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APPLICATION NUMBER:
125409Orig1s0051

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology/Pharmacometrics Review

BLA	125409
Submission Date:	May 01, 2013
Applicant:	Genentech
Brand Name:	Perjeta[®]
Generic Name:	Pertuzumab
Strength:	420 mg/14 mL pertuzumab in a single use vial
OCP/PM Reviewer:	Pengfei Song, Ph.D.
OCP Team Leader:	Qi Liu, Ph.D.
PM Team Leader:	Kevin Krudys, Ph.D.
OCP Division:	Division of Clinical Pharmacology 5
ORM Division:	Division of Oncology Products 1 (DOP1)
Submission Type	sBLA-51; Efficacy Supplement
Indication:	Neoadjuvant treatment of breast cancer, in combination with trastuzumab and docetaxel, for patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer greater than 2 cm in diameter as part of a complete early breast cancer regimen
Dosing Regimen:	PERJETA (Initially 840 mg IV infusion, followed by 420 mg Q3W), trastuzumab (Initially 8 mg/kg IV followed 6 mg/kg Q3W), and docetaxel (75 mg/m² Q3W IV infusion) should be administered for 4 cycles as part of a complete early breast cancer regimen. Following surgery, patients should continue to receive trastuzumab to complete 1 year of treatment.

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1 EXECUTIVE SUMMARY

PERJETA was approved for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer on June 8, 2012. In the current efficacy supplement submission, the applicant seeks to expand the use of pertuzumab to the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer greater than 2 cm in diameter.

The applicant conducted a randomized Phase 2 trial NEOSPHERE (WO20697) to support the approval. Treatment with PERJETA plus trastuzumab and docetaxel has a statistically significantly improved pathological complete response (pCR) rate of 39.3% (90% CI [30.0, 49.2], $P=0.0063$), compared to a pCR rate of 21.5% (90% CI [14.1, 30.5]) following treatment with trastuzumab plus docetaxel.

The updated population PK analysis results suggested that pertuzumab exposure in patients with early breast cancer in trial NEOSPHERE was similar to exposure in other historical patient types including first-line metastatic breast cancer. No significant exposure-response relationship was identified between predicted pertuzumab trough serum concentration and the probability of pCR response, the primary efficacy endpoint of the Trial NEOSPHERE.

2 RECOMMENDATIONS

This efficacy supplement of BLA125409 is acceptable from a clinical pharmacology perspective, provided that a satisfactory agreement is reached between the Applicant and the Agency regarding labeling language.

3 SUMMARY OF FINDINGS

3.1 Background

PERJETA is a HER2/neu receptor antagonist approved for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer on June 8, 2012. In the current efficacy supplement submission, the applicant seeks to expand the use of pertuzumab to the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer greater than 2 cm in diameter.

The applicant conducted a Phase 2 trial NEOSPHERE (WO20697) to support the approval. NEOSPHERE is a randomized trial conducted in 417 patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d) who were scheduled for neoadjuvant therapy. Patients were randomly allocated to receive 1 of 4 neoadjuvant regimens prior to surgery as follows: trastuzumab plus docetaxel (Arm A, N=107), PERJETA plus trastuzumab and docetaxel (Arm B, N=107), PERJETA plus trastuzumab (Arm C, N=107), or PERJETA plus docetaxel (Arm D, N=96).

In trial NEOSPHERE, PERJETA [initially 840 mg, followed by 420 mg IV infusion every three weeks (Q3W)], trastuzumab (initially 8 mg/kg IV followed 6 mg/kg Q3W), and docetaxel (75 mg/m² Q3W IV infusion) were administered for 4 cycles. Following surgery, all patients received 3 cycles of 5-fluorouracil (600 mg/m²), epirubicin (90 mg/m²), and cyclophosphamide (600 mg/m²) (FEC) given intravenously every 3 weeks and trastuzumab administered intravenously every 3 weeks to complete 1 year of therapy. After surgery, patients in the PERJETA plus trastuzumab arm received docetaxel every 3 weeks for 4 cycles prior to FEC.

