Bijal Joshi
National Institute for Health and Clinical Excellence
10 Spring Gardens
London
SW1A 2BU

BY EMAIL

14 May 2013

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

Dear Bijal,

Please find attached our response to the clarification questions for the above mentioned appraisal. As noted in previous responses to clarification questions such as these, we are concerned that the majority of these requests do not seek 'clarification' but instead, ask for significant amounts of patient level data from the CLEOPATRA study without context or explanation. We do not believe these data requests are within the remit, or spirit, of the STA process.

We note that KM data for patients with non-visceral disease (NVD) has been requested. Given our previous experience with LRiG we anticipate that this will form the basis of a *de novo* cost effectiveness analysis in this group. We do not believe this to be legitimate due to:

(1) The lack of biologic rationale for separate consideration of the NVD group,

(2) The imbalances in prognostic characteristics between the two arms of this subgroup,

(3) The small sample size in this patient population,

(4) The low event rate associated with this better prognosis population, and

(5) The wide confidence intervals surrounding this data.

Roche Products Limited
6 Falcon Way
Shire Park
Welwyn Garden City
Hertfordshire
AL7 1TW
Health Economics and Strategic Pricing
Tel. +44(0)1707 361032
Fax +44(0)1707 384123

As a result, Roche consider the modeling of the NVD population of CLEOPATRA to be inappropriate. In addition, we note we have received no clarification questions on our cost-effectiveness analysis.

In the interests of transparency we have provided the majority of the data requested (including the KM data for patients with NVD). However we request the ERG and Committee consider the significant limitations associated with any analysis based upon the NVD KM data provided.

We would be happy to provide clarification on our submission if requested.

Yours Sincerely

Lee Moore

Health Economics and Strategic Pricing Director

Section A: Clarification on effectiveness data

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

Please find the full updated Clinical Study Reports attached. The 2011 Clinical Study Report includes data from the 13 May 2011 data-cut. The 2012 Clinical Study Report includes data from the 14 May 2012 data-cut.

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

a) These can be found on page 349 and page 451 of the 2012 Clinical Study Report.

b) These can be found on page 469 of the 2012 Clinical Study Report.

c) These can be found in section 5.11 (page 96), and page 1422 of the 2012 Clinical Study Report.

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)

These tables refer to different Medical Dictionary for Regulatory Activities (MedDRA) terms for these adverse events.

The values for participants who experienced rash and leukopenia in Table 17 of the main submission are derived from the use of the MedDRA Adverse Event Grouped Term (AEGT) "**EGFR Associated Rash**" for rash adverse events and the use of the Standardised MedDRA Query (SMQ) (narrow) "**Haematopoietic leukopenia**" for leukopenia adverse events.

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The values for participants who experienced rash and leukopenia in Table 18 of the main submission are derived from the use of the MedDRA Preferred Terms "**rash**" (compared to "EGFR Associated Rash" in Table 17) and "**leukopenia**" (compared to Haematopoietic leukopenia in Table 17). All of these groupings are in keeping with the pre-specified safety analysis for the study.

Table 17 of the main submission includes the number and percentages of participants in each treatment arm who experienced rash and leukopenia at both data cut-offs for grades 3 and 4, and for all grades. Grades 1 and 2 can be calculated by subtracting the number of grade 3 and 4 events from all grades.

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.

At the time of the second data cut-off (14 May 2012), 20.0% of participants in the trastuzumab and docetaxel arm compared with 41.5% of participants in the pertuzumab, docetaxel and trastuzumab arm received antidiarrheal medication during the study. The majority of participants in both arms were treated with loperamide; 19.2% of participants in the trastuzumab and docetaxel arm and 39.8% in the pertuzumab-based arm.

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 10: Progression-free survival forest plot (Investigator assessed 14 May 2012)
c) Figure 8: Overall survival forest plot (Independently assessed 14 May 2012)

The results of the statistical tests for interaction for all pre-specified subgroup analyses for the forest plots in Figure 6, 8 and 10 of the main submission are presented in Tables 5, 6 and 7 below.

