26 April 2018
EMA/CHMP/366182/2018
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Perjeta

International non-proprietary name: pertuzumab

Procedure No. EMEA/H/C/002547/II/0034

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
AUC_{ss}	area under the concentration versus time curve at steady state
BIG	Breast International Group
bpCR	breast pathologic complete response
BrEAST	Breast European Adjuvant Study Team
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
$C_{max,ss}$	maximum concentration at steady state
$C_{min,ss}$	minimum concentration at steady state
CSR	clinical study report
DFS	disease-free survival
DRFI	distant recurrence-free interval
EBC	early breast cancer
ESMO	European Society for Medical Oncology
EtM	event to monitor
FEC	5-fluorouracil, epirubicin, cyclophosphamide
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRQoL	health-related quality of life
IDFS	invasive disease-free survival
IDFS-SPNBC	invasive disease-free survival including second primary non-breast cancer
IDMC	Independent Data Monitoring Committee
ITT	intent-to-treat
LVEF	left ventricular ejection fraction
LVD	left ventricular systolic dysfunction
MBC	metastatic breast cancer
NYHA	New York Heart Association
OS	overall survival
pCR	pathologic complete response
PCTT	post-chemotherapy targeted therapy
PFS	progression-free survival
PK	pharmacokinetic
PAM	post-approval measure
popPK	population pharmacokinetic
PRO	patient-reported outcome
PT	preferred term
q3w	every 3 weeks
RFI	recurrence-free survival
SAE	serious adverse event
sBLA	supplemental Biologics License Application
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SOC	system organ class
TCH	docetaxel (Taxotere®), carboplatin and Herceptin
tpCR	total pathologic complete response
TTTC	targeted therapy + taxane chemotherapy

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 23 August 2017 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication for Perjeta in combination with trastuzumab and chemotherapy for the adjuvant treatment of adult patients with HER2-positive early breast cancer. The submission is based on the primary analysis of efficacy and safety data from the pivotal Phase III study BIG-4-11/BO25126/TOC4939g (APHINITY). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.
The RMP version 10.2 has also been submitted.

The variation proposed amendments to the SmPC, and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMA/973755/2011, CW/1/2011, dated 19/12/2011 on the granting of a class waiver in the treatment of breast carcinoma.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. Please refer to separate assessment report.

Scientific advice

Scientific Advice was given from CHMP/SAWP on the study design of the BIG 4-11 / BO25126 / TOC4939g (APHINITY) study, dated 21 October 2010 (EMEA/H/SA/897/3/210/III).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Daniela Melchiorri

Timetable	Actual dates
Submission date	23 August 2017
Start of procedure:	16 September 2017
CHMP Rapporteur Assessment Report	10 November 2017
CHMP Co-Rapporteur Assessment Report	24 November 2017
PRAC Rapporteur Assessment Report	16 November 2017
Updated PRAC Rapporteur Assessment Report	24 November 2017
PRAC Outcome	30 November 2017
CHMP members comments	4 December 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	8 December 2017
Request for supplementary information (RSI)	14 December 2017
CHMP Rapporteur Assessment Report	26 March 2018
PRAC Rapporteur Assessment Report	28 March 2018
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	12 April 2018
CHMP members comments	16 April 2018
Updated CHMP Rapporteur Assessment Report	19 April 2018
Opinion	26 April 2018
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Perjeta in comparison with existing therapies (Appendix 1)	26 April 2018

2. Scientific discussion

2.1. Introduction

Pertuzumab (rhuMab 2C4, Perjeta®) is a recombinant, humanized immunoglobulin (Ig)G1κ monoclonal antibody, which targets the human epidermal growth factor receptor 2 (HER2, also known as c-erbB-2), a transmembrane glycoprotein with intrinsic tyrosine kinase activity. By binding to the subdomain 2 epitope of the extracellular domain of HER2, it prevents heterodimerization of HER2 with other members of the HER family (HER1, HER3 and HER4), and as a result, ligand-activated downstream signalling is blocked by pertuzumab. Pertuzumab is also capable of activating antibody-dependent cell-mediated cytotoxicity.

Perjeta was first granted marketing authorization in the United States (US) on 08 June 2012 and in the European Union (EU) on 04 March 2013, for use in combination with trastuzumab (Herceptin®) and docetaxel in patients with HER2-positive metastatic breast cancer (MBC). The approval was based on data

from the pivotal Phase III study, WO20698/TOC4129g (CLEOPATRA), which showed compelling evidence of clinical benefit in patients with HER2-positive MBC, with a statistically significant and clinically relevant increase in progression-free survival (PFS) and overall survival (OS). In addition, supportive data was submitted from more than 15 other clinical studies of Perjeta.

A Type II variation was subsequently submitted in the EU on 15 August 2014 seeking an extension of the indication to include use of Perjeta in the neoadjuvant setting in patients with HER2-positive early breast cancer (EBC), based on the results from two randomized Phase II studies WO20697 (NEOSPHERE) and BO22280 (TRYPHAENA). Results of the pivotal NEOSPHERE study in patients with HER2-positive inflammatory, locally advanced or EBC showed that the addition of Perjeta to standard neoadjuvant therapy with Herceptin and docetaxel resulted in a significantly higher rate of pathological complete response (pCR) compared to either Perjeta or Herceptin alone in combination with docetaxel, with little additional toxicity (Gianni et al, 2012). TRYPHAENA, designed as a cardiac tolerability study, evaluated Perjeta and Herceptin in combination with clinically established anthracycline- and non-anthracycline-based regimens; pCR was a secondary endpoint. The pCR rates reported in this study compared favorably with published data. The Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion recommending the use of Perjeta in the neoadjuvant setting and this was followed by an EU Commission Decision on 28 July 2015 for the following indication:

Use in combination with trastuzumab and chemotherapy in the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.

Perjeta has been approved in more than 100 countries worldwide for the treatment of patients with HER2-positive MBC, and in more than 80 countries for the neoadjuvant treatment of patients with HER2-positive EBC.

The purpose of this Type II variation is to seek approval for the use of Perjeta in the adjuvant treatment of patients with HER2-positive EBC, and to reflect in the PI the results of the study agreed as Annex IID obligation to the approval for the neoadjuvant indication of Perjeta granted on 28 July 2015.

This application is based on the primary analysis of efficacy and safety data from the pivotal (confirmatory) Phase III study, BIG 4-11/BO25126/TOC4939g (hereafter referred to as ″APHINITY″). This is a randomized multicenter, double-blind, placebo-controlled study comparing Perjeta plus Herceptin plus standard chemotherapy (Ptz+H+Chemo) versus placebo plus Herceptin plus standard chemotherapy (Pla+H+Chemo) as adjuvant therapy in patients with operable HER2-positive EBC. The Applicant considers that the efficacy and safety data from APHINITY submitted with this Type II variation support a positive benefit-risk assessment in a population with a high unmet medical need. APHINTY showed that the addition of 1 year (up to 18 cycles) of Perjeta to standard Herceptin and chemotherapy in the adjuvant setting demonstrated a statistically significant and clinically meaningful benefit in invasive disease-free survival (IDFS) in a setting with curative intent. Based on these results, the Applicant now proposes the following revised wording of the indication.

Early Breast Cancer

Perjeta is indicated for use in combination with trastuzumab and chemotherapy in:

- *the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence (see section 5.1)*

HER2 Positive Breast Cancer

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related deaths in women worldwide. An estimated 1.7 million new breast cancer cases were diagnosed in 2012 (25% of all cancers in women) and there were 521,900 deaths (Ferlay et al, 2015; DeSantis et al, 2015).

The HER2 receptor has emerged as an important target for the treatment of breast cancer. HER2 is involved in regulating cell growth, survival, and differentiation (Sundaresan et al, 1999). Amplification and/or overexpression of HER2 occurs in around 15% – 20% of breast cancers (Wolff et al, 2007; Chia et al, 2008; Ross et al, 2009) and is associated with increased tumor aggressiveness, higher rates of recurrence, and increased mortality (Borg et al, 1990; Ross et al, 1998; Menard et al, 2001; Brown et al, 2008; Curigliano et al, 2009; Ross et al, 2009).

Current Treatment of HER2-Positive Breast Cancer

Approval of Herceptin for adjuvant use was based on data generated from four large studies, which showed that adjuvant Herceptin reduces the (relative) risk of relapse by about 50% and the risk of death by about 30% in patients with HER2-positive EBC (HERA/BO16348 [Piccart-Gebhart et al, 2005]; NSABP B-31 and NCCTG N9831 [Romond et al, 2005]; BCIRG 006 [Slamon et al, 2009]). Additional studies have been conducted in patients with HER2-positive EBC, in which adjuvant treatment with Herceptin-based therapy was the control arm therapy, notably the BO20906 (BETH) and ALTTO studies (Report No.1056851 [clinical cut-off date: 30 June 2013]; Piccart-Gebhart et al. 2016). These studies showed similar high rates of disease-free survival (DFS) as seen in the HERA, BCIRG006, NSABP B-31 and NCCTG N9831 studies.

Perjeta also targets HER2 and when combined with Herceptin provides a more complete blockade of the HER2 pathway and greater anti-cancer activity. Perjeta in combination with Herceptin + Chemotherapy has now become the recommended standard of care in MBC and for neoadjuvant use in patients with high risk EBC undergoing neoadjuvant therapy (NCCN Guidelines, Version 1.2017 [Gradishar et al, 2017]; European Society for Medical Oncology [ESMO] guidelines [Senkus et al, 2015]). Apart from Herceptin and Perjeta, trastuzumab emtansine (ado-trastuzumab emtansine, T-DM1; Kadcyla®) and lapatinib (Tykerb®; Tyverb®) are HER2-targeted agents currently approved in many countries for the treatment of patients with HER2-positive MBC. However, neither is approved for adjuvant use in patients with EBC. In addition, results have been reported from a study with the investigational agent, neratinib (a tyrosine kinase inhibitor), in the extended adjuvant EBC setting after completion of one year of adjuvant Herceptin (ExteNET study; Chan et al, 2016). In this study, extended adjuvant treatment with 12 months of neratinib in patients who had previously received adjuvant Herceptin and chemotherapy, improved the 2-year IDFS rate.

2.2. Non-clinical aspects

2.2.1. Introduction

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.2. Ecotoxicity / environmental risk assessment

Pertuzumab is a recombinant humanised IgG1 monoclonal antibody. Proteins and peptides are exempted from the need to provide an ERA, because they are unlikely to result in significant risk to the environment. Neither Perjeta as finished product (420 mg concentrate for solution for infusion) including its excipients, poses a significant risk to the environment.

Thus, in accordance with the "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA, 2006), the justification presented by the MAH for the not providing an ERA in the context of the current extension of indication, is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

All clinical trials carried out outside the European Union meet the ethical requirements of the EU Clinical Trial Directive [2001/20/EC].

The Application is based on the APHINITY study (pivotal study).

2.3.2. Pharmacokinetics

For the present application, the following analyses have been presented:

- PK data from the APHINITY study
- Comparison of PK data from APHINITY with the developed popPK model for pertuzumab
- Comparisons of observed pertuzumab and trastuzumab data from APHINITY with data from previous studies and indications
- A DDI assessment
- Results of an exploratory E-R analysis

PK data from the APHINITY study

A total of 72 patients consented to participate in the global PK sub-study, of whom 38 patients were randomized to the Ptz+H+Chemo arm and 34 patients were randomized to Pla+H+Chemo. The blood sample collection time points were Cycle 1 pre- and post-infusion, Cycle 2 pre-infusion, Cycle 10 pre- and post-infusion, and Cycle 15 pre- and post-infusion. There were 36 PK evaluable patients from the Ptz+H+Chemo arm and 34 PK evaluable patients from the Pla+H+Chemo arm, defined as a patient who had received at least one active pertuzumab and/or trastuzumab treatment and had at least one PK sample collected. Thirty-five patients in the Ptz+H+Chemo arm contributed pertuzumab PK samples to the PopPK analysis. Summary statistics of serum pertuzumab peak and trough concentrations are summarized in the table below:

Table 1 Summery of Pertuzumab Pharmacokinetic Paramerters

Treatment Group		Cycle 1 C_{max} (µg/mL)	Cycle 1 C_{min} (µg/mL)	Cycle 10 C_{min} (µg/mL)	Cycle 10 C_{max} (µg/mL)	Cycle 15 C_{min} (µg/mL)	Cycle 15 C_{max} (µg/mL)
Pertuzumab + Trastuzumab	N	33	31	31	29	27	24
	Mean (SD)	237 (118)	68.0 (16.6)	88.1 (34.4)	222 (92.2)	95.5 (51.5)	206 (94.9)

SD=Standard deviation.

Cycle 1, 10, and 15 C_{max} = post-infusion serum concentration; Cycle 1 C_{min}=predose serum concentration concentration at Cycle 2; Cycle 10 C_{min} = predose serum concentration at Cycle 10; Cycle 15 C_{min}=predose serum concentration at Cycle 15.

Following IV administrations of a pertuzumab 840-mg loading dose and subsequent 420-mg maintenance doses, every 3 weeks, the mean observed trough concentrations increased over time and the mean observed peak concentrations remained roughly equivalent over time. In this study, serum pertuzumab exposure reached steady-state by Cycle 10. However, due to the sparse sampling design of the study, the onset of steady-state could not be assessed. The PK data in patients with HER2-positive EBC was comparable to PK data observed in patients with HER2-positive MBC.

Observed pertuzumab peak and trough serum concentrations at Cycles 1, 10, and 15 from APHINITY were compared with observed pertuzumab peak and trough serum concentrations at Cycles 3, 9, and 15 in the previous MBC trial CLEOPATRA, to assess the impact of disease stage on pertuzumab PK.

Table 2 Pertuzumab Serum C_{min} and C_{max} (in the presence of Trastuzumab and / or Chemotherapy in Patients with EBC and MBC

APHINITY (EBC)					CLEOPATRA (MBC)				
Cycle	n	C_{min} (µg/mL) Arithmetic Mean±SD	n	C_{max} (µg/mL) Arithmetic Mean±SD	Cycle	n	C_{min} (µg/mL) Arithmetic Mean±SD	n	C_{max} (µg/mL) Arithmetic Mean±SD
1	30	65.9±12.4	30	291±99.1	3	18	63.4±48.1	18	183±33.5
10	30	91.0±30.9	28	230±83.4	9	16	75.5±22.1	14	196±66.3
15	24	98.4±39.6	21	233±64.6	15	11	94.1±30.6	9	221±32.0

C_{max} = maximum concentration; C_{min} = minimum concentration; EBC = early breast cancer; MBC = metastatic breast cancer.

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Pharmacokinetic interaction

Of the 72 patients who participated in the global PK sub-study, 70 patients received at least one dose of trastuzumab (36 in Ptz+H+Chemo arm and 34 in Pla+H+Chemo arm). The blood sample collection time points were Cycle 1 pre- and post-infusion, Cycle 2 pre-infusion, Cycle 10 pre- and post-infusion, and Cycle 15 pre- and post-infusion.