Treatment with PERJETA plus trastuzumab and docetaxel has a statistically significantly improved pathological complete response (pCR) rate of 39.3% (90% CI [30.0, 49.2], $P=0.0063$),

compared to a pCR rate of 21.5% (90% CI [14.1, 30.5]) following treatment with trastuzumab plus docetaxel.

The applicant submitted new PK data from NEOSPHERE and the results of an exposure–response analysis to support the extension of pertuzumab use in the neoadjuvant treatment of patients with HER2-positive early breast cancer.

3.2 Key Review Questions

The purpose of this clinical pharmacology/pharmacometric review is to address the following key questions:

3.2.1 Is there evidence for different pertuzumab exposure in patients with early stage breast cancer and patients with metastatic breast cancer?

No. The population PK analysis results suggested similar pertuzumab exposure in patients with early breast cancer in trial NEOSPHERE and other historical patient types including the first-line metastatic breast cancer.

The previously developed popPK model based on historical patient types including first-line metastatic breast cancer reasonably predicted the observed pertuzumab serum concentrations in trial NEOSPHERE stratified by the treatment arms (B) trastuzumab + docetaxel + pertuzumab, (C) trastuzumab + pertuzumab, and (D) pertuzumab + docetaxel (Figure 1).

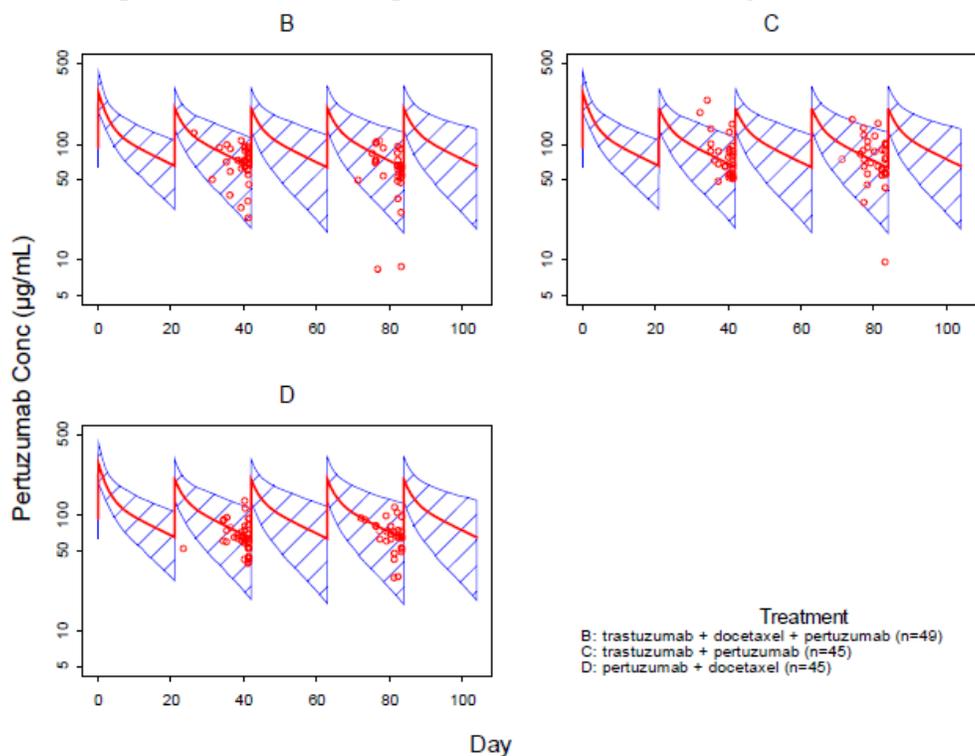
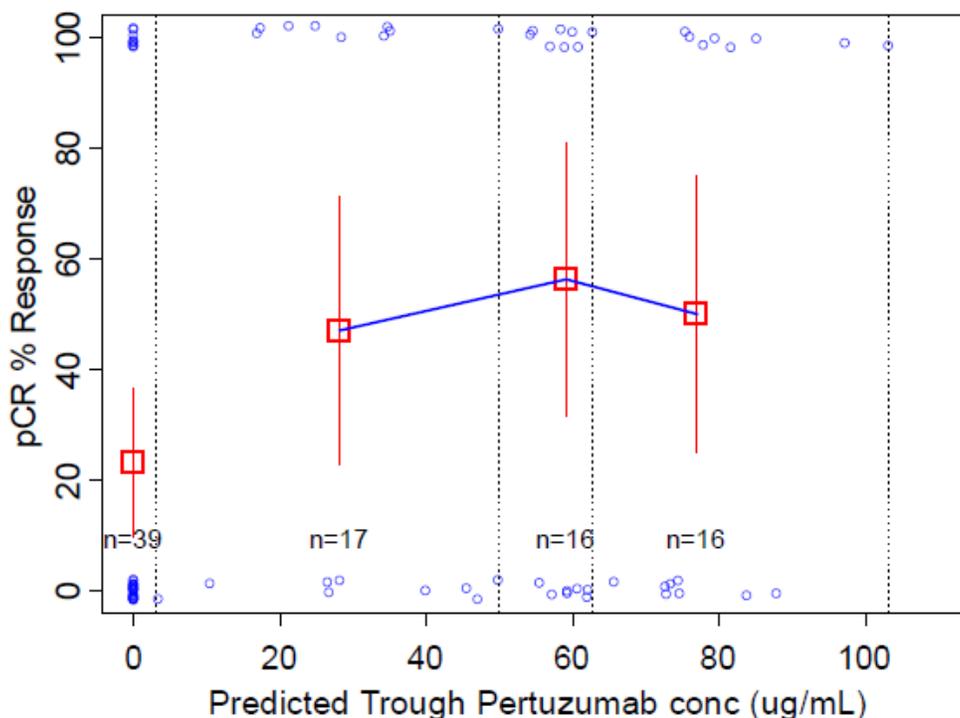