Table 1 Results of statistical tests - Progression-free survival forest plot hazard (Independently assessed 13 May 2011)

Interaction of treatment effect	**p-value**
Prior treatment status	0.8960
Prior trastuzumab therapy	0.9263

Docetaxel dose escalation to 100 mg	0.8543
Region	0.3381
Age group (>=65 vrs <65)	0.4180
Age group (>=75 vrs <75)	0.3104
Race	0.8037
Visceral disease status	0.0332
HER2 IHC status	0.1252
FISH status	0.0254
ER/PgR status	0.1277
ECOG status	0.2132
Previous taxane use	0.7970
IHC, Immunohistochemistry; FISH, fluorescence in situ hybridization; ER, estrogen receptors; PgR: progesterone receptors; ECOG, Eastern Cooperative Oncology Group.	

Table 2 Results of statistical tests - Progression-free survival forest plot (Investigator assessed 14 May 2012)

Interaction of treatment effect	**p-value**
Prior treatment status	0.7888
Prior trastuzumab therapy	0.586
Docetaxel dose escalation to 100 mg	0.6007
Region	0.4171
Age group (>=65 vrs <65)	0.1388
Age group (>=75 vrs <75)	0.7296

Race	0.4196
Visceral disease status	0.1064
HER2 IHC status	0.1931
FISH status	0.0241
ER/PgR status	0.1646
ECOG status	0.6586
Previous taxane use	0.5485
IHC, Immunohistochemistry; FISH, fluorescence in situ hybridization; ER, estrogen receptors; PgR: progesterone receptors; ECOG, Eastern Cooperative Oncology Group.	

Table 3 Results of statistical tests - Overall survival forest plot (Independently assessed 14 May 2012)

Interaction of treatment effect	**p-value**
Prior treatment status	0.9892
Prior trastuzumab therapy	0.9207
Docetaxel dose escalation to 100 mg	0.8124
Region	0.8575
Age group (>=65 vrs <65)	0.3190
Age group (>=75 vrs <75)	0.6862
Race	0.6425
Visceral disease status	0.0138
HER2 IHC status	0.6987
FISH status	0.1900

ER/PgR status	0.3272
ECOG status	0.5854
Previous taxane use	0.7076
IHC, Immunohistochemistry; FISH, fluorescence in situ hybridization; ER, estrogen receptors; PgR: progesterone receptors; ECOG, Eastern Cooperative Oncology Group.	

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

A full listing of the CLEOPATRA trial protocol violations can be found in Section 3.1.4 of the 2011 Clinical Study Report, and Section 3.4 and page 2464 of the 2012 Clinical Study Report.

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.

An Eligibility Screening Form documenting the participant's fulfilment of the entry criteria was completed by the investigator/designee for all participants considered for the study and subsequently included or excluded. All Eligibility Screening forms were kept in the study files at the sites. Additionally, copies of records of all prior trastuzumab dosing and ECHO/MUGA reports were retained with the study files at the investigative sites, for randomized and screen-failure participants.

An Interactive Voice Response System (IVRS) was used to collect participant screening information and to randomise eligible participants in a 1:1 ratio to one of the two treatment arms. The patient identification numbers were allocated sequentially in the order in which the participants are enrolled using the IVRS. The investigator or designee entered the participants' data into the eCRF, which was used for electronic data capture (EDC). A Patient Enrolment and Identification Code List was maintained by the investigator. The treatment randomisation list was generated by the Sponsor and incorporated into IVRS. The password-protected and/or encrypted electronic drug kit number randomisation list was kept in a central repository by the Sponsor's unblinding statistician. An open key to the code was not available at the study site, to the Sponsor's monitors, project statisticians or project team.