In order to evaluate the **impact of pertuzumab on trastuzumab** Cmin or Cmax when the two antibodies were administered concurrently in combination with an EBC chemotherapy regimen, the exposures of the two drugs are summarised below:

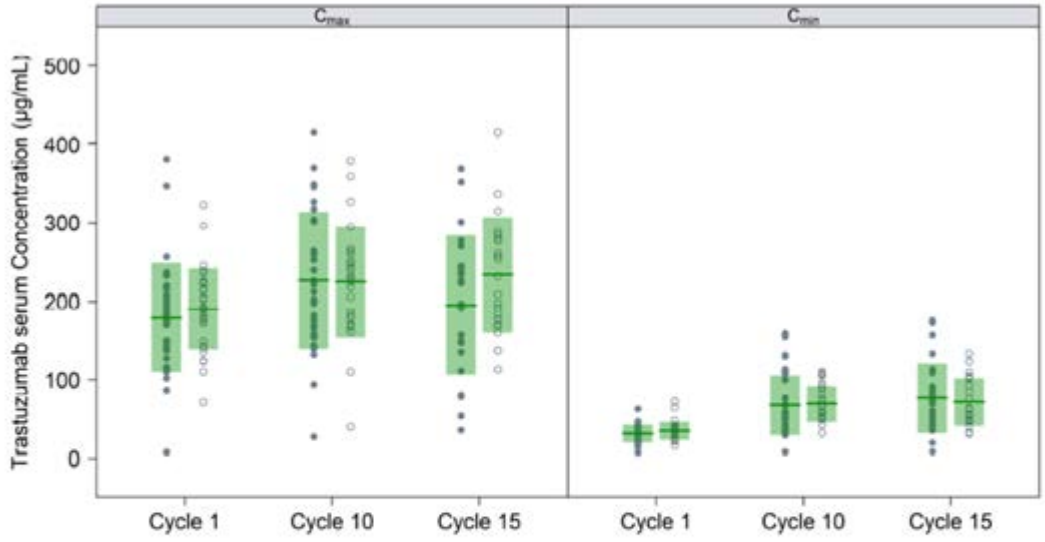
Table 3 Summery of Serum C_{min} and C_{max} of Trastuzumab with Pertuzumab or Placebo

Timepoint	n	Ptz+H+Chemo Arithmetic Mean (±SD)	n	Pla+H+Chemo Arithmetic Mean (±SD)	Mean Ratio [a] (90% CI)
Cycle 1 C_{max} (µg/mL)	34	179 (±69.1)	33	190 (±51.6)	0.873 (0.713-1.07)
Cycle 1 C_{min} (µg/mL)	31	30.8 (±11.3)	31	34.1 (±11.4)	0.874 (0.745-1.03)
Cycle 10 C_{max} (µg/mL)	32	226 (±87.4)	27	225 (±70.7)	0.978 (0.797-1.20)
Cycle 10 C_{min} (µg/mL)	32	67.0 (±38.5)	26	68.4 (±23.0)	0.878 (0.711-1.09)
Cycle 15 C_{max} (µg/mL)	24	195 (±88.6)	21	234 (±73.5)	0.765 (0.605-0.968)
Cycle 15 C_{min} (µg/mL)	26	75.7 (±44.6)	22	71.0 (±30.4)	0.967 (0.737-1.27)

C_{max} = maximum concentration; C_{min} = minimum concentration ; Pla+H+Chemo = placebo plus Herceptin plus chemotherapy; Ptz+H+Chemo = Perjeta plus Herceptin plus chemotherapy.

[a] Ratios of geometric means.

Figure 1 Serum C_{min} and C_{max} of Trastuzumab with or without Pertuzumab



C_{max} = maximum concentration; C_{min} = minimum concentration ; Pla+H+Chemo = placebo plus Herceptin plus chemotherapy; Ptz+H+Chemo = Perjeta plus Herceptin plus chemotherapy.

Closed circles = Ptz+H+Chemo; open circles = Pla+H+Chemo; solid green line = arithmetic mean for each timepoint and treatment arm; shaded area = arithmetic mean ± 1 SD.

Steady-state concentrations of trastuzumab from patients in the APHINITY study were compared with data from a previous study of adjuvant trastuzumab in patients with EBC. After confirming a lack of PK DDI between pertuzumab and trastuzumab in APHINITY as summarized above, trastuzumab PK data from both arms of the APHINITY study were compared with historical observed PK data from the Study BO16348 (HERA). The HERA study was a pivotal, randomized Phase III study in which patients were treated with 1 year of adjuvant trastuzumab monotherapy or placebo after completion of standard adjuvant chemotherapy (Report No. 1066908). Patients also received adjuvant hormonal therapy if clinically indicated, after completion of chemotherapy. The table below shows comparable observed trastuzumab Cmin and Cmax between APHINITY and HERA at similar cycles.

Table 4 Summery of Serum C_{min} and C_{max} of Trastuzumab (in the Presence of Chemotherapy and Pertuzumab or Placebo) in Two EBS Studies

APHINITY					HERA				
	C_{min} (µg/mL)		C_{max} (µg/mL)			C_{min} (µg/mL)		C_{max} (µg/mL)	
Cycle	Arithmetic Mean±SD	n	Arithmetic Mean±SD	n	Cycle	Arithmetic Mean±SD	n	Arithmetic Mean±SD	n
10	67.7±32.2	58	226±79.5	59	10	66.0±39	3	203±7.0	3
15	73.6±38.4	48	213±83.3	45	12	72.3±46	15	237±12.0	15

C_{max} = maximum concentration; C_{min} = minimum concentration; EBC = early breast cancer.

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These findings further support a lack of impact of pertuzumab on trastuzumab PK.

Following IV administrations of a trastuzumab 8 mg/kg loading dose and subsequent 6 mg/kg maintenance doses, every 3 weeks, the mean observed trough concentrations increased over time and the mean observed peak concentrations remained roughly equivalent over time. In this study, serum trastuzumab exposure reached steady-state by Cycle 10. However, due to the sparse sampling design of the study, the onset of steady-state could not be assessed. Trastuzumab PK data was comparable to prior observations in patients with HER2-positive EBC.

Since all patients in the APHINITY study received concurrent pertuzumab and trastuzumab, the potential **effect of trastuzumab on the PK of pertuzumab** could not be assessed using data from the APHINITY study alone. Instead, it was assessed by comparing the observed pertuzumab concentrations in APHINITY with the popPK model predictions. In contrast to the APHINITY study, the majority of the PK data (>95%) used to build the popPK model came from patients treated with pertuzumab without concomitant trastuzumab. Additionally, patients in 7 of the 12 studies in the popPK model were treated with pertuzumab as monotherapy (without concomitant chemotherapy or targeted therapies).

Observed pertuzumab data from APHINITY were compared to the observed pertuzumab data from the previous MBC trial CLEOPATRA, table below:

Table 5 Summery of Serum C_{min} and C_{max} of Pertuzumab (in the Presence of Trastuzumab +/- Chemotherapy) in Patients with EBC and MBC

APHINITY (EBC)					CLEOPATRA (MBC)				
Cycle	C_{min} ($\mu g/mL$)	n	C_{max} ($\mu g/mL$)	n	Cycle	C_{min} ($\mu g/mL$)	n	C_{max} ($\mu g/mL$)	n
1	65.9±12.4	30	291.2±99.1	30	3	63.4±48.1	18	183±33.5	18
10	91.0±30.9	30	229.8±83.4	28	9	75.5±22.1	16	196±66.3	14
15	98.4±39.6	24	232.8±64.6	21	15	94.1±30.6	11	221±32.0	9

Serum Cmin and Cmax in APHINITY (Cycles 1, 10, and 15) are comparable to PK data from the CLEOPATRA study (Cycles 3, 9, and 15).

Paclitaxel and carboplatin

For patients in the anthracycline cohort receiving Ptz+H with paclitaxel, a total of 18 blood samples of 5 mL each were needed for PK evaluation and these were collected over a period of 15 cycles (21 days/cycle). For patients in the non-anthracycline cohort receiving Ptz+H with docetaxel and carboplatin, a total of 20 blood samples of 5 mL each were needed for PK evaluation and these were collected over a period of 15 cycles (21 days/cycle). For paclitaxel, blood samples were collected during Cycle 1 only at pre-infusion, and 3, 5, and 24 hours after the start of infusion. For carboplatin, blood samples were collected during Cycle 1 only at pre-infusion, end-of-infusion, and 1, 2, 4, and 5 hours after the end-of-infusion.

The potential effect of pertuzumab on the PK of paclitaxel and carboplatin was assessed by comparing the arithmetic means of the carboplatin or paclitaxel plasma Cmax and AUClast in Cycle 1 between the Ptz+H+Chemo and Pla+H+Chemo treatment arms. Paclitaxel and paclitaxel metabolite PK parameters and 90% CI of the geometric mean ratios in the Ptz+H+Chemo and Pla+H+Chemo treatment arms are summarized below:

Table 6 Summery of Paclitaxel PK Parameters (in the Presence of Trastuzumab) with or without Pertuzumab

	Ptz+H+chemo (±SD)	Pla+H+chemo (±SD)	Mean Ratio* (90% CI)
n	23	21	
C_{max}	665.3 (±494.8)	834.6 (±495.5)	0.639 (0.387-1.06)
AUC_{last}	3901.2 (±3073.5)	4816.7 (±3859.9)	0.731 (0.485-1.1)

Arithmetic means. Plasma C_{max} in ng/mL. Plasma AUC_{last} in ng·h/mL. * Ratios of Geometric Means.

The 90% CI of the mean ratio of PK parameters were wide and most probably affected by the variability in PK parameters and the low statistical power associated with the small sample sizes of the treatment groups. The results suggest that there is no impact of pertuzumab on the PK of paclitaxel, as expected since there is no apparent mechanistic basis for a PK DDI between these agents. The 6-alpha-hydroxy metabolite of paclitaxel was also measured in the global PK substudy and there were detectable levels at 3 and 5 hours post-dose. The Cmax of the paclitaxel metabolite in the Ptz+H+Chemo and Pla+H+Chemo arms was compared and the mean ratio (90% CI) was 0.882 (0.587-1.33), supporting that in addition to no impact of pertuzumab on the PK of paclitaxel, there is no impact on paclitaxel's 6-alpha-hydroxy metabolite.

Carboplatin PK parameters and 90% CIs of the geometric mean ratios in the Ptz+H+Chemo and Pla+H+Chemo treatment arms are showed below:

Table 7 Summery of Carboplatin PK Parameters (in the Presence of Trastuzumab) with Pertuzumab or without Pertuzumab (Placebo)

	Ptz+H+Chemo Arithmetic Mean (±SD)	Pla+H+Chemo Arithmetic Mean (±SD)	Mean Ratio [a] (90% CI)
N	6	12	-
C_{max} (ng/mL)	25100 (±3450)	27300 (±8880)	0.959 (0.795-1.16)
AUC_{last} (ng*h/mL)	30000 (±18900)	36900 (±20800)	0.833 (0.307-2.26)

AUC_{last} = area under the concentration versus time curve over all concentration measurements; C_{max} = maximum concentration; PK = pharmacokinetic; Pla+H+Chemo = placebo plus Herceptin plus chemotherapy; Ptz+H+Chemo = Perjeta plus Herceptin plus chemotherapy.

[a] Ratios of geometric means.

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Similar to paclitaxel, the 90% CI of the mean ratio of PK parameters were wide and most probably affected by the variability in PK parameters and the low statistical power associated with the small sample sizes of the treatment groups. The results suggest that there is no impact of pertuzumab on the PK of carboplatin, as expected since there is no apparent mechanistic basis for a PK DDI between these agents.

2.3.3. Pharmacodynamics

Mechanism of action

Perjeta is a recombinant humanised monoclonal antibody that specifically targets the extracellular dimerization domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2), and thereby, blocks ligand-dependent heterodimerisation of HER2 with other HER family members, including EGFR, HER3 and HER4. As a result, Perjeta inhibits ligand-initiated intracellular signalling through two major signal pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signalling pathways can result in cell growth arrest and apoptosis, respectively. In addition, Perjeta mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

2.3.4. PK/PD modelling

The Global PK Substudy included 72 patients of whom 38 were in the Ptz+H+chemo treatment arm and 35 contributed pertuzumab concentration data for the PopPK analysis as detailed below:

Table 8 Summery of Pertuzumab PK Sampling and Patients Included in the Global PK Substudy

	Global PK Substudy
N patients	72
Patients exposed to pertuzumab treatment	38
Patients contributing pertuzumab PK samples for the analysis	35
PK Sampling	
Cycle 1:	pre- and post-infusion
Cycle 2:	pre-infusion only
Cycle 10:	pre- and post-infusion
Cycle 15:	pre- and post-infusion

For more information consult the clinical study protocol.

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Pertuzumab data was completely removed for 3 patients: Patient 2093020006 did not have any recorded pertuzumab data (no pertuzumab doses or observations), Patient 2099570001 had non-plausible PK data, and Patient 2469040007 had blank time records for the pertuzumab observations.

A PK model previously developed for pertuzumab based on a large database of patients with solid tumors, including MBC, was subjected to external validation to examine whether it is appropriate for patients included in the APHINITY study.

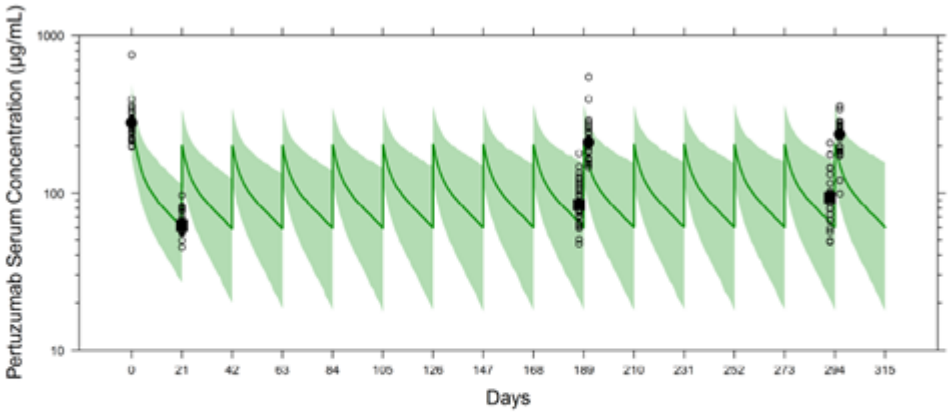
The previously developed PopPK model was built on data from 5 Phase I/Ib studies, 6 Phase II studies, and 1 pivotal Phase III study. In contrast to the current study, the majority of the data (>95%) used to build the PopPK model was based on pertuzumab without concomitant trastuzumab treatment. Additionally, 7 of the 12 studies in the PopPK model investigated pertuzumab as monotherapy (without concomitant chemotherapy or targeted therapies).

Pertuzumab PK was described by a two-compartment linear model with a clearance (CL), central volume of distribution (Vc), and terminal elimination half life (t1/2) of 0.235 L/ day, 3.11 L, and 18 days, respectively. LBW and baseline serum albumin (ALBU) were identified as statistically significant covariates inuencing pertuzumab PK.

The PopPK analysis was carried out using NONMEM (Version 7.3, ICON Development Solutions, Elicott City, MD, USA). The NONMEM installation was validated according to qPharmetra information system and information technology (ISIT) Policies. Post-processing of NONMEM analysis results was carried out in R version 3.2.2. Estimation of individual PK parameters was carried out using first order conditional estimation with Interaction (FOCE-I).

Pertuzumab PK results from patients in APHINITY were compared with those predicted from the pertuzumab popPK model that was developed using data from 481 patients in 12 clinical studies. The observed pertuzumab peak and trough serum concentrations (black circles) from the APHINITY patients and the covariate-adjusted, model-predicted median serum concentrations for the population (green line) and the 5th through 95th percentiles (green shaded area; 95% prediction interval) are showed in the figure below:

Figure 2 Observed versus Model-Simulated Pertuzumab Peak and Trough Concentrations in APHINITY



C_{max} = maximum concentration; C_{min} = minimum concentration.

Open circles = observed serum concentrations; filled circles = median observed serum C_{max}; filled squares = median observed serum C_{min}; solid green line = predicted median serum concentration; shaded area = 95% prediction interval.

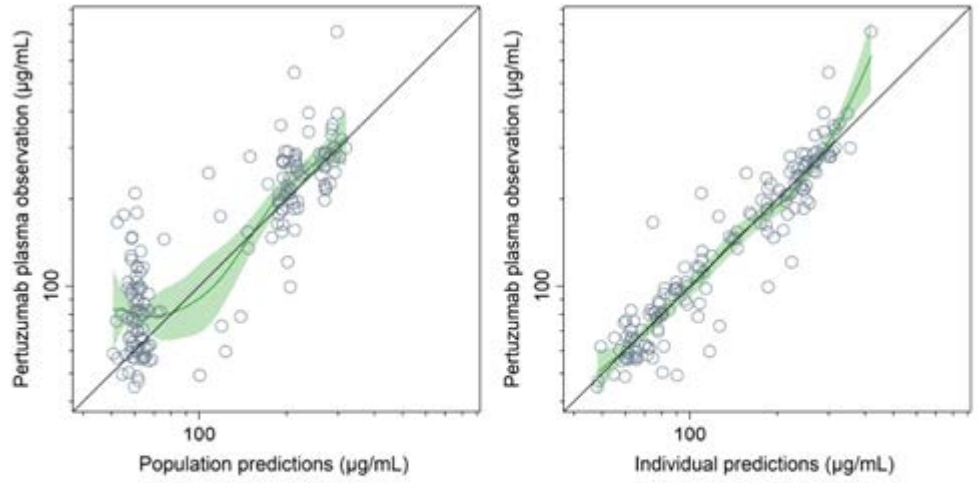
Note: The symbols have been shifted slightly on the x-axis to make it easier to distinguish the pre-dose and post-infusion observation in Cycles 10 and 15.