Figure 1. Observed versus model-simulated pertuzumab serum concentrations by treatment groups. The blue-shaded areas represent the 2.5th–97.5th percentiles based on simulations by the popPK model and the observed lean body weight and albumin distributions in NEOSPHERE. The red lines are the popPK model predictions for a typical patient, i.e., the median values of lean body weight and albumin for each treatment group. The red circles represent trough serum concentrations observed for NEOSPHERE patients.

Source: Figures A of the study report entitled ‘Pharmacokinetic Analysis and Exposure-Response of Pertuzumab in Combination with Trastuzumab and Docetaxel in the Neoadjuvant Setting’

3.2.2 Is there a significant exposure-efficacy relationship for pertuzumab?

No significant exposure-response relationship ($p=0.751$) was identified between predicted pertuzumab trough serum concentration (3.4–103.8 $\mu\text{g/mL}$) and the probability of pCR response, the primary efficacy endpoint of the Trial NEOSPHERE.



pCR = pathological complete response.

Figure 2. Cycle 4 pCR percent response versus predicted pertuzumab serum concentration in combination with trastuzumab and docetaxel. Square symbols represent % pCR of the patients grouped by pertuzumab serum concentration into third tiles (separated by vertical dashed lines). The group with zero pertuzumab serum concentration is all patients in Arm A. Error bars represent $2 \times$ standard error ($2 \times \sqrt{p*(1-p)/n}$). The blue circles represent the response status of individual patients (0% = non-responder, 100% = responder).

Source: Figures F of the study report entitled 'Pharmacokinetic Analysis and Exposure-Response of Pertuzumab in Combination with Trastuzumab and Docetaxel in the Neoadjuvant Setting'

4 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. Double underlines indicate the content that was added by the Applicant to the originally approved label or by the Agency to the applicant's proposed label, and ~~strikethroughs~~ indicate contents taken out by the applicant from the originally approved label or by the Agency from the applicant's proposed label.