A complete block randomization scheme was applied to achieve balance in treatment assignment within each of the eight strata, as defined by prior treatment status (de novo vs. prior adjuvant or neo-adjuvant therapy) and region (Europe, North America, South America, and Asia). Unblinding of treatment assignment was not permitted during the study except for safety issues arising during

study treatment. An approval from the Sponsor‘s medical monitor(s) had to be obtained prior to any unblinding of treatment code. Under no circumstances were participants who enrolled in this study permitted to be re-randomised and enrolled for a second course of treatment in the study

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).

The 2011 and 2012 Clinical Study Reports include the FACT-B analyses specified in the CLEOPATRA protocol.

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

Due to the significant amount of data requested and a short time frame, and the fact that this request is not marked as being a ‘priority’, this request has not been conducted.

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.

This is not a clarification question. The KM requested is provided within the economic model submitted. We have not conducted the analysis with the 'alternate' censoring rule requested. This request appears to be significantly flawed. By censoring patients at the date of data-cut off, and not of last observation, this request would consider patients who had been lost to follow up, to have remained progression free, and alive, for the course of the study. We do not believe this to be reasonable (a view shared by the vast majority of the statistical and regulatory community).

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).

This is not a clarification question. This request suggests that LR*i*G intend to develop a *de novo* cost-effectiveness analysis in patients with non-visceral disease. We do not believe this to be legitimate due to:

(1) The lack of biologic rationale for separate consideration of the NVD group,

(2) The imbalances in prognostic characteristics between the two arms of this subgroup,

(3) The small sample size in this patient population,

(4) The low event rate associated with this better prognosis population, and

(5) The wide confidence intervals surrounding this data.

The question of whether there the visceral/non-visceral disease patient populations should be evaluated separately was raised in the EMA assessment of pertuzumab. This question and Roche's subsequent response is provided below.

CHMP Question

Patients with non-visceral disease (n=178) appeared to get the smallest benefit from the addition of pertuzumab based on this subgroup analysis (HR=0.96 (0.61; 1.52). This is somewhat unexpected from a mechanistic point of view as HER2 blockade is also known to be efficacious in earlier disease stages. The relatively wide confidence intervals reveal that the estimate is not very precise in this subpopulation. The applicant should try to explain the observed result in this subpopulation (number of outliers, chance finding, others). In addition to this, the Applicant should elaborate on possible mechanisms that could explain differences of pertuzumab activity on visceral and non-visceral disease status. Visceral disease status was the only significant interaction term when test for interaction term was performed. Thus, the Applicant should perform the multivariate Cox regression analysis by adding the interaction term of treatment effect with visceral disease status and discuss the observed results.

Roche Response to CHMP Question

Results of (original) visceral/non-visceral sub-group analysis

The Statistical Analysis Plan for the WO20698/TOC4129g study pre-specified that descriptive subgroup analyses of 21 baseline factors would be performed to explore the consistency of the primary endpoint results. These subgroups were selected as potentially important prognostic and/or predictive, patient and disease characteristics. Two of the baseline factors analyzed were visceral and non-visceral disease. Non-visceral disease was classified as tumors located in the breast, bone, bone marrow, lymph nodes, skin and soft tissue. All other locations were classified as visceral disease. Patients with both visceral and non-visceral disease (e.g. a patient with a tumor in the liver and bone lesions) were classified as having visceral disease for the purposes of the analysis.

Overall, the 21 pre-specified analyses showed that the IRF-PFS treatment effect was consistent across subgroups. As shown in Table 1 , the estimate of the IRF-PFS HR among patients with visceral and non-visceral disease both favored treatment with pertuzumab. For the subgroup of patients with non-visceral disease the point estimate of the HR was 0.96 (95% CI 0.61; 1.52) and in the subgroup of patients with visceral disease the point estimate of the HR was 0.55 (95% CI

0.45; 0.68). As highlighted in the question, the confidence interval around the IRF-PFS HR for patients with non-visceral disease was wide and thus a benefit for pertuzumab, trastuzumab and docetaxel cannot be excluded.

