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APPLICATION NUMBER:

125409Orig1s000

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

Clinical Pharmacology Review

BLA	125409
Submission Date	December 08, 2011
Brand Name	XXX TM
Generic Name	Pertuzumab (rhuMAb 2C4)
Dosage Form / Strength	Pertuzumab 420 mg/14 mL concentrate in a single use vial
Related IND	9900
Applicant	Genentech, Inc.
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OCP Division	Division of Clinical Pharmacology 5
ORM Division	Division of Oncology Products 1
Submission Type; Code	Original BLA; New Biologic Entity
Dosing Regimen	Initial dose of 840 mg over 60 minutes intravenous infusion, followed every 3 weeks thereafter by 420 mg over 30-60 minutes intravenous infusion, in combination with trastuzumab and docetaxel
Indication	HER2-positive breast cancer

Table of contents

1	Executive Summary	4
1.1	Recommendations	4
1.2	Post-Marketing Requirements	4
1.3	Clinical Pharmacology Summary	5
2	Question Based Review	6
2.1	General Attributes	6
2.2	General Clinical Pharmacology	7
2.3	Intrinsic Factors	14
2.4	Extrinsic Factors	20
2.5	General Biopharmaceutics	27
2.6	Analytical Section	27
	Detailed Labeling Recommendations	31
3	Pharmacometric Review	35
4	Genomics Review	48

List of Tables

Table 1. Pertuzumab general properties	6
Table 2. Clinical trials with pertuzumab pharmacokinetic analysis	8
Table 3. Summary of pertuzumab PK parameters (mean ± SD) following IV infusion as a single-agent or in combination with other therapies in patients with advance tumors	10
Table 4. Patients with positive ATA in the Phase 3 trial WO20698/TOC4129g	18
Table 5. Summary of efficacy by ATA status in the Phase 3 trial WO20698/TOC4129g.....	19
Table 6. Impact of ATA on pertuzumab trough concentrations in study WO20698/TOC4129g.	19
Table 7. Comparisons of trastuzumab pharmacokinetics between pertuzumab arm and placebo arm	22
Table 8. Comparisons of docetaxel pharmacokinetics between pertuzumab + trastuzumab + docetaxel arm (N=14) and placebo + trastuzumab + docetaxel arm (N=18)	23
Table 9. Comparison of the pharmacokinetics of pertuzumab when used as single agent and used in combination with capecitabine, docetaxel, and erlotinib	24
Table 10. Comparison of pertuzumab pharmacokinetics when pertuzumab is used as single agent in studies TOC2682g and TOC2572g, and used in combination with gemcitabine in study TOC3258g.....	24
Table 11. Study BO17003: Mean pharmacokinetic parameters of capecitabine given alone (on pre-cycle Day -7) and in combination with pertuzumab (Day 1 of the same cycle).	25
Table 12. Study BO17021: Summary of pharmacokinetic parameters for docetaxel alone and in combination with pertuzumab	25
Table 13. Study BO17021: Summary of pharmacokinetic parameters for docetaxel alone and in combination with pertuzumab	26
Table 14. Study TOC3258g: AUC ₅₋₃₀ for gemcitabine (upper) and AUC _{all} for dFdU (lower) when administered with or without pertuzumab	26
Table 15. Composition of pertuzumab drug product	27
Table 16. Assay performance of validated pharmacokinetic assays used in clinical studies	28
Table 17. Assay performance of validated anti-therapeutic antibody assays used in clinical studies	29

List of Figures

- Figure 1: Mean serum pertuzumab concentration time profiles for the first two treatment cycles in Phase 1 dose escalation studies TOC2297g and JO17076. 12
- Figure 2: Pertuzumab C_{max} (left) and $AUC_{last\ Day0-21}$ (right) in the first treatment cycle (Day 0 -21) increased with doses with a slope of 0.89 (0.80, 0.98) for C_{max} and 0.97 (0.86, 1.07) for $AUC_{last\ Day0-21}$ from 2 mg/kg to 25 mg/kg single dose of pertuzumab. The shaded area is the 90% confidence interval of the slope. The dots represents the observed C_{max} or calculated $AUC_{last, Day0-21}$ from 27 patients in Phase 1 dose escalation trials TOC2297g and JO17076. 13
- Figure 3: Pertuzumab serum concentrations following IV Infusion of 420 mg after a loading dose of 840 mg (left) in 40 patients with metastatic breast cancer or following IV Infusion of 1050 mg in 37 patients with metastatic breast cancer (right) every three weeks (Study 16934). Serum samples were taken at baseline, before and within 15 min of the end of pertuzumab infusion for all cycles, and once on days 8 and 15 for Cycles 1 and 2..... 13
- Figure 4: Baseline body weight and trough concentrations of pertuzumab at steady state for a loading dose of 840 mg followed by 420 mg every 3 weeks. 15
- Figure 5: The box-plot of simulated steady-state trough concentrations for a loading dose of 840 mg followed by 420 mg every three weeks using Bayes posthoc PK parameters versus renal function groups. Based on each patient's baseline creatinine clearance (CrCL), renal function was grouped as normal renal function ($CLcr > 80$ mL/min, $N=241$), mild (50 mL/min $<$ creatinine clearance ($CLcr$) ≤ 80 mL/min, $N=158$), moderate (30 mL/min $\leq CLcr < 50$ mL/min, $N=38$), and severe ($CLcr < 30$ mL/min, $N=3$) renal impairment. Points are individual values and box plots show the median, 25th and 75th percentiles. 16
- Figure 6: Observed and population PK predicted serum concentrations of pertuzumab. The observed serum concentrations of pertuzumab were obtained from 20 patients in a PK sub-study of the Phase 3 trial WO20698/TOC4129g. The population PK model was based on PK data of 12 clinical studies. 22
- Figure 7: Mean (\pm SD) plasma concentration-time profiles of docetaxel (in the presence of trastuzumab) – with either placebo ($N=18$) or pertuzumab ($N=14$) in Cycle 1 of the PK sub-study in Phase 3 trial WO20698/TOC4129g. 23

1 EXECUTIVE SUMMARY

Pertuzumab (rhuMAb 2C4) is a recombinant, humanized, IgG1 monoclonal antibody targeting the human epidermal growth factor receptor 2 (HER2). The applicant seeks the approval of pertuzumab for use in combination with trastuzumab and docetaxel as a first-line treatment of HER2-positive breast cancer. The proposed pertuzumab dosage is a loading dose of 840 mg administered as an intravenous infusion, followed thereafter by 420 mg maintenance dose every 3 weeks.

The pivotal Phase 3 trial in patients with HER2-positive breast cancer demonstrated a significantly improved progression free survival (PFS) in the pertuzumab plus trastuzumab and docetaxel arm (median: 18.5 months) compared to the placebo plus trastuzumab and docetaxel arm (median: 12.4 months), with a hazard ratio of 0.62 (95% CI: 0.51, 0.75; P<0.0001). Most common adverse reactions in the pertuzumab arm were diarrhea, alopecia, and neutropenia.

Pertuzumab demonstrated linear pharmacokinetics (PK) at a dose range of 2-25 mg/kg. With the proposed dosing regimen, steady-state concentration of pertuzumab was reached following the first maintenance dose. A population PK analysis estimated clearance and terminal elimination half-life of pertuzumab as 0.235 L/day and 18 days, respectively. 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. Based on the population PK analysis, dose adjustments are not needed for renal impairment. No significant drug interactions were observed when pertuzumab was co-administered with docetaxel and trastuzumab, as well as with other chemotherapeutic agents (gemcitabine, capecitabine, or erlotinib). No large changes in mean QTc intervals (i.e., > 20 ms) were detected at the proposed pertuzumab dosing regimen.

The incidence of positive anti-therapeutic antibodies (ATAs) to pertuzumab was 2.8% in the pertuzumab arm as compared to 6.2% in the placebo arm. The presence of ATAs had no known association with hypersensitivity reactions and anaphylaxis. Although the presence of ATAs appeared to be associated with shorter PFS and lower response rate, the benefit of pertuzumab treatment seemed to be preserved within both ATA-positive and ATA-negative subgroups.

1.1 RECOMMENDATIONS

This BLA is acceptable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language.

1.2 POST-MARKETING REQUIREMENTS

None.

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1.3 CLINICAL PHARMACOLOGY SUMMARY

Pertuzumab (rhuMAb 2C4) is a recombinant, humanized, IgG1 monoclonal antibody targeting the human epidermal growth factor receptor 2 (HER2). In this original BLA, the applicant seeks the approval of pertuzumab for use in combination with trastuzumab and docetaxel as a first-line treatment of HER2-positive breast cancer.

In the pivotal Phase 3 trial (W020698/TOC4129g), patients with HER2-positive breast cancer were randomized to receive either pertuzumab plus trastuzumab and docetaxel (n=402) or placebo (n=406) plus trastuzumab and docetaxel. Pertuzumab was administered as intravenous infusion, with a loading dose of 840 mg, followed by a 420 mg maintenance dose every 3 weeks. Progression free survival (PFS), the primary efficacy endpoint, was significantly improved in the pertuzumab arm (median: 18.5 months) compared to the placebo arm (median: 12.4 months), with a hazard ratio of 0.62 (95% CI: 0.51, 0.75; P<0.0001). Most common adverse reactions (> 50%) in pertuzumab arm were diarrhea, alopecia, and neutropenia.

Pertuzumab demonstrated a linear PK at a dose range of 2-25 mg/kg in terms of dose proportionality and time-independence. With a loading dose of 840 mg and a 420 mg maintenance dose every three weeks, the steady-state concentrations of pertuzumab were reached after the first maintenance dose. Based on a population PK analysis using data from 12 clinical trials, clearance (CL), central volume of distribution (V_c), and terminal elimination half-life of pertuzumab are 0.235 L/day, 3.11 L, and 18 days, respectively. Inter-individual variability of CL and V_c expressed as CV% are 34.9% and 18.7%, respectively. Though lean body weight and baseline serum albumin level were identified as significant covariates on the pertuzumab PK, the fixed dosage was acceptable, as their impacts on the pertuzumab PK were considered as marginal. The population PK analysis did not identify age, race, gender, or mild/moderate renal impairment as significant covariates on the PK of pertuzumab.

No significant drug interactions were observed between pertuzumab and docetaxel (in the presence of trastuzumab) or between pertuzumab and trastuzumab (in the presence of docetaxel). Furthermore, no significant drug interactions were observed when pertuzumab was co-administered with other small molecule chemotherapeutic agents (gemcitabine, capecitabine, erlotinib, or docetaxel).

The incidence rate of positive anti-therapeutic antibodies (ATAs) to pertuzumab was 2.8% in the pertuzumab arm as compared to 6.2% in the placebo arm. The presence of ATAs has no known association with hypersensitivity reactions, anaphylaxis or other adverse safety findings. Although ATA-positive patients appeared to have shorter PFS and lower response rate than ATA-negative patients, the benefit of pertuzumab treatment was preserved within both ATA-positive and ATA-negative subgroups.

IRT-QTc review team concluded that no large changes in mean QTc intervals (i.e., > 20 ms) were detected at the proposed pertuzumab therapeutic dose.

Inadequate PK data in the pivotal Phase 3 trial (available in 20 out of 407 patients receiving pertuzumab) precluded the exposure-response relationship analysis.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Pertuzumab is a recombinant humanized monoclonal antibody based upon the human IgG1(κ) framework sequence. It is composed of two light chains consisting of 214 amino acid residues and two heavy chains consisting of 448 or 449 amino acid residues. Pertuzumab differs from Herceptin[®] (trastuzumab) in the complementarity-determining regions (CDRs) of the light chain (12 amino acid differences) and the heavy chain (29 amino acid differences).

The physico-chemical properties of pertuzumab is summarized below (Table 1):

Table 1. Pertuzumab general properties

Property	Molecule Details
Structure	Pertuzumab is a recombinant humanized monoclonal antibody based upon the human IgG1(κ) framework sequence.
Amino Acid Composition	Refer to Figure 3.2.S.1.2-1 and Figure 3.2.S.1.2-2 for the amino acid sequences of the light chain and heavy chain, respectively.
Binding Site	Refer to Figure 3.2.S.1.2-1 and Figure 3.2.S.1.2-2 for the complementarity-determining regions.
Molecular Weight	The molecular mass of intact pertuzumab is approximately 148 088 Daltons (b) (4)
Extinction Coefficient	(b) (4)
Isoelectric Point	(b) (4)
Glycosylation	(b) (4)
Biological Activity	Pertuzumab acts by blocking the association of HER2 with the other HER family members, including HER1 (EGFR), HER3, and HER4. Pertuzumab can also prevent formation of HER2 homodimerization. As a result, pertuzumab inhibits ligand-initiated intracellular signaling pathways, mitogen-activated protein (MAP) kinase, and phosphoinositide 3 (PI3) kinase. Inhibition of these signaling pathways can result in growth arrest and apoptosis.
Potency Assay	(b) (4)
Clinical Experience	Clinical experience with pertuzumab in patients with metastatic breast cancer has shown that it is well tolerated and effective.

Source: Table 3.2.S.1.3-1 of Module 3 Quality

[Tradename], the drug product, is supplied in a single-dose vial containing preservative free liquid concentrate, at a concentration of 30 mg/mL ready for infusion. Each vial of [Tradename] contains a total of 420 mg pertuzumab. Vials should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Indication: Pertuzumab is a HER2 dimerization inhibitor indicated in combination with trastuzumab and docetaxel for patients with HER2-positive metastatic (b) (4) breast cancer, who have not received previous treatment (b) (4)

Mechanism of action: Pertuzumab is a recombinant humanized monoclonal IgG1 antibody that targets HER2 by binding to the subdomain 2 of HER2 (not subdomain 4 where trastuzumab binds to). Binding of pertuzumab to the HER2 on human epithelial cells prevents HER2 from forming complexes with other members of the HER receptor family (including EGFR, HER3, HER4) and forming HER2 homodimers, resulting in inhibition of cell proliferation and survival. In addition, both pertuzumab and trastuzumab are capable of inducing antibody-dependent cell-mediated cytotoxicity (ADCC).

2.1.3 What are the proposed dosage and route of administration?

Pertuzumab was proposed to be administered in combination with trastuzumab and docetaxel using the following dosage and route of administration:

Pertuzumab: initial dose of 840 mg over 60 minutes IV infusion, followed every 3 weeks thereafter by 420 mg over 30–60 minutes IV infusion

Trastuzumab: initial dose of 8 mg/kg followed thereafter by a dose of 6 mg/kg every 3 weeks via IV infusion.

Docetaxel: initial dose of 75 mg/m² administered as an IV infusion, an dose of 100 mg/m² every 3 weeks allowed if the initial dose is well tolerated.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The proposed dosing regimen of pertuzumab is the same with that was used in the pivotal Phase 3 trial. To support the approval, the results of a pivotal Phase 3 trial (W020698/TOC4129g) and three supportive Phase 2 trials (WO20697, BO17929, BO16934) were submitted. In the pivotal Phase 3 trial, patients with HER2-positive breast cancer were randomized to receive either pertuzumab plus trastuzumab and docetaxel (n=402) or placebo (n=406) plus trastuzumab and docetaxel. Pertuzumab arm demonstrated a significantly improved PFS (median: 18.5 months) compared to placebo arm (median: 12.4 months), with a hazard ratio of 0.62 (95% CI: 0.51, 0.75; P<0.0001).

A population PK report for pertuzumab based on pooled data from 444 cancer patients in 12 clinical studies with PK data available (Table 2) provided the characterization of pertuzumab PK across different dose levels and tumor types, assessment of factors associated with PK variability, and support for a fixed dosage.

Though no dedicated drug-drug interactions studies have been conducted, a sub-study of the pivotal Phase 3 trial in 37 patients evaluated the potential for drug interactions between pertuzumab and docetaxel/trastuzumab. Additionally, the drug interaction potential between

pertuzumab and co-administered drugs was assessed in Phase I/II studies with docetaxel (BO17021), gemcitabine (TOC3258g), capecitabine (BO17003), or erlotinib (WO20024).

The immunogenic effects of pertuzumab were evaluated by measuring ATAs to pertuzumab using validated bridging immunoassays. A “tiered strategy” was used for ATA sample analysis. The incidence of ATAs was compiled from 366 patients in eleven Phase I/II clinical trials and 758 patients in the Phase 3 pivotal trial. The impact of the presence of ATAs on the PK, safety, and efficacy were explored.