Applicant's Proposal	Agency's Edits
<p>(b) (4)</p>	<p>12.3 Pharmacokinetics</p> <p>Pertuzumab demonstrated linear pharmacokinetics at a dose range of 2 – 25 mg/kg. Based on a population PK analysis that included 481 patients, the median clearance (CL) of pertuzumab was 0.24 L/day and the median half-life was 18 days. With an initial dose of 840 mg followed by a maintenance dose of 420 mg every three weeks thereafter, the steady-state concentration of pertuzumab was reached after the first maintenance dose.</p> <p>The population PK analysis suggested no PK differences based on age, gender, (b) (4) ethnicity (Japanese vs. non-Japanese) <u>or disease status (neoadjuvant vs. metastatic settings)</u>. Baseline serum albumin level and lean body weight as covariates only exerted a minor influence on PK parameters. Therefore, no dose adjustments based on body weight or baseline albumin level are needed.</p> <p>No drug-drug interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel in a sub-study of 37 patients in Study 1.</p> <p>No dedicated renal impairment trial for PERJETA has been conducted. Based on the results of the population pharmacokinetic analysis, pertuzumab exposure in patients with mild (CLcr 60 to 90 mL/min, n=200) and moderate renal impairment (CLcr 30 to 60 mL/min, n=71) were similar to those in patients with normal renal function (CLcr greater than 90 mL/min, n=200). No relationship between CLcr and pertuzumab exposure was observed over the range of observed CLcr (27 to 244 mL/min).</p> <p>(b) (4)</p>

5 APPLICANT'S ANALYSES

No independent analyses have been conducted by the FDA. The following summary of the applicant's analyses are excerpted from the study report entitled 'Pharmacokinetic Analysis and Exposure-Response of Pertuzumab in Combination with Trastuzumab and Docetaxel in the Neoadjuvant Setting'.

5.1 Objectives

The goals of the exposure-response (ER) and pharmacokinetic (PK) analyses were:

- To compare pertuzumab pharmacokinetics between the neoadjuvant population (early breast cancer [EBC]) in NEOSPHERE and those of other tumor types including the first-line mBC population
- To explore the potential PK drug-drug interaction (DDI) between pertuzumab and trastuzumab and the potential effect of docetaxel on the pertuzumab + trastuzumab combination
- To explore the relationship between pertuzumab exposure (in combination with trastuzumab and docetaxel) and pCR

5.2 Methods

Study WO20697 (NEOSPHERE) is a 4-arm study evaluating the efficacy and safety of neoadjuvant (naïve to chemotherapy and prior to surgery) treatment regimens in female patients with locally advanced, inflammatory or early-stage HER2-positive breast cancer. Before surgery, patients were randomized to receive four cycles of one of the following four treatment arms: (A) trastuzumab + docetaxel, (B) trastuzumab + docetaxel + pertuzumab, (C) trastuzumab + pertuzumab, and (D) pertuzumab + docetaxel.

Pertuzumab serum concentrations were measured at Cycles 2 and 4 on Days 14 up to 21 post-dose (window of collection; 2 samples per patients were planned). Samples were obtained from 139 patients: Arm B, n = 49; Arm C, n = 45; and Arm D, n = 45. The PK data were compared with the simulations from a pertuzumab population pharmacokinetic (popPK) model previously developed from 481 patients in 12 clinical studies.

Trastuzumab serum concentrations were also measured on Days 14 to 21 post-dose of Cycle 2 and Cycle 4 in NEOSPHERE. Samples were obtained from 135 patients: Arm A, n = 41; Arm B, n = 49; and Arm C, n = 45. The PK data were compared with simulations from a trastuzumab popPK model previously developed from 595 patients in Study BO22227 (HANNAH).

DDIs between pertuzumab, trastuzumab, and docetaxel were examined by empirical Bayesian estimates (EBEs) of the individual PK parameters using exploratory plots and analysis of variance (ANOVA) with a significance level of < 0.01.

The ER relationship of pCR versus pertuzumab exposure (in combination with trastuzumab and docetaxel) was evaluated based on Arm B data. PopPK-predicted trough serum concentrations were used as a measure of exposure to reduce the differences in serum concentrations resulting from differences in sampling times within the Day 14 to 21 sampling window. Significance was ascertained at the 0.05 level of significance using a log-likelihood criteria.