Overall, the popPK model predicted the observed serum concentrations of pertuzumab reasonably well across cycles after correcting for baseline differences in weight and albumin concentrations. A slight increase in observed pertuzumab concentrations (minimum concentration [Cmin]) was seen in later cycles although the majority of the observed pertuzumab concentrations were within the 95% prediction interval.

According to the MAH, the ability of the popPK model to predict the pertuzumab serum concentrations in the APHINITY study suggests that trastuzumab does not affect pertuzumab PK. These results are consistent with previous results from the CLEOPATRA and NEOSPHERE studies, which showed no impact of trastuzumab on pertuzumab PK.

Graphical assessment of the match between observed and model predicted pertuzumab concentrations, as well as conditional weighted residuals, suggested an adequate fit of the model to the data, although trends can be seen for low pertuzumab population predictions. Diagnostic plots of observed data vs. population prediction (PRED) and individual prediction (IPRED) were examined for adequate fit. Plots of conditional weighted residual (CWRES) versus PRED and versus time (time after last dose as well as time after first dose) are reported below:

Figure 3 Observed Versus Model-Simulated Pertuzumab Serum Concentrations



Solid Black Line: Line of identity. **Solid Green Line and Shaded Green Area**: Gaussian Loess smooth with 95% CI. Left Panel: **Circles**: Individual observations / Population predictions, Right Panel: **Circles**: Individual observations / Individual predictions.

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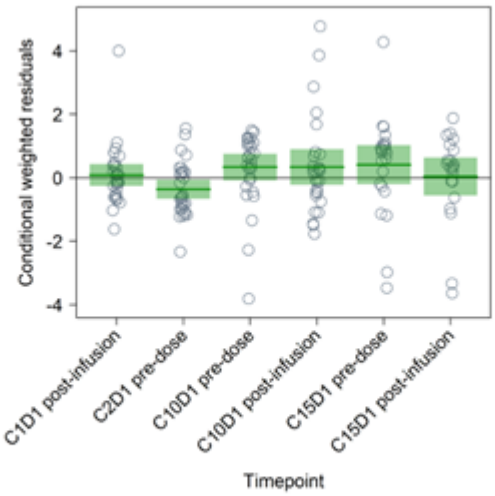
Figure 4 Conditional Weighted Residuals – by Time Point



Circles: Individual CWRES, **Solid Green Line**: Mean CWRES for each timepoint **Shaded Area**: The shaded areas indicate the 95% CI for the mean CWRES.

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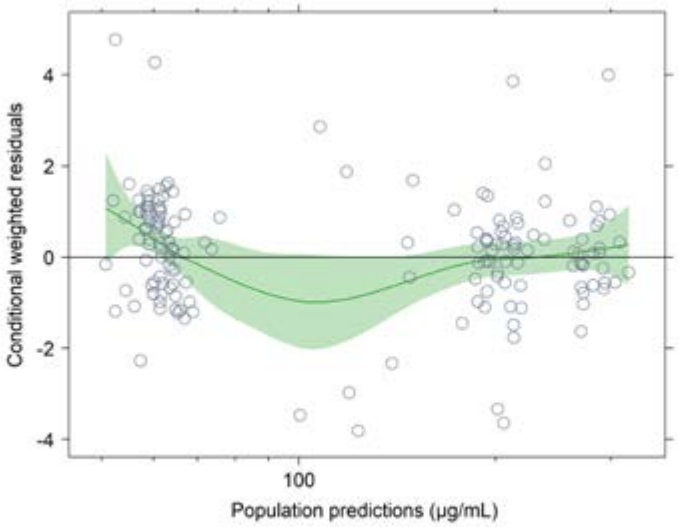
Figure 5 Conditional Weighted Residuals Versus Population Predictions



Circles: Individual CWRES Solid Green Line and Shaded Green Area: Gaussian Loess smooth with 95% CI.

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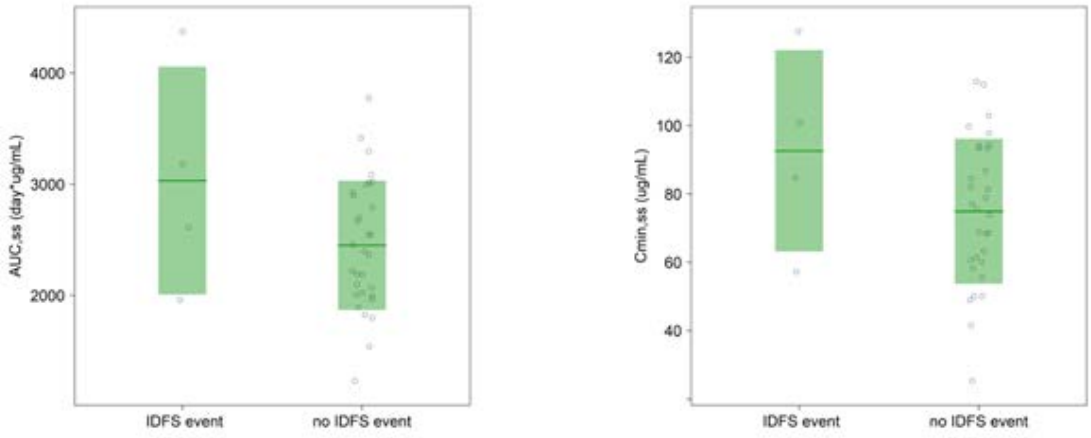
Exposure-response Analysis

To generate individual pertuzumab exposure for patients in the Ptz+H+chemo treatment arm of the Global PK Substudy, a simulation dataset was constructed based on estimated individual parameters for the PopPK model. For all patients with at least one available valid concentration measurement of pertuzumab, predictions of Cmax;ss, Cmin;ss and AUCss were derived. The simulation dataset consisted of a loading dose and 3 maintenance doses. The loading dose, including infusion duration, was taken from the NONMEM dataset for each patient in the Ptz+H+chemo treatment arm in the Global PK Substudy, thereafter, 3 doses of 420 mg pertuzumab were administered using a 30 minute infusion with 3 weeks dosing interval. Individual predictions of concentration at the end of infusion (Cmax;ss) and before next dose (Cmin;ss) were generated following the third maintenance dose for all patients.

The efficacy endpoint in the exposure-efficacy analysis was the primary study endpoint, IDFS, defined as the time from randomization until the date of first occurrence of one of the following events: ipsilateral invasive breast tumor recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death attributable to any cause. Patients who had not had an event at the time of data analysis were censored at the date they were last known to be event free. The primary exposure metrics used in the exposure-efficacy analysis were individual predicted Cmin;ss and AUCss.

A total of 35 patients in the Ptz+H+chemo arm with predicted AUCss and Cmin;ss were included in the exposure-efficacy analysis.

Figure 6 Pertuzumab AUC_{ss} and $C_{min, ss}$ for Patients with or without an IDFS event (Ptz+H+chemo Treated Patients



Solid Green Line: Arithmetic mean for each group **Shaded Area**: Arithmetic mean $\pm 1SD$

Selection of adverse events (AEs) to be included in the safety-exposure analysis was based on the APHINITY data (overall safety population). AEs were considered if there was a difference of ≥5% in the incidence of Grade ≥ 3 AEs between the Ptz+H+chemo and Pla+H+chemo arms. Furthermore, to be considered for the analysis, pertuzumab PK data was required for 5-10 patients experiencing the AE, and "Any Grade ≥ 3 AE" (incidence 64.25% in the Ptz+H+chemo arm and 57.3% in the Pla+H+chemo arm) and Grade ≥ 3 diarrhea (incidence 9.9% in th Ptz+H+chemo arm and 3.7% in the Pla+H+chemo arm) met these criteria.

Table 9 Number of Patients (%) with Grade ≥ 3 AE in the Global PK Substudy by Treatment Arm

Treatment	Number of subjects	Any AE	Diarrhea
Pla+H+chemo	34	25 (73.5%)	2 (5.9%)
Ptz+H+chemo	35	27 (77.1%)	7 (20.0%)

The occurrence of Grade ≥3 AEs for the Pla+H+chemo treated patients and for the Ptz+H+chemo treated patients with pertuzumab exposure (AUCss or Cmax;ss) below or above median are summarized below:

Table 10 Number of Patients (%) with Grade ≥ 3 AE in the Global PK Substudy by AUC_{ss} Group

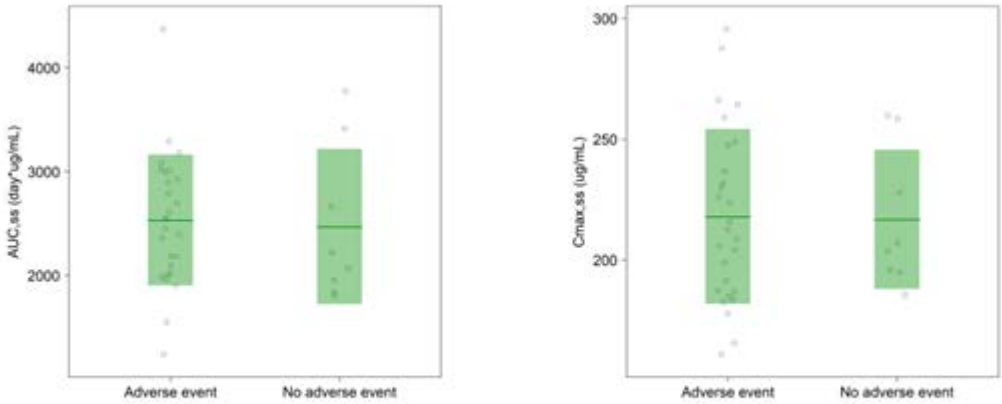
AUC group	Number of subjects	Any AE	Diarrhea
placebo	34	25 (73.5%)	2 (5.9%)
Pertuzumab below median AUC	18	13 (72.2%)	4 (22.2%)
Pertuzumab above median AUC	17	14 (82.4%)	3 (17.6%)

Table 11 Number of Patients (%) with Grade ≥ 3 AE in the Global PK Substudy by $C_{max.ss}$ Group

C_{max} group	N total	Any AE	Diarrhea
placebo	34	25 (73.5%)	2 (5.9%)
Pertuzumab below median C_{max}	18	13 (72.2%)	4 (22.2%)
Pertuzumab above median C_{max}	17	14 (82.4%)	3 (17.6%)

The figure below presents the possible relationships between AUCss or Cmax;ss and occurrence of any Grade ≥3 AE:

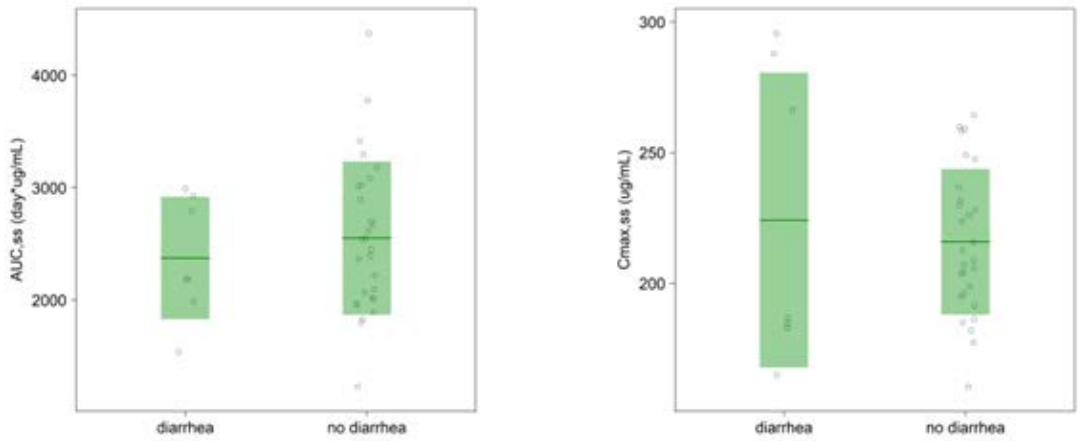
Figure 7 Pertuzumab AUC_{ss} and $C_{max,ss}$ for Ptz+H+chemo-treated Patients with or without any Grade ≥ 3 AE



Solid Green Line: Arithmetic mean for each group **Shaded Area**: Arithmetic mean $\pm 1SD$

The figure below presents the possible relationships between AUCss or Cmax;ss and occurrence of Grade ≥3 diarrhea:

Figure 8 Pertuzumab AUC_{ss} and $C_{max,ss}$ for Ptz+H+chemo-treated Patients with or without Grade ≥ 3 Diarrhea



Solid Green Line: Arithmetic mean for each group **Shaded Area**: Arithmetic mean $\pm 1SD$

According to the MAH, the incidence of Grade ≥ 3 AEs (any AE) was similar in the Pla+H+chemo and Ptz+H+chemo-treated patients in the Global PK Substudy and the incidence of Grade ≥ 3 AEs was similar in high and low pertuzumab exposure groups (10% difference but a difference of only 1 patient in two groups). The incidence of Grade ≥ 3 diarrhea was more frequent in Ptz+H+chemo-treated patients than in Pla+H+chemo-treated patients but the occurrence of Grade ≥3 diarrhea does not increase with increasing pertuzumab exposure. It should be noted that grouping of patients based on AUCss or Cmax;ss was identical, i.e. all patients with AUCss above the median also had a Cmax;ss above the median. Hence, results are identical for Cmax;ss and AUCss.

2.3.5. Discussion on clinical pharmacology

New PK data and analyses from Study BO25126 (APHINITY/BIG 4-11/TOC 4939G) have been submitted to support extension of the Perjeta indication to include its use in combination with Herceptin and chemotherapy for the adjuvant treatment of patients with HER2-positive EBC.

Comparing pertuzumab peak and trough serum concentrations at Cycles 1, 10, and 15 between EBC patients (APHINITY study) and MBC patients (CLEOPATRA study), it has been observed that, after the first cycles, pertuzumab mean Cmax value was slightly higher in EBC patients. This is not considerate clinically relevant, therefore, tumour burden not seems to affect the PK profile.

Results from the pertuzumab popPK model suggest that trastuzumab does not affect pertuzumab PK. Diagnostic plots of observed data vs. population prediction (PRED) and individual prediction (IPRED) as well as plots of conditional weighted residual (CWRES) versus PRED and versus time show some uncertainties in the model performance. Observed data vs. individual prediction plot results in the best fit and the VPC show a good fit of the data. A systematic lack of fit can be excluded, even if information derived from the developed pop PK can be considered only supportive.

Findings and analyses presented support a lack of DDI between pertuzumab and trastuzumab. No dosage adjustment is needed also for paclitaxel and carboplatin.

The exposure-efficacy analysis showed that higher exposure to pertuzumab, namely higher mean AUCss and Cmin values, were not associated with low number of IDFS events. MAH's conclusion on exposure-safety relationship are supported: no relationship is suggested from available data.

2.3.6. Conclusions on clinical pharmacology

Based on PK data from the Global PK Substudy (APHINITY study), no dose adjustment is needed either for pertuzumab, paclitaxel or carboplatin when administered in combination with trastuzumab. Overall, the clinical pharmacology data support the proposed variation application.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

An exposure-response analysis was performed based on a PopPK model. The efficacy endpoint in the exposure-efficacy analysis was the primary study endpoint, IDFS, defined as the time from randomization until the date of first occurrence of one of the following events: ipsilateral invasive breast tumor recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death attributable to any cause. Patients who had not had an event at the time of data analysis were censored at the date they were last known to be event free. The primary exposure metrics used in the

exposure-efficacy analysis were individual predicted Cmin;ss and AUCss. Results showed that higher exposure to pertuzumab was not associated with low number of IDFS events

The safety-exposure analysis was based on the APHINITY data (overall safety population). AEs were considered if there was a difference of ≥5% in the incidence of Grade ≥ 3 AEs between the Ptz+H+chemo and Pla+H+chemo arms. No relationship is suggested from available data.

For further details, see Section 2.3.

2.4.2. Main study

The APHINITY study

The **APHINITY** study: Phase III, prospective, two-arm randomized, multicenter, multinational, double-blinded, placebo-controlled study in patients with HER2-positive primary breast cancer who have had their primary tumor excised.