Table 2. Clinical trials with pertuzumab pharmacokinetic analysis

Study	Phase	Indication	Dose ^a /Regimens	Patients Treated	Status ^b
Single-agent studies					
<u>Phase I, dose escalation</u>					
TOC2297g	Ia	Advanced solid tumors	0.5, 2.0, 5.0, 10.0, and 15.0 mg/kg q3wk	21	Completed
JO17076 ^c	I	Advanced solid tumors	5.0, 10.0, 15.0, 20.0 and 25.0 mg/kg q3wk	18	Completed
<u>Phase II</u>					
TOC2689g	II	Advanced ovarian cancer	Cohort 1: 420 mg qw3k ^a Cohort 2: 1050 mg qw3k ^a	61 62	Completed
BO16934	II	MBC with low HER2 expression	Arm A: 420 mg qw3k ^a Arm B: 1050 mg qw3k	41 37	Completed
BO17004	II	HRPC, chemotherapy naive	Cohort 1: 420 mg qw3k ^a Cohort 2: 1050 mg qw3k ^a	35 33	Completed
TOC2682g	II	CRPC pretreated with docetaxel	420 mg qw3k ^a	41	Completed
TOC2572g	II	Advanced, recurrent NSCLC	420 mg qw3k ^a	43	Completed
Combination Therapy Studies					
<u>Phase I studies</u>					
BO17003	Ib	Advanced solid tumors	Cohort 1: pertuzumab: 1050 mg q3wk docetaxel: 60 mg/m ²	18	Completed
BO17021	Ib	Advanced solid tumors	Cohort 2: pertuzumab: 1050 mg q3wk docetaxel and 75 mg/m ² Cohort 2A: pertuzumab: 420 mg q3wk docetaxel: 75 mg/m ²	19	Completed
WO20024	Ib	Advanced NSCLC	pertuzumab: 420 mg q3wk Cohort 1: erlotinib: 100 mg/day Cohort 2: erlotinib 150 mg/day	15	Completed
<u>Phase II randomized studies</u>					
TOC3258g	II	Platinum-resistant ovarian, peritoneal, or fallopian tube cancer	gemcitabine: 800 mg/m ² ± pertuzumab: 420 mg q3wk	Gemcitabine + Pertuzumab: 65 Gemcitabine: 65	Completed
<u>Pivotal Phase III, randomized study</u>					
WO20698/TOC4129g (CLEOPATRA)	III	HER2-positive MBC (first-line treatment)	Placebo + docetaxel + trastuzumab Pertuzumab: 420 mg + docetaxel + trastuzumab	357 ^d 407	Completed

CSR= clinical study report; CRPC= castrate-resistant prostate cancer; HRPC= hormone-refractory prostate cancer; MBC= metastatic breast cancer; NSCLC= non-small cell lung cancer; qwk= weekly; q3wk= every 3 weeks.

^a Pertuzumab given q3wk – the 420 mg dose is given after an initial 840-mg loading dose, trastuzumab given 6 mg/kg q3wk (loading dose 8 mg/kg).

^b “Completed” indicates end of trial (as defined in protocol) has been reached.

^c Japanese studies sponsored by (b) (4)

^d The PK/QTc sub-study, enrolled 37 patients

Source: Table 1 of Summary of Clinical Pharmacology

2.2.2 What is the basis of the dose selection?

The pivotal Phase 3 trial used the fixed (non-weight-based) dosage of 840 mg loading dose followed by a 420 mg maintenance dose every three weeks (840 mg/420 mg Q3W), in combination with trastuzumab and docetaxel. This fixed dosage with a loading dosing strategy was selected based on clinical studies of pertuzumab administered as a single agent or in combination with a range of therapeutic agents in a variety of oncology indications.

In two Phase 1 dose escalation studies (TOC2297 and JO17076), pertuzumab was dosed on a weight-based basis (mg/kg) at doses ranging from 0.5 to 25 mg/kg. A maximum tolerated dose was not achieved during this escalation and a favorable safety profile was observed. The lack of

safety observations in addition to an assessment of the PK characteristics of pertuzumab (long half-life) in relation to the target concentration led to an adoption of a fixed (non-weight-based) dosage for future clinical trials. Two dosages were adopted for further evaluation: 1) 840 mg/420 mg Q3W and 2) 1050 mg Q3W.

The serum pertuzumab concentration of 20 µg/mL was set as a target serum concentration based on the observation that the maximum suppression of tumor growth was achieved at ~5 - 25 µg/mL in xenograft mouse models. A population PK analysis predicted that > 90% of patients receiving the 840 mg /420 mg Q3W regimen would have steady-state trough serum concentrations higher than > 20 µg/mL. Since the target concentrations were achieved by 840 mg /420 mg Q3W regimen, the higher dosage of 1050 mg Q3W was not selected for the pivotal trial.

2.2.3 What are the clinical endpoints used to assess efficacy in the pivotal clinical efficacy study? What is the clinical outcome in terms of efficacy and safety?

The primary efficacy endpoint of the pivotal Phase 3 trial was progression free survival (PFS). PFS was defined as the time from randomization to the first documented radiographical progressive disease, as determined by an independent review facility (IRF) using Evaluation Criteria in Solid Tumors (RECIST), or death from any cause, whichever occurred first.

In the pivotal Phase 3 trial, patients with HER2-positive breast cancer were randomized to receive either pertuzumab plus trastuzumab and docetaxel (n=402) or placebo (n=406) plus trastuzumab and docetaxel. The pertuzumab arm demonstrated a significantly improved PFS (median: 18.5 months) compared to the placebo arm (median: 12.4 months), with a hazard ratio of 0.62 (95% CI: 0.51, 0.75; P<0.0001). Most common adverse reactions (> 50%) in pertuzumab arm were diarrhea, alopecia and neutropenia.

2.2.4 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Serum concentrations of pertuzumab were appropriately measured by ELISA methods to assess PK parameters.

See Section 2.6.

2.2.5 Exposure-response

2.2.5.1 Can exposure-response relationships be established for the efficacy and safety in the pivotal Phase 3 trial?

No. Inadequate PK data from the pivotal Phase 3 trial (20 out of 407 patients receiving pertuzumab) precluded the efforts to establish the exposure-response relationship for PFS.

See Pharmacometrics review (Section 3) by Dr. Kevin Krudys for more information.

2.2.5.2 Does pertuzumab prolong the QT or QTc interval?

IRT-QTc review team concluded that no large changes in mean QTc intervals (i.e., > 20 ms) were detected at the proposed pertuzumab therapeutic dose in the QTc sub-study of pivotal Phase 3 trial (17 patients in the placebo arm, 20 patients in the pertuzumab arm). Although the largest upper bound of the 2-sided 90% CI for the mean difference between pertuzumab arm and

placebo arm was 17.5 ms, the point estimate was 6.0 ms. Due to study design limitations (e.g. lack of positive control, confounding of effects of concomitant treatments on the QT interval, underlying disease in patient population, and slightly higher QTcF baseline in the placebo group compared to that in the pertuzumab treatment group), precise effect of pertuzumab on QT interval can not be estimated. Because of the lack of demonstrated assay sensitivity, the results should be interpreted as having ruled out an effect of about 20 ms.

Please see IRT-QTc review by Dr. Jiang Liu (dated March 20, 2012 in DARRTs) for more information.

2.2.5.3 Is the fixed dosing regimen acceptable? Are there any unresolved dosing or administration issues?

Yes, the fixed dosing, without regard to body weight, is acceptable in breast cancer patients. There are no outstanding unresolved dosing or administration issues from a clinical pharmacology perspective.

Please also see 2.3.2.2 and the pharmacometrics review (Section 3) by Dr. Kevin Krudys.

2.2.5.4 Are the proposed dose modifications in the case of delayed or missed doses acceptable?

Yes, the proposed dose modifications in the case of delayed or missed doses are acceptable.

The applicant proposed to administer the 420 mg dose in patients if the time between two sequential infusions was less than 6 weeks. If the time between two sequential infusions was 6 weeks or more, the initial 840 mg dose should be re-administered. This was the strategy used in the pivotal trial. Simulations showed that for a typical patient, this dosing strategy ensured that trough concentrations were reasonably restored to levels which would have been observed if the patient had not missed a dose.

See the pharmacometrics review (Section 3) by Dr. Kevin Krudys.

2.2.6 Pharmacokinetic characteristics of pertuzumab in humans

2.2.6.1 What are the pharmacokinetic parameters of pertuzumab across studies?

Pertuzumab demonstrated a linear pharmacokinetics in humans in terms of dose proportionality and time-independence at a dose range of 2-25 mg/kg in two Phase 1 dose escalation studies (TOC2297 and JO17076).

Across all seven studies where pertuzumab was administered as a single agent, pertuzumab doses of 2.0 mg/kg and higher showed linear kinetics. In studies where PK parameters were obtained, the estimated mean values for CL, V_{ss} and t_{1/2} ranged from 0.232 - 0.329 L/day, 3.53 - 7.05 L, and 11.1 - 22.3 days, respectively (Table 3). The lowest tested dose level was 0.5 mg/kg, where pertuzumab is cleared at a much faster rate than doses above 2 mg/kg (Figure 1).

Population PK analysis using a two-compartment linear model with first-order elimination from the central compartment described serum pertuzumab PK in the dose range 2.0 to 25.0 mg/kg. The population elimination clearance (CL), the central compartment volume (V_c), and terminal elimination half-life were estimated as 0.235 L/day, 3.11 L, and 18.0 days.

Table 3. Summary of pertuzumab PK parameters (mean ± SD) following IV infusion as a

single-agent or in combination with other therapies in patients with advance tumors

Study	Dose ^a Group (Cycle; No. of PK-Evaluable Patients)	CL (L/day)	V _{ss} (L)	t _{1/2} (days)
Single-agent studies				
<u>Phase I, dose-escalation</u>				
TOC2297g ^{b, c} (advanced solid tumors)	0.5 mg/kg (1; n=3)	0.917±0.385	3.05 ^d ±0.32	2.6±0.9
	2.0 mg/kg (1; n=3)	0.299±0.102	5.56±1.10	14.9±1.1
	5.0 mg/kg (1; n=4)	0.275±0.070	5.78±2.37	17.2±10.3
	10.0 mg/kg (1; n=3)	0.258±0.088	7.05±1.31	22.3±9.9
	15.0 mg/kg (1; n=8)	0.232±0.093	5.37±2.31	18.6±8.8
JO17076 ^c (advanced solid tumors)	5.0 mg/kg (1; n=3)	0.308±0.094	4.89±1.21	11.1±0.5
	10.0 mg/kg (1; n=3)	0.269±0.105	5.31±2.14	14.4±2.7
	15.0 mg/kg (1; n=3)	0.245±0.066	5.35±1.18	16.8±4.0
	20.0 mg/kg (1; n=3)	0.270±0.012	5.56±0.76	15.0±2.6
	25.0 mg/kg (1; n=6)	0.254±0.072	5.42±0.77	16.3±5.9
<u>Phase II</u>				
TOC2689g ^e (ovarian cancer)	420 mg (n=56)	NA	NA	NA
	1050 mg (n=55)	NA	NA	NA
BO16934 (MBC)	420 mg (1; n=38)	0.270±0.113	4.12±1.65	12.2±3.8
	1050 mg (1; n=36)	0.247±0.088	3.53±1.38	11.4±4.1
BO17004 (HRCP, chemo naïve)	420 mg (1; n=35)	0.270±0.078	4.45±1.16	13.7±5.3
	1050 mg (1; n=33)	0.253±0.089	5.23±1.25	19.3±13.0
TOC2682g ^e (CRPC, pretreated with docetaxel)	420 mg (n=40)	NA	NA	NA
TOC2572g ^e (NSCLC)	420 mg (n=43)	NA	NA	NA
Combination therapy studies				
<u>Phase I</u>				
BO17003 (+ capecitabine) (advanced solid tumors)	1050 mg (1; n=18)	0.283±0.098	5.20±1.01	14.6±4.1
BO17021 (+ docetaxel) (advanced solid tumors)	420 mg (1; n=11)	0.329±0.097	5.36 ^f ±1.68	12.1±5.4
	1050 mg (1; n=8)	0.282±0.083	5.21 ^f ±1.39	13.4±4.2
WO20024 (+ erlotinib) (advanced NSCLC)	420 mg (2; n=8)	0.240±0.050	4.90±1.3	17.9±2.2
<u>Phase II, randomized</u>				
TOC3258g ^e (+ gemcitabine) (platinum-resistant ovarian, peritoneal, or fallopian tube cancer)	420 mg (n=21)	NA	NA	NA
<u>Pivotal Phase III, randomized</u>				
WO20698/TOC4129g (CLEOPATRA) ^g (+trastuzumab + docetaxel)	420 mg (n=20)	NA	NA	NA

CL = systemic clearance; CRPC = castration-resistant prostate cancer; HRPC = hormone-resistant prostate cancer; IV = intravenous; MBC = metastatic breast cancer; NA = not analyzed; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; t_{1/2} = terminal half-life; V_c = volume of the central compartment; V_{ss} = steady-state volume of distribution; V_Z = volume of distribution in the terminal phase.

^a Pertuzumab given q3wk – the 420 mg dose is given after an initial 840-mg loading dose.
^b PK parameters estimated by two-compartment model except for the 0.5 mg/kg dose group for which a one-compartment model was used.

^c CL and V_{ss} adjusted due to dosing per kg using median body weight of 70, 80, 78, 96, and 63 kg for dose groups 0.5, 2, 5, 10, and 15 mg/kg, respectively for Study TOC2297g, and using individual body weights in all dose levels for Study JO17076.

^d V_c reported.

^e PK parameters were not calculated for Studies TOC2689g, TOC2682g, TOC2572g, TOC3258g, and WO20698/TOC4129g as only peak and trough samples were collected.

^f V_Z reported.

Source: Table 20 of Summary of Clinical Pharmacology (BLA 125409)

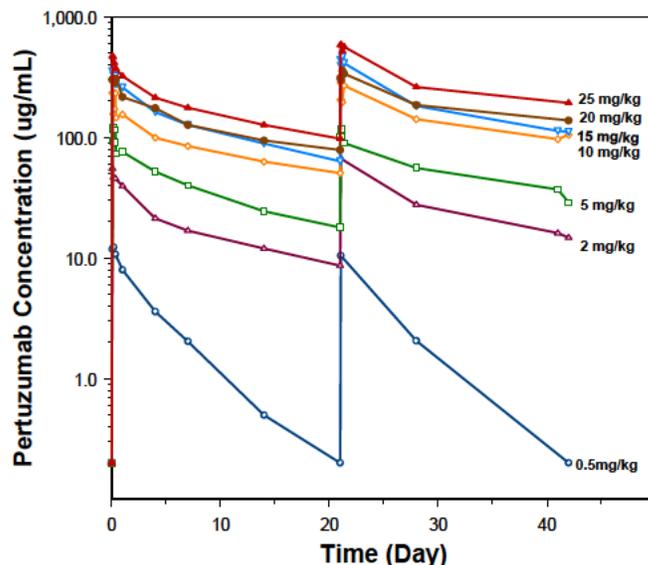


Figure 1: Mean serum pertuzumab concentration time profiles for the first two treatment cycles in Phase 1 dose escalation studies TOC2297g and JO17076.

2.2.6.2 How does the PK of the pertuzumab in healthy volunteers compare to that in patients?

It is unknown whether the PK of pertuzumab in healthy volunteers differs from that in patients, as pertuzumab has only been tested in patients with advanced tumors (breast cancer, non-small cell lung cancer, prostate cancer, ovarian cancer, or other solid tumors). Population PK analysis did not identify the presence of metastatic breast cancer as a significant covariate.

2.2.6.3 Based on PK parameters, what is the degree of linearity or non-linearity based on the dose-concentration relationship?

Pertuzumab demonstrated a linear PK at a dose range of 2.0-25.0 mg/kg in terms of dose proportionality and time-independence after multiple doses. However, at the 0.5 mg/kg dose, pertuzumab was cleared at a faster rate than that at doses above 2 mg/kg dose.

See Section 2.2.6.1.