The HR (0.96 vs. 0.62 for the whole study population) and wide confidence interval in the non-visceral subgroup of patients may have been influenced by the slower event rate observed in patients with non-visceral disease, the low number of events, and the generally better outcome (notably in median IRF-PFS) observed in both treatment arms for this subgroup of patients. Only 73 patients with non-visceral disease (41% of the 178 patients with non-visceral disease) had had an IRF-PFS event at the time of the primary analysis (37 in the trastuzumab and docetaxel arm and 36 in the pertuzumab, trastuzumab and docetaxel arm), compared to 360 (57% of the 630 patients with visceral disease) in the visceral sub-group (205 in the trastuzumab and docetaxel arm and 155 in the pertuzumab, trastuzumab and docetaxel arm). In addition, median IRF-PFS duration in both treatment arms was longer than in the visceral subgroup and the overall patient population (See Table 1).

The non-visceral subgroup of patients in the trastuzumab and docetaxel arm had a particularly good median IRF-PFS (17.3 months compared with 12.4 months for the overall patient population treated with trastuzumab and docetaxel). Importantly, despite the limited number of events the subgroup of patients with non-visceral disease randomized to pertuzumab, trastuzumab and docetaxel still experienced an improvement in median IRF-PFS compared with the placebo arm, but the difference was smaller than that for the overall patient population (3.5 month improvement compared with 6.1 months).

Table 1 Summary of IRF-Assessed Progression-free Survival by Visceral/Non-Visceral disease status

	Trastuzumab and docetaxel	Pertuzumab, trastuzumab and docetaxel
Overall		
Patients included in the analysis	406	402
Patients with an event	242 (59.6)	191 (47.5)
Median Time to event (months)	12.4	18.5
p-value (Log-Rank test)	<0.0001	
Hazard Ratio	0.62 [0.51; 0.75]	
Visceral		
Patients included in the analysis	316	314
Patients with an event	205 (64.9)	155 (49.4)
Median Time to event (months)	10.4	17.2
Hazard Ratio	0.55 [0.45; 0.68]	
Non-Visceral		
Patients included in the analysis	90	88
Patients with an event	37 (41.1)	36 (40.9)
Median Time to event (months)	17.3	20.8
Hazard Ratio	0.96 [0.61; 1.52]	
Derived from t_ttev_str_irf_pfs_i and t_ttev_irf_vnd_pfs_i.(in the WO20698/TOC4129g CSR)		

Possible reasons for these findings

Baseline demographic and disease characteristics

The Applicant has examined baseline data to explore whether the results observed for patients with non-visceral disease might be due to unexplained imbalances in baseline demographic and disease characteristics between patients with non-visceral disease and patients with visceral disease (Table 2), or between treatment arms (Table 3).

Baseline demographic and disease characteristics were compared for patients with non-visceral and visceral disease (regardless of treatment arm) (Table 2). As would be expected, patients with non-visceral disease (as defined earlier) were less likely to have metastases, had fewer lesions and fewer organ sites, and a lower measurable disease burden, than patients with visceral disease. They also tended to have a better ECOG performance. The pattern of metastatic sites was also very different between the two groups of patients (t_ufmets_vnd in Q127 Appendices). These differences (which are expected based on the definition of visceral disease) explain the relatively favorable outcome of patients with non-visceral disease compared with patients with visceral disease, regardless of treatment regimen.

Table 2 Key Baseline Demographic and Disease Characteristics in Patients With Non-Visceral Vs Visceral Disease

	Non-visceral n= 178	**Visceral n=630**
Metastatic disease	164 (92.1)	623 (99.2)
Median no. lesions (target + non-target)	3.0	6.0
Only 1 lesion	48 (27.0)	22 (3.5)
2 lesions	27 (15.2)	53 (8.4)
3 lesions	37 (20.8)	73 (11.6)
≥ 4 lesions	66 (37.0)	482 (76.5)
No. of organs involved		
1 organ	73 (41.0)	70 (11.1)
2 organs	67 (37.6)	158 (25.1)
3 organs	37 (20.8)	183 (29.0)
≥ 4 organs	1 (0.6%)	219 (34.8)
Median measurable tumor burden (investigator assessed)	68.0 mm	83.0 mm
ECOG 0	126 (70.8)	396 (62.9)
ECOG 1	52 (29.2)	230 (36.5)
ER/PR +	92 (51.7)	296 (47.0)