Methods

Study design

The **APHINITY** study is an ongoing, Phase III, prospective, two-arm randomized, multicenter, multinational, double-blinded, placebo-controlled study in patients with HER2-positive primary breast cancer who have had their primary tumor excised.

The primary objective of the study is to compare invasive disease-free survival (IDFS) in patients with HER2-positive early breast cancer (EBC) randomized to adjuvant treatment with Perjeta plus Herceptin and chemotherapy (Ptz+H+Chemo) or placebo plus Herceptin and chemotherapy (Pla+H+Chemo).

The primary tumour had to be confirmed as HER2-positive by a central pathology laboratory prior to enrollment. For each individual patient, the Investigator in consultation with the patient selected one of the standard anthracycline-based or non-anthracycline-based regimen defined in the protocol before randomization.

A total of 4805 patients were randomized in a 1:1 ratio to one of the two treatment arms. One patient was excluded from all analyses due to unreliable data, resulting in a total of 4804 patients being included in efficacy analyses and the following treatment allocations:

Perjeta plus Herceptin and chemotherapy (Ptz+H+Chemo) (2400 randomized patients):

- Herceptin: loading dose of intravenous (IV) 8 mg/kg, followed by 6 mg/kg IV every three weeks (q3w)
- Perjeta: loading dose of 840 mg/kg IV, followed by 420 mg/kg IV q3w

Placebo plus Herceptin and chemotherapy (Pla+H+Chemo) (2404 randomized patients):

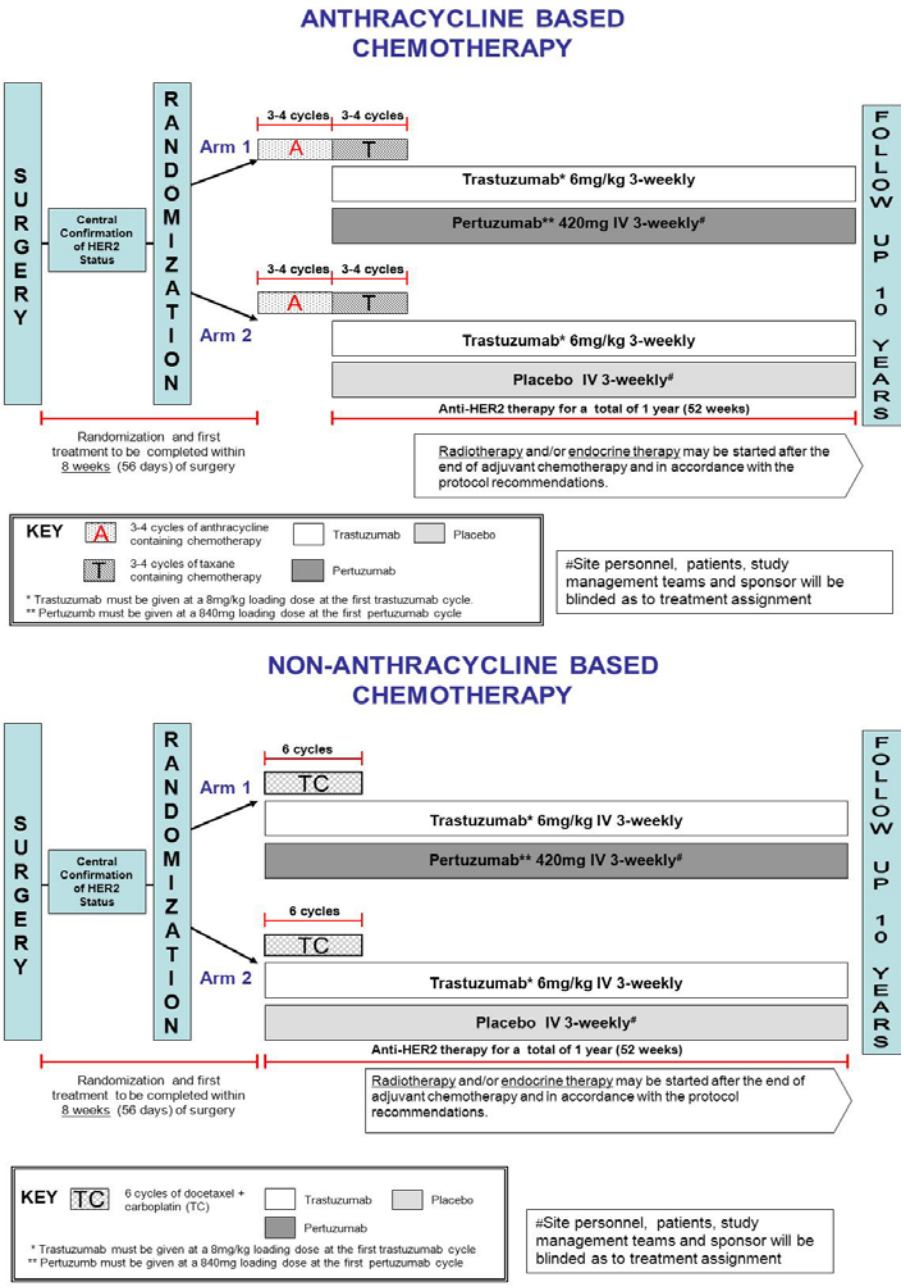
- Herceptin: loading dose of 8 mg/kg IV, followed by 6 mg/kg IV q3w
- Placebo: IV infusion q3w

Patients were stratified according to nodal status, type of standard adjuvant chemotherapy regimen (anthracycline-based versus non-anthracycline-based), hormone receptor status, geographical region and protocol version (Protocol A versus Protocol Version B). Protocol version (A versus B) was introduced as a stratification factor at the time of the first protocol amendment (Version B, dated 20 November 2012).

Randomized HER2-targeted treatment (Herceptin plus Perjeta OR Herceptin plus placebo) had to start concurrently with the taxane component of chemotherapy. All patients were required to have a screening

left ventricular ejection fraction (LVEF) ≥ 55% prior to randomization. Patients receiving anthracyclines were required to have an LVEF of ≥ 50% after completion of anthracyclines and prior to commencing HER2-targeted treatment. HER2-targeted treatment was administered for a total of up to 52 weeks (i.e., 18 cycles within 1 year).

Figure 9 Study Design



Study participants

Main inclusion and exclusion criteria

Inclusion Criteria

- Non-metastatic, histologically confirmed primary invasive breast carcinoma that had been adequately excised
- Node-positive disease (any tumor size except T0) or node-negative disease (only under Protocol Version A) were allowed to enroll. For patients with node-negative disease, one of the following conditions had to be met:
    - Tumor size > 1cm
    - Tumor size > 0.5 cm and ≤ 1cm and at least one of the following three features:
        - Histologic/nuclear Grade 3, OR
        - Negative for ER and PgR, OR
        - Age < 35 years.

  Enrollment of patients with node-negative tumors ≤ 1.0 cm was limited to < 10% of the total number of randomized patients.
- The hormone receptor status of the tumor (ER and PgR) had to be known.
- Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 1
- HER2-positivity of the breast cancer had to be confirmed by a central laboratory.
- Baseline left ventricular ejection fraction (LVEF) ≥ 55%
-

Exclusion Criteria

- History of any prior invasive breast carcinoma or a history of non-breast malignancies within 5 years prior to study entry (although certain exceptions were permitted to the prior malignancies clause)
- Any clinical T4 tumor (including inflammatory breast cancer)
- Any node-negative tumor
- Any previous systemic chemotherapy for cancer or radiotherapy for cancer
- Prior use of anti-HER2 therapy for any reason or other prior biologic or immunotherapy for cancer
- Serious cardiac or cardiovascular disease or condition
- Other concurrent serious diseases that may interfere with planned treatment including severe pulmonary conditions/illness
- Abnormal laboratory tests immediately prior to randomization
- Pregnant or lactating women

Treatments

The Perjeta dosing regimen used in APHINITY (i.e., 840 mg intravenous (IV) loading dose, followed by a maintenance dose of 420 mg IV every 3 weeks [q3w]) is the approved Perjeta dosing regimen for patients with HER2-positive MBC and for the neoadjuvant treatment of patients with locally advanced, inflammatory and EBC. Perjeta/placebo was administered for a total of 52 weeks plus a window of 3 days (i.e., maximum of 18 cycles within 1 year).

Herceptin was administered IV as an 8 mg/kg loading dose followed by 6 mg/kg q3w. This regimen is licensed in many countries for Herceptin in the adjuvant breast cancer setting. Herceptin was administered for a total of 52 weeks, plus a window of 3 days (i.e., maximum of 18 cycles within 1 year).

The anthracycline-based and non-anthracycline-based chemotherapy regimens were based on published data, clinical guidelines, and routine clinical practice, see table 12.

Table 12 Protocol Approved Chemotherapy Regimens (Investigators' Choice)

All study treatments were given intravenously.
For all regimens, the maximum allowed cumulative dose of doxorubicin was 360 mg/m^2 and of epirubicin was 720 mg/m^2.

REGIMEN	DOSE	FREQUENCY
Anthracycline therapy: FEC (or FAC) → T		
3 or 4 cycles x FEC (or FAC) → 3 or 4 cycles x docetaxel	F: 500 to 600mg/m^2 E: 90 to 120mg/m^2 or A: 50mg/m^2 C: 500 to 600mg/m^2	q3w
	Followed by: Docetaxel: 100mg/m^2 OR Docetaxel: 75mg/m^2 for 4 cycles [a] OR Docetaxel: 75mg/m^2 in the first cycle, escalating to 100mg/m^2 in subsequent cycles	q3w q3w q3w
3 or 4 cycles x FEC (or FAC) → 12 weekly cycles of paclitaxel	F: 500 to 600mg/m^2 E: 90 to 120mg/m^2 or A: 50mg/m^2 C: 500 to 600mg/m^2	q3w
	Followed by: Paclitaxel: 80mg/m^2	q1w
Anthracycline therapy: AC (or EC) → T		
4 cycles x AC [b] (or EC) → 3 or 4 cycles x docetaxel	A: 60mg/m^2 or E: 90 to 120mg/m^2 C: 500 to 600mg/m^2	q3w
	Followed by: Docetaxel: 100mg/m^2 OR Docetaxel: 75mg/m^2 for 4 cycles [a] OR Docetaxel: 75mg/m^2 in the first cycles, escalating to 100mg/m^2 in subsequent cycles	q3w
4 cycles x AC [b] (or EC) → 12 weekly cycles of paclitaxel	A: 60mg/m^2 or E: 90 to 120mg/m^2 C: 500 to 600mg/m^2	q3w
	Followed by: Paclitaxel: 80mg/m^2	q1w

Non-Anthracycline therapy: Docetaxel and Carboplatin as in BCIRG006		
6 x docetaxel + carboplatin	Docetaxel: 75mg/m^2 Carboplatin AUC 6 (max 900 mg)	q3w

A = doxorubicin; AUC = area under the curve; C = cyclophosphamide, E = epirubicin, F=5-fluorouracil; T=taxane; q1w=every week; q3w=every 3 weeks.

[a] If docetaxel 75 mg/m^2 was used and not escalated to 100mg/m^2, then 4 cycles had to be given.

[b] EC or AC could be given at the same dose (A: 60mg/m^2 or E: 90 to 120mg/m^2) every 2 weeks (dose dense) with G-CSF support, for a total of 4 cycles.

All patients entering the study were to receive radiotherapy and/or adjuvant hormone therapy, if indicated, according to standard practice. Before actively enrolling patients, each center had to define their radiotherapy and hormone therapy policies for APHINITY trial patients at their site.

In the responses to the LOQ, radiotherapy use was analyzed according to surgery type (mastectomy or breast conserving surgery [BCS]) and according to nodal status, as these are two key factors which determine the need for adjuvant radiotherapy. Finally, radiotherapy use has also been compared by geographic region.

Table 13 Randomization Stratification Factors by Treatment Regimen Adjuvant Radiotherapy (ITT Population)

Randomization Stratification Factors by Treatment Regimen, Adjuvant Radiotherapy, ITT Population
Protocol: BIG 4-11/BO25126/TOC4939G

	Pertuzumab + Trastuzumab + Chemotherapy (N=1746)	Placebo + Trastuzumab + Chemotherapy (N=1735)
Nodal status		
n	1746	1735
0 positive nodes and tumor <= 1cm*	60 (3.4%)	58 (3.3%)
0 positive nodes and tumor > 1cm*	517 (29.6%)	506 (29.2%)
1-3 positive nodes	634 (36.3%)	638 (36.8%)
>= 4 positive nodes	535 (30.6%)	533 (30.7%)
Adjuvant chemotherapy regimen (randomized)		
n	1746	1735
Anthracycline containing regimen	1403 (80.4%)	1401 (80.7%)
Non-anthracycline containing regimen	343 (19.6%)	334 (19.3%)
Hormone receptor status (central)		
n	1746	1735
Negative (ER and PgR negative)	607 (34.8%)	587 (33.8%)
Positive (ER and/or PgR positive)	1139 (65.2%)	1148 (66.2%)
Geographical Region		
n	1746	1735
USA	192 (11.0%)	188 (10.8%)
Canada/Western Europe/Australia-New Zealand/South Africa	1050 (60.1%)	1060 (61.1%)
Eastern Europe	124 (7.1%)	136 (7.8%)
Asia Pacific	346 (19.8%)	316 (18.2%)
Latin America	34 (1.9%)	35 (2.0%)
Protocol Version		
n	1746	1735
Protocol A	1299 (74.4%)	1282 (73.9%)
Protocol Amendment B	447 (25.6%)	453 (26.1%)

* Protocol A only

Program: /opt/BIOSTAT/prod/odp11450/r25126a/ah_sa973.sas
Output: /opt/BIOSTAT/prod/od11450g/j25126a/reports/ah_sa973_TRT1P_ADJRY_IT.out
11JAN2018 15:21 Page 1 of 1 ¶

Table 14 Sites of Radiotherapy in Patients who underwent Breast Conserving Surgery by Geographic Region

	Geographic Region					
	Western Europe[a]	US	Eastern Europe	Asia-Pacific	Latin America	Total across all Regions
Site of Radiotherapy	Ptz (n = 778) vs. Pla (n = 750)	Ptz (n = 100) vs. Pla (n = 116)	Ptz (n = 62) vs. Pla (n = 72)	Ptz (n = 165) vs. Pla (n = 121)	Ptz (n = 13) vs. Pla (n = 17)	Ptz (n = 1118) vs. Pla (n = 1076)
Breast	92.7% vs. 93.3%	91.0% vs. 86.2%	90.3% vs. 90.3%	98.2% vs. 96.7%	92.3% vs. 94.1%	93.2% vs. 92.8%
Axilla/LNs	30.6% vs. 25.3%	22.0% vs. 26.7%	41.9% vs. 33.3%	29.1% vs. 24.0%	7.7% vs. 35.3%	30.0% vs. 26.0%
Breast and axilla/LNs	30.1% vs. 24.9%	22.0% vs. 25.9%	41.9% vs. 33.3%	29.1% vs. 23.1%	7.7% vs. 35.3%	29.6% vs. 25.6%
Chest wall	1.3% vs. 1.1%	0 vs. 0.9%	3.2% vs. 1.4%	0 vs. 0	0 vs. 0	1.1% vs. 9.3%
Chest & axilla/LNs	0.8% vs. 0.4%	0 vs. 0.9%	1.6% vs. 0	0 vs. 0	0 vs. 0	0.6% vs. 0.4%
Breast, chest and axilla/LNs	0.5% vs. 0.3%	0 vs. 0.9%	1.6% vs. 0	0 vs. 0	0 vs. 0	0.4% vs. 0.3%

LNs = lymph nodes; Pla =Placebo+Herceptin+Chemo arm; Ptz =Perjeta+Herceptin+Chemo arm..
[a] Western Europe also includes Canada, South Africa, Australia and New Zealand.
Note: patients may be counted in more than one category. For example, a patient counted in the 'Breast & axilla/LNs' category is also counted in both the individual 'Breast' and 'Axilla/LNs' categories.
Source: ah_sa993_EUR_SB_IT; ah_sa993_USA_SB_IT; ah_sa993_EEUR_SB_IT; ah_sa993_APA_SB_IT; ah_sa993_LAM_SB_IT.

