NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2-positive metastatic breast cancer [ID523]

[redacted]

The Evidence Review Group, Liverpool Reviews & Implementation Group, and the technical team at NICE have now had an opportunity to take a look at the submission received on 3 April by Roche products. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on 14 May 2013. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

[redacted]

Yours sincerely

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Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. **Priority Question:** Please provide the complete and updated Clinical Study Reports for the CLEOPATRA trial.

A2. **Priority Question:** Please provide the following data on adverse events (AEs) from the CLEOPATRA trial for the May 2012 data cut-off in tabular format (similar to Tables 67 and 71 in the draft EPAR):

a) Serious adverse events (SAEs)
b) Treatment-related SAEs
c) AEs leading to discontinuation of any study medication

A3. It is unclear from the submission how many patients experienced rash and leukopenia in the CLEOPATRA trial as Tables 17 and 18 appear to present conflicting information for these AEs. Please clarify the number and percentage of patients in each treatment arm who experienced rash and leukopenia at both the May 2011 and May 2012 data cut-offs (Grade 1-2, Grade 3+ and All)

A4. Table 68 on page 134 of the draft EPAR provides data on 'Diarrhoea requiring treatment' (see final row). Please provide the same data from the CLEOPATRA trial for the May 2012 data cut-off and, if possible, provide additional data on the type of treatment received by treatment arm, for example, treatment requiring hospitalisation.

A5. Please provide the results of the statistical tests for interaction for all pre-specified subgroup analyses presented in the following forest plots in the submission:

a) Figure 6: Progression-free survival forest plot hazard (Independently assessed 13 May 2011)
b) Figure 8: Overall survival forest plot (Independently assessed 14 May 2012)
c) Figure 10: Progression-free survival forest plot (Investigator assessed 14 May 2012)

A6. Please provide a full listing of CLEOPATRA trial protocol violations.

A7. The submission (including the table on quality assessment of RCTs in section 10.3) does not provide detail on how treatment was allocated in the CLEOPATRA trial. Please describe the allocation procedure used.

A8. Please provide the full results for all the quality of life analyses specified in the CLEOPATRA trial protocol, including the FACT-B subscale results (mean and standard deviation scores and number of patients in each treatment arm who completed each assessment) at every protocol assessment (every 3 cycles) up to the May 2012 data cut-off (if available).

A9. For only those patients who completed the FACT-B questionnaires at every protocol assessment (every 3 cycles) until independently assessed disease progression or death, please provide the number of patients completing the questionnaire as well as

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the mean (standard deviation) TOI-PFB scores for these patients at each assessment.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question:** Please provide full Kaplan-Meier analysis results (see SAS output table for example below) showing Kaplan-Meier survival estimates at each event time, for each treatment arm in the CLEOPATRA trial for Overall Survival (OS), Progression-Free Survival (PFS), Time to Off Treatment (TTOT) and Post-Progression Survival (PPS). These analyses should use the May 2012 data cut-off, be based on investigator assessments of disease progression, and any patient still at risk at the date of data cut should be censored at the date of data cut-off, *not* the date of last contact/assessment.

B2. **Priority Question:** Please provide full Kaplan-Meier analysis results (see SAS output table for example below) showing Kaplan-Meier survival estimates at each event time, for each treatment arm in the CLEOPATRA trial, by the following sub-groups:

a) Patients with visceral disease
b) Patients with non-visceral disease

The same analyses for OS, PFS, TTOT and PPS should be carried out as for Question B1 (i.e. using same definition of disease progression, same data cut-off and censoring rule).

B3. **Priority Question:** Please provide an analysis of the number of investigator-assessed progression events in each treatment arm of the CLEOPATRA trial in terms of fatal and non-fatal events (a non-fatal event requires the patient to survive at least one day beyond the date of the progression event).

B4. **Priority Question:** Please provide a table of body weight (number of patients, mean body weight and standard deviation) and body surface area (number of patients, mean body surface area and standard deviation) by region of origin (Europe, North America, Asia and South America).

B5. **Priority Question:** Please provide a table showing for each treatment arm the number of patients receiving docetaxel by treatment cycle, and for each cycle, the number of patients receiving each allowed dosing level (75mg/m^2, 100mg/m^2 and 55mg/m^2).

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Example from SAS of typical output requested from analyses specified in questions B1 and B2:

Product-Limit Survival Estimates						
SURVIVAL		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP...		0.8548	0.1452	0.0447	9	53
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

Section C: Missing references

C1. The ERG appreciates the references provided by the manufacturer. However, there are five references that are referred to in the submission that were not provided and which the ERG has been unable to locate. Please provide the complete citations and documents for the following references (for references 1 and 4, see also Priority Question A1):

1) Clinical Study Report –WO20698C/TOC4129g – A Phase III, Randomised, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer – Report No. 1046288, October 2011.

2) Fujiwara K, Kohno I, Tanaka K, et al. Phase II dose escalation: a novel approach to balancing efficacy and toxicity of anticancer agents. Japanese Docetaxel Ovarian Cancer Study Group. Anticancer Res 1999; 19(1B): 639-644.

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3) Tumorregister-Muenchen, 2012 (see submission, p122)

4) Update Clinical Study Report – WO20698C/TOC4129g - A Phase III, Randomised, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer – Report No. 1053649, November 2012

5) Verrill M, Lee J, Cameron DA, Agrawal R, Coleman RE, McAdam K et al. (2007) Anglo-Celtic IV: First results of a UK National Cancer Research Network randomised phase 3 pharmacogenetic trial of weekly versus 3 weekly paclitaxel in patients with locally advanced or metastatic breast cancer (ABC). J Clin Oncol; 25: 18S (June 20 Suppl), LBA1005.