IHC 3+	156 (88.1)	565 (89.8)
IHC 2+	19 (10.7)	60 (9.5)
Prior (neo) adjuvant therapy	83 (46.6)	293 (46.5)
Prior trastuzumab	22 (12.4)	66 (10.5)
Median treatment-free interval (months)*	31.5	29.5

Derived from t_dm11_db_v_nv, t_dm11_i_nvis, t_uhist1_vnd_i, t_ufmets_vnd_i and t_dm11_i_vis (in the WO20698/TOC4129g CSR)

*Treatment-free interval was defined as the time from completion of systemic therapy (chemotherapy or biological therapy) to the date of metastatic disease for patients who received prior (neo)adjuvant therapy

Key baseline demographic and disease characteristics are compared by treatment arm in Table 3. The most notable difference between the two treatment arms within the non-visceral subset was the duration of treatment-free interval (median 42.0 months for patients in the trastuzumab and docetaxel arm vs 28.0 months for patients in the pertuzumab, trastuzumab and docetaxel arm). This was also considerably longer than the treatment-free interval for patients with visceral disease (28.0 months in the trastuzumab and docetaxel arm and 32.0 months in the pertuzumab, trastuzumab and docetaxel arm). This finding suggests that, by chance, patients in the trastuzumab and docetaxel arm in the non-visceral subgroup had more indolent disease and/or had responded particularly well to prior (neo)adjuvant therapy compared with other patients. This also suggests that they had chemo-sensitive disease.

Patients in the trastuzumab and docetaxel arm in the non-visceral subgroup also generally had fewer lesions (target and non-target), fewer organ sites involved, and a lower measurable tumor burden than patients in the pertuzumab, trastuzumab and docetaxel arm in the non-visceral subgroup. Other baseline factors with a difference in incidence of >5% between the two treatment arms (within the non-visceral subset) were as follows:

- More patients in the trastuzumab and docetaxel arm had bone-only disease (26.7% versus 15.9%)
- More patients in the trastuzumab and docetaxel arm had IHC3+ disease (92.2% versus 83.9%)
- More patients in the pertuzumab, trastuzumab and docetaxel arm had IHC2+ disease (13.8% versus 7.8%)
- More patients in the pertuzumab, trastuzumab and docetaxel arm had ER/PR+ disease (54.5% versus 48.9%)

- More patients in the pertuzumab, trastuzumab and docetaxel arm had received prior trastuzumab (15.9% versus 8.9%)

Overall, these differences are likely to account for the slow event rate and favorable response to study treatment (trastuzumab and docetaxel) in patients treated with trastuzumab and docetaxel in the non-visceral subgroup.

Table 3 Key Baseline Demographic and Disease Characteristics in the Two Treatment Arms (By Visceral/Non-Visceral Disease Status)

	Non-Visceral n (%)		**Visceral n (%)**	
	Trastuzumab and docetaxel (N= 90)	**Pertuzumab, trastuzumab and docetaxel (N= 88)**	**Trastuzumab and docetaxel (N= 316)**	**Pertuzumab, trastuzumab and docetaxel (N= 314)**
ECOG 0	65 (72.2)	61 (69.3)	183 (57.9)	213 (67.8)
ECOG 1	25 (27.8)	27 (30.7)	132 (41.8)	98 (31.2)
ER/PR +	44 (48.9)	48 (54.5)	155 (49.1)	141 (44.9)
ER/PR -	42 (46.7)	39 (44.3)	154 (48.7)	173 (55.1)
IHC 3+	83 (92.2)	73 (83.9)	288 (91.4)	277 (88.2)
IHC 2+	7 (7.8)	12 (13.8)	25 (7.9)	35 (11.1)
Prior (neo) adjuvant therapy	41 (45.6)	42 (47.7)	151 (47.8)	142 (45.2)
Prior trastuzumab	8 (8.9%)	14 (15.9%)	33 (10.4%)	33 (10.5%)
Median treatment-free interval (months)*	42.0	28.0	28.0	32.0
Bone-only disease	24 (26.7)	14 (15.9)	0	0
Bone + another site	25 (27.8)	33 (37.5)	NA	NA