S-PLUS 6.2 and NONMEM (Version 7.1) were used for the analyses.

5.3 Results

Pertuzumab Pharmacokinetic Analysis

The observed pertuzumab serum concentrations were in good agreement with the popPK model predictions in all study arms after correcting for significant covariate differences (see Figure A). These significant covariates were identified as lean body weight (LBW) and albumin (ALBU) at baseline.

Individual pertuzumab PK parameters (clearance [CL], volume of distribution for the peripheral compartment [Vp], and volume of distribution for the central compartment [Vc]) were similar among different treatment groups (see Figure B). Trastuzumab and docetaxel did not appear to cause any DDIs with pertuzumab (Arm B versus Arm D) and (Arm B versus Arm C), respectively.

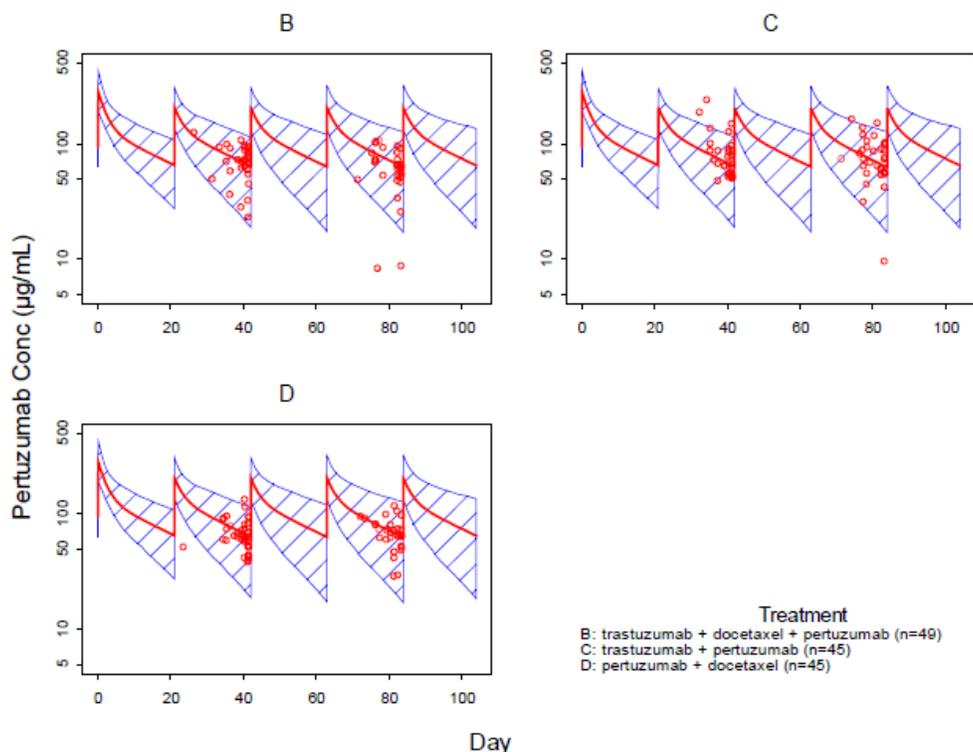


Figure 1. Observed versus model-simulated pertuzumab serum concentrations by treatment groups. The blue-shaded areas represent the 2.5th–97.5th percentiles based on simulations by the popPK model and the observed lean body weight and albumin distributions in NEOSPHERE. The red lines are the popPK model predictions for a typical patient, i.e., the median values of lean body weight and albumin for each treatment group. The red circles represent trough serum concentrations observed for NEOSPHERE patients.