Dose proportionality following the first dose of pertuzumab

Using C_{max} and $AUC_{Day0-21}$ in the first treatment cycle in Phase 1 dose escalation trials TOC2297g and JO17076, a power model was applied to test the dose proportionality. The slope of the power model on logarithmic scale was 0.89 for C_{max} with a 90% confidence interval of (0.80, 0.98), and was 0.97 for $AUC_{Day0-21}$ with a 90% confidence interval of (0.86, 1.07). Therefore, the systemic exposure of pertuzumab increases with dose in a proportional manner

over a dose range from 2 mg/kg to 25 mg/kg. The dose level of 0.5 mg/kg was not included in the analyses due to obvious nonlinearity.

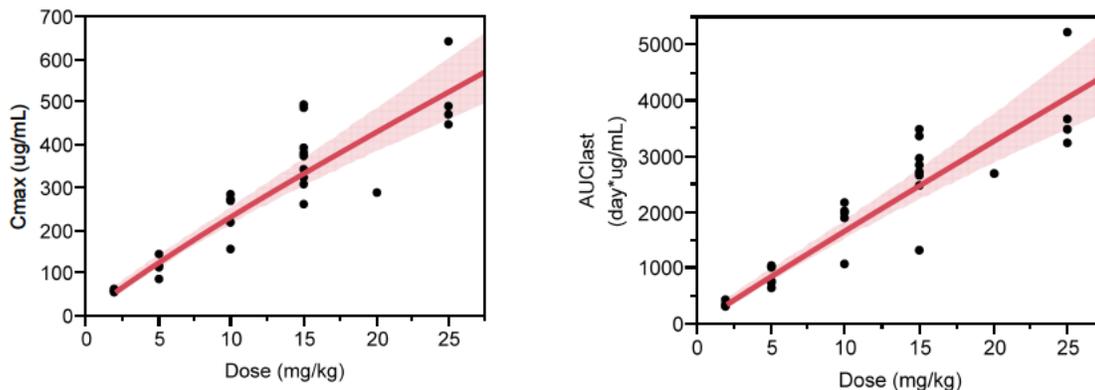


Figure 2: Pertuzumab C_{max} (left) and $AUC_{last, Day0-21}$ (right) in the first treatment cycle (Day 0 -21) increased with doses with a slope of 0.89 (0.80, 0.98) for C_{max} and 0.97 (0.86, 1.07) for $AUC_{last, Day0-21}$ from 2 mg/kg to 25 mg/kg single dose of pertuzumab. The shaded area is the 90% confidence interval of the slope. The dots represents the observed C_{max} or calculated $AUC_{last, Day0-21}$ from 27 patients in Phase 1 dose escalation trials TOC2297g and JO17076.

Steady-state following multiple doses

Trough serum pertuzumab concentrations appeared to plateau more rapidly for the 840 mg/420 mg Q3W dosage, as compared to the 1050 mg dosage (Figure 3). With the loading dose, the approximate steady-state concentration was reached following the first maintenance dose of the 840 mg/420 mg dosage, whereas it was reached after about 4 doses of the 1050 Q3W dosage.

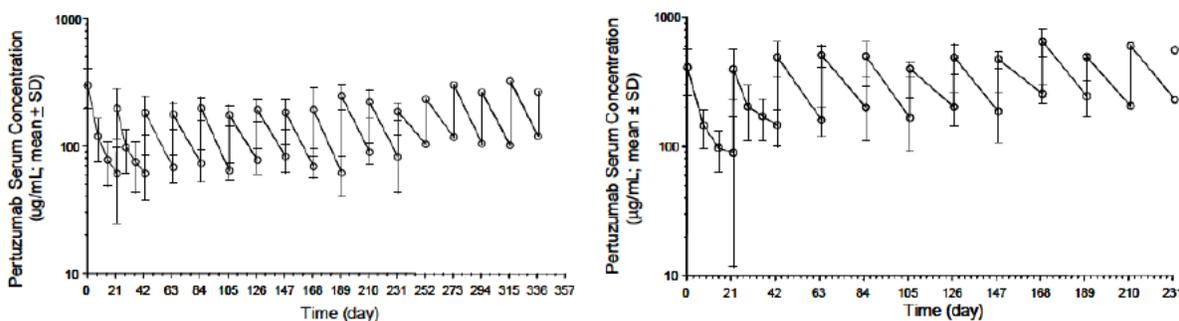


Figure 3: Pertuzumab serum concentrations following IV Infusion of 420 mg after a loading dose of 840 mg (left) in 40 patients with metastatic breast cancer or following IV Infusion of 1050 mg in 37 patients with metastatic breast cancer (right) every three weeks (Study 16934). Serum samples were taken at baseline, before and within 15 min of the end of pertuzumab infusion for all cycles, and once on days 8 and 15 for Cycles 1 and 2.

2.2.6.4 What is the inter- and intra-subject variability of PK parameters in patients, and what are the major causes of variability?

Moderate variability in pertuzumab PK parameters in patients with advanced solid tumors was estimated in the population PK analysis. Inter-individual variability (expressed as CV%) in CL

and V_c were 34.9% and 18.7%, respectively. The median distribution and terminal elimination half-lives were 1.6 days (95% range: 1.1-2.4 days) and 18 days (95% range: 9.6-30 days) respectively.

Population PK analysis identified serum albumin concentration and lean body weight as significant covariates on pertuzumab PK parameters. CL decreased in patients with higher albumin concentrations and increased in patients with greater lean body weight. After inclusion of albumin and lean body weight in the final model, the inter-individual variance in CL decreased from 39.9% to 34.9%. Inclusion of lean body weight in the final model decreased the inter-individual variability of V_c from 23.3% to 18.7% and in V_p from 51.2% to 48.3%.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

No formal studies have been conducted to assess the effect of age, gender, race, body weight, height, body surface area (BSA), disease, genetic polymorphism, pregnancy, renal or hepatic dysfunction on pertuzumab PK.

Population PK analysis evaluates the impact of age, gender, race, lean body weight, performance status, presence/absence of MBC, number of metastatic sites, liver metastases, and concomitant chemotherapy, as well as baseline serum concentrations of total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, creatinine, and albumin, on the PK of pertuzumab. Lean body weight and serum albumin concentration have a statistically significant effect on pertuzumab PK. CL decreases in patients with higher albumin concentrations and increases in patients with greater lean body weight.

Although albumin and lean body weight are statistically significant covariates, the magnitude of their effects on pertuzumab exposure (AUC and C_{max}) was marginal compared to the inter-individual variability of the population.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosing regimen adjustments, if any, are recommended for each of these groups? If dosing regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Based on the clinical pharmacology data, no dose adjustments are recommended for specific patient populations.

2.3.2.1 Pediatric patients

Safety and effectiveness of pertuzumab have not been established in pediatric patients. Breast cancer is rare in children.

2.3.2.2 Body size

Higher lean body weight may be related with increased pertuzumab clearance and subsequent

lower systemic exposure. Bayes post-hoc PK parameters were simulated for a loading dose of 840 mg followed by 420 mg every three weeks. Median $C_{\min,ss}$ was 58.4 $\mu\text{g/mL}$ in the lightest 25% of the patients compared to 40.8 $\mu\text{g/mL}$ in the heaviest 25% of the patients (Figure 4). Furthermore, the effect of the baseline body weight on the PFS was explored. The PFS was stratified by four body weight quartiles for patients receiving pertuzumab in the pivotal trial. The results do not show a trend between body weight and PFS. Therefore, there is no evidence to suggest that heavier patients had substantially worse outcomes. See Pharmacometrics review (Section 3) by Dr. Kevin Krudys for more information.

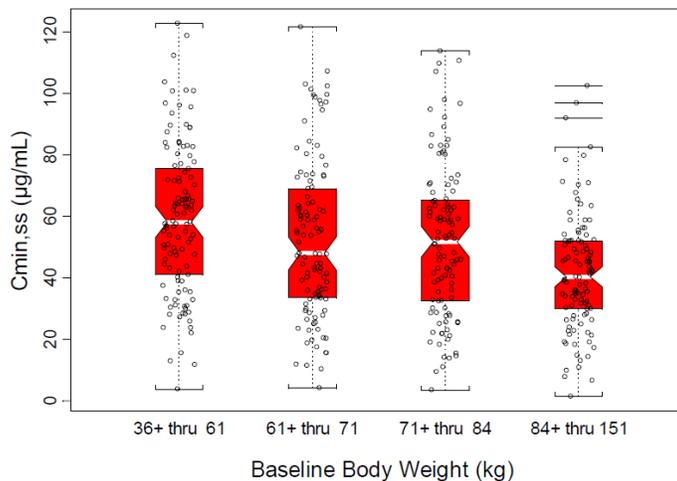


Figure 4: Baseline body weight and trough concentrations of pertuzumab at steady state for a loading dose of 840 mg followed by 420 mg every 3 weeks.

2.3.2.3 Sex

Sex was not identified as a significant covariate in population pharmacokinetic analysis with data from 300 females and 181 males.

2.3.2.4 Elderly

Age was not identified as a significant covariate in population pharmacokinetic analysis. No significant difference was observed in the pharmacokinetics of pertuzumab between patients < 65 years ($n=306$) and patients ≥ 65 years ($n=175$). Of 402 patients with previously untreated MBC who received pertuzumab in the pivotal trial, 60 patients (15%) were ≥ 65 years of age and 5 patients (1%) were ≥ 75 years of age. No overall differences in efficacy and safety of pertuzumab were observed between these patients and younger patients.

2.3.2.5 Hepatic impairment

No formal hepatic impairment trials have been conducted. Population PK analysis did not select serum concentrations of transaminases as significant covariates influencing pertuzumab PK. Hepatic impairment is unlikely to be a major factor to impact the PK of pertuzumab as IgG is catabolized by ubiquitous proteolytic enzymes.

2.3.2.6 Renal impairment

Dose adjustments are not needed in patients with various degrees of renal impairment.

No formal trial has been conducted in patients with renal impairment. Renal function, measured as creatinine clearance (CrCL), was not a significant predictor of pertuzumab exposure in the population pharmacokinetic analysis. Although there were only 3 patients in the dataset with severe renal impairment (CrCL < 30 mL/min), a trend between CrCL and pertuzumab exposure was not observed over the range of observed CrCL (27 to 244 mL/min). Therefore, patients with severe renal impairment are unlikely to have increased pertuzumab exposure relative to patients with normal renal function, which is consistent with the current knowledge that intact IgG is not cleared through the kidneys.

Also see the Pharmacometrics review (Section 3) by Dr. Kevin Krudys.

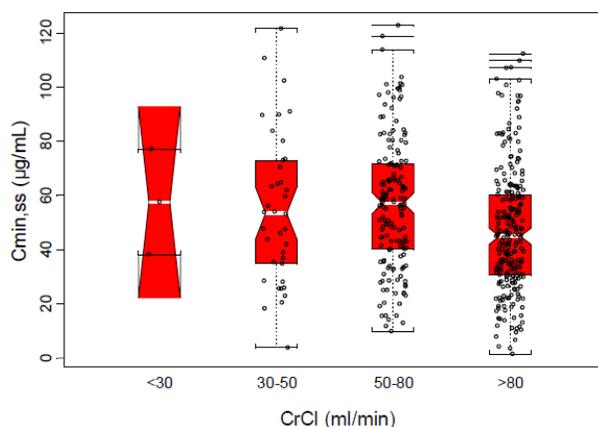


Figure 5: The box-plot of simulated steady-state trough concentrations for a loading dose of 840 mg followed by 420 mg every three weeks using Bayes posthoc PK parameters versus renal function groups. Based on each patient's baseline creatinine clearance (CrCL), renal function was grouped as normal renal function (CLcr > 80 mL/min, N=241), mild (50 mL/min < creatinine clearance (CLcr) ≤ 80 mL/min, N=158), moderate (30 mL/min ≤ CLcr < 50 mL/min, N=38), and severe (CLcr < 30 mL/min, N=3) renal impairment. Points are individual values and box plots show the median, 25th and 75th percentiles.

2.3.2.7 Race/Ethnicity

Race/ethnicity was not identified as a significant covariate in population pharmacokinetic analysis.

Racial difference in febrile neutropenia incidence

In the pivotal Phase 3 trial, febrile neutropenia (≥ grade 3) was 14% in pertuzumab (plus trastuzumab and docetaxel) arm versus 8% in placebo (plus trastuzumab and docetaxel) arm. The incidence of ≥ grade 3 febrile neutropenia was 26% in Asians in pertuzumab arm and 12% in Asians in placebo arm. The incidence of ≥ grade 3 febrile neutropenia was 8.2% in Non-Asians in pertuzumab arm and 5.7% in non-Asians in placebo arm. Overall, despite making up only 32% of the trial population, Asian patients accounted for 56% of the cases of febrile neutropenia.

No underlying mechanisms can be identified at this time for the difference in febrile neutropenia between two treatment arms, as well as between Asian and non-Asians, because:

- As no patients experienced febrile neutropenia in the pertuzumab plus trastuzumab arm in the Phase 2 trial 20697 (n=108), febrile neutropenia in the Phase 3 pivotal trial appeared to be caused by docetaxel.
- Docetaxel dose intensity was similar in the two arms (median docetaxel dose of 24.8 mg/m² per week in patients receiving placebo versus 24.6 mg/m² per week in patients receiving pertuzumab). A higher proportion of patients in the placebo arm received 100 mg/m² docetaxel at any cycle compared with patients in the pertuzumab arm (15.4% versus 11.8%, respectively).
- The PK profiles and geometric means of docetaxel AUC and C_{max} with and without pertuzumab in the presence of trastuzumab suggested that the co-administration of pertuzumab (in the presence of trastuzumab) has no significant impact on docetaxel PK (Section 2.4.2.5)
- Subjects enrolled in Asia are balanced in two arms (128 in placebo arm and 125 in pertuzumab arm).
- Among a total of 808 subjects in the pivotal trial, 6 out of 261 Asian patients (5 in the placebo arms), compared to 103 out of 547 non-Asian patients, received 100 mg/m² docetaxel.
- The docetaxel label states that "Mean total body clearance for Japanese patients dosed at the range of 10-90 mg/m² was similar to that of European/American populations dosed at 100 mg/m², suggesting no significant difference in the elimination of docetaxel in the two populations."

Of note, febrile neutropenia has been previously associated with docetaxel exposure (docetaxel label), and polymorphisms in CYP3A5 and ABCB1 as well as in glutathione-S-transferase (GST) have been associated with docetaxel exposure and safety profile (PMID: 16765145). However, a potential underlying pharmacogenetic association with febrile neutropenia was not explored by the applicant.

Also see Genomics review (Section 4) by Dr. Christian Grimstein.

2.3.2.8 Immunogenicity

The immunogenicity pertuzumab was evaluated during the drug development.

2.3.2.8.1 How was the immunogenicity of pertuzumab evaluated?

The serum samples were collected at baseline, and every 9 weeks at the time of tumor assessment, and at the treatment discontinuation. At least one post-dose serum samples for ATA analysis were available for 366 patients (out of 628 patients) in all Phase 1 /2 trials, 372 (out of 397 patients) in the placebo arm and 386 (out of 407 patients) in the pertuzumab arm in the pivotal Phase 3 trials.

A "tiered strategy" was used for ATA sample analysis. Serum samples were first screened in a bridging enzyme-linked immunosorbent assay (ELISA) assay. Samples that screened positive

were further analyzed by competitive binding with pertuzumab to confirm the positivity. Samples that were confirmed positive were then diluted further to obtain a value in titer units.

A conservative approach was taken for calculating the incidence of ATA so that any patient confirmed to have an ATA positive sample after dosing was considered positive for ATA, regardless of baseline status.

See 2.6.2 for more information on ATA bioassays.

2.3.2.8.2 What is the ATA incidence of pertuzumab?

In the phase 3 trial WO20698/TOC4129g, the ATA incidence to pertuzumab is 6.2% in the placebo arm compared to 2.8% in the pertuzumab treatment arm (Table 4). In the Phase I/II studies, two of the 366 pertuzumab treated patients (0.5%) were tested positive for ATA to pertuzumab.

Table 4. Patients with positive ATA in the Phase 3 trial WO20698/TOC4129g

Results of ATA testing	No of Patients (Pla+T+D arm)	No. of Patients (Ptz+T+D arm)
Post-baseline samples available	372	386
Positive at baseline (regardless of post-baseline result)	7	5
Positive at baseline, negative post-baseline	1	4
Positive at baseline, positive post-baseline	6	1
Negative at baseline, positive post-baseline	15	10
Baseline unknown, positive post-baseline	2	0
Total positive post-baseline ¹	23	11

Note: Any patient confirmed to have an ATA positive sample after dosing was considered positive for ATA, regardless of baseline status.

