumab group. This regimen also demonstrated an objective response rate (ORR) of 80.2% in the pertuzumab group. This PFS & ORR clinical benefit is larger than any biologic & chemotherapy combinations observed thus far in this population. This clinically and statistically significant benefit is achieved with no increase in cardiac toxicity.	Comment noted. The innovative nature of pertuzumab will be considered by the Committee during the course of the appraisal.
	GlaxoSmithKline	No comment	Comment noted.
	Lancashire & South Cumbria Cancer Network	This is a treatment which is to be added to the current standard treatment. Although it has a slightly different mode of action, (as well as the fact that it is unusual to treat using 2 monoclonal antibodies) I wouldn't consider this to be a "step change"	Comment noted. The innovative nature of pertuzumab will be considered by the Committee during the course of the appraisal.
	CSAS	No response received	No response received.
	Breakthrough Breast Cancer	Preliminary data from the CLEOPATRA trial has been published with very promising findings. Patients on the experimental arm of the trial (those who received pertuzumab plus trastuzumab plus a taxane) had 6.1	Comment noted. The innovative nature of pertuzumab will be considered by the Committee during the course of the appraisal.

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		months longer progression free survival (PFS) than patients receiving trastuzumab and taxane with a placebo (18.5 months vs 12.4 months). This result was statistically significant and demonstrates a clinically meaningful improvement in PFS. Furthermore, interim analysis of overall survival showed a strong trend in favour of patients who received pertuzumab as part of their treatment. Although some side effects were reported to be higher in the pertuzumab group the safety profile between both groups was comparable and there was no increase in cardiac toxic events in the experimental arm of the trial. The findings of the CLEOPATRA study thus far certainly demonstrate pertuzumab to be an innovative technology. A drug which can offer a 6.1 month improvement in PFS in this setting represents a highly attractive option for patients and shows potential to make a substantial impact on health-related benefits.	
Other considerations	Roche Products	Given the approaching implementation of Value-based Pricing, and in the spirit of the government response to the VBP consultation, we would like to formally propose that pertuzumab be considered as one of the early testers for this new pricing system (Section 5.19 of the Government Response to Consultation). Asides from the timing of regulatory approval which suggest a NICE appraisal of pertuzumab may straddle 2013/2014; the value-based pricing of pertuzumab would be an interesting and important case study in the implications of valuing treatment regimens containing multiple biological agents (e.g. pertuzumab and trastuzumab). [redacted]	NICE is unable to conduct any pilot projects which consider the VBP scheme until further information on VBP is issued by the Department of Health. This will proceed as a single technology appraisal under the usual NICE process.

Section	Consultees	Comments	Action
		[redacted] An opportunity for further dialogue on this HTA and pricing challenge with the institute would be most welcomed.	
	GlaxoSmithKline	No comment	Comment noted.
	Lancashire & South Cumbria Cancer Network	No comments	Comment noted.
	CSAS	No response received	Response noted.
	Breakthrough Breast Cancer	No comment	Comment noted.
Questions for consultation	Roche Products	There are no subgroups known which are expected to be more clinically effective or more cost effective.	Comment noted, no action required.
	GlaxoSmithKline	No comment	Comment noted.
	Lancashire & South Cumbria Cancer Network	No comments	Comment noted.
	CSAS	No response received	Response noted.
	Breakthrough Breast Cancer	No response received	Response noted.

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

Department of Health
Healthcare Improvement Scotland
Medicines and Healthcare products Regulatory Agency
Royal College of Nursing
Royal College of Pathologists

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer

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.	Remove the following: • Abraxis Bioscience (paclitaxel) • Actavis UK (docetaxel, paclitaxel) • Bristol-Myers Squibb Pharmaceuticals (paclitaxel) • Celgene (paclitaxel) • Dabur oncology (paclitaxel) • GlaxoSmithKline (lapatinib) • Hospira UK (paclitaxel) • Medac UK (paclitaxel) • Roche Products (trastuzumab) • Sandoz (docetaxel, paclitaxel) • Sanofi-Aventis (docetaxel) • Teva UK (docetaxel, paclitaxel) • Wockhardt UK (paclitaxel)	NICE Secretariat		Removed	Pertuzumab is an add-on treatment to trastuzumab and a taxane (docetaxel).