Source: Figures A of the study report entitled ‘Pharmacokinetic Analysis and Exposure-Response of Pertuzumab in Combination with Trastuzumab and Docetaxel in the Neoadjuvant Setting’

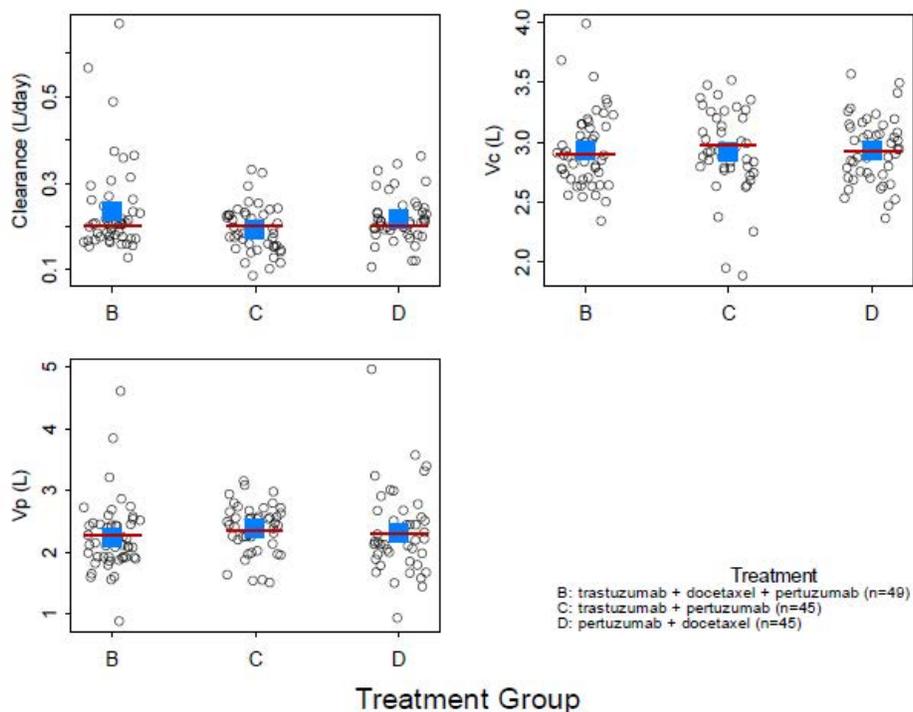


Figure 3. Pertuzumab Individual Pharmacokinetic Parameters by Treatment Group. The black circles represent individual pharmacokinetic parameter values for the NEOSPHERE patients, and the blue squares represent mean values per group. The red lines represent the pharmacokinetic parameter values for a typical patient, i.e., the median values of lean body weight and albumin of each of the treatment groups predicted by the population pharmacokinetic model.

Source: Figures B of the study report entitled 'Pharmacokinetic Analysis and Exposure-Response of Pertuzumab in Combination with Trastuzumab and Docetaxel in the Neoadjuvant Setting'

Trastuzumab Pharmacokinetic Analysis

The modeled PK profiles over-predicted the observed trastuzumab serum concentrations in the study arms, even after correcting for covariate differences (see Figure 4). Measured trough trastuzumab serum concentrations were 32.4% lower than the modeled values. The potential cause for the lower trastuzumab serum concentrations in the NEOSPHERE samples (i.e., assay difference and other factors) is currently being investigated by the applicant. Individual trastuzumab PK parameters were similar among treatment groups within this study (see Figure 5). Trastuzumab PK parameters were not affected by the addition of pertuzumab (Arm A versus Arm B) or docetaxel (Arm B versus Arm C).