Source: Table 73 in the CSR of Phase 3 Trial W020698/TOC4129g

2.3.2.8.3 What are possible reasons for positive ATAs to pertuzumab in placebo arm?

Possible reasons for the false positive ATA incidence include:

1. Antibodies against the framework of trastuzumab in the pertuzumab antibody ELISA assay: Trastuzumab and pertuzumab share the same human IgG1(κ) framework structure, differing only in the complementarity determining region (CDR). Though specific for CDR region of pertuzumab, the ELISA assay can detect ATAs directed against epitopes contained within pertuzumab that are shared with trastuzumab in the common framework regions.
2. HER2 extracellular domain (ECD) cross-reactivity: Using recombinant HER2 ECD, validation data demonstrated that cross-reactivity was observed at ≥ 100 ng/mL, but not at ≤ 10 ng/mL of recombinant HER2 ECD. Herceptin label states that “Sixty-four percent (286/447) of women with metastatic breast cancer had detectable circulating extracellular domain of the HER2 receptor (shed antigen), which ranged as high as 1880 ng/mL (median 11 ng/mL).

2.3.2.8.4 Is the positive ATA incidence related to the inferior progression free survival (PFS) and objective response rate (ORR)?

ATA-positive patients within both study arms appeared to be associated with shorter PFS and lower ORR (Table 5). However, the improvement in PFS and ORR seen with pertuzumab treatment seemed to be preserved within both ATA-positive and ATA-negative subgroups.

Table 5. Summary of efficacy by ATA status in the Phase 3 trial WO20698/TOC4129g

	Pla+T+D arm		Ptz+T+D arm	
	ATA -ve	ATA +ve	ATA -ve	ATA +ve
n	349	23	375	11
IRF-PFS (median in months)	12.5	6.3	18.7	12.5
95% CI	[10; 14]	[4; 17]	[16; 25]	[2; 14]
ORR	73.2%	45.0%	81.7%	45.5%
95% CI	[67.7; 78.1]	[23.1; 68.5]	[77.1; 85.7]	[16.7; 76.6]

ORR = Objective response rate; IRF-PFS = progression-free survival according to IRF

Source: Table 76 in the CSR of Phase 3 Trial W020698/TOC4129g

2.3.2.8.5 Is the positive ATA incidence related to safety?

Positive ATA did not appear to be related to safety in the pivotal Phase 3 trial. Among ATA-positive patients in the pertuzumab arm in the pivotal Phase 3 trial, treatment discontinuation occurred in only one patient (who experienced a Grade 4 anaphylactic reaction on Day 2 in association with trastuzumab and docetaxel and before the development of detectable ATA).

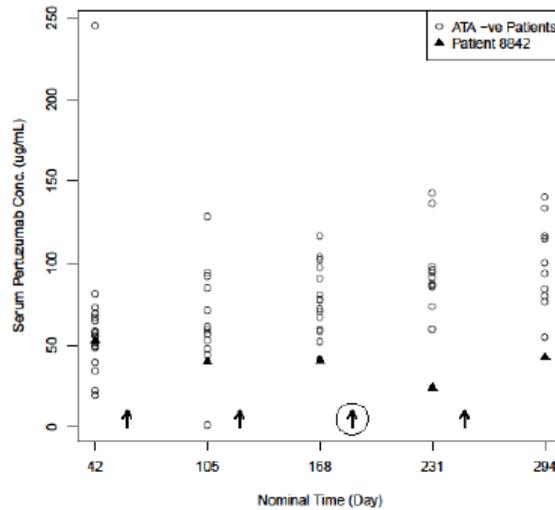
However, both of two patients tested as ATA-positive in Phase 1/2 trials experienced hypersensitivity reactions. In study TOC2572g with single-agent pertuzumab, one patient (3164) had an early termination sample (early termination due to a serious adverse event) that was determined to have a positive ATA result.

2.3.2.8.6 Does ATA incidence affect the PK of pertuzumab or trastuzumab?

Conclusion can not be drawn at this time due to inadequate data.

Only four ATA-positive patients were included in the PK sub-study, and among them, only one patient (164992/8842) was in the pertuzumab arm, who had positive ATA on only one occasion (Study Day 192, Cycle 9). This patient had slightly lower trough concentrations compared with the mean trough concentration for ATA-negative patients throughout treatment (Table 6).

Table 6. Impact of ATA on pertuzumab trough concentrations in study



Arrows represent ATA sampling time points. Circled arrow represents ATA +ve sample for Patient 8842. Patient 9961 excluded: patient received 6 mg/kg trastuzumab IV on Day 1 of Cycle 1, instead of 8 mg/kg trastuzumab IV. Patient 6451 data excluded postdose Cycle 6: patient received 840 mg pertuzumab IV instead of the scheduled 420 mg pertuzumab IV in Cycle 6.

Source: Table 26 in the Summary of Clinical Pharmacology of BLA125409 (Section 2.7.2)

In addition, PK data were available for one of two patients tested as ATA-positive in Phase 1/2 trials. Trough concentration for ATA-positive patient in study TOC2572g showed a pertuzumab concentration of 2.71 $\mu\text{g/mL}$, compared to a mean concentration of 45.8 $\mu\text{g/mL}$ for all samples taken at that time point. No PK samples were collected for the second ATA-positive patients in trial BO17931 where pertuzumab was administered with chemotherapy.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

No significant drug interactions were observed between pertuzumab and docetaxel (in the presence of trastuzumab) or between pertuzumab and trastuzumab (in the presence of docetaxel). Furthermore, no significant drug interactions were observed when pertuzumab was administered in combination with other small molecule chemotherapeutic agents (gemcitabine, capecitabine, erlotinib, or docetaxel).

None of the other extrinsic factors including herbal products, diet, smoking, and alcohol use were studied for their influence on pertuzumab exposure and/or response.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in-vivo* drug-drug interactions?

No.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Unlikely.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Unlikely.

2.4.2.4 Are there metabolic/transporter pathways that may be important?

Unlikely. Metabolism studies are not generally performed for biological protein products. As proteins are degraded into amino acids that are subsequently recycled into other proteins, the classical biotransformation studies for small molecule drugs are not applicable.

2.4.2.5 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Yes. The label specifies that pertuzumab should be administered in combination with trastuzumab and docetaxel. In a PK sub-study of the pivotal Phase 3 trial, no significant drug interactions were observed between pertuzumab and docetaxel (in the presence of trastuzumab) or between pertuzumab and trastuzumab (in the presence of docetaxel).

Blood samples for PK evaluations of pertuzumab were drawn within 15 minutes before the infusion and at the end of infusion on Day 1 of Cycles 1, 3, 6, 9, 12, 15, 18, and at the treatment discontinuation. Blood samples for PK evaluations of trastuzumab were drawn pre- and post-trastuzumab infusion at Cycles 1 and 3. Blood samples for docetaxel PK were drawn within 15 min before the infusion and up to 24 hours following docetaxel infusion at Cycle 1. Of 40 patients enrolled, PK data were available for pertuzumab, trastuzumab, and docetaxel in 20, 37, and 37 patients, respectively.

Pertuzumab PK

No significant pertuzumab PK changes were observed when pertuzumab was combined with trastuzumab and docetaxel. No significant deviation in the observed serum pertuzumab concentrations in the PK sub-study was noticed when compared to the population PK model predicted concentrations (Figure 6). Of note, population PK analysis did not identify any of the concomitant chemotherapies as a significant covariate.

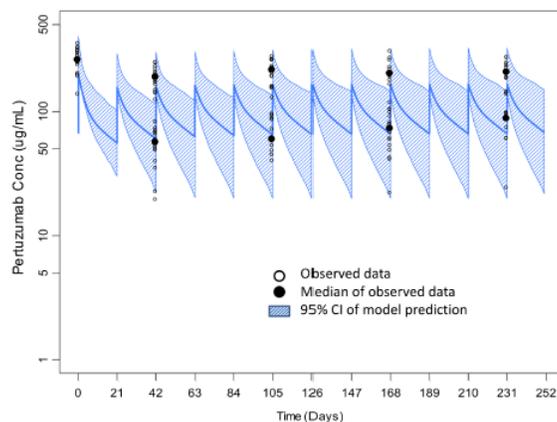


Figure 6: Observed and population PK predicted serum concentrations of pertuzumab. The observed serum concentrations of pertuzumab were obtained from 20 patients in a PK sub-study of the Phase 3 trial WO20698/TOC4129g. The population PK model was based on PK data of 12 clinical studies.

Trastuzumab PK

The observed C_{max} (in Cycles 1 and 3) and C_{min} (at pre-dose of Cycle 3) suggested that the co-administration of pertuzumab (in the presence of docetaxel) has no significant impact on trastuzumab PK. Of note, the large 90% confidence interval of geometric mean ratios for the C_{max} and C_{min} values were probably due to large PK variability and small sample sizes.

Table 7. Comparisons of trastuzumab pharmacokinetics between pertuzumab arm and placebo arm

Parameters	Cycle	Geometric LSmeans		Ratio of Geometric LSmeans x100 (90% CI) Pertuzumab + Trastuzumab + Docetaxel arm/ Placebo + Trastuzumab + Docetaxel arm
		Pertuzumab + Trastuzumab + Docetaxel (µg/mL)	Placebo + Trastuzumab + Docetaxel (µg/mL)	
C_{max}	1	174	193	90.29 (78.15-104.33)
C_{min}^b	3	21.0	21.9	95.94 (70.72-130.13)
C_{max}	3	119	147	81.02 (62.68-104.71)

Note: ^b C_{min} is the serum trastuzumab concentration at the pre-dose of Cycle 3.

N=17 and 18 in Cycles 1 and 3, respectively, in pertuzumab arm; N=15 for both Cycles 1 and 3 in placebo arm

Source: Table 19 and 22 in the Summary of Clinical Pharmacology of BLA125409 (Section 2.7.2)

Docetaxel PK

The PK profiles and geometric means of docetaxel AUC and C_{max} with and without pertuzumab in the presence of trastuzumab suggested that the co-administration of pertuzumab (in the presence of trastuzumab) has no significant impact on docetaxel PK.

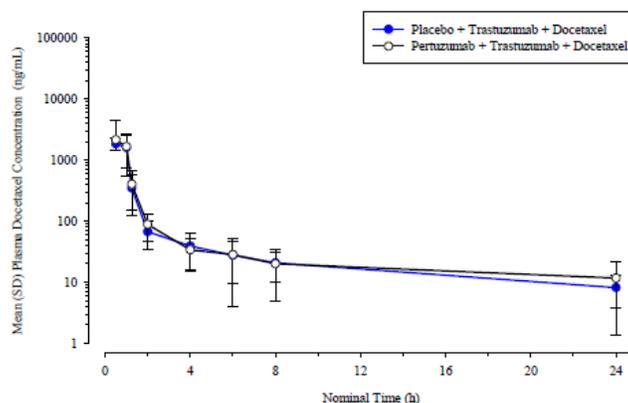


Figure 7: Mean (\pm SD) plasma concentration-time profiles of docetaxel (in the presence of trastuzumab) – with either placebo (N=18) or pertuzumab (N=14) in Cycle 1 of the PK sub-study in Phase 3 trial WO20698/TOC4129g.

Table 8. Comparisons of docetaxel pharmacokinetics between pertuzumab + trastuzumab + docetaxel arm (N=14) and placebo + trastuzumab + docetaxel arm (N=18)

Parameters	Geometric LSmeans		Ratio of Geometric LSmeans x 100 (90% CI)
	Pertuzumab + Trastuzumab + Docetaxel	Placebo + Trastuzumab + Docetaxel	Pertuzumab + Trastuzumab + Docetaxel arm/ Placebo + Trastuzumab + Docetaxel arm
AUC _{0-t}	2190	2088	104.90 (73.90 – 148.90)
AUC _{0-∞}	2660	2622	101.42 (75.66 – 135.96)
C _{max}	1881	2034	92.50 (65.22 – 131.18)

Note: The units for AUC and C_{max} are ng*h/mL and ng/mL, respectively.

Source: Table 23 and 24 in the Summary of clinical pharmacology

2.4.2.6 What is the drug-drug interaction potential between pertuzumab and other chemotherapies?

No significant drug-drug interactions were observed when pertuzumab was administered in combination with other small molecule chemotherapeutic agents (capecitabine, erlotinib, docetaxel, or gemcitabine).

Though no dedicated drug-drug interaction studies have been conducted, the drug-drug potential between pertuzumab and chemotherapies were evaluated by comparing the PK parameters in combination trials to those in pertuzumab single-agent trials. When PK parameters of pertuzumab in trials BO17003 (pertuzumab + capecitabine), BO17021 (pertuzumab + docetaxel), WO20024 (pertuzumab + erlotinib) were compared to those in single-agent trials BO16934 and BO17004 (Table 9), no significant impact of the co-administration of capecitabine, docetaxel, or erlotinib on the PK parameters of pertuzumab were observed. Similarly, when C_{max} and C_{min} concentrations of pertuzumab in cycle 1 and cycle 3 in trials TOC3258g (pertuzumab + gemcitabine) were compared to those in single-agent trials

Table 1), no significant impact of the gemcitabine co-administration on the pertuzumab PK was observed.

Table 9. Comparison of the pharmacokinetics of pertuzumab when used as single agent and used in combination with capecitabine, docetaxel, and erlotinib

Study	Drug	T _{1/2} (day)	C _{max} (ug/mL)	AUC _{last} (ug-day/mL)	AUC _∞ (ug-day/mL)	CL (mL/day)	V _{ss} (mL)
Study BO16934	Pertuzumab 1050 mg (n=36*)	11.4 (36)	409 (39)	3465 (30)	4750 (32)	247 (36)	3527 (39)
Study BO17004	Pertuzumab 1050 mg (n=35)	19.3 (69)	294 (24)	2626 (28)	5097 (71)	253 (35)	5227 (24)
Study BO17003	Pertuzumab 1050 mg + Capecitabine (n=18)	14.6 (28)	355 (19)	2740 (27)	4010 (32)	283 (35)	5202 (19)
Study BO17021	Pertuzumab 1050 mg + Docetaxel (n=8)	13.4 (31)	301 (31)	2390 (24)	3951 (23)	282 (29)	5214 (27)
Study WO20024	Pertuzumab 420 mg** + Erlotinib (n=8)	17.9 (12)	231 (24)	1780 (19)	3000 (27)	240 (21)	4900 (27)

Note: * n=37 for C_{max} and AUC_{last}

** Pertuzumab cycle two after 840 mg loading dose in cycle 1

Source: Adapted from Tables 6, 7, 10, 12 and 14 in the Summary of Clinical Pharmacology

Table 10. Comparison of pertuzumab pharmacokinetics when pertuzumab is used as single agent in studies TOC2682g and TOC2572g, and used in combination with gemcitabine in study TOC3258g.

Cycle	Sampling Event	Study TOC2682g		Study TOC2572g		Study TOC3258g	
		N	Pertuzumab Conc (ug/mL)	N	Pertuzumab Conc (ug/mL)	N	Pertuzumab Conc (ug/mL)
1	Day 1: pre-dose	40	LTR	37	LTR	21	LTR
1	Day 1: post-dose	38	255 ± 46.9	37	265 ± 69.9	16	306 ± 88.0
2	Day 22: pre-dose	33	52.4 ± 15.2	31	45.8 ± 17.9	16	57.1 ± 18.9
2	Day 22: post-dose	31	176 ± 34.7	24	156 ± 52.6	15	188 ± 56.1
3	Day 43: pre-dose	26	53.1 ± 19.5	22	38.0 ± 15.0	17	54.4 ± 16.4
3	Day 43: post-dose	23	176 ± 32.4	10	174 ± 30.8	16	192 ± 27.7

LTR = less than reportable; MQC = minimum quantifiable concentration.

Note: LTR ≤ MQC (0.25–0.40 mg/mL of serum pertuzumab).

Pertuzumab was administered with 840 mg loading dose in cycle 1 and followed by 420 mg every three weeks

Source: Table 18 in Summary of Clinical Pharmacology

On the other side, the impact of pertuzumab on the PK of co-administered capecitabine, docetaxel, erlotinib, and gemcitabine were evaluated (Table 11, Table 12, Table 13, and Table 14, respectively) by comparing the PK parameter of these drugs with and without pertuzumab. No significant impact of the co-administration of pertuzumab on the PK of these co-administered drugs.