Soft tissue disease	41 (45.6)	41 (46.6)	NA	NA
Total no. lesions**				
1	30 (33.3)	18 (20.5)	10 (3.2)	12 (3.8)
2	14 (15.6)	13 (14.8)	27 (8.5)	26 (8.3)
3	14 (15.6)	23 (26.1)	34 (10.8)	39 (12.4)
≥ 4	32 (35.6)	34 (38.6)	245 (77.5)	237 (75.5)
No. organ sites				
1	42 (46.7)	31 (35.2)	37 (11.7)	33 (10.5)
2	32 (35.6)	35 (39.8)	88 (27.8)	70 (22.3)
3	16 (17.8)	21 (23.9)	87 (27.5)	96 (30.6)
≥ 4	0	1 (1.1)	104 (32.9)	115 (36.6)
Median measurable tumor burden	65.5 mm	70.0 mm	84.0 mm	82.5 mm

Derived from t_dm11_i_nvis, t_dm11_db_nvis, t_uhist1_vis_i, t_uhist1_nvis_i, t_nvis_nvis_i, t_ufmets_vis_i, t_ufmets_nvis_i and t_dm11_i_vis, t_dm11_db_vis (in the WO20698/TOC4129g CSR)

NA: not assessed

*Treatment-free interval was defined as the time from completion of systemic therapy (chemotherapy or biological therapy) to the date of metastatic disease for patients who received prior (neo)adjuvant therapy

** Target and non-target

Inclusion of bone-only disease in the sub-set of patients with non-visceral disease

Assessment of response and progression of bone lesions is generally more difficult than assessment of soft tissue disease in patients with breast cancer, and physicians may rely more on accompanying signs and symptoms of progressive disease to trigger or confirm the findings of a radiological assessment. Therefore, the proportion of patients with bone-only disease was compared in the two arms (Table 3) to see if an imbalance in the proportion of patients with bone-only disease could explain the relatively long IRF-PFS duration in the trastuzumab and docetaxel arm in the non-visceral subgroup (see Table 4). Within the non-visceral patient subgroup, a higher proportion of patients had bone-only disease in the trastuzumab and docetaxel arm (26.7%) compared with the pertuzumab, trastuzumab and docetaxel arm (15.9%). Therefore additional exploratory analyses of IRF-PFS were conducted in which patients with bone-only disease and other patterns of non-visceral involvement were excluded from the analyses. Excluding patients with bone-only disease from the IRF-PFS analysis did not significantly change the hazard ratio or median IRF-PFS duration in the trastuzumab and docetaxel arm (see Table 4). Overall therefore,

inclusion of patients with bone-only disease does not explain the smaller difference in PFS benefit seen with pertuzumab, trastuzumab and docetaxel in patients with non-visceral disease compared to patients with visceral disease. In fact, the difference in IRF-PFS between treatment arms for the subgroup analysis of non-visceral patients in whom there was bone involvement was larger than for that observed in any other subgroup analysis (median 16.6 months on the trastuzumab and docetaxel arm and 28.9 months in the pertuzumab, trastuzumab and docetaxel arm).