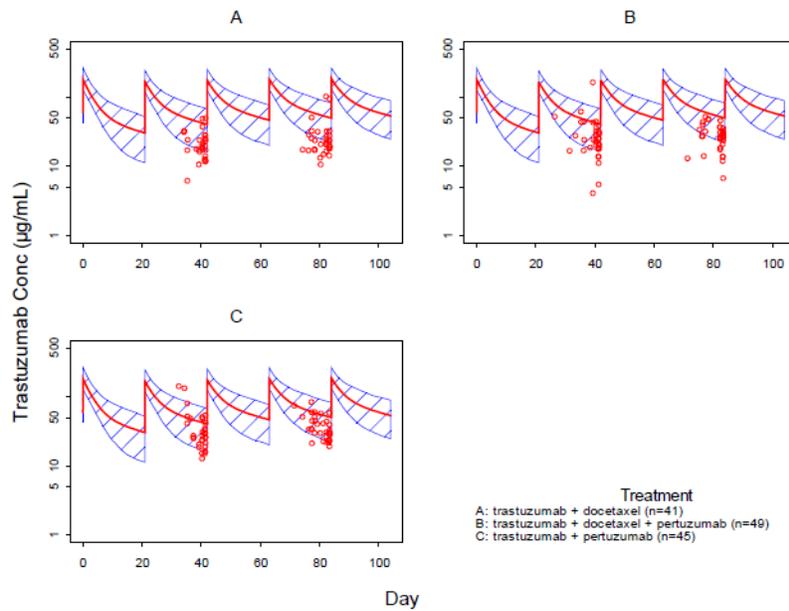


Figure 4. Observed versus Model-Simulated Trastuzumab Serum Concentration by Treatment Group. The blue-shaded areas represent the 2.5th–97.5th percentiles based on simulations by the popPK model and the observed body weight and serum SGPT distributions in NEOSPHERE. The red lines are the PK model predictions for a typical patient i.e., the median values of body weight and serum SGPT for each treatment group. The red circles represent the trough serum concentrations observed for NEOSPHERE patients.

Source: Figures C of the study report entitled ‘Pharmacokinetic Analysis and Exposure-Response of Pertuzumab in Combination with Trastuzumab and Docetaxel in the Neoadjuvant Setting’

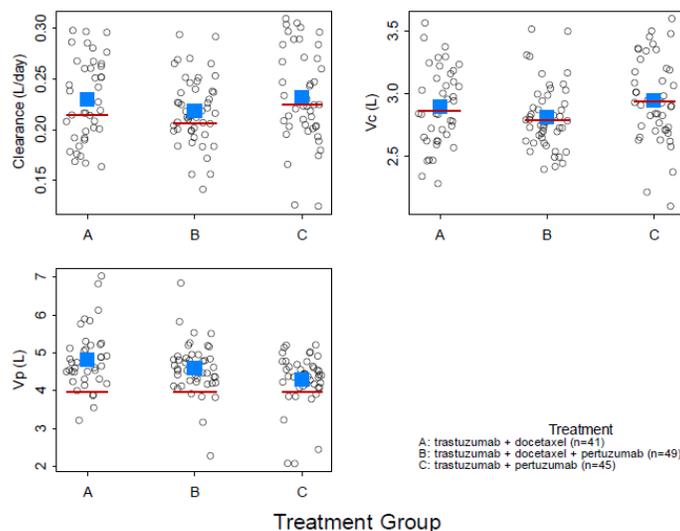
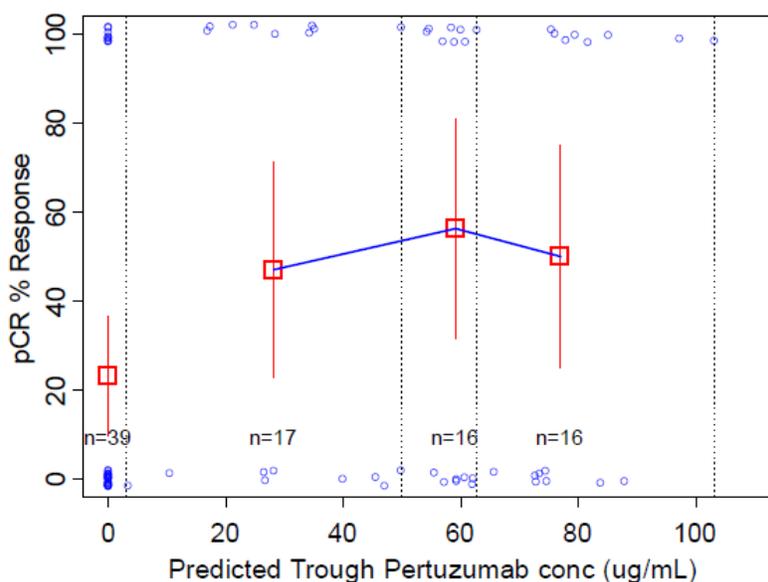


Figure 5. Trastuzumab Individual Pharmacokinetic Parameters by Treatment Groups. The black circles represent individual pharmacokinetic parameter values for the NEOSPHERE patients, and the blue squares represent the mean value of these for each group. The red lines represent the pharmacokinetic parameter values for a typical patient, i.e., the median values of body weight and serum SGPT of each of the treatment groups predicted by the population pharmacokinetic model.

Source: Figures D of the study report entitled ‘Pharmacokinetic Analysis and Exposure-Response of Pertuzumab in Combination with Trastuzumab and Docetaxel in the Neoadjuvant Setting’

Exposure-Response Analyses

The exposure-response relationship of percent pCR versus the predicted trough pertuzumab serum concentration is illustrated in Figure F. The patients included in this analysis were from Arms A and B in which all patients were treated with trastuzumab and docetaxel. Most (45 of 49) patients treated with pertuzumab (Arm B) had a predicted trough pertuzumab serum concentration > 20 µg/mL the target efficacious exposure based on nonclinical efficacy models. The pCR rate was higher in patients treated with pertuzumab plus trastuzumab and docetaxel (Arm B) relative to trastuzumab and docetaxel alone (Arm A). Within Arm B, there was no significant impact ($p = 0.751$) of predicted pertuzumab serum concentration (3.4–103.8 µg/mL) on the probability of pCR response.



pCR = pathological complete response.

Figure 3. Cycle 4 pCR percent response versus predicted pertuzumab serum concentration in combination with trastuzumab and docetaxel. Square symbols represent % pCR of the patients grouped by pertuzumab serum concentration into third tiles (separated by vertical dashed lines). The group with zero pertuzumab serum concentration is all patients in Arm A. Error bars represent $2 \times$ standard error ($2 \times \sqrt{p*(1-p)/n}$). The blue circles represent the response status of individual patients (0% = non-responder, 100% = responder).

Source: Figures F of the study report entitled 'Pharmacokinetic Analysis and Exposure-Response of Pertuzumab in Combination with Trastuzumab and Docetaxel in the Neoadjuvant Setting'

5.4 Conclusion

The pertuzumab PK results in NEOSPHERE were consistent with the previous popPK model predictions, suggesting similarity in pertuzumab pharmacokinetics between the EBC population in NEOSPHERE and other historical patient types including the first-line MBC population.

- The majority of patients (137 of 139) in Arms B, C, and D of NEOSPHERE had an observed pertuzumab trough serum concentration > 20 µg/mL at Cycle 2.
- The trastuzumab PK results were similar across the three arms in NEOSPHERE. Notably, the observed trastuzumab serum concentrations in NEOSPHERE were lower than the predictions

from the previous popPK model, which was derived from HANNAH, and were not explained by the identified covariates. The reasons for the systematic lower serum concentrations in the NEOSPHERE samples are currently being explored, including an investigation into the assays.

- On the basis of comparisons between arms, there did not appear to be an effect of trastuzumab on pertuzumab pharmacokinetics; nor was there an effect of pertuzumab on trastuzumab pharmacokinetics.
- Docetaxel did not appear to affect the pharmacokinetics of pertuzumab and trastuzumab as a combination or as single agents.
- The pCR rate was higher in patients treated with pertuzumab + trastuzumab + docetaxel (Arm B) compared with those treated with trastuzumab + docetaxel (Arm A). An ER relationship was not observed for pertuzumab in the pertuzumab + trastuzumab + docetaxel arm. Thus, it follows that pertuzumab serum concentrations > 20 µg/mL in serum did not result in increases in pCR rates.

Reviewer's comments:

The applicant's population PK analysis and exposure-response analyses are reasonable. The overall conclusion is consistent with the Population PK analysis reviewed and accepted in the original submission (See Pharmacometrics review by Dr. Kevin Krudys that was collated in the clinical pharmacology review dated May 10, 2012 in Dartrts under BLA125409). As the treatment with pertuzumab plus tratuzumab and docetaxel (Arm B) demonstrated improved efficacy than tratuzumab and docetaxel treatment (Arm A), the decrease of trastuzumab exposure due to unknown reasons is not considered as clinical importantly. There was no exposure-response relationship observed.

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