Capecitabine PK

Table 11. Study BO17003: Mean pharmacokinetic parameters of capecitabine given alone (on pre-cycle Day -7) and in combination with pertuzumab (Day 1 of the same cycle)

Capecitabine Dose mg/m ²	Analyte	Day -7 Capecitabine Alone				Day 1 Capecitabine + Pertuzumab			
		t _{1/2} (h)	t _{max} (h)	C _{max} (ng/mL)	AUC (ng.h/mL)	t _{1/2} (h)	t _{max} (h)	C _{max} (ng/mL)	AUC (ng.h/mL)
825 N=5	5'-DFCR	0.89	1.3	4508	7446	0.78	0.9	4909	7739
	5'-DFUR	0.75	1.3	5274	8568	0.62	1	5736	9672
	5-FU	0.67	1.3	201	306	0.73	0.9	219	321
	Capecitabine	0.54	1.2	4802	5813	0.42	0.7	8060	6400
	FBAL	2.54	2.4	3214	16872	2.59	2.6	3674	17440
1000 N=6	5'-DFCR	0.82	0.84	7687	12096	0.76	1.42	3917	9987
	5'-DFUR	0.76	1.09	7657	11309	0.73	2	4103	8805
	5-FU	0.64	1.09	355	575	0.67	1.84	187	397
	Capecitabine	0.4	0.76	9112	9083	0.62	1.17	3367	5144
	FBAL	2.69	2.16	3963	18588	2.58	3.16	3498	18374
1250 N=7	5'-DFCR	0.82	1.05	8647	12792	0.75	1.86	6569	11097
	5'-DFUR	0.66	1.05	10311	15263	0.79	1.86	8683	13888
	5-FU	0.7	1.05	369	567	0.8	1.93	345	502
	Capecitabine	0.36	0.77	7543	7397	0.54	1.15	4731	6252
	FBAL	3.08	2.21	5290	28637	2.81	2.5	5136	27739

Source: Table 11 in Summary of Clinical Pharmacology

Docetaxel PK

Table 12. Study BO17021: Summary of pharmacokinetic parameters for docetaxel alone and in combination with pertuzumab

Dose Group	Cycle		t _{1/2} (h)	t _{max} (h)	C _{max} (ng/mL)	AUC _{0-∞} (ng.h/mL)	V _{ss} (mL/m ²)	CL (mL/h/m ²)
Docetaxel 60 mg/m ² alone	1	N	6	6	6	6	6	6
		Mean	16.9	0.63	1642	1838	786981	33128
	2	SD	5.22	0.21	274	244	218139	4396
		Min	7.31	0.50	1250	1523	415471	27592
		Median	17.7	0.50	1710	1814	808655	33177
		Max	22.7	0.90	1960	2175	999994	39407
		CV%	31.0	32.6	16.7	13.3	27.7	13.3
		GeoMean	15.9	0.61	1622	1825	756383	32885
Docetaxel 60 mg/m ² + Pertuzumab 1050 mg	2	N	6	6	6	6	6	6
		Mean	19.7	0.89	1695	1734	1023569	35813
	1	SD	4.65	0.24	331	409	335711	6216
		Min	12.5	0.50	1320	1512	644842	23415
		Median	19.7	0.90	1630	1580	1068651	37997
		Max	27.1	1.25	2270	2562	1544809	39686
		CV%	23.6	26.6	19.5	23.6	32.8	17.4
		GeoMean	19.2	0.86	1670	1702	977134	35261
Docetaxel 75 mg/m ² alone	1	N	6	6	6	6	6	6
		Mean	12.7	0.57	3128	3744	410174	22013
	2	SD	3.46	0.16	859	1304	184216	7031
		Min	9.56	0.50	2210	2386	178928	12970
		Median	12.0	0.50	3030	3386	409216	22412
		Max	19.4	0.90	4580	5783	697069	31433
		CV%	27.3	28.8	27.5	34.8	44.9	31.9
		GeoMean	12.3	0.55	3036	3567	374188	21027
Docetaxel 75 mg/m ² + Pertuzumab 420 mg	2	N	6	6	6	6	6	6
		Mean	15.2	0.83	2722	3496	566759	23747
	1	SD	5.11	0.16	912	1211	361946	8175
		Min	9.62	0.50	1480	2178	203630	14668
		Median	13.8	0.90	2895	3312	451340	22643
		Max	23.8	0.90	3830	5113	1107162	34440
		CV%	33.5	19.6	33.5	34.6	63.9	34.4
		GeoMean	14.6	0.82	2579	3323	475096	22572
Docetaxel 100 mg/m ² alone	1	N	5	5	5	5	5	5
		Mean	9.59	0.90	5450	5930	254233	18913
	2	SD	2.34	0.00	1867	2137	85054	7245
		Min	7.49	0.90	3160	3522	157907	11957
		Median	8.92	0.90	5900	6003	306743	16658
		Max	13.5	0.90	7740	8364	325552	28389
		CV%	24.4	0.00	34.3	36.0	33.5	38.3
		GeoMean	9.39	0.90	5175	5606	241518	17838
Docetaxel 100 mg/m ² + Pertuzumab 420 mg	2	N	4	4	4	4	4	4
		Mean	12.8	0.70	4705	5218	428863	22976
	1	SD	6.13	0.23	1871	2216	283977	12679
		Min	8.04	0.50	2210	2409	163614	12782
		Median	11.8	0.70	5020	5320	395572	18809
		Max	21.4	0.90	6570	7823	760696	41503
		CV%	48.0	33.0	39.8	42.5	66.2	55.2
		GeoMean	11.8	0.67	4360	4805	354475	20811

Source: Table 13 in Summary of Clinical Pharmacology

Erlotinib PK

Table 13. Study BO17021: Summary of pharmacokinetic parameters for docetaxel alone and in combination with pertuzumab

Analyte	Patient ID/ Statistic	C _{max} (ng/mL)	t _{max} (h)	t _{1/2} (h)	AUC ₀₋₂₄ (h.ng/mL)	V _{ss} (mL)	CL _{ss} (ml/h)
Erlotinib 100mg alone Cycle 1 Day -1	N	6	6	6	6	6	6
	Mean	1460	2.77	24.5	23400	159000	4380
	SD	361	1.76	11.9	3800	97500	759
	Min	1020	1.50	12.2	18500	78800	3600
	Median	1410	2.25	23.0	24500	133000	4090
	Max	2070	6.00	43.7	27700	341000	5410
CV%	24.8	63.5	48.4	16.3	61.4	17.3	
Erlotinib 100mg With Pertuzumab Cycle 2	N	5	5	3	3	3	3
	Mean	1200	3.32	53.3	19100	346000	4460
	SD	398	1.67	34.0	7700	243000	539
	Min	694	1.52	18.2	10800	122000	3850
	Median	1150	3.00	55.9	20500	311000	4650
	Max	1800	6.08	85.9	26000	605000	4880
CV%	33.2	50.3	63.7	40.4	70.4	12.1	
Erlotinib 150mg alone Cycle 1 Day -1	N	9	9	6	6	6	6
	Mean	2300	4.89	97.8	37900	731000	4010
	SD	886	7.34	113	18300	983000	2620
	Min	1090	0.500	10.6	19600	41000	0.00
	Median	2250	3.00	37.6	35000	221000	3230
	Max	3770	24.0	255	66900	2540000	7670
CV%	38.7	150.0	115.9	48.1	134.5	65.5	
Erlotinib 150mg With Pertuzumab Cycle 2	N	4	4	1	2	1	2
	Mean	2940	4.63	17.2	54000	64500	2790
	SD	324	3.74	-	5210	-	270
	Min	2730	0.00	17.2	50300	64500	2600
	Median	2800	5.36	17.2	54000	64500	2790
	Max	3420	7.80	17.2	57600	64500	2980
CV%	11.0	80.7	-	9.7	-	9.7	

Source: Table 15 in Summary of Clinical Pharmacology

Gemcitabine PK

Table 14. Study TOC3258g: AUC₅₋₃₀ for gemcitabine (upper) and AUC_{all} for dFdU (lower) when administered with or without pertuzumab

Gemcitabine

Treatment	AUC ₅₋₃₀ (min.ng/mL)				Geometric Mean Ratio (90% CI) ^a
	Mean ± SD	Geometric Mean	95% LCL	95% UCL	
Gemcitabine + placebo (n = 11)	77,800 ± 27,700	70,200	48,000	103,000	-
Gemcitabine + pertuzumab (n = 16)	69,200 ± 31,600	62,200	47,900	80,700	0.886 (0.625, 1.26)

AUC₅₋₃₀ = area under the concentration-time curve from 5 to 30 minutes post-infusion; LCL = lower confidence limit; UCL = upper confidence limit.

^a The geometric mean ratio and 90% confidence interval for AUC₅₋₃₀ comparing the gemcitabine + placebo arm with the gemcitabine + pertuzumab arm.

dFdU

Treatment	AUC _{all} (min.ng/mL)				Geometric Mean Ratio (90% CI) ^a
	Mean ± SD	Geometric Mean	95% LCL	95% UCL	
Gemcitabine + placebo (n = 12)	3,320,000 ± 579,000	3,270,000	2,910,000	3,670,000	-
Gemcitabine + pertuzumab (n = 17)	3,230,000 ± 668,000	3,160,000	2,850,000	3,510,000	0.968 (0.854, 1.10)

AUC_{all} = area under the concentration-time curve from 5 to 125 minutes post-infusion; LCL = lower confidence limit; UCL = upper confidence limit.

^a The geometric mean ratio and 90% confidence interval for AUC_{all} comparing the gemcitabine + pertuzumab arm with the gemcitabine + placebo arm.

Source: Table 18 in Summary of clinical pharmacology

2.4.2.7 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Unknown.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 What moieties should be assessed in biocomparability studies?

Pertuzumab, the active ingredient of the drug product, should be assessed in biocomparability studies, based on the current knowledge.

2.5.2 What is the composition of the to-be-marketed formulation?

The commercial formulation of pertuzumab is provided as a sterile liquid and contains no preservatives. Each single-use, 20 mL vial contains 420 mg (nominal) pertuzumab for intravenous infusion. The to-be-marketed Drug Substance manufacturing process, drug product formulation, and vial configuration are the same as that used for the Phase 3 clinical trial.

The composition of the to-be-marketed pertuzumab formulation is listed in Table 15.

Table 15. Composition of pertuzumab drug product

Ingredients	Amount per Vial ^a	Concentration per Vial	Component Function	Pharmacopeial Specification
Pertuzumab	420 mg	30 mg/mL	Active Ingredient	—
L-Histidine (b) (4)			(b) (4)	USP/Ph. Eur.
				USP/Ph. Eur.
Sucrose				NF/Ph. Eur.
Polysorbate 20 (b) (4)				NF/Ph. Eur.
				USP/Ph. Eur.

NA = not applicable; NF = National Formulary.

^a Amounts listed depict the extractable content.

Source: BLA submission Section 3.2.P.1 drug product

2.6 ANALYTICAL SECTION

2.6.1 What bioanalytical methods are used to assess serum concentrations of pertuzumab?

The serum concentrations of primary active moiety pertuzumab were appropriately assessed in 12 clinical pharmacology studies (Table 2).

Three validated enzyme-linked immunosorbent assays (ELISA) were used to measure serum pertuzumab in studies without concurrent trastuzumab, serum pertuzumab in the presence of trastuzumab in study WO20698/TOC4129g, and serum trastuzumab in the presence of pertuzumab in study WO20698/TOC4129g. The performance of these assays are summarized in (Table 16).

Table 16. Assay performance of validated pharmacokinetic assays used in clinical studies

PK Assay	Validation Report No.	Validation and Sample Analysis Site	Standard Curve Reporting Range		Accuracy ^a (% Recovery)	Intra-assay Precision (%CV)	Inter-assay Precision (%CV)
			(ng/mL)	MQC (ng/mL)			
Pertuzumab	4.2C4.4_AVR_1	Genentech, Inc.	4 to 120	400	81 to 132	6 to 12	5 to 15
Pertuzumab (in the presence of trastuzumab)	BA.MET.2C4.013.AVR_0	Genentech, Inc.	3 to 80	150	88 to 124	2 to 11	4 to 14
trastuzumab (in the presence of pertuzumab)	BA.MET.HH2.015.AVR_0	Genentech, Inc.	2 to 60	200	92 to 116	2 to 27	3 to 13

MQC = minimum quantifiable concentration in neat serum samples (corrected for the minimum dilution of the assay); %CV = percent coefficient of variation.

^a Accuracy assessed in individual human serum samples. Refer to the validation reports for more information on testing and results.

Source: BLA 125409 Table 6 of Section 2.7.1 "Summary of biopharmaceutical studies and associated analytical methods"

Method 4.2C4.4_AVR_1 was used to measure serum pertuzumab concentrations in studies without concurrent trastuzumab. The assay used recombinant HER2-extracellular domain (ECD) to capture pertuzumab from serum samples. Bound pertuzumab was detected with a mouse anti-human IgG Fc conjugated to horseradish peroxidase (HRP), (b) (4)

Method BA.MET.2C4.013.AVR_0 used a monoclonal anti-idiotypic antibody against pertuzumab to capture pertuzumab from serum samples in the presence of trastuzumab. Bound pertuzumab was detected with a biotinylated monoclonal antibody against Genentech IgG framework and HRP-Avidin D conjugate. (b) (4)

The presence of trastuzumab did not interfere with the accurate quantification of pertuzumab in this assay.

Method BA.MET.HH2.015.AVR_0 was used to measure trastuzumab in the presence of pertuzumab in serum samples from patients in Study WO20698/TOC4129g. The assay used a monoclonal anti-idiotypic antibody against trastuzumab to capture trastuzumab from serum samples. Bound trastuzumab was detected with goat anti-human IgG (gamma) conjugated to HRP, (b) (4) The MQC in human serum was 200 ng/mL. The presence of pertuzumab did not interfere with the accurate quantification of trastuzumab in this assay.

2.6.2 What bioanalytical methods are used to detect Anti-Therapeutic Antibody (ATA) to Pertuzumab?

Three validated methods were developed to detect serum anti-therapeutic antibodies (ATAs) to pertuzumab, as summarized below (Table 17).

Table 17. Assay performance of validated anti-therapeutic antibody assays used in clinical studies

Assay	Validation Report No.	Validation and Sample Analysis Site	Relative Sensitivity (ng/mL)	Pertuzumab Interference	Intra-Assay Precision (%CV)	Inter-Assay Precision (%CV)	Studies
Pertuzumab Antibody ELISA	4.2C4.5.AVR_0	Genentech, Inc.	30	≥10 µg/mL ^a ≥100 ng/mL ^a	2 to 11	2 to 8	TOC2297g, BO16934 BO17004
Pertuzumab Antibody ECLA	4.2C4.10.AVR_1	Genentech, Inc.	18	See footnote ^b	4 to 11	4 to 12	BO17931, JO17076 TOC2572g, TOC2664g TOC2682g, TOC2689g TOC3258g, WO20024
Pertuzumab Antibody ELISA	BA.MET.2C4.012.AVR_0	Genentech, Inc.	8	See footnote ^c	3 to 4	4 to 16	WO20698/TOC4129g

%CV = percent coefficient of variation.

^a A concentration of 10 µg/mL of pertuzumab reduced the response of a high titer sample (3.5 titer units) to negative. A concentration of 100 ng/mL of pertuzumab reduced the response of a low titer sample (1.9 titer units) to negative.

^b Pertuzumab concentrations of 25 µg/mL, 50 µg/mL, and 100 µg/mL reduced the relative sensitivity of the assay to 245 ng/mL, 148 ng/mL, and 764 ng/mL, respectively.

^c In the presence of 100 µg/mL of pertuzumab, the assay can detect 500 ng/mL of the anti-idiotypic monoclonal antibodies.

Source: BLA 125409 Table 7 of Section 2.7.1 "Summary of biopharmaceutical studies and associated analytical methods"

Method 4.2C4.5.AVR_0 is a step-wise bridging ELISA using pertuzumab to capture antibodies to pertuzumab from serum samples. Bound anti-pertuzumab antibodies were detected with biotinylated pertuzumab and Streptavidin HRP conjugate. (b) (4)

With affinity purified cynomolgus monkey anti-pertuzumab polyclonal antibodies, the relative sensitivity was determined to be 30 ng/mL (in the absence of pertuzumab).