Table 15 Sites of Radiotherapy in Patients who underwent Mastectomy by Geographic Region

	Geographic Region					
	Western Europe[a]	US	Eastern Europe	Asia-Pacific	Latin America	Total across all Regions
Site of Radiotherapy	Ptz (n = 514) vs. Pla (n = 538)	Ptz (n = 196) vs. Pla (n = 1786)	Ptz (n = 138) vs. Pla (n = 128)	Ptz (n = 385) vs. Pla (n = 436)	Ptz (n = 47) vs. Pla (n = 47)	Ptz (n = 1280) vs. Pla (n = 1327)
Breast	4.1% vs.7.4%	13.8% vs. 19.7%	9.4% vs. 6.3%	2.6% vs. 2.5%	2.1% vs. 0	5.6% vs. 7.1%
Axilla/LNs	46.1% vs. 47.6%	35.7% vs. 33.7%	42.8% vs. 46.9%	43.1% vs. 40.1%	21.3% vs. 17.0%	42.3% vs. 42.1%
Breast and axilla/LNs	3.1% vs.5.9%	10.7% vs.15.7%	8.0% vs. 5.5%	2.3% vs. 1.8%	2.1% vs. 0	4.5% vs. 5.7%
Chest wall	61.7% vs. 63.8%	50.0% vs. 47.2%	34.8% vs. 43.0%	47.3% vs. 44.5%	44.7% vs. 38.3%	52.0% vs. 52.3%
Chest & axilla/LNs	45.1% vs. 45.4%	34.7% vs. 32.6%	31.2% vs. 34.4%	42.6% vs. 39.4%	19.1% vs. 14.9%	40.3% vs. 39.6%
Breast, chest and axilla/LNs	2.7% vs. 4.8%	10.7% vs. 15.7%	2.9% vs. 2.3%	2.3% vs. 1.8%	0 vs. 0	3.8% vs. 4.9%

LNs = lymph nodes; Pla =Placebo+Herceptin+Chemo arm; Ptz =Perjeta+Herceptin+Chemo arm.
[a] Western Europe also includes Canada, South Africa, Australia and New Zealand.
Note: patients may be counted in more than one category. For example, a patient counted in the 'Breast & axilla/LNs' category is also counted in both the individual 'Breast' and 'Axilla/LNs' categories.
Source: ah_sa993_EUR_SM_IT; ah_sa993_USA_SM_IT; ah_sa993_EEUR_SM_IT; ah_sa993_APA_SM_IT; ah_sa993_LAM_SM_IT.

Table 16 Sites of Radiotherapy in Patients with Node-Positive Disease by Geographic Region

	Geographic Region					
	Western Europe[a]	US	Eastern Europe	Asia-Pacific	Latin America	Total across all Regions
Site of Radiotherapy	Ptz (n = 778) vs. Pla (n = 773)	Ptz (n = 182) vs. Pla (n = 182)	Ptz (n = 142) vs. Pla (n = 142)	Ptz (n = 365) vs. Pla (n = 366)	Ptz (n = 36) vs. Pla (n = 39)	Ptz (n = 1503) vs. Pla (n = 1502)
Breast	49.9% vs. 49.4%	36.8% vs. 44.0 %	31.7% vs. 31.0%	23.3% vs. 16.7%	8.3% vs. 20.5%	39.1% vs. 38.3%
Axilla/LNs	58.4% vs. 56.1%	50.5% vs. 47.8%	57.7% vs. 56.3%	57.0% vs. 55.2%	30.6% vs. 30.8%	56.4% vs. 54.3%
Breast and axilla/LNs	30.7% vs. 27.2%	23.6% vs. 29.7%	24.6% vs. 19.0%	14.5% vs. 9.8%	5.6% vs. 12.8%	24.8% vs. 22.1%
Chest wall	36.0% vs. 39.5%	51.6% vs. 44.0%	33.1% vs. 38.7%	48.8% vs. 51.4%	58.3% vs. 38.5%	41.3% vs. 42.8%
Chest & axilla/LNs	29.2% vs. 31.2%	37.4% vs. 31.3%	31.0% vs. 31.0%	44.1% vs. 46.4%	25.0% vs. 15.4%	33.9% vs. 34.5%
Breast, chest and axilla/LNs	2.2% vs. 3.2%	11.5% vs. 14.8%	3.5% vs. 2.1%	2.2% vs. 2.2%	0 vs. 0	3.4% vs. 4.2%

LNs = lymph nodes; Pla =Placebo+Herceptin+Chemo arm; Ptz =Perjeta+Herceptin+Chemo arm.
[a] Western Europe also includes Canada, South Africa, Australia and New Zealand.
Note: patients may be counted in more than one category. For example, a patient counted in the 'Breast & axilla/LNs' category is also counted in both the individual 'Breast' and 'Axilla/LNs' categories.
Source: ah_sa975_NPOS_EUR_IT; ah_sa975_NPOS_USA_IT; ah_sa975_NPOS_EEUR_IT; ah_sa975_NPOS_APA_IT; ah_sa975_NPOS_LAM_IT; ah_sa975_NPOS_IT.

Table 17 Sites of Radiotherapy in Patients with Node-Positive Disease by Geographic Region

	Geographic Region					
	Western Europe[a]	US	Eastern Europe	Asia-Pacific	Latin America	Total across all Regions
Site of Radiotherapy	Ptz (n = 516) vs. Pla (n = 516)	Ptz (n = 114) vs. Pla (n = 112)	Ptz (n = 58) vs. Pla (n = 58)	Ptz (n = 185) vs. Pla (n = 191)	Ptz (n = 24) vs. Pla (n = 25)	Ptz (n = 897) vs. Pla (n = 902)
Breast	68.8% vs. 69.6%	44.7% vs. 49.1%	41.4% vs. 50.0%	47.0% vs. 35.1%	41.7% vs. 32.0%	58.8% vs. 57.4%
Axilla/LNs	4.1% vs. 2.5%	0 vs. 3.6%	5.2% vs. 6.9%	3.2% vs. 1.0%	0 vs. 8.0%	3.3% vs. 2.8%
Breast and axilla/LNs	2.1% vs. 1.9%	0 vs. 3.6%	3.4% vs. 6.9%	2.2% vs. 0	0 vs. 4.0%	1.9% vs. 2.1%
Chest wall	9.5% vs. 8.9%	3.5% vs. 4.5%	5.2% vs. 1.7%	2.2% vs. 3.1%	0 vs. 12.0%	6.7% vs. 6.8%
Chest & axilla/LNs	2.1% vs 1.2%	0 vs. 1.8%	0 vs. 0	1.6% vs. 1.0%	0 vs. 4.0%	1.6% vs. 1.2%
Breast, chest and axilla/LNs	0.2% vs. 0.6%	0 vs. 1.8%	0 vs. 0	0.5% vs. 0	0 vs. 0	0.2% vs. 0.6%

LNs = lymph nodes; Pla =Placebo+Herceptin+Chemo arm; Ptz =Perjeta+Herceptin+Chemo arm.
[a] Western Europe also includes Canada, South Africa, Australia and New Zealand
Note: patients may be counted in more than 1 category. For example, a patient counted in the 'Breast & axilla/LNs' category is also counted in both the individual 'Breast' and 'Axilla/LNs' categories.
Source: ah_sa975_NNEG_EUR_IT; ah_sa975_NNEG_USA_IT; ah_sa975_NNEG_EEUR_IT; ah_sa975_NNEG_APA_IT; ah_sa975_NNEG_LAM_IT; ah_sa975_NNEG_IT.

Table 18 Randomization Stratification Factors by Treatment Regimen, Adjuvant Hormone Therapy and Central Hormone Receptor Positive Cohort (ITT Population)

Randomization Stratification Factors by Treatment Regimen, Adjuvant Hormone Therapy and Central Hormone Receptor Positive Cohort, ITT Population
Protocol: BIG 4-11/BO25126/TOC4939G

	Pertuzumab + Trastuzumab + Chemotherapy (N=1311)	Placebo + Trastuzumab + Chemotherapy (N=1337)
Nodal status		
n	1311	1337
0 positive nodes and tumor <= 1cm*	34 (2.6%)	35 (2.6%)
0 positive nodes and tumor > 1cm*	472 (36.0%)	483 (36.1%)
1-3 positive nodes	507 (38.7%)	523 (39.1%)
>= 4 positive nodes	298 (22.7%)	296 (22.1%)
Adjuvant chemotherapy regimen (randomized)		
n	1311	1337
Anthracycline containing regimen	1013 (77.3%)	1056 (79.0%)
Non-anthracycline containing regimen	298 (22.7%)	281 (21.0%)
Hormone receptor status (central)		
n	1311	1337
Positive (ER and/or PgR positive)	1311 (100.0%)	1337 (100.0%)
Geographical Region		
n	1311	1337
USA	169 (12.9%)	159 (11.9%)
Canada/Western Europe/Australia-New Zealand/South Africa	765 (58.4%)	781 (58.4%)
Eastern Europe	106 (8.1%)	112 (8.4%)
Asia Pacific	249 (19.0%)	262 (19.6%)
Latin America	22 (1.7%)	23 (1.7%)
Protocol Version		
n	1311	1337
Protocol A	998 (76.1%)	1021 (76.4%)
Protocol Amendment B	313 (23.9%)	316 (23.6%)

* Protocol A only

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/ah_sa973.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/ah_sa973_TRT1P_CHRP_ADJHY_IT.out
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Objectives

Outcomes / endpoints

Primary objective/endpoint

The primary efficacy endpoint was IDFS (Invasive Disease-Free Survival), defined as the time from randomization to the first occurrence of one of the following events:

- Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion)
- Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast)
- Distant recurrence (i.e., evidence of breast cancer in any anatomic site – other than the two above mentioned sites—that was either histologically confirmed or clinically diagnosed as recurrent invasive breast cancer)
- Death attributable to any cause including breast cancer, non-breast cancer, or unknown cause (but cause of death was specified if at all possible)

- Contralateral invasive breast cancer

All second primary non-breast cancers and in situ carcinomas (including DCIS and LCIS) and non-melanoma skin cancer were excluded as an event in this endpoint. If a patient experienced an event on the same day as randomization their time from randomization to event was set as 1 day. Patients who did not have an event at the time of data analysis were censored at the date they were last known to be alive and event-free.

Note: this definition of IDFS (which excludes second primary non-breast cancers as events) is not the same as IDFS defined by Hudis et al. (2007) (which includes second primary non-breast cancers as events).

Secondary objectives/endpoints

The secondary efficacy endpoints included IDFS-including second primary non-breast cancer (IDFS-SPNBC), disease-free survival (DFS), overall survival (OS), recurrence-free interval (RFI), and distant recurrence-free interval (DRFI).

- IDFS-SPNBC, was defined in the same way as IDFS but including second primary non-breast invasive cancer as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site). This definition of IDFS is often the primary endpoint for breast cancer adjuvant therapy trials since i) it can be difficult to distinguish second primaries from breast cancer metastasis and ii) second cancers may be treatment related.
- DFS was defined as the time between randomization and the date of the first occurrence of an invasive disease-free survival event including second primary non-breast cancer events or contralateral or ipsilateral DCIS. Patients who did not have an event at the time of data analysis were censored at the date last known to be alive and event free.
- OS was defined as the time from randomization to death attributable to any cause. Patients who were alive (including lost to follow-up) at the time of the analysis were censored at the last known alive date.
- RFI was defined as the time between randomization and the date of local, regional or distant breast cancer recurrence. Patients who did not have a recurrence event at the time of data analysis were censored at the date last known to be alive or at date of death.
- DRFI was defined as the time between randomization and the date of distant breast cancer recurrence. Patients who did not have a distant recurrence event at the time of data analysis were censored at the date last known to be alive or at date of death. DRFI was included since distant recurrence was anticipated to account for the majority of first disease recurrence events based on previous published trials.

Exploratory efficacy endpoints

An assessment of breast cancer-free interval (BCFI) was also performed. BCFI was defined as the time between randomization and the date of local, regional or distant breast cancer recurrence, invasive contralateral breast cancer or DCIS (contralateral or ipsilateral). Patients who did not have a recurrence event at the time of data analysis were censored at the date when they were last known to be alive or at their date of death.

HRQoL was defined as symptoms of therapy, patient functioning, and global health status and assessed by the EORTC QLQ-C30, QLQ-BR23, and EQ-5D questionnaires. Patients were to complete patient-reported outcome (PRO) measures until recurrence or until 36 months after randomization, regardless of whether the patient completed study treatment or not. The timing of the chemotherapy PRO assessment was tailored to the patient's treatment regimen to ensure that PROs were assessed at key time points, namely the end of anthracycline treatment (only in patients receiving an anthracycline-based regimen), the end of taxane therapy (all patients), and the end of HER2-targeted treatment (all patients).

Assessment of disease

Physical examinations were performed at screening, during the HER2-targeted treatment period (every 3 months at a minimum) and at the end of treatment safety follow-up visit. Thereafter, physical examinations were performed at least every 3 months in Year 2 after the start of treatment, every 6 months during Year 3-5, and annually during Year 6-10.

A mammogram or breast magnetic resonance image (MRI) and chest X-ray/computed tomography (CT)/MRI/positron emission tomography (PET) had to be completed within 6 months prior to randomization. Bone scan and liver imaging was performed at screening if clinically indicated to exclude metastatic disease.

Mammograms or breast MRIs were repeated at yearly intervals, as per routine clinical practice. All mammograms/breast MRIs were bilateral, unless the patient had had a mastectomy. After the screening period, chest X-rays/CT/MRI/PET, bone scan, and liver imaging were only performed if clinically indicated. Additional assessments could be performed at any time, if clinically indicated (for suspected disease recurrence).

Patients who had disease recurrence at any time were followed for survival and new relapse events, annually (starting 1 year after the first relapse) until Year 10 after randomization of the last patient. Post-recurrence anticancer-related therapies were also collected.

Confirmation of Disease Recurrence

The diagnosis of a first breast cancer recurrence or second primary cancer was made only when clinical, radiological and laboratory findings met specific 'acceptable' criteria as defined in the protocol. In cases of diagnostic doubt (e.g., ill-defined, palpable mass in an irradiated breast), histological or cytological confirmation of recurrence was to be obtained whenever possible. If a patient developed a suspected recurrence that led to death before relapse was confirmed, efforts were made to obtain an autopsy report.

The earliest date of diagnosis of recurrent disease was recorded, based on clinical, radiological, histological or cytological evidence. The date of recurrence of disease was the date of the first diagnosis of a lesion (i.e., an objective finding), not the date of occurrence of the first symptom. Recurrent disease included local, regional, distant recurrence and contralateral breast cancer (see Table below). The following events were not considered recurrent disease as per protocol: ipsilateral and contralateral lobular carcinoma in situ (LCIS); ipsilateral and contralateral ductal carcinoma in situ (DCIS); carcinoma in situ of the cervix; and basal or squamous cell carcinoma of the skin.

Second primary non-breast malignancies had to be confirmed histologically and were reportable as SAEs throughout the study. Myelodysplastic syndrome was not considered a progression event but had to be reported as an SAE.

Types of recurrent disease [a]	Acceptable methods of confirmation of recurrence
Local invasive recurrence	
In the ipsilateral breast after previous lumpectomy	Positive histology or cytology
Ipsilateral after previous mastectomy	Positive histology or cytology
Regional recurrence	Positive histology or cytology, or Chest X-ray, CT-scan or MRI (especially in case of internal mammary lymph nodes if no biopsy was performed)
Distant recurrence Skin, subcutaneous tissue, and lymph nodes (other than local or regional)	Positive cytology, aspirate or biopsy, OR radiological (by CT scan or MRI or ultrasound) evidence of metastatic disease
Bone	X-ray, CT scan, or MRI evidence of lytic or blastic lesions consistent with bone metastasis, OR bone scan (required additional radiological investigation, alone not acceptable in case of diagnostic doubt), OR biopsy proof of bone metastases or cytology
Bone marrow	Positive cytology or histology or MRI scan
Lung	Radiologic evidence of multiple pulmonary nodules consistent with pulmonary metastases; OR positive cytology or histology (practically rarely performed with the exception of solitary nodules)
Liver	Abdominal CT scan, liver scan, ultrasound, or MRI consistent with liver metastases, OR liver biopsy or fine needle aspiration.
Central Nervous System	Positive MRI or CT scan, usually in a patient with neurologic symptoms, OR biopsy or cytology
Contralateral invasive breast cancer	Positive cytology or histology
Second primary malignancy (breast or other cancer)	Histology

CT = computed tomography; MRI = magnetic resonance imaging. [a] The following events were NOT considered recurrent disease as per protocol, but had to be recorded on the follow-up eCRF: ipsilateral and contralateral LCIS; ipsilateral and contralateral DCIS; carcinoma in situ of the cervix; basal or squamous cell carcinoma of the skin.