Table 4 Summary of Further Exploratory Subgroup Analyses of IRF-Assessed Progression-Free Survival in Patients With Non-Visceral Disease

	Trastuzumab and docetaxel	Pertuzumab, trastuzumab and docetaxel
Overall		
Patients included in the analysis	406	402
Patients with an event	242 (59.6%)	191 (47.5%)
Median Time to event (months)	12.4	18.5
p-value (Log-Rank test)	<0.0001	
Hazard Ratio	0.62 [0.51; 0.75]	
Non-Visceral		
Patients included in the analysis	90	88
Patients with an event	37 (41.1%)	36 (40.9%)
Median Time to event (months)	17.3	20.8
p-value (Log-Rank test)	0.8626	
Hazard Ratio	0.96 [0.61; 1.52]	
Non-Visceral (excluding bone only)		
Patients included in the analysis	66	74
Patients with an event	28 (42.4%)	31 (41.9%)
Median Time to event (months)	17.3	18.7
p-value (Log-Rank test)	0.7283	
Hazard Ratio	0.91 [0.55; 1.52]	
Non-Visceral (including bone only and bone+other lesions)		
Patients included in the analysis	49	47
Patients with an event	22 (44.9%)	18 (38.3%)
Median Time to event (months)	16.6	28.9

p-value (Log-Rank test)	0.4990	
Hazard Ratio	0.81 [0.43; 1.51]	
Non-Visceral (no bone lesion component)		
Patients included in the analysis	41	41
Patients with an event	15 (36.6%)	18 (43.9%)
Median Time to event (months)	Not reached	16.9
p-value (Log-Rank test)	0.6438	
Hazard Ratio	1.18 [0.59; 2.33]	
Derived from t_ttev_irf_pfs_nvis_i and t_ttev_irf_pfs_nvis_t_i , and from t_ttev_irf_str_pfs_i and t_ttev_irf_vnd_pfs_i (in the WO20698/TOC4129g CSR).		

Multivariate Cox regression analysis adding the interaction term of treatment effect with visceral disease status

Exploratory analyses of the interaction between treatment and pre-defined baseline characteristics were described in the CSR. These were performed through univariate Cox regression analyses which included in the model only: the baseline characteristic, treatment and their interaction. The results are discussed in Section 3.2.2.3 of CSR. In summary it was found that there was a significant interaction (p= 0.0332) between treatment and disease status (visceral or non-visceral), but based on a cut-off for statistical significance of 0.1, no further significant covariate by treatment interactions were identified.

As requested by the CHMP, a multivariate Cox regression analysis has also been performed, where covariates were included in the model for all the pre-defined baseline characteristics, and additionally the treatment by disease status interaction was included. In this model, the interaction term was statistically significant at the 10% level (p=0.0513). However, inclusion of this interaction term in the multivariate model did not affect the overall conclusions of the multivariate model discussed in the CSR Section 3.2.2.3, with the same covariates deemed statistically significant (p<0.05), namely disease status, ER/PgR status, HER2 IHC status (2+ vs 3+) and ECOG status.

Similarly, when the interaction term was added to the final multivariate model, selected via stepwise regression, including the covariates treatment, visceral disease status, ECOG status and HER2 IHC status, the interaction term between treatment and disease status was statistically significant (p=0.0384) and all other covariates also remained statistically significant (p<0.05).

Overall, the conclusions from the multivariate Cox regression analyses of IRF-PFS were unaltered by the addition of the interaction term between treatment and disease status to the models.

Summary and Conclusions

Overall, the observed HR of 0.96 (0.61; 1.52) in the non-visceral subgroup of patients in the WO20698/TOC429g study may have been due to a chance imbalance in baseline factors. Patients in the trastuzumab and docetaxel arm in the non-visceral subgroup appeared to be a particularly favorable subgroup with a longer treatment-free interval (suggesting more indolent disease and/or better chemo-responsiveness), fewer lesions, fewer organ sites involved, and a lower tumor burden than patients in the pertuzumab, trastuzumab and docetaxel arm. They were also more likely to have HER2 3+ disease (by immunohistochemistry) and bone-only disease, and less likely to have ER/PR-positive disease and to have received prior trastuzumab, than patients in the pertuzumab, trastuzumab and docetaxel arm. Altogether, these factors probably account for the slow event rate, prolonged PFS, and good response to trastuzumab + docetaxel treatment in the trastuzumab and docetaxel arm of the non-visceral subgroup.