Method 4.2C4.10.AVR_1 is an electrochemiluminescence assay (ECLA) uses pertuzumab labeled with biotin and pertuzumab labeled with ruthenium. Using affinity purified cynomolgus monkey anti-pertuzumab polyclonal antibodies as positive controls, the relative sensitivity was determined to be 18 ng/mL (in the absence of pertuzumab).

Method BA.MET.2C4.012.AVR_0 is a homogeneous ELISA assay utilizing pertuzumab labeled with biotin and pertuzumab labeled with digoxigenin. This assay was used in Study WO20698/TOC4129g. Using an anti-idiotypic monoclonal antibody directed against pertuzumab, the relative sensitivity was determined to be 8 ng/mL (in the absence of pertuzumab).

Per FDA's request, the applicant clarified that the above assays may not be able to distinguish the ATAs against pertuzumab from those against trastuzumab. Trastuzumab and pertuzumab share the same human IgG1(κ) framework structure, differing only in the complementarity determining region (CDR). Though specific for CDR region of pertuzumab, the ELISA assay can detect ATAs directed against epitopes contained within pertuzumab that are shared with trastuzumab in the common framework regions.

During the pre-study validation of the pertuzumab antibody ELISA, cross-reactivity of HER2 ECD was tested to assess the potential of interference of HER2 ECD. Using recombinant HER2 ECD, validation data demonstrated the following:

- Cross-reactivity was observed at ≥ 100 ng/mL of recombinant HER2 ECD
- Cross reactivity was not observed at ≤ 10 ng/mL of recombinant HER2 ECD

The cross-reactivity may contribute to the false positive ATA, as Herceptin label states that “Sixty-four percent (286/447) of women with metastatic breast cancer had detectable circulating extracellular domain of the HER2 receptor (shed antigen), which ranged as high as 1880 ng/mL (median 11 ng/mL).

DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. Underlines indicate the content that was added to the proposed label by the Agency and ~~strikethroughs~~ indicate content taken out from the proposed label by the Agency.

(b) (4)

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3 PHARMACOMETRIC REVIEW

APPEARS THIS WAY ON
ORIGINAL

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

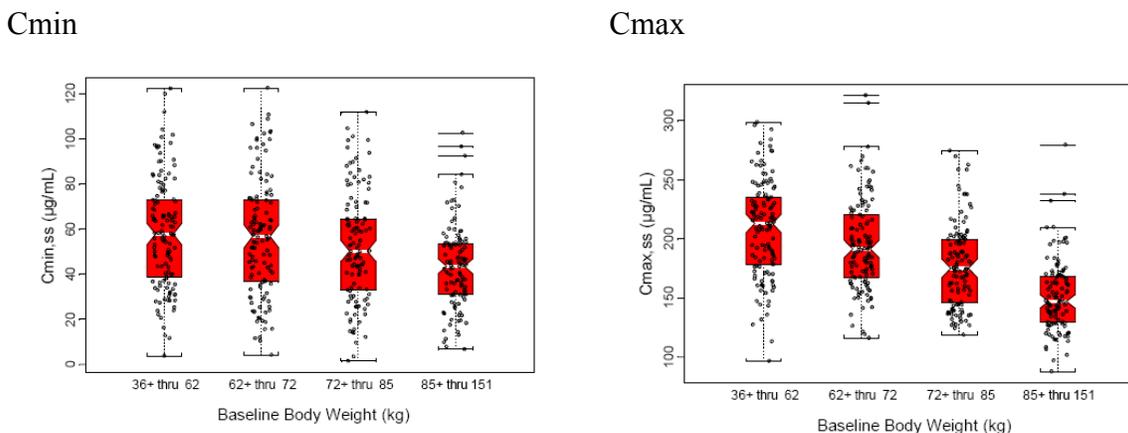
1.1.1 Is fixed dosing acceptable in breast cancer patients?

Yes, fixed dosing, without regard to body weight, is acceptable in breast cancer patients.

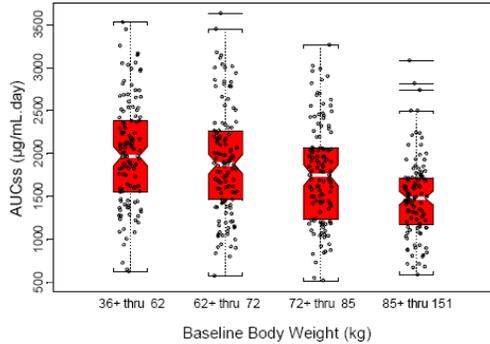
Lean body weight was found to have a significant influence on pertuzumab exposure, with heavier patients having lower $C_{min,ss}$, $C_{max,ss}$ and AUC values than lighter patients (Figure 1). In the population pharmacokinetic dataset, patients in the heaviest weight quartile (85 to 151 kg) are predicted to have $C_{min,ss}$ values that are 25% lower than patients in the lightest weight quartile (37 to 62 kg).

The impact of lower pertuzumab exposure in heavier patients on efficacy is difficult to predict because exposure-response analysis could not be conducted due to limited pharmacokinetic data collected in the pivotal trial; PK data was collected in 20 out of 407 patients. Furthermore, dose-ranging studies were not performed. To address this question, the primary endpoint (progression free survival) was stratified by four weight quartiles for patients in the pivotal trial receiving pertuzumab. Note that the weight quartiles for the pivotal trial are different than those for the population pharmacokinetic analysis because patients enrolled in the pivotal trial tended to weigh less than patients in the pharmacokinetic database. The results are illustrated in Figure 2 and do not show a trend between body weight and progression free survival. Therefore, there is no evidence to suggest that heavier patients had substantially worse outcomes.

Figure 1: Pertuzumab Exposure at Steady State for a Loading Dose of 840 mg Followed by 420 mg q3w from Expanded Dataset

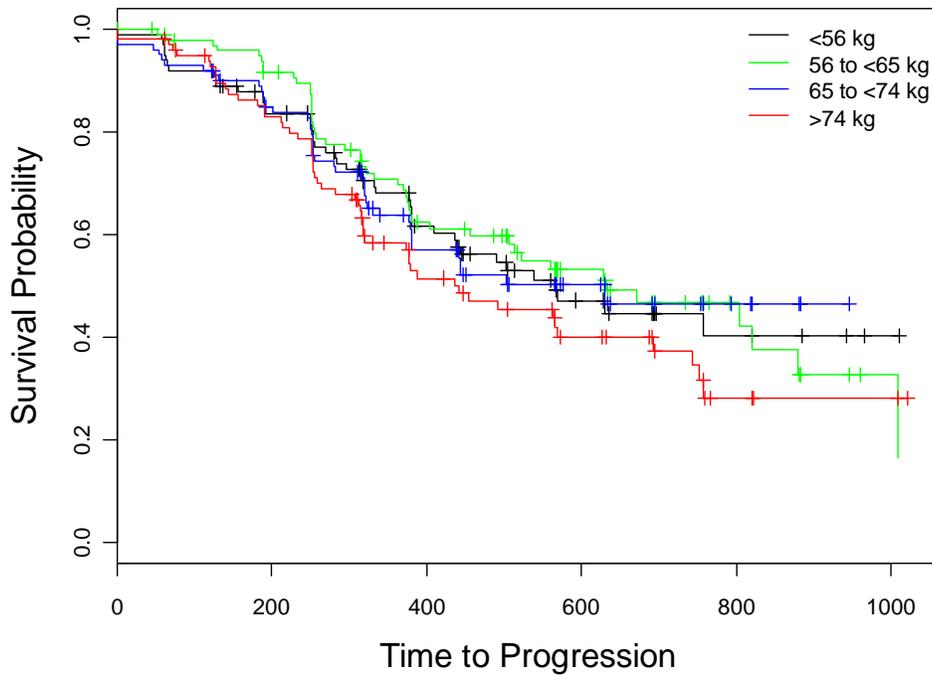


AUC



Source: Figure 4 from Sponsor's report 11-2998 Addendum I of population pharmacokinetic analysis of pertuzumab in cancer patients

Figure 2: Progression Free Survival by Quartiles of Body Weight in Patients Receiving Pertuzumab in Pivotal Trial



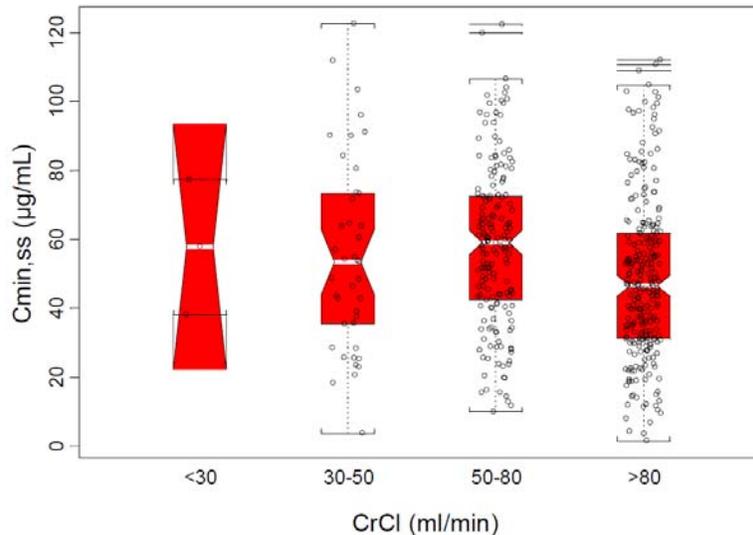
1.1.2 Is dose adjustment recommended for patients with renal impairment?

No, dose adjustment is not needed in patients with renal impairment.

Renal function, measured as creatinine clearance (CrCL), was not found to be a significant predictor of pertuzumab exposure in the population pharmacokinetic analysis. Although there were only 3 patients in the dataset with severe renal impairment (CrCL < 30 ml/min), a trend between CrCL and pertuzumab exposure was not observed over the

range of observed CrCL (27 to 244 ml/min). Therefore, patients with severe renal impairment are not expected to have increased pertuzumab exposure relative to patients with normal renal function. A plot of predicted pertuzumab $C_{min,ss}$ in all patients in the population pharmacokinetic dataset receiving the recommended dosing regimen is provided in Figure 3.

Figure 3: Steady State C_{min} Concentrations versus CrCL



Source: Figure 5 from Sponsor's report 11-2998 Addendum I of population pharmacokinetic analysis of pertuzumab in cancer patients

1.1.3 Is the Sponsor's proposal for dose modification in the case of delayed or missed doses acceptable?

Yes, the Sponsor's proposal for dose modification in the case of delayed or missed doses is acceptable.

The Sponsor has proposed to administer the 420 mg dose in patients if the time between two sequential infusions is less than 6 weeks. If the time between two sequential infusions is 6 weeks or more, the initial 840 mg dose should be re-administered. This was the strategy used in the pivotal trial. Simulations show that for a typical patient, this dosing strategy ensures that trough concentrations are reasonably restored to levels which would have been observed if the patient had not missed a dose.

1.2 Recommendations

Dose adjustment is not recommended for body weight or renal function.

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

12.2 Pharmacokinetics

2 PERTINENT REGULATORY BACKGROUND

A Biologics License Application (BLA 125409) was submitted for pertuzumab on December 6, 2011. Pertuzumab is a recombinant, humanized, immunoglobulin (Ig)G1 κ monoclonal antibody targeting the human epidermal growth factor receptor 2 (HER2). The Applicant is seeking an indication for pertuzumab in combination with Herceptin and docetaxel for patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received previous treatment [REDACTED] (b) (4)

[REDACTED] On February 27, 2012, an addendum to the population pharmacokinetic report was submitted. The Applicant added pharmacokinetic data which had been inadvertently excluded from the original population pharmacokinetic report.

3. RESULTS OF SPONSOR'S ANALYSIS

3.1. Population PK Analysis

Sponsor performed a population PK analysis using data from 12 studies in cancer patients including 5 Phase I trials, 6 Phase II trials and 1 pivotal Phase III trial. A weight-based dose regimen (0.5-25mg/kg) was used in 2 Phase I studies and fixed dose regimens were used in all other 10 studies. Pertuzumab was given as an 840 mg intravenous infusion over 60 minutes as a loading dose followed by a 420 mg intravenous infusion over 30 – 60 minutes as a maintenance dose q3w in the pivotal Phase III trial. The main objectives of the population PK analysis include (1) describing the disposition of pertuzumab in cancer patients, (2) confirming the selection of fixed dose regimen in the pivotal trial and (3) comparing the PK of pertuzumab in metastatic breast cancer in the pivotal Phase III trial to the various cancer settings in the 11 Phase I/II trials.

3.1.1. Methods

Originally, a total of 3890 PK samples from 444 cancer patients in 12 clinical studies were used for population PK analysis in Report 11-2998. Later, sponsor added new data from 2 of the 12 studies to the original PK dataset and formed an expanded dataset including 4525 PK samples from 481 cancer patients in Report 11-2998 Addendum I. Although the number of patients was increased by 8% and the number of PK samples

was increased by 16% in the expanded dataset compared to the original dataset, patient characteristics were similar across the datasets.

The original PK dataset was used to develop the population PK model of pertuzumab using a nonlinear mixed effects model with the first-order conditional estimation method using NONMEM 7, version 7.1.2. The PK data of the weight-based dose regimen of 0.5 mg/kg were not included in model development due to the nonlinearity at that dose level. A base model was built based on graphical examination of pertuzumab concentration time profiles. The relationship between 18 covariates and PK parameters were screened by visualization, linear regression (continuous covariates) and ANOVA tests (categorical covariates). The relationship was considered significant at a p value less than 0.01. Next, a stepwise forward addition and backward elimination process was used to select the relationships between covariates and PK parameters for the final model. The relationship was considered significant at a p value less than 0.01 in forward addition and less than 0.001 in backward elimination. The model diagnostics included objective function, goodness of fit plots, accuracy and precision of population and individual PK estimates, and the size of residual error. The model fit was evaluated by bootstrap, visual predictive check and numerical predictive check.

Sponsor performed sensitivity analyses to examine the consistency of PK results across original and expanded datasets. The sensitivity analyses consisted of an external validation using new data and reproduction of population PK analysis using the expanded dataset.

3.1.2. Results

The pharmacokinetics of pertuzumab in cancer patients was described with a two-compartment model with first order elimination from the central compartment. An exponential model was used to describe the inter-individual variability. A log-additive model was selected to describe the residual error. After forward addition and backward elimination for covariate selection, the impact of lean body weight (LBW) and serum albumin on elimination clearance (CL) and the impact of LBW on both central volume (V_c) and peripheral volume (V_p) were deemed as significant and remained in the final population PK model. CL decreased in cancer patients with high serum albumin and low LBW. The results of sensitivity analysis using 90% range of albumin and LBW demonstrated that albumin had a bigger effect on CL, C_{min} and AUC than LBW and LBW had a bigger effect on V_c, V_p and C_{max} than albumin.

The population PK model was re-fitted to the expanded dataset using the same method as described in section 3.1.1. The PK parameter estimates were comparable between the original and expanded datasets, as shown in Table 1. The four significant covariate-parameter relationships seen in the original dataset remained the same in the expanded dataset and no other significant relationship was found.