Sample size

It is assumed that the true HR is 0.75. In order to have 80% power to identify a statistically significant difference on a 2-sided 5% significance level, approximately 379 IDFS events are required.

A total of 3806 patients was initially planned assuming a 10% drop-out rate.

During the enrollment phase, it was observed that the monthly recruitment rate was more than 50% higher than expected an, the proportion of patients with node-negative disease was nearly twice that expected based on the BCIRG 006 study, resulting in a population inconsistent with the protocol assumptions upon which the protocol design was based. Hence, the protocol was amended to cap recruitment of patients with node-negative disease, the total planned sample size was increased to 4800 patients, and statistical

assumptions were adjusted accordingly. The decision to amend the protocol and changes to the sample size were made on the basis of overall recruitment rates into the study, without unblinding of any study personnel.

Original protocol (Version A dated 28 June 2011) recruitment rate and event rate assumptions were as follows:

– It was foreseen when the protocol was designed that the study would enroll a similar population to the adjuvant Herceptin trial BCIRG 006 (Slamon et al, 2006; Slamon et al, 2009). Therefore, based on the data from that trial, the Kaplan-Meier estimate of IDFS at 3 years for the Herceptin control group for this study was estimated to be 88%, regardless of the chemotherapy regimen (with annual decreases in Kaplan–Meier estimates of 2% during the first year after randomization, 5% during Years 2 and 3, and 2% during Year 4 and beyond). Based on this and a projected monthly accrual rate of 0.29 patients at 700 sites, it was estimated that with 3806 patients, enrolled in approximately 27 months, 379 IDFS events would occur at around 55 months.

The following revised sample size assumptions became applicable with Protocol Version B (dated 20 November 2012):

– The annual decrease in Kaplan–Meier estimates of the IDFS function in the Herceptin control group (regardless of the chemotherapy regimen) was anticipated to be 1.9% during the first year after randomization, 4.5% during Year 2, 4.4% during Year 3, and 1.8% during Year 4 and beyond. Therefore, the Kaplan–Meier estimate of IDFS at 3 years for the Herceptin control group was 89.2%. These assumptions were based on 5-year follow up data from BCIRG 006. Under the alternative hypothesis and with the assumption that IDFS for both groups was exponentially distributed, the magnitude of treatment effect in terms of increase in IDFS at 3 years was 2.6%, meaning a Kaplan-Meier estimate of IDFS at 3 years for the Perjeta group of 91.8%. The smallest estimated difference detectable at a 5%, 2 sided significance level was HR= 0.818, under which the magnitude of treatment effect would be 1.9%. Under these assumptions, it was planned that 4800 patients would be enrolled over an estimated 25 months, and assuming a 10% drop-out rate, the 379 IDFS events required for the primary analysis would occur at 46 months.

Randomisation

A total of 4805 patients were randomized in a 1:1 ratio to one of the two treatment arms using a web-based randomization system. Patients were stratified according to nodal status (0 positive nodes and tumour ≤ 1cm, 0 positive nodes and tumour > 1 cm, 1-3 positive nodes, ≥ 4 positive nodes), type of standard adjuvant chemotherapy regimen (anthracycline-based versus non-anthracycline-based), hormone receptor status (ER and PgR negative, ER and/or PgR positive), geographical region (USA, Canada/Western Europe/Australia-New-Zealand/South Africa) and protocol version (Protocol A versus Protocol Version B). Protocol version (A versus B) was introduced as a stratification factor at the time of the first protocol amendment (Version B, dated 20 November 2012).

Blinding (masking)

The trial was a double-blind placebo-controlled trial. Pertuzumab and placebo were both given as IV. The formulation of the placebo pertuzumab was equivalent to pertuzumab but without the active agent.

Unblinding should only be considered if deemed essential. For instance, the sponsor will not routinely unblind the investigator in case of for SAEs. Unblinding for ongoing safety monitoring is performed through an independent data-coordinating centre. All entities directly involved in the study will remain blinded until the final analysis of the primary efficacy endpoint.

Statistical methods

Analysis strategy:

The primary analysis takes place after 379 IDFS events have occurred. If the result of the analysis is statistically significant, then secondary endpoints are tested in the following hierarchical order: IDFS-SPNBC, DFS, and OS. The secondary endpoints RFI and DRFI will be tested but not included in the multiplicity adjustment.

The primary analysis after 379 IDFS events is the first interim analysis for OS. In addition, two interim analyses will be performed approximately 4-5 years, and 7-8 years, after last patient was randomized. The final OS analysis will be performed when 640 OS events have occurred. Thus, there are in total 4 OS analyses. The overall alpha-level for these analyses will be controlled at 0.05 according to O'Brien-Fleming Lan-DeMets.

Table 19 Planned OS Analysis Timings

Analysis	Timing of Analysis	Percent Information	Adjusted two-sided alpha level	Cumulative Power
1st – at IDFS final	379 IDFS events (~2-3 years after Last patient randomized)	26%	<0.00001	0%
2nd	~ 4–5 years after Last patient randomized	49%	0.0027	17.4%
3rd	~7–8 years after Last patient randomized	70%	0.0139	47.9%
4th	640 OS events (~9-10 years after Last patient randomized)	100%	0.0453	80%

If the OS analyses are stopped early for efficacy, safety follow-up will still continue until approximately 10 years after randomization of the last patient.

At the time of each of the 2nd, 3rd, and 4th OS analysis, exploratory analyses of IDFS for the ITT population and in key demographic subgroups will also be performed.

Endpoints:

The primary endpoint as well as all secondary and exploratory endpoints are time-to-event endpoints, which are defined as the time from randomization to first occurrence of the relevant event.

Analysis populations:

ITT**:** All randomized subjects. Analysed as randomized. All efficacy analyses will be based on the ITT population.

Safety Population: All randomized subjects who have received any amount of study drug. Analysed as treated. All safety analyses will be based on the Safety Population.

Missing data handling:

For the time-to-event analyses, patients not experiencing an event will be censored at the date when they were last known to be alive and event-free. Randomized patients with no post-baseline data will be censored at the day of randomization plus 1 day. Other ways of censoring will be explored in the sensitivity analyses for the primary endpoint.

Primary endpoint:

Statistical analysis of primary endpoint:

The primary endpoint, IDFS, defined as time from randomization to first occurrence of either ipsilateral invasive breast tumor recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant

recurrence, death, or contralateral invasive breast cancer, will be compared between the two treatment groups using the stratified log-rank test. The stratification factors are the same as the ones used in the randomization, apart from geographical region, which is not included. The Kaplan-Meier plot of the IDFS rates will be presented, and so will the hazard ratios estimated from the stratified Cox proportional hazards model with the corresponding 95% confidence intervals.

Sensitivity analyses:

Two types of sensitivity analyses are planned. First descriptive analyses to assess whether there are imbalances in number of assessments or in follow-up time between the two treatment arms. Then analyses to assess the robustness of the primary endpoint with respect to the impact of imbalances. The specific descriptive analyses are:

1. Kaplan-Meier plot of time to censoring
2. Number of assessments per treatment group
3. Reason for withdrawal
4. Time between event and previous assessment

The analysis to assess robustness, all using the ITT population and the same analysis method as the primary analysis, unless otherwise stated, are:

1. Censoring patients when they begin a new anti-cancer therapy
2. Considered start of new anti-cancer therapy as event
3. Censoring patients who withdraw from the protocol-specified assessments
4. Considering events to have occurred at the planned assessment date for patients who have missed this date but relapsed or died later
5. Considering patients who withdraw due to toxicity as having an event one day after they were last known to be event free
6. Considering patients with incomplete follow-up according to the protocol-defined schedule as having an event one day after the tie they were event free
7. The primary analysis but without stratification
8. Including actual chemotherapy regimen as stratification factor instead of planned chemotherapy regimen
9. Including stratification factors reported in the IxRS system instead of the ones reported in the eCRF

Statistical analysis of secondary endpoints: analysed in analogy with the primary endpoint. Similar sensitivity analyses are also planned.

Statistical analysis of exploratory endpoints: analysed in analogy with the primary endpoint.

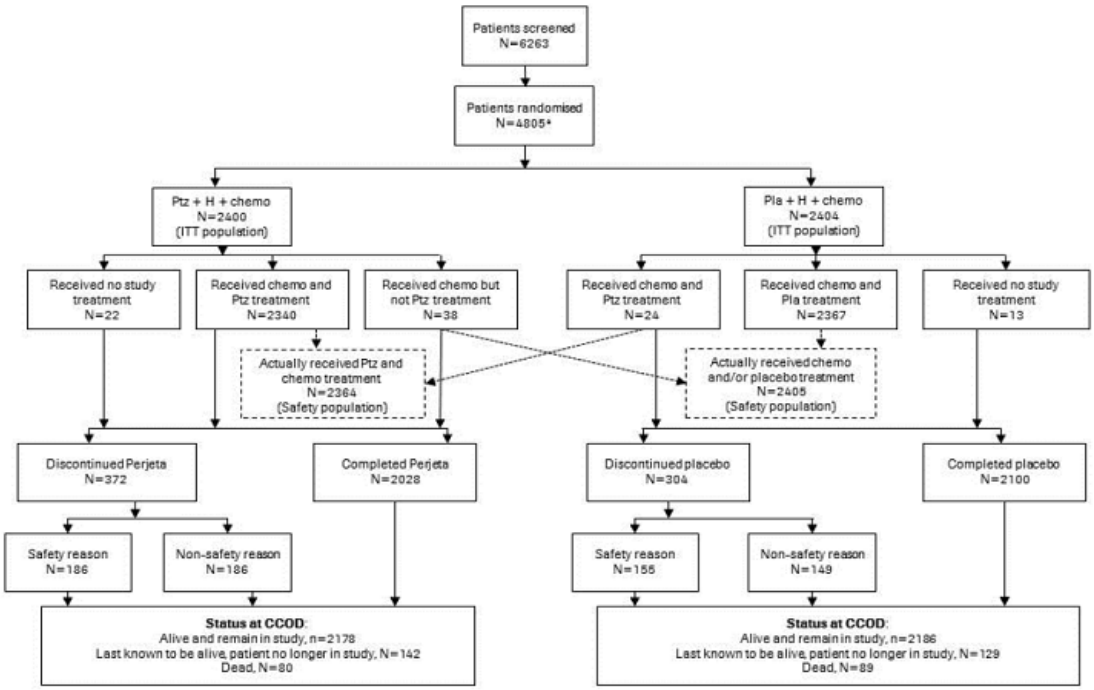
Results

Participant flow

A total of 6263 patients were screened for the study. Patient enrollment took place over a period of 22 months, from 08 November 2011 (first patient in) to 31 August 2013 (last patient in), in 548 centers from 42 countries. Of the patients screened, 4805 patients were randomized in a 1:1 ratio to one of the two treatment arms (2400 patients to the Ptz+H+Chemo arm and 2405 patients to the Pla+H+Chemo arm); see

Figure 10. The most common cause of screen failure was lack of confirmation of HER2-positivity by the central laboratory, which accounted for approximately half of the screen failures.

Figure 10 Disposition of Patients



H=Herceptin; FUP=follow up; Pla=placebo; Ptz=Perjeta
[a] Patient No. 250848-2508480020 in the Pla+H+Chemo arm was randomized but not included in the ITT population (due to provision of some false personal information by the patient)
Source: t_ds_pp_RA; l_ds_ixrs; t_ds_pstat_IT; t_ef_fut_IT and list of screen failures

Of the randomized patients, 22 in the Ptz+H+Chemo arm and 13 in the Pla+H+Chemo did not receive any study treatment. In the majority of cases, in both treatment arms, the reason for not receiving any study treatment was the patient's decision to withdraw from the study. Of the 4805 patients randomized, 14 patients in the Ptz+H+Chemo arm and 24 patients in the Pla+H+Chemo arm received at least one dose of non-randomized treatment in error. The 14 patients in the Ptz+H+Chemo arm received only 1 cycle of placebo in error and, therefore, remain in the pertuzumab arm for safety analyses. However, the 24 patients in the Pla+H+Chemo arm who received at least 1 dose of pertuzumab are included in the Ptz+H+Chemo arm for safety analyses.

Table 20 Patient Disposition during Treatment Period by Treatment Regimen (Randomized Patients)

Patient Disposition during Treatment Period by Treatment Regimen, Randomized Patients
Protocol: BIG 4-11/BO25126/TOC4939G

Status	Pertuzumab + Trastuzumab + Chemotherapy (N=2400)	Placebo + Trastuzumab + Chemotherapy (N=2404)
Completed Pertuzumab/placebo treatment	2028 (84.5%)	2100 (87.4%)
Discontinued Pertuzumab/placebo treatment	372 (15.5%)	304 (12.6%)
Safety	186 (7.8%)	155 (6.4%)
Adverse event	176 (7.3%)	149 (6.2%)
Death	9 (0.4%)	6 (0.2%)
Pregnancy	1 (<0.1%)	0
Non-Safety	186 (7.8%)	149 (6.2%)
Lost to follow-up	0	1 (<0.1%)
Non-compliance with study drug	44 (1.8%)	29 (1.2%)
Physician decision	30 (1.3%)	15 (0.6%)
Protocol violation	1 (<0.1%)	3 (0.1%)
Recurrence of disease	20 (0.8%)	29 (1.2%)
Contralateral breast cancer	2 (<0.1%)	0
Withdrawal by subject	55 (2.3%)	47 (2.0%)
Other	34 (1.4%)	25 (1.0%)

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ds_pp.sas
Output: /opt/BIOSTAT/prod/cdl1450g/j25126a/reports/t_ds_pp_RA.out
25FEB2017 11:54 Page 1 of 1

At the time of clinical cut-off, 2368 patients (98.7%) in the Ptz+H+Chemo arm had entered the follow-up period, and 370 (15.4% of randomized patients) had subsequently discontinued from follow-up. Similarly, in the Pla+H+Chemo treatment arm 2381 patients (99.0%) had entered the follow-up period and 399 (16.6%) had subsequently discontinued. The main reasons for discontinuing during the follow-up period were withdrawal by patient (6.8% of patients in the Ptz+H+Chemo arm vs. 6.2% in the Pla+H+Chemo arm) and recurrence of disease (5.5% of patients in the Ptz+H+Chemo arm vs. 7.1% in the Pla+H+Chemo arm).

Table 21Patient Disposition during Follow-Up by Treatment Regimen (Randomized Patients)

Patient Disposition during Study by Treatment Regimen, Randomized Patients
Protocol: BIG 4-11/BO25126/TOC4939G

Status	Pertuzumab + Trastuzumab + Chemotherapy (N=2400)	Placebo + Trastuzumab + Chemotherapy (N=2404)
Number entering follow-up period	2368 (98.7%)	2381 (99.0%)
Completed Follow-up	0	0
Discontinued from Follow-up	370 (15.4%)	399 (16.6%)
Adverse event	10 (0.4%)	16 (0.7%)
Death	17 (0.7%)	17 (0.7%)
Lost to follow-up	19 (0.8%)	20 (0.8%)
Physician decision	10 (0.4%)	8 (0.3%)
Recurrence of disease	132 (5.5%)	171 (7.1%)
Contralateral breast cancer	5 (0.2%)	11 (0.5%)
Withdrawal by subject	163 (6.8%)	148 (6.2%)
Other	14 (0.6%)	8 (0.3%)

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Output: /opt/BIOSTAT/prod/cdl1450g/j25126a/reports/t_ds_fu_RA.out
21MAR2017 19:27

Recruitment

Patient enrollment took place over a period of 22 months, from 08 November 2011 (first patient in) to 31 August 2013 (last patient in), in 548 centers from 42 countries. The top recruiting countries were the United States (US), France and Germany, each recruiting more than 450 patients. Only three countries (Argentina, El Salvador, and Slovenia) recruited less than 10 patients. Individual centers recruited between 1 and 94 patients. The top recruiting individual centers were in China (94 patients), South Korea (59 patients) and Poland (51 patients).

Conduct of the study

There were three amendments to the study protocol. A summary of the protocol amendments, including the rationale and key changes, is provided in Table 22. Version A dated 28 June 2011 was the original protocol.

Table 22 Summary of Protocol Amendments

Protocol Amendment (Date)	Rationale and Key Changes
Version B (dated 20 November 2012)	This amendment was made mainly to adjust for a higher than expected rate of recruitment of node-negative patients. Statistical assumptions in the original protocol (Version A) were based on the proportion of node-negative/node-positive patients and recruitment rates seen in prior Herceptin adjuvant studies (particularly BCIRG-006). However, the patient population enrolled in APHINITY in September 2012 was not consistent with these assumptions. Therefore, the trial sample size was increased from N = 3806 to N = 4800 and node-negative patients were no longer permitted to enroll. The recruitment period was adjusted (from 27 to 25 months) and a clause was included to ensure that the primary analysis did not take place until at least 30 months after the last patient enrolled. Additional protocol revisions are detailed in the protocol amendment history for Version B and include the following: • The time from randomization to first treatment was increased from 7 weeks to 8 weeks to allow patients more time to enter the study. • The number of centers was reduced from 700 to 600. • The number of cycles of FEC/FAC was made more flexible (3 or 4) to more closely reflect local practice. • Reporting of non-breast second primary malignancies was added, in line with protocol-specified endpoints. • The minimum observation period after administration of Perjeta was adjusted to align with the current Perjeta label. • The order of administration of TCH was updated in line with current practice, in addition to clarifying the dose and time period of administration. • Criteria for highly effective contraception were adjusted to include surgical sterilization and to allow patients with a previously implanted progesterone-coated intra-uterine device to continue to use this for contraception. Exclusion of patients receiving estrogen-replacement therapy was added. • A range of clarifications were added including to the eligibility criteria (examples of concurrent serious diseases added), the requirements for patients undergoing sentinel lymph node biopsies, the reporting of concomitant medications and prior treatments for breast cancer, the information to be collected at the time of partial withdrawal from the study, and to the timing of assessments and sample collection

FAC = Standard therapy for breast cancer consisting of 5-fluorouracil, doxorubicin and cyclophosphamide;
FEC = Standard therapy for breast cancer consisting of 5 fluorouracil, epirubicin and cyclophosphamide;
TCH= docetaxel (Taxotere®), carboplatin and Herceptin

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Summary of Protocol Amendments (Cont.)

Protocol Amendment (Date)	Rational and Key Changes
Version C (dated 3 December 2013)	This amendment consisted mainly of clarifications, corrections of minor inconsistencies and minor adjustments, as follows: • A 3-day window for the last dose of targeted therapy was added at the end of 52 weeks. • The IMP terminology was clarified to refer specifically to Perjeta ('targeted treatment' referred to Perjeta + Herceptin; 'study drugs' referred to Perjeta + Herceptin + chemotherapy). • Due to multiple queries from sites, the language associated with the Investigators' choice of adjuvant chemotherapy was revised, and information on excluded anti-cancer agents was added. • Follow-up of AEs was clarified (until resolution or end of study); also the assessment schedules for patients according to treatments received. Footnotes to the schedule of assessment tables were also added or revised, for example relating to the requirements for yearly mammograms • Mentions of optional cores from the original tumor block for non-heritable factors were removed Additional protocol revisions are detailed in the protocol amendment history for Version C.
Version D (2 February 2015)	This amendment was made primarily to include details of enhanced measures for reporting of pregnancies that occur during study treatment or within 6 months after completion of Perjeta treatment. In addition, the following changes were made: • The washout period for Herceptin was increased to 7 months based on updated half-life data for trastuzumab • Related warnings (pregnancy exclusion and cardiac toxicity risk) were revised based on the updated Herceptin washout period • Endocrine therapy recommendations were revised (to allow endocrine therapy administration as per local practice) • An additional plasma sample at disease recurrence was added • Various clarifications were made (to sample collection, definitions and reporting requirements). Additional protocol updates are detailed in the protocol amendment history for Version D .

AE = adverse event; IMP = investigational medicinal product.

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Protocol deviations

Major protocol deviations were reported in relation to inclusion/exclusion criteria, and on study procedures and assessments. Approximately 28% of patients in each treatment arm had at least one major protocol deviation reported, with a similar incidence observed in the two treatment arms, regardless of the protocol deviation category (Table 23). The most common deviations were: time interval between definitive surgery for breast cancer and randomization outside protocol-specified criteria; inability to start treatment within 1 week of randomization (an inclusion criterion); completion of all necessary baseline laboratory and radiographic investigations prior to randomization (an inclusion criterion); and abnormal laboratory results immediately prior to randomization (an exclusion criterion).

Of note, one major protocol deviation led to a patient being excluded from both the efficacy and safety analysis populations. This patient (Patient 2508480020) was excluded after she had completed study treatment because she was found to have used some false personal information when consenting to the

study. The patient did this in an attempt to use her sister's medical insurance (as she did not have medical insurance herself). This patient does not appear in Table 23 and no safety or efficacy data from this patient are included in this report, as they are considered unreliable.

Two patients were randomized despite the presence of metastatic disease at baseline. Patient 2324810007 did not start study treatment and Patient 2470700009 completed study treatment. For both patients, a decision was made not to consider them as having an IDFS event in the primary analysis. For all other efficacy endpoints, except for overall survival, the patient was censored at the date of randomization. A listing of patients with protocol deviations was also provided, but is not shown here.

Table 23 Major Protocol Deviations by Treatment Regimen, Randomized Patients

Major Protocol Deviations by Treatment Regimen, Randomized Patients
Protocol: BIG 4-11/BO25126/TOC4939G

	Pertuzumab + Trastuzumab + Chemotherapy (N=2400)	Placebo + Trastuzumab + Chemotherapy (N=2404)
No. of Patients with at least one Major Protocol Deviation	674 (28.1%)	688 (28.6%)
Protocol Deviations		
Number of Major Inclusion Criteria Deviations	310	308
Number of Major Exclusion Criteria Deviations	192	211
Number of Major On-study Deviations	402	432
No. Violating at least one Inclusion Criterion		
Total Number of Patients with at least one Major Inclusion Deviation	285 (11.9%)	280 (11.6%)
Baseline LVEF >=55% measured by echocardiography (preferred) or MUGA scan	3 (0.1%)	9 (0.4%)
Completion of all necessary baseline laboratory and radiologic investigations prior to randomization.	101 (4.2%)	109 (4.5%)
HER2-positive breast cancer confirmed by a central laboratory.	0	1 (<0.1%)
Interval between definitive surgery for breast cancer and randomisation at least 3 weeks but no more than 7 weeks and patient is willing and able to start treatment within 1 week of randomization	123 (5.1%)	114 (4.7%)
Non-metastatic operable primary invasive carcinoma of the breast that is Adequately excised	0	2 (<0.1%)
Non-metastatic operable primary invasive carcinoma of the breast that is Histologically confirmed	1 (<0.1%)	0
Non-metastatic operable primary invasive carcinoma thats node negative (pN0) and either tumor size <= 1cm or for > 0.5cm must be histologic/nuclear grade 3 or negative ER and PgD or age <35 years	12 (0.5%)	8 (0.3%)
Signed informed consent.	30 (1.3%)	24 (1.0%)
Women of childbearing potential (or male partners) agree to use highly-effective, non-hormonal form of contraception during study treatment and for at least 6 months after the last study treatment	40 (1.7%)	41 (1.7%)
No. Violating at least one Major Exclusion Criterion		
Total Number of Patients with at least one Major Exclusion Deviation	189 (7.9%)	200 (8.3%)
Any clinical T4 tumor as defined by TNM, including inflammatory breast cancer.	1 (<0.1%)	0
Any of the following abnormal laboratory tests immediately prior to randomization: Total bilirubin; ALAT and/or ASAT; ALP; Serum creatinine; WBC; ANC; Platelets.	107 (4.5%)	113 (4.7%)
Any previous systemic chemotherapy (eg, neo-adjuvant or adjuvant) for cancer OR radiation therapy for cancer	1 (<0.1%)	1 (<0.1%)
History of any prior (ipsi- and/or contralateral) invasive breast carcinoma.	0	2 (<0.1%)
History of non-breast malignancies within the 5 years prior to study entry (with exceptions)	1 (<0.1%)	0
Pregnant, lactating or women of childbearing potential without a negative pregnancy test (serum), within 7 days prior to randomization, irrespective of the method of contraception used	80 (3.3%)	90 (3.7%)
Serious cardiac illness or medical conditions.	2 (<0.1%)	5 (0.2%)

Table continues

Major Protocol Deviations by Treatment Regimen, Randomized Patients (cont.)

Major Protocol Deviations by Treatment Regimen, Randomized Patients
Protocol: BIG 4-11/BO25126/TOC4939G

	Pertuzumab + Trastuzumab + Chemotherapy (N=2400)	Placebo + Trastuzumab + Chemotherapy (N=2404)
No. Violating at least one On-study Criterion		
Total Number of Patients with at least one Major On-study Deviation	332 (13.8%)	340 (14.1%)
2 or more consecutive LVEF assessments missed	18 (0.8%)	19 (0.8%)
2 or more consecutive visits missed	7 (0.3%)	9 (0.4%)
Biomarker sample not taken prior to first dose	40 (1.7%)	24 (1.0%)
Chemotherapy given despite ANC <1000 (paclitaxel)	1 (<0.1%)	0
Chemotherapy given despite ANC <1500 (docetaxel)	9 (0.4%)	16 (0.7%)
Chemotherapy given if ANC or platelets not known	26 (1.1%)	20 (0.8%)
Completion of baseline assessments (other)	0	1 (<0.1%)
Did not receive chemotherapy	3 (0.1%)	1 (<0.1%)
Dosage: Not modified according to LVEF algorithm	2 (<0.1%)	5 (0.2%)
Dosage: Overdosage - pertuzumab	0	1 (<0.1%)
Dosage: Overdosage - trastuzumab	8 (0.3%)	3 (0.1%)
Dosage: Treatment beyond 1 year	50 (2.1%)	47 (2.0%)
End of anthracycline LVEF not done	2 (<0.1%)	1 (<0.1%)
Inadequate end of anthracycline LVEF or not done	33 (1.4%)	32 (1.3%)
Missed pregnancy (if inadequate contraception)	10 (0.4%)	11 (0.5%)
No HER2 targeted treatment administered	10 (0.4%)	9 (0.4%)
Not following the cardiac algorithm	11 (0.5%)	15 (0.6%)
Not repeating LVEF as per cardiac algorithm	5 (0.2%)	11 (0.5%)
OS1 No HER2 targeted treatment administered	2 (<0.1%)	3 (0.1%)
OS1 Received incorrectly assigned ptz/pla	0	1 (<0.1%)
OS10 Missed pregnancy (if inadequate contraception	3 (0.1%)	4 (0.2%)
OS5 Inadequate end of anthracycline LVEF or not do	1 (<0.1%)	4 (0.2%)
Pregnancy - no baseline test	0	2 (<0.1%)
Pregnancy within 7 months of treatment	1 (<0.1%)	4 (0.2%)
Prohibited concomitant medication (anti-cancer)	13 (0.5%)	12 (0.5%)
Prohibited concomitant medication (other)	65 (2.7%)	93 (3.9%)
QoL not performed prior to first dose	29 (1.2%)	36 (1.5%)
Received incorrectly assigned ptz/pla	52 (2.2%)	47 (2.0%)
Two or more consecutive LVEF assessments missed	1 (<0.1%)	0
Two or more consecutive visits missed	0	1 (<0.1%)

Patients may have deviations for more than one reason, therefore the same patient may be counted in different categories.

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Baseline data

An overview of the key demographic data, baseline disease characteristics and stratification factors is provided in Table 24.

Table 24 Key Demographic Data, Baseline Disease Characteristics and Stratification Factors, ITT Population

		Ptz + H + Chemo N = 2400	Pla + H + Chemo N = 2404
Demo-graphics	**Age, median, range (yrs)**	51.0 (22 – 86)	51.0 (18 – 85)
	< 65 years	2085 (86.9%)	2111 (87.8%)
	≥ 65 years	315 (13.1%)	293 (12.2%)
	Weight, median, range (kg)	65 (37–154)	65 (37–162)
	Sex, female/male	99.9/ 0.1%	99.7/ 0.3%
	Race, White/ Asian/ Other	71.2/ 24.7/ 4.1%	70.5/ 24.9/ 4.6%
Baseline Breast Cancer Characteristics	**Histologic grade of Primary tumor**[a]		
	Grade 1	53 (2.2%)	42 (1.7%)
	Grade 2	770 (32.0%)	764 (31.7%)
	Grade 3	1493 (62.1%)	1506 (62.5%)
	Unevaluable	87 (3.6%)	94 (3.9%)
	Unknown	0	2 (<0.1%)
	HER2 status by Central lab (IHC Result)[a,b]		
	0	6 (0.3%)	2 (<0.1%)
	1+	16 (0.7%)	9 (0.4%)
	2+	193 (8.0%)	200 (8.3%)
	3+	2184 (91.0%)	2190 (91.2%)
	Type of Primary Surgery[c]		
	Mastectomy	1280 (53.3%)	1327 (55.2%)
	Breast Conserving Surgery	1118 (46.7%)	1076 (44.8%)
Randomization Stratification Factors	**Nodal status**		
	0 positive nodes and tumor ≤ 1 cm [d]	90 (3.8%)	84 (3.5%)
	0 positive nodes and tumor > 1 cm [d]	807 (33.6%)	818 (34.0%)
	1-3 positive nodes	907 (37.8%)	900 (37.4%)
	≥ 4 positive nodes	596 (24.8%)	602 (25.0%)
	Adjuvant Chemotherapy Regimen (randomized)		
	Anthracycline containing regimen	1865 (77.7%)	1877 (78.1%)
	Non-anthracycline containing regimen	535 (22.3%)	527 (21.9%)
	Hormone receptor status (central)		
	Negative (ER and PgR negative)	864 (36.0%)	858 (35.7%)
	Positive (ER and/or PgR positive)	1536 (64.0%)	1546 (64.3%)
	Geographic Region		
	USA	296 (12.3%)	294 (12.2%)
	Canada/Western Europe/Australia-New Zealand/South Africa	1294 (53.9%)	1289 (53.6%)
	Eastern Europe	200 (8.3%)	200 (8.3%)
	Asia-Pacific	550 (22.9%)	557 (23.2%)
	Latin America	60 (2.5%)	64 (2.7%)
	Protocol Version		
	Protocol A	1828 (76.2%)	1827 (76.0%)
	Protocol Amendment B	572 (23.8%)	577 (24.0%)

[a] For patients with bilateral tumors, the grade and HER2 status for each tumor was counted separately.
[b] Tumors that were anything other than IHC3+, had to be HER2-positive according to FISH.
[c] Mastectomy included radical mastectomy, modified radical mastectomy and simple mastectomy. Breast conserving surgery included partial mastectomy and breast lumpectomy and others that did not meet the criteria for mastectomy. Information on type of surgery was not available for 3 patients (2 in Ptz+H+Chemo arm and 1 in Pla+H+Chemo arm).
[d] Randomized under Protocol Version A only.

Source: Primary CSR.in module 5.3.5.1

Table 25 Randomization Stratification Factors by Treatment Regimen, ITT population Protocol: BIG 4-11/BO25126/TOC4939G

Randomization Stratification Factors by Treatment Regimen, ITT Population
Protocol: BIG 4-11/BO25126/TOC4939G

	Pertuzumab + Trastuzumab + Chemotherapy (N=2400)	Placebo + Trastuzumab + Chemotherapy (N=2404)
Nodal status		
n	2400	2404
0 positive nodes and tumor <= 1cm*	90 (3.8%)	84 (3.5%)
0 positive nodes and tumor > 1cm*	807 (33.6%)	818 (34.0%)
1-3 positive nodes	907 (37.8%)	900 (37.4%)
>= 4 positive nodes	596 (24.8%)	602 (25.0%)
Adjuvant chemotherapy regimen (randomized)		
n	2400	2404
Anthracycline containing regimen	1865 (77.7%)	1877 (78.1%)
Non-anthracycline containing regimen	535 (22.3%)	527 (21.9%)
Hormone receptor status (central)		
n	2400	2404
Negative (ER and PgR negative)	864 (36.0%)	858 (35.7%)
Positive (ER and/or PgR positive)	1536 (64.0%)	1546 (64.3%)
Geographical Region		
n	2400	2404
USA	296 (12.3%)	294 (12.2%)
Canada/Western Europe/Australia-New Zealand/South Africa	1294 (53.9%)	1289 (53.6%)
Eastern Europe	200 (8.3%)	200 (8.3%)
Asia Pacific	550 (22.9%)	557 (23.2%)
Latin America	60 (2.5%)	64 (2.7%)
Protocol Version		
n	2400	2404
Protocol A	1828 (76.2%)	1827 (76.0%)
Protocol Amendment B	572 (23.8%)	577 (24.0%)

* Protocol A only

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Pathological characteristics of primary tumour

The treatment arms were well balanced with respect to patients' breast cancer history. The majority of patients had primary tumours that were at least 2 cm in diameter. Most patients (91% of patients in either treatment arm) had tumours that were HER2 3+ based on immunohistochemistry and Grade 2 or 3, histologically.

Breast Cancer Surgery

The majority of patients underwent mastectomy (53.3% vs. 55.2%). The majority of patients underwent sentinel lymph node biopsy (SLNB), with a median of 2 sentinel lymph nodes examined. The majority of patients underwent axillary dissection with a median of 15 lymph nodes examined. There were no apparent imbalances in lymph node surgery between treatment arms.

Previous and Concurrent Diseases Other than Primary Breast Cancer

The treatment arms were comparable with respect to the proportion of patients with previous disorders/conditions other than breast cancer (26.8% vs. 27.9%). Infections and Infestations (6.3% vs. 7.0%) and Gastrointestinal Disorders (3.6% vs 3.6%) were the most common classes of previous disorders/conditions, and the incidence was similar in the two treatment arms.

Twenty-eight patients (1.2%) vs 24 patients (1.0%) reported previous Cardiac Disorders, most commonly, palpitations (8 patients [0.3%] vs. 2 [<0.1%]), supraventricular tachycardia (2 patients [<0.1%] vs. 4 [0.2%]) and myocardial infarction (2 patients [<0.1%] vs. 3 [0.1%]). All other cardiac disorders (preferred term) occurred in 2 or less patients.

Around 67% of patients in each treatment arm reported concurrent disorders/conditions other than breast cancer at baseline and there were no notable differences between the treatment arms. The most frequently reported class of concurrent disorders/conditions was vascular disorders (594 patients [24.8%] vs. 605 [25.2%]), in particular, hypertension (523 patients [21.8%] vs. 513 [21.3%]).

The frequency of diabetes, hypertension, coronary artery disease and/or hyperlipidemia (that are commonly accepted risk factors for cardiovascular disease,) was similar in the two treatment arms.

Table 26

	Pertuzumab + Trastuzumab + Chemotherapy (N=2400)	Placebo + Trastuzumab + Chemotherapy (N=2404)
Diabetes		
n	2400	2404
Yes	138 (5.8%)	137 (5.7%)
No	2262 (94.3%)	2267 (94.3%)
Hypertension		
n	2400	2404
Yes	544 (22.7%)	539 (22.4%)
No	1856 (77.3%)	1865 (77.6%)
Coronary artery disease		
n	2400	2404
Yes	21 (0.9%)	21 (0.9%)
No	2379 (99.1%)	2383 (99.1%)
Hyperlipidaemia		
n	2400	2404
Yes	247 (10.3%)	255 (10.6%)
No	2153 (89.7%)	2149 (89.4%)

Diabetes identified using HLGT Glucose metabolism disorders (incl diabetes mellitus)
Hypertension identified using SMQ (wide) Hypertension
Coronary artery disease identified using SMQ (wide) Ischaemic heart disease
Hyperlipidaemia identified using SMQ (wide) Dyslipidaemia

Concurrent treatments

Adjuvant Radiotherapy

The majority of patients in both treatment arms (72.8% vs. 72.2%) received adjuvant radiotherapy. Of these patients, around half received radiation to the right side and the other half to the left side (as would be expected). About 20% of patients received radiotherapy to the left chest wall (Table 27).

Table 27 Summary of Adjuvant Radiotherapy for Primary Breast Cancer by Treatment Regimen
Protocol: BIG 4-11/BO25126/TOC4939G

	Pertuzumab + Trastuzumab + Chemotherapy (N=2400)	Placebo + Trastuzumab + Chemotherapy (N=2404)
Adjuvant radiotherapy		
No	654 (27.3%)	669 (27.8%)
Yes	1746 (72.8%)	1735 (72.2%)
Side		
n	1746	1735
Left only	897 (51.4%)	877 (50.5%)
Right only	846 (48.5%)	857 (49.4%)
Bilateral	3 (0.2%)	1 (<0.1%)
Left chest wall		
n	357 (20.4%)	370 (21.3%)

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_dm_adj.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_dm_adj_IT.out
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Adjuvant Hormone Therapy

The great majority of patients with central hormone receptor-positive disease received adjuvant hormone therapy (1317/1508 [87.3%] vs. 1330/1551 [85.8%]; Table 28).

Table 28 Summary of Adjuvant Hormone Therapy by Treatment Regimen
Summary of Hormone Therapy: Central Hormone Receptor Positive Cohort, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

	Pertuzumab + Trastuzumab + Chemotherapy (N=1508)	Placebo + Trastuzumab + Chemotherapy (N=1551)
Patients with no Adjuvant Hormone Therapy	191 (12.7%)	221 (14.2%)
Patients with Adjuvant Hormone Therapy	1317 (87.3%)	1330 (85.8%)
SERM alone	663 (44.0%)	681 (43.9%)
AI alone	440 (29.2%)	412 (26.6%)
Ovarian Suppression alone	5 (0.3%)	4 (0.3%)
SERM -> AI or AI -> SERM	63 (4.2%)	71 (4.6%)
Ovarian Suppression + SERM	92 (6.1%)	96 (6.2%)
Ovarian Suppression + AI	21 (1.4%)	17 (1.1%)
Other	33 (2.2%)	49 (3.2%)

AI: Aromatase Inhibitor; LHRH: Luteinizing hormone releasing hormone;
SERM: Selective estrogen receptor modulator; ->: followed by; +: concurrent
Total line may exceed sum of individual lines because sex hormones are not included in any subclass of hormone therapies.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_cm_ht.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_cm_ht_CHRP_SE.out
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Numbers analysed

Randomized Population– Intent-to-Treat (ITT)

The primary analysis population for all efficacy endpoints was the intent-to-treat (ITT) population. All randomized patients were included in the ITT population. Patients were grouped according to the treatment assigned at randomization. Patients who received any amount of study medication (chemotherapy, Perjeta/ placebo, or Herceptin) were included in the safety population. Patients were analysed as treated: patients who received at least one full or partial dose of Perjeta were included in the Perjeta arm; all other treated patients were included in the control arm.

Outcomes and estimation

Primary endpoint

Table 29 Summary of Time to First IDFS Event, Stratified Analysis (ITT Population)

Summary of Time to First IDFS Event by Treatment Regimen, Stratified Analysis, ITT Population
Protocol: BIG 4-11/BO25126/TOC4939G

Invasive Disease Free Survival	Pertuzumab + Trastuzumab + Chemotherapy (N=2400)		Placebo + Trastuzumab + Chemotherapy (N=2404)
Patients with event (%)	171 (7.1%)		210 (8.7%)
Patients without event (%)	2229 (92.9%)		2194 (91.3%)
Stratified Analysis			
p-value (log-rank)		0.0446	
Hazard Ratio		0.81	
95% CI		(0.66, 1.00)	
3 year duration			
Patients remaining at risk	2101		2108
Event Free Rate (%)	94.06		93.24
95% CI	(93.09, 95.03)		(92.21, 94.26)

Time to IDFS Event (months) - Censoring: IDFS (1=censored, 0=event).
Strata are: nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen.
Hazard ratios were estimated by Cox regression.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ef_tte.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ef_tte_STR1_IDFS_IT.out
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Figure 11 Kaplan-Meier Plot of IDFS (ITT Population)

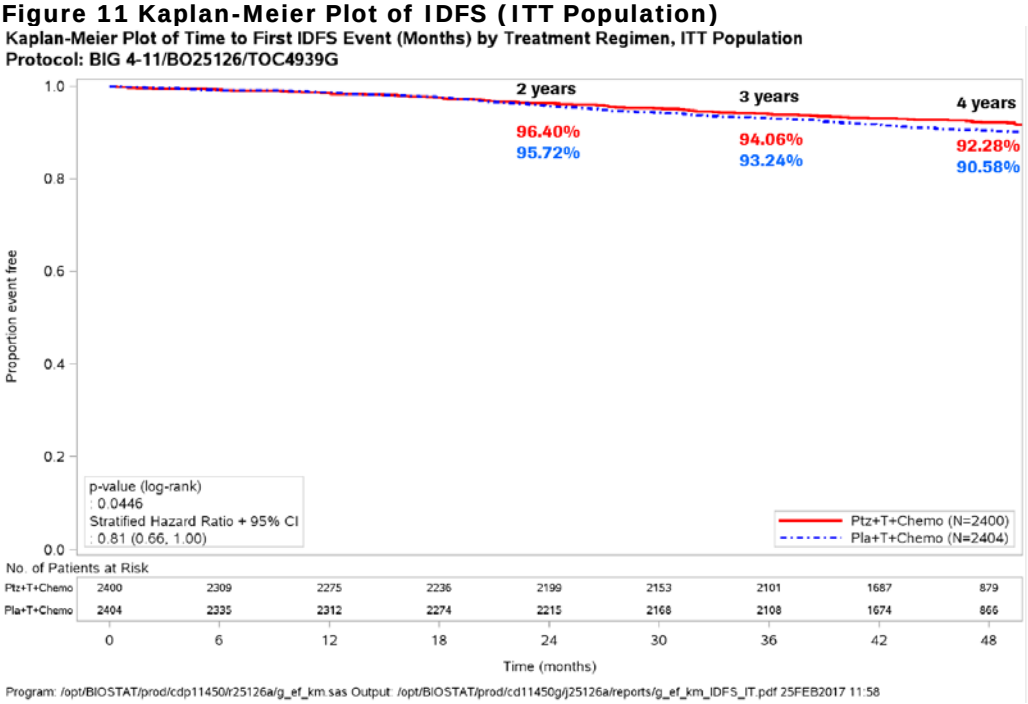

Table 30 Summary of First Occurrence of an IDFS Event Applying Hierarchy and Time Window

Summary of First Occurrence of an IDFS Event Applying Hierarchy and Time Window by Treatment Regimen, ITT Population
Protocol: BIG 4-11/BO25126/TOC4939G

	Pertuzumab + Trastuzumab + Chemotherapy (N=2400)	Placebo + Trastuzumab + Chemotherapy (N=2404)
Total Patients with IDFS Event: n (%)	171 (7.1%)	210 (8.7%)
Category of IDFS Event: n (%)		
Distant recurrence	112 (4.7%)	139 (5.8%)
CNS metastases	45 (1.9%)	44 (1.8%)
Locoregional recurrence	26 (1.1%)	34 (1.4%)
Contralateral breast cancer	5 (0.2%)	11 (0.5%)
Death without prior event	28 (1.2%)	26 (1.1%)

Patients who experience additional IDFS event(s) within 61 days of their 1st IDFS event are reported in the category according to the following hierarchy: [1] Distant recurrence; [2] Locoregional recurrence; [3] Contralateral breast cancer; [4] Death without prior event. CNS metastases is a subset of Distant recurrence.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ef_fo.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ef_fo_FTIDFS_IT.out
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Secondary endpoints

As required by the SAP, since the result for the primary endpoint, IDFS, showed statistical significance, key secondary endpoints were tested sequentially at an overall two-sided significance level of 5% by use of a hierarchical testing procedure in the following order:

1. IDFS including second primary non-breast cancer (IDFS-SPNBC)
2. DFS
3. OS.

RFI and DRFI were tested but not included in the multiplicity adjustment.

IDFS including second primary non-breast cancer (IDFS-SPNBC)

Table 31 Summary of Time to First IDFS Including Second Primary Non-breast Cancer Event, Stratified Analysis (ITT Population)

Summary of Time to First IDFS Including Second primary non-breast Cancer Event by Treatment Regimen, Stratified Analysis, ITT Population
Protocol: BIG 4-11/BO25126/TOC4939G

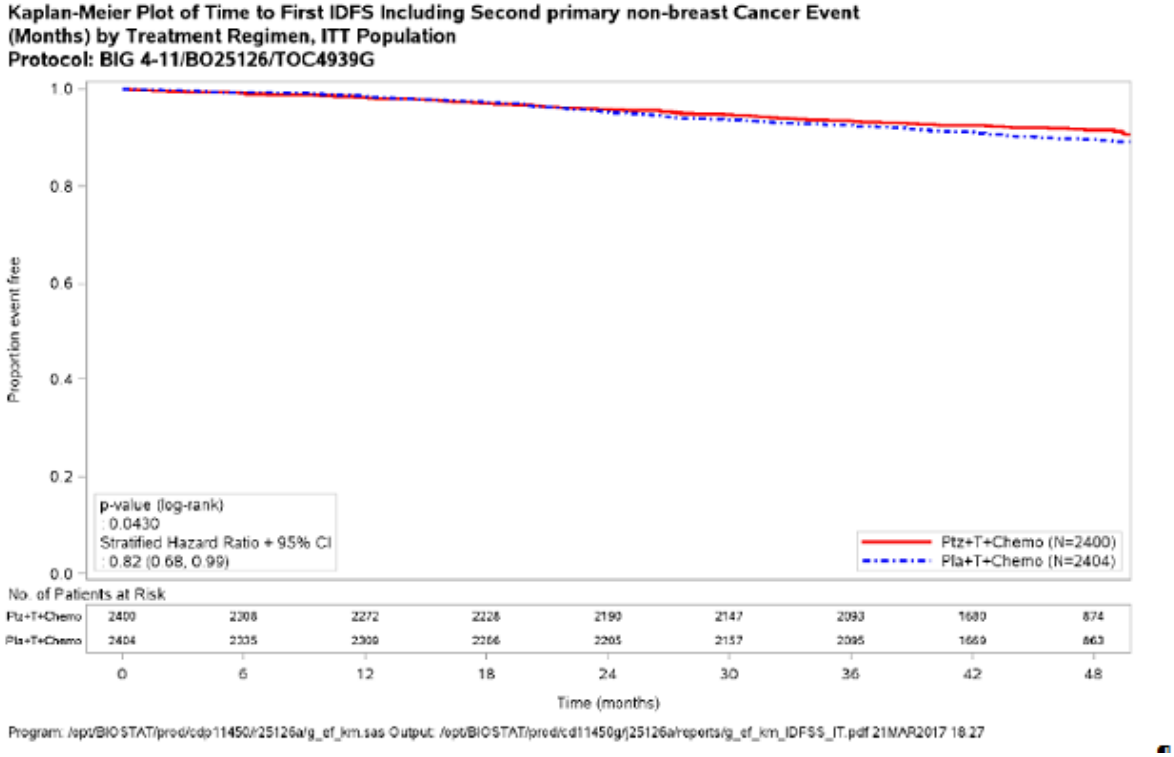
IDFS including second primary non-breast cancer

	Pertuzumab + Trastuzumab + Chemotherapy (N=2400)		Placebo + Trastuzumab + Chemotherapy (N=2404)
Patients with event (%)	189 (7.9%)		230 (9.6%)
Patients without event (%)	2211 (92.1%)		2174 (90.4%)
Stratified Analysis			
p-value (log-rank)		0.0430	
Hazard Ratio		0.82	
95% CI		(0.68, 0.99)	
3 year duration			
Patients remaining at risk	2093		2095
Event Free Rate (%)	93.50		92.51
95% CI	(92.49, 94.51)		(91.43, 93.58)

Time to IDFS including second primary non-breast cancer (IDFS-SPNBC) event (months)
Censoring: IDFS-SPNBC (1=censored, 0=event).
Strata are: nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen. Hazard ratios were estimated by Cox regression.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ef_tte.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ef_tte_STR1_IDFSS_IT.out
25FEB2017 12:13 Page 1 of 1

Figure 12 Kaplan-Meier Plot of IDFS-SPNBC (ITT Population)



Disease-Free Survival (DFS)

Table 32 Summary of Time to First DFS Event, Stratified Analysis (ITT Population)