Furthermore, there is no clear biological reason why the addition of pertuzumab should not have efficacy in patients with non-visceral HER2-positive metastatic breast cancer. Consistent improvements in response rates were observed in patients with visceral and non-visceral disease when trastuzumab was added to docetaxel in the M77001 study (Marty et al. 2005 [10165]), and data from the WO20697 (NEOSPHERE) study, clearly showed that pertuzumab, trastuzumab and docetaxel has improved activity in patients with purely non-visceral (soft tissue and lymph node) disease. When comparing the pathological complete response rates between patients receiving trastuzumab and docetaxel versus patients receiving pertuzumab, trastuzumab and docetaxel, there was a clinically meaningful and statistically significant improvement in the pathological complete response rate in the breast (pCR) with the addition of pertuzumab (pCR rate 29.0% in the T+D arm compared to 45.8% in the pertuzumab, trastuzumab and docetaxel arm: difference in pCR rates = 16.8%: 95% CI = 3.5; 30.1, p= 0.0141). This benefit was also observed when pCR rate in breast and lymph nodes was assessed (pCR rate 21.5% in the T+D arm compared to 39.3% in the pertuzumab, trastuzumab and docetaxel arm).

The CI for the hazard ratio in the non-visceral subgroup of the WO20698/TOC4129g study does not exclude a true hazard ratio in this subgroup that is consistent with the ITT population.

Given the above considerations and uncertainties around the true estimate of the treatment effect in the subgroup of patients with non-visceral disease, the Sponsor does not believe there is strong evidence to suggest that patients with non-visceral only disease do derive, or would derive, a smaller benefit from the addition of pertuzumab.

In light of the information provided above we do not believe the CLEOPATRA NVD data can form the basis of a cost-effectiveness analysis. However, in the interests of transparency the data for this subgroup is provided in the attached excel file.

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).

The number and percentage of investigator-assessed progression events that were fatal and non-fatal in each treatment arm of the CLEOPATRA trial taken from the May 14 2012 data-cut are presented in Table 5.

Table 5 Events for Investigator assessed Progression Free Survival (Independently assessed 14 May 2012)

Event	**Trastuzumab and docetaxel (N=406)**	**Pertuzumab, trastuzumab and docetaxel (N=402)**
Fatal PFS event	16 (3.9%)	8 (2.0%)
Non-fatal PFS event	280 (69.0%)	249 (61.9%)
Censored	110 (27.1%)	145 (36.1%)
PFS, Progression Free Survival.		

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).

The number of participants and the average weight and body surface area, by region of origin of the intention to treat participants in the CLEOPATRA trial are provided in Table 6.

Table 6 Bodyweight and body surface area

Region	Number of participants	Average Weight in Kg	Standard Deviation of Weight in Kg	Average of BSA	Standard Deviation of BSA
Asia	253	57.0	9.07	1.55	0.119
Europe	306	71.4	14.84	1.74	0.198
North America	135	74.0	17.41	1.77	0.198
South America	114	66.2	11.97	1.66	0.142
Total	**808**	**66.6**	**15.05**	**1.68**	**0.192**
BSA, body surface area; kg, kilograms.					

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).

Details of the docetaxel dosing regimen of each participant is presented in the attached excel file.

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.

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.

The Clinical Study Reports, Fujiwara et al (1999) and Verrill et al (2007) are provided as PDFs.
The reference for tumorregister-Muenchen registry data is:

Munich Cancer Registry (MCR) of the Munich Cancer Center (MCC) at the Institute for med. Informatics, Biometry and Epidemiology (IBE) University Hospital Großhadern Ludwig-Maximilians-University (LMU) Munich, Marchioninistr. 15, D-81377 Munich (http://www.tumorregister-muenchen.de/facts/spec/spec_C50f__08_20130207_met_her2).