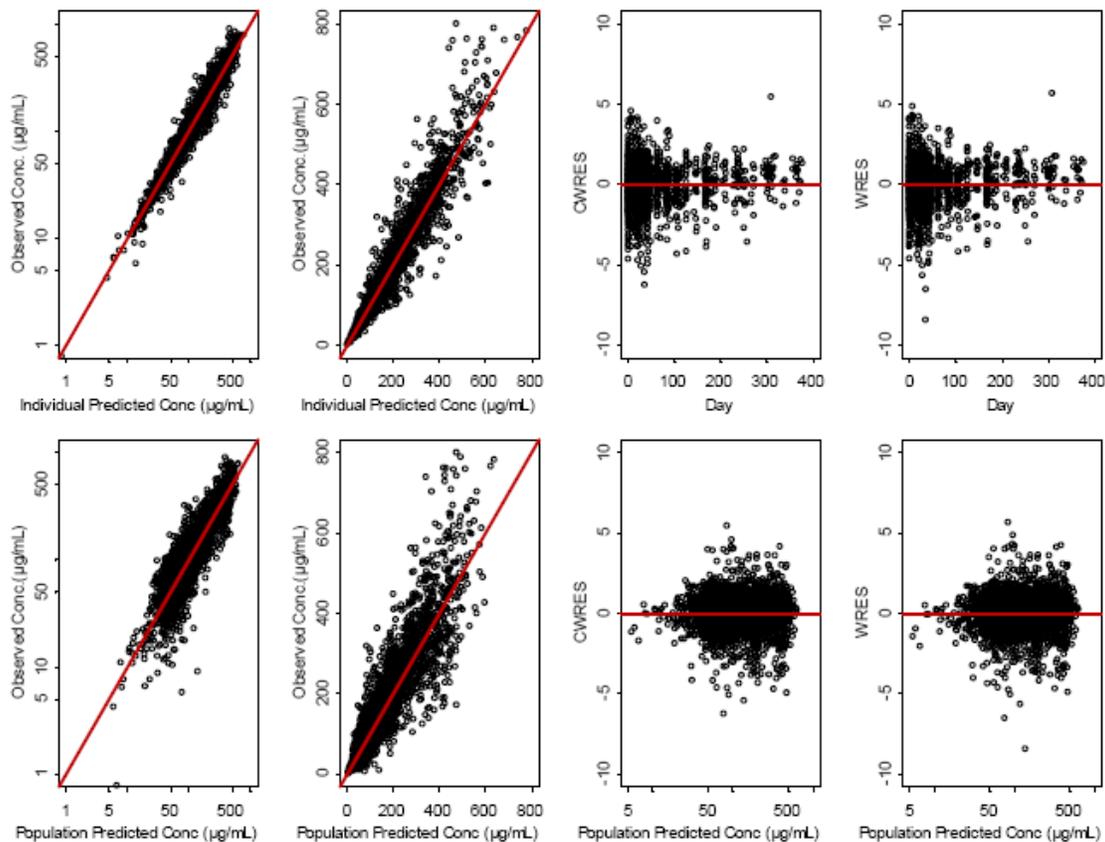
Table 1 Population PK Parameters Estimated from the Original Dataset and the Expanded Dataset

Parameters		Final PopPK Model Estimates		Inter-individual variability (%)	
		Original [95% CI]	Expanded [95% CI]	Original	Expanded
θ_1	Elimination clearance, CL (L/day)	0.239 [0.229, 0.249]	0.235 [0.226, 0.244]	34.5	34.1
θ_5	Influence of LBW on CL	0.519 [0.346, 0.692]	0.516 [0.348, 0.684]		
θ_7	Influence of ALBU on CL	-1.05 [-1.28, -0.821]	-1.06 [-1.28, -0.842]		
θ_2	Volume of central compartment, Vc (L)	3.07 [3.00, 3.14]	3.11 [3.04, 3.18]	19.3	18.5
θ_6	Influence of LBW on Vc	0.674 [0.555, 0.793]	0.747 [0.637, 0.857]		
θ_3	Distribution clearance, Q (L/day)	0.558 [0.466, 0.65]	0.534 [0.462, 0.606]		
θ_4	Volume of peripheral compartment, Vp (L)	2.36 [2.2, 2.52]	2.46 [2.31, 2.61]	45.3	45.9
θ_8	Influence of LBW on Vp	0.7 [0.402, 0.998]	0.83 [0.516, 1.14]		
$T_{1/2}$	Elimination half-life (day)	17.2	18.0		
σ	Intra-individual variability	17.7%	18.1%		

Source: Table 5 from Sponsor's report 11-2998 Addendum I of population pharmacokinetic analysis of pertuzumab in cancer patients

The goodness-of-fit plots for both original and expanded datasets demonstrated an adequate fit of the PK model to pertuzumab concentrations. No bias was found in the residual plots. The goodness-of-fit plots for the expanded dataset are shown in Figure 4. The results from bootstrap, visual predictive check and numerical predictive check also supported the reliability of the population PK model (data not shown here).

Figure 4: Goodness-of-fit Diagnostic Plots for the Model Based on the Expanded Dataset



Source: Figure 21 from Sponsor’s report 11-2998 Addendum I of population pharmacokinetic analysis of pertuzumab in cancer patients

Sponsor performed a sensitivity analysis to confirm the selection of the fixed dose regimen in pivotal Phase III trial. The pertuzumab exposure (C_{min} , C_{max} and AUC) at steady state was simulated and grouped by baseline body weight into 4 quartiles. The results are shown in Figure 1. The number of patients with a trough concentration $< 20 \mu\text{g/mL}$ in expanded dataset is summarized in Table 2. Sponsor considered $20 \mu\text{g/mL}$ to be the threshold to demonstrate treatment efficacy, which was derived from mouse studies. The percentage of patients not achieving the threshold increased from 3.3% in the low weight quartile group to 10.6% in high weight quartile group. Overall, 93.6% of patients in expanded dataset had C_{min} at steady state above $20 \mu\text{g/mL}$, and 6.4% were below. The body weight of patients with HER2-positive metastatic breast cancer in the pivotal trial was slightly lower (39 to 129 kg) than the entire study population, so the percentage of patients not achieving the threshold in the heaviest weight group is expected to be lower than 6.4%.

Table 2 Percentage of Patients with Steady State Trough Concentration below 20 $\mu\text{g/mL}$ from the Expanded Dataset

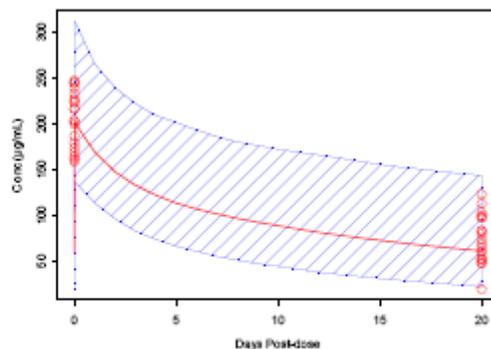
Model	Baseline Body Weight (kg)	Number of patients*	Median $C_{\text{min,ss}}$ ($\mu\text{g/mL}$)	Number of patients < 20 $\mu\text{g/mL}$	% patients < 20 $\mu\text{g/mL}$
Expanded dataset	36.5+ thru 61.8	120	58	4	3.3
	61.8+ thru 72.0	122	56	9	7.4
	72.0+ thru 85.0	122	51	11	9
	85.0+ thru 150.6	113	43.4	12	10.6

*Number of patients is not even because some patients with weights on the boundary were disproportionately assigned to a single group.

Source: Table 7 from Sponsor's report 11-2998 Addendum I of population pharmacokinetic analysis of pertuzumab in cancer patients

Only twenty patients in the pivotal Phase III study, who had pertuzumab PK data, contributed to the development of population PK model. Although these patients had a lower LBW and higher albumin level compared to the entire population, the pertuzumab exposure were within the range of model prediction after adjusting for the covariate effects (Figure 5).

Figure 5: Pertuzumab Exposure in 20 Patients in Phase III Trial with Model Predictions



Median (red) and 95% range (blue) of the model prediction normalized to the typical covariate values of the study.

Source: Figure 21 from Sponsor's report 11-2998 of population pharmacokinetic analysis of pertuzumab in cancer patients

2.1 Sponsor's Conclusions

- The pharmacokinetic of pertuzumab in the dose range of 2-25 mg/kg was described by a two-compartment linear model with first-order elimination. The fixed dose regimen of 840 mg loading dose followed by 420 mg q3w is within the dose range used for PK model.
- LBW and albumin were identified as the statistically significant covariates on pertuzumab PK parameters. Pertuzumab CL decreased with increasing albumin. Extremes in albumin lead to 40% variability in PK parameters and C_{\min} . The impact of LBW on pertuzumab concentration was minimal.
- The selection of a fixed dose regimen in Phase III trial for clinical routine use was supported by the sensitivity analyses and the fact that more than 90% of patients reached the target concentration above 20 $\mu\text{g/mL}$.
- No noticeable difference was detected between the pertuzumab PK in the Phase III trial and Phase I/II trials.

Reviewer's comments on Sponsor's Population PK Analysis:

- *Sponsor's population PK analysis is generally reasonable.*
- *The inclusion of additional data submitted in the addendum to the population pharmacokinetic report did not change the results from the original report. For completeness, this review uses the expanded dataset.*
- *The exclusion of the 0.5 mg/kg data is reasonable because PK is nonlinear at this dose and the dose is substantially lower than the therapeutic dose*
- *The sponsor's target level of 20 $\mu\text{g/mL}$ derived from mouse studies is a reasonable target to guide dose selection for the pivotal trial but is not sufficient to guide dose adjustment in breast cancer patients.*
- *The significant relationships of covariate and PK parameters identified in the final model are reasonable.*
- *Sponsor's selection of fixed dose regimen is reasonable*

4. RESULTS OF REVIEWER'S ANALYSIS

4.1. Objective

The primary objective was to explore the pharmacokinetic consequences of the sponsor's recommendations for dose modification for delayed or missed doses as described in the label. Sponsor claimed that 420 mg of pertuzumab should be administered if the time between two sequential infusions is less than 6 weeks; the initial dose of 840 mg should be re-administered followed by 420 mg q3w if the time between two sequential infusions is 6 weeks or more.

4.2. Method

4.2.1. Data Sets

Data sets uses are summarized in Table 3.

Table 3: Reviewer’s Analysis Data Sets

Study Number	Name	Link to EDR
Population PK Analysis	PTZ_PPK_sim.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pertuzumab_BLA125409_KMK_RJ\PPK Analyses\PPK simulation

4.2.2. Software

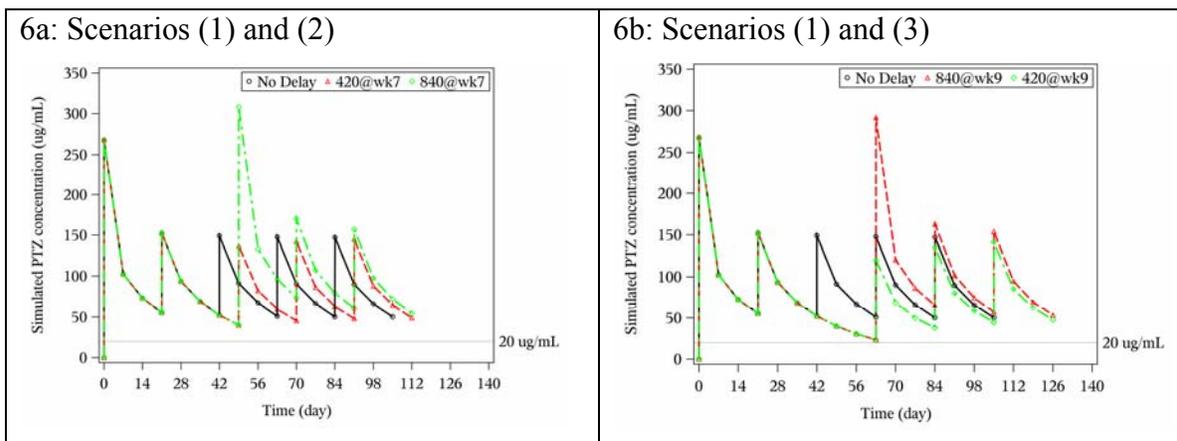
NONMEM 7 and SAS 9.2 were used for the reviewer’s analyses.

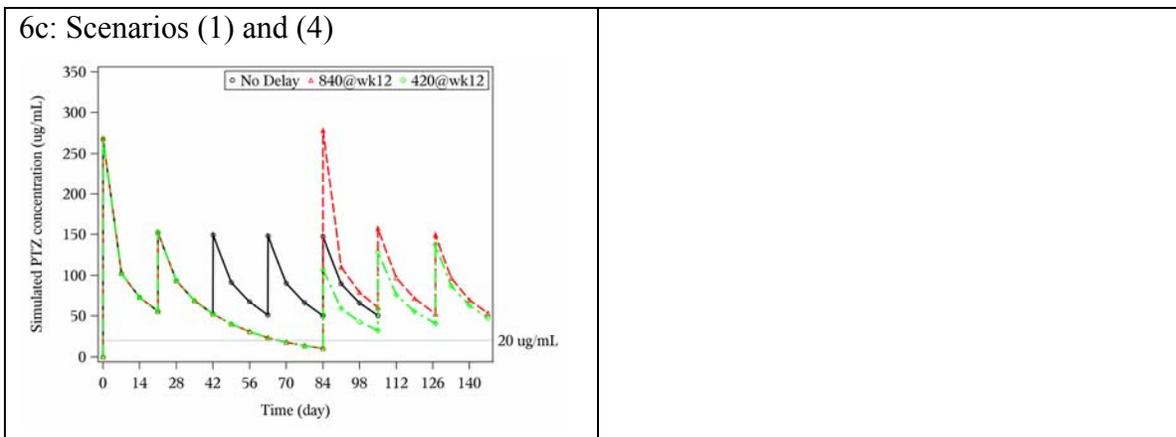
4.3. Results

The mean pertuzumab concentration time profile was simulated for a typical patient with LBW of 48 kg and serum albumin of 3.9 g/dL. Sponsor’s final population PK model was used for simulation. For routine clinical dosing (840 mg loading, 420 mg q3w), 5 cycles were simulated. For delayed or missing dosing scenarios, the subsequent dose was assumed to occur at cycle 3 because steady state is reached after the first two cycles. For the subsequent dose, both 840 mg and 420 mg were simulated. The scenarios of the simulated dose administration included (1) routine clinical dose: (840 mg loading dose followed by 420 mg q3w) (2) 4 weeks delayed/missing dose (time between sequential doses is 4 weeks) (3) 6 weeks delayed/missing dose (time between sequential doses is 6 weeks) (4) 9 weeks delayed/missing dose (time between sequential doses is 9 weeks).

The comparison of the mean pertuzumab concentrations time profile between scenarios (1) and (2) is presented in Figure 6a. The comparison between scenarios (1) and (3) is presented in Figure 6b. The comparison between scenarios (1) and (4) is presented in Figure 6c. In scenario (2), the dose is administered at week 7. In scenario (3), the dose is administered at week 9. In scenario (4), the dose is administered at week 12.

Figure 6: Mean Pertuzumab Concentration between Routine Dose and Dose Modification at 4 Weeks Apart (6a), 6 Weeks Apart (6b) and at 9 Weeks Apart (6c)





As shown in Figure 6a, for a typical patient with 4 weeks between subsequent doses, there is no need to re-administer the 840 mg loading dose. Steady state trough concentrations are maintained with the 420 mg dosing (red line). As seen in Figure 6b, when the 420 mg dose is administered after a 6 week delay, trough concentrations (Day 84) are ~24% lower than for the routine clinical dosing scenario. When the 840 dose is administered after a 6 week delay, trough concentrations (Day 84) are ~32% higher than for the routine clinical dosing scenario. As seen in Figure 6c, when the 420 mg dose is administered after a 9 week delay, trough concentrations (Day 105) are ~36% lower than for the routine clinical dosing scenario. When the 840 dose is administered after a 9 week delay, trough concentrations (Day 105) are ~20% higher than for the routine clinical dosing scenario.

Based on the comparison in the typical pertuzumab concentration profile among different scenarios of dose modification in Figure 6, the sponsor's proposal of re-administering the 840 mg dose after a 6 week delay in dosing is reasonable. The strategy is based on the goal of maintaining trough concentrations at least as high as those expected for the routine clinical dosing scenario. More importantly, this was the strategy employed in the pivotal trial.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
PTZ_newPPK_base_reviewer.ctf	Base Model (NONMEM control file)	Reviews\Ongoing PM Reviews\Pertuzumab_BLA125409_KMK_RJ\PPK Analyses\Structure Model
PTZ_newPPK_reviewer_base output.lst	Base Model (NONMEM output file)	Reviews\Ongoing PM Reviews\Pertuzumab_BLA125409_KMK_RJ\PPK Analyses\Structure Model
PTZ_newPPK_final_reviewer.ctf	Final Model (NONMEM control file)	Reviews\Ongoing PM Reviews\Pertuzumab_BLA125409_KMK_RJ\PPK Analyses\Final Model
PTZ_newPPK_reviewer_final output.lst	Final Model (NONMEM output file)	Reviews\Ongoing PM Reviews\Pertuzumab_BLA125409_KMK_RJ\PPK Analyses\Final Model

npoppkal_reviewer.csv	Population PK dataset	Reviews\Ongoing PM Reviews\Pertuzumab_BLA125409_KMK_RJ\PPK Analyses\Structure Model
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4 GENOMICS REVIEW

APPEARS THIS WAY ON
ORIGINAL

**OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW**

NDA/BLA Number	125409
Submission Date	12/08/11
Applicant Name	Genentech
Generic Name	Pertuzumab
Proposed Indication	Metastatic breast cancer
Primary Reviewer	Christian Grimstein, Ph.D.
Secondary Reviewer	Issam Zineh, Pharm.D., M.P.H

Executive Summary

The purpose of our review is to identify baseline biomarkers that are correlated with cardiac events in the pivotal phase III trial (Study WO20698/TOC4129g) using patient level data submitted by the sponsor. The assessed biomarkers are related to cardiac biology (i.e. HER signaling) or associated with the mechanism of action of anti-HER2 monoclonal antibodies (i.e. antibody-dependant cell-mediated cytotoxicity (ADCC) activity). Specifically, our correlative safety analyses evaluated the association between baseline levels of HER ligands, shed HER2-ECD (sHER2), and germline Fc-gamma receptor (FCGR) polymorphisms with cardiac events observed in the study. Our assessment did not show a consistent relationship between the evaluated biomarkers and cardiac events. We also intended to determine whether on-treatment changes in these biomarkers were correlates of safety risk. After discussions with the sponsor, it was determined that, while samples exist, the sponsor has not yet assayed the biomarkers beyond the baseline timepoint. No labeling recommendations or post-approval decision actions are warranted at this time.

1 Background

Pertuzumab is an IgG1 humanized monoclonal antibody that specifically targets the extracellular domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2-ECD). It blocks ligand-dependant heterodimerization of HER2 with other HER family members, including HER1 (EGFR), HER3 and HER4. It also mediates ADCC. The proposed indication for pertuzumab in combination with trastuzumab and docetaxel is the treatment of patients with HER2 positive metastatic (b) (4) breast cancer.

Different from pertuzumab, trastuzumab targets subdomain IV of the HER2 receptor and inhibits ligand independent HER2 signaling, in addition to mediating ADCC through Fc-gamma receptors. Trastuzumab inhibits HER2-ECD cleavage and formation of a residual truncated and constitutively active form of the receptor (PMID: 22124364). HER2 is a co-receptor for HER4, which is activated by the epidermal-like growth factor neuregulin-1 (NRG-1). Because NRG-1/HER signaling in the heart is associated with cardioprotective effects, therapies that block HER signaling such as trastuzumab or pertuzumab may be expected to induce cardiac adverse events (PMID: 20056944). Trastuzumab therapy may lead to sub-clinical and clinical cardiac failure manifesting as congestive heart failure (CHF) and decreased left ventricular ejection fraction (LVEF) with greater risk when administered concurrently with anthracyclines (trastuzumab

label). Patients receiving trastuzumab as a single agent or in combination with chemotherapy have a 4-6 fold increase of symptomatic myocardial dysfunction compared to patients who do not receive trastuzumab. Also, as anticipated, cardiac toxicities, especially left ventricular dysfunction (LVD) were observed in the pivotal phase III trial (for details, refer to the clinical review). Of note, potential biomarkers of cardiotoxicity associated with anti-HER2 therapies are not well established.

2 Submission Contents Related to Genomics

The applicant collected serum, tumor tissue and germline DNA at baseline in the pivotal phase III study WO20698/TOC4129g for exploratory correlative analyses of selected biomarkers with efficacy endpoints. Evaluated biomarkers, analytical methods and corresponding sample acquisition rates are shown in Table 1.

Table 1: Biomarker assessed in phase III (Study WO20698/TOC4129g)

Sample	Biomarker	Sample acquisition rates*
Tumor tissue	qRT-PCR: HER2, HER3, EGFR, amphiregulin (AREG), betacellulin, PI3KCA IHC: HER3, IGFR-1R, PTEN, pAKT FISH: c-myc; Taqman: PIK3CA	>99% (HER2 IHC) Remaining: 60% (IHC) or 70-90% (PCR, FISH, Taqman)
Serum	shed HER2 (sHER2), EGF, TGF-alpha, amphiregulin	~90%
Whole blood	FCGR germline polymorphism (FCGR3A-V158F; FCGR2A-H131R; FCGR2B-I232T)	~90%

FCGR: Fc-gamma receptor; *acquisition rates were similar between treatment arms

Among the biomarkers presented in Table 1, the following were assessed in our safety analyses based on the relationship with HER2-signaling and the mode of action of pertuzumab and trastuzumab (Table 2). Also, if shown to have clinical utility, these biomarkers may be easily evaluated in clinical practice due to convenient access to specimen used for analyses.

Table 2: Biomarkers tested for correlation with cardiac events

Biomarker	Specimen source	Genotype	Samples available
sHER2	serum	n/a	729
TGF-alpha			721
AREG			714
EGF			727
FCGR3A-V158F (V= high affinity)	germline DNA	V/V	76
		V/F	339
		F/F	324
FCGR2A-H131R (H= high affinity)	germline DNA	H/H	251
		H/R	346
		R/R	142
FCGR2B-I232T (T= low affinity)	germline DNA	T/T	53
		T/I	169
		I/I	495

sHER2: Elevated sHER2 levels have been correlated with a more aggressive clinical disease course, although results are not consistent (PMIDs: 18661530; 21549508). Furthermore, serum sHER2 levels were shown to be increased in chronic heart failure patients and correlated inversely with left ventricular ejection fraction (PMID: 16860598).

Serum TGF-alpha/AREG/EGF: AREG, EGF and TGF-alpha are EGFR (HER1) ligands involved in HER signaling (PMID: 17962208).

FCGR polymorphisms: ADCC is regulated by different polymorphic FCGR isoforms e.g., FCGR3A, FCGR2A and FCGR2B. Polymorphisms in these receptors lead to different affinities for their target Fc domains, potentially leading to different ADCC activity levels (PMID: 19707318). For example, the commonly studied polymorphisms V158F (FCGR3A), H131R (FCGR2A) and I232T (FCGR2B) are associated with lower FCGR affinity for human IgG (PMID: 18064051). Consistently, FCGR2A and 3A have been associated with decreased response of trastuzumab therapy (PMIDs: 21109570, 18347005).

3 Key Questions and Summary of Findings

3.1 Do mechanism-based biomarkers robustly correlate with left ventricular dysfunction/heart failure events in pertuzumab (P) + trastuzumab (T) + docetaxel (D) therapy?

No, our analyses did not show a robust correlation of assessed biomarkers with LVD/CHF in the trial. However, we identified a potential subpopulation [patients who have low sHER2 levels (< 25.53ng/mL)] who may be at a decreased risk for developing LVD/CHF events while on P/T/D therapy. Nonetheless, the results are considered exploratory since a similar result was not observed in the T/D treatment arm and results are mechanistically difficult to explain; replication of the observation would increase confidence in the results.

In the pivotal phase III study (WO20698/TOC4129g), metastatic breast cancer patients were randomized 1:1 to P/T/D vs. T/D. The treatment arms were balanced for demographic factors and cardiac risk factors (e.g. race, prior anthracycline therapy, prior radiation therapy). In both treatment arms ~43% of patients had previously received radiotherapy, ~39% received prior anthracycline therapy. Among enrolled patients, 59.4% were White, 32.3% were Asians, and 3.7% were Black. The median age was 54 years, and over 80% of patients in both arms were aged < 65 years.

Cardiac events included in the analysis consisted of asymptomatic and symptomatic LVD or diastolic dysfunction as assessed by the investigator. If a particular patient had more than one LVD/CHF related event, only the most severe event was considered. The population used in our correlative analysis corresponded to the safety population which included 407 patients who received P/T/D and 397 patients who received T/D. Results were similar for investigator assessed or CRC adjudicated datasets and also when only cardiac events considered treatment related by the investigator were included in the analysis (Table 3). Notably, the incidence of LVD/CHF related cardiac events was lower in the pertuzumab containing arm compared to control (4.7% vs. 8.3%, Table 3). While there may not be a specific cardiac safety concern for the addition of pertuzumab to T/D therapy, our biomarker assessment may help to identify

biomarkers that can be used to inform safety monitoring in patients receiving P/T/D.

Table 3: Investigator assessed LVD/CHF events by treatment arm in phase III

Cardiac event	Treatment	All investigator assessed LVD/CHF events- N [incidence]	Investigator assessed, treatment related LVD/CHF events - N [incidence]
LVD	All (N=804)	52 (6.5%)	46 (5.7%)
	P/T/D (N=407)	19 (4.7%)	17 (4.2%)
	T/D (N=397)	33 (8.3%)	29 (7.3%)
Diastolic dysfunction*	All (N=804)	2 (0.2%)	0
	P/T/D (N=407)	1 (0.2%)	0
	T/D (N=397)	1 (0.3%)	0

*if patient also had LVD, only LVD was considered; P/T/D: pertuzumab + trastuzumab + docetaxel; T/D trastuzumab + docetaxel; LVD: left ventricular dysfunction

Reviewer's analysis:

Methods:

A logistic regression model was developed to assess biomarker relationships with LVD/CHF risk. A multivariate model of clinical features was developed based on factors that were significantly associated with a LVD or CHF event ($p \leq 0.05$) in univariate analyses. Variables included in univariate analysis were age, gender, smoking status, diabetes status, race category, hypertension, ECOG status, prior anthracycline therapy, and prior radiation therapy. The final multivariate model included 1) prior anthracycline therapy, 2) prior radiation therapy, 3) race category (white, black, asian, others) and 4) treatment arm. Individual biomarkers (see Table 2) were then added one at a time as a covariate in the multivariate model of clinical features to test for association with LVD/CHF events. Serum levels of sHER2, AREG, EGF and TGF-alpha were log-transformed (ln) and included in the multivariate model as 1) continuous variable and 2) as a dichotomized variable based on the optimal cutpoint defined in ROC analysis. The ROC curves for AREG, EGF and TGF-alpha were considered unimpressive (ROC curve AUC < 0.55) and therefore dichotomous data of these biomarkers were not further evaluated. Of note, the ROC curve AUC of sHER2 was 0.59.

Results:

The odds ratios (OR, 95% CI) for developing LVD/CHF associated with each biomarker are shown in Table 4. Patients with increased baseline sHER2 levels and patients who were FCGR2A - H allele carriers had a 2-3 fold increased risk for developing LVD/CHF in the phase III trial while controlling for prior anthracycline therapy, prior radiation therapy, race, and study treatment received (Table 4).

Table 4: Risk for developing LVD/CHF event based on biomarker status

Biomarker	Parameterization (% samples above cut-off)	LVD/CHF risk – investigator assessed	
		OR	95% CI
sHER2* †	continuous	1.30	1.02, 1.65
	> 25.53 ng/mL (50%)	2.54	1.32, 5.11
AREG*	continuous	1.04	0.79, 1.31
EGF*	continuous	1.07	0.76, 1.54
TGF-alpha*	continuous	0.92	0.58, 1.46

Biomarker	Parameterization (% samples above cut-off)	LVD/CHF risk – investigator assessed	
		OR	95% CI
FCGR3A-V158F	V-carrier (vs. Non-V carrier)	1.00	0.55, 1.84
	V/V vs. F/F	0.33	0.05, 1.18
	V/F vs. F/F	1.19	0.65, 2.23
FCGR2A- H131R	H-carrier (vs. Non-H carrier)	2.69	1.11, 8.09
	H/H vs. RR	2.67	0.96, 8.73
	H/R vs. RR	2.70	1.08, 8.25
FCGR2B-I232T	T-carrier (vs. Non-T carrier)	0.82	0.40, 1.60
	T/T vs. I/I	0.52	0.08, 1.83
	T/I vs. I/I	0.92	0.43, 1.86

* log-transformed (ln) prior to analysis to normalize; † dichotomized variable based on ROC analysis

In addition, the correlation of biomarkers with LVD/CHF in each treatment arm was evaluated. An OR (95%CI) of 6.85 (2.04, 31.51) was observed for patients on P/T/D therapy who had high sHER2 baseline levels [> 25.53 ng/mL (= ln (3.24))] compared to patients on P/T/D therapy with low sHER2 baseline levels (Table 5). Of note, the OR seems to be driven by a low event rate in the P/T/D sHER2 low group [3/193 (1.6%)] rather than a high event rate in the P/T/D sHER2 high group [14/180 (7.8%)] since event rates in the T/D arm [T/D sHER2 low group [11/173(6.4%); T/D sHER2 high group [17/182 (9.3%)] were comparable to those in the P/T/D sHER2 high group. Thus, the data indicate that there may be a subpopulation of patients [patients on P/T/D therapy with low sHER2 levels], who experiences less LVD/CHF events compared to other patients in the trial. In addition, our analysis also showed that FCGR2A -131 H carriers who received T/D therapy had a ~5 fold increased risk of developing LVD/CHV compared to 131- non-H allele carriers on T/D therapy. However, this trend was not observed in the P/T/D arm. None of the other evaluated serum biomarker and FCGR polymorphisms assessed showed a significant association with LVD/CHF events.

Table 5: Risk for developing LVD/CHF event based on biomarker status and treatment

Biomarker	Parameterization	LVD/CHF risk - Pertuzumab arm		LVD/CHF risk - Placebo arm	
		OR	95% CI	OR	95% CI
sHER2* †	continuous	1.39	0.95, 2.03	1.27	0.92,1.75
	> 25.53 ng/mL (high vs. low)	6.84	2.04, 31.51	1.60	0.71, 3.71
AREG*	continuous	1.04	0.65, 1.58	1.02	0.71,1.39
EGF*	continuous	1.05	0.62, 1.87	1.15	0.75,1.85
TGF*	continuous	0.56	0.25, 1.25	1.18	0.67, 2.13
FCGR3A-V158F	V-carrier (vs. Non-V carrier)	0.77	0.27, 2.18	1.03	0.49, 2.26
FCGR2A- H131R	H-carrier (vs. Non-H carrier)	1.40	0.37, 7.10	5.37	1.48, 35.02
	H/H vs. RR	1.11	0.22, 6.45	6.02	1.41, 42.43
	H/R vs. RR	1.62	0.40, 8.69	5.13	1.36, 33.91
FCGR2B-I232T	T-carrier (vs. Non-T carrier)	1.05	0.26, 3.49	0.84	0.35,1.89

* log-transformed (ln) prior to analysis to normalize; † dichotomized variable based on ROC analysis

We also intended to determine whether on-treatment changes in these biomarkers were correlates of safety risk. However, while samples exist, the sponsor has not yet assayed the biomarkers beyond the baseline timepoint.

3.2 Additional issues associated with genomics

The incidence of \geq grade 3 febrile neutropenia was highly increased in Asians receiving P/T/D compared to Asians receiving T/D (26% vs. 12%). This difference was not observed in other race groups. No biological rationale for this observation was identified. Of note, febrile neutropenia has been previously associated with docetaxel exposure (docetaxel label), and polymorphisms in CYP3A5 and ABCB1 as well as in glutathione-S-transferase (GST) have been associated with docetaxel exposure and safety profile (PMID: 16765145). In any case, it is unlikely that polymorphisms associated with docetaxel exposure would explain the higher rate of febrile neutropenia in Asians receiving P/T/D compared to T/D, since both arms included docetaxel and the study arms were balanced for demographic and clinically relevant factors. Of note, the sponsor did not explore a potential underlying pharmacogenetic association with febrile neutropenia.

4 Summary and Conclusions

Our correlative safety analysis did not show a robust correlation of assessed baseline biomarkers with LVD/CHF in the pivotal trial. However, we may have identified a subpopulation [patients on P/T/D therapy who have low baseline sHER2 levels ($< 25.53\text{ng/mL}$)] who is at a decreased risk for developing LVD/CHF events. The results could be useful if confirmed in future trials. At this point, there is no apparent biological mechanism that explains the potential association of low HER2 levels with decreased risk for LVD/CHF in P/T/D therapy. Also, we did not observe the association in the T/D arm which may be surprising given the similar MOA of pertuzumab and trastuzumab. A potential cardioprotective role of pertuzumab for T/D therapy can also not be excluded at this time but additional studies are necessary to support this hypothesis. On-treatment changes of assessed biomarkers as potential correlates of safety risk could not be evaluated since the sponsor has not yet assayed the biomarkers beyond the baseline timepoint.

The observed correlation of FCGR2A-131 genotype with LVD/CHF in patients receiving only T/D may further be explored in future studies and should be considered exploratory at this time. Considering that ADCC is included in the MOA for both drugs, pertuzumab and trastuzumab, it is currently unclear why an association with FCGR polymorphisms was not also observed in the P/T/D arm.

5 Recommendations

BLA 125409 is acceptable for approval from the OCP Genomics Group perspective. No labeling or post-approval decision actions are proposed at this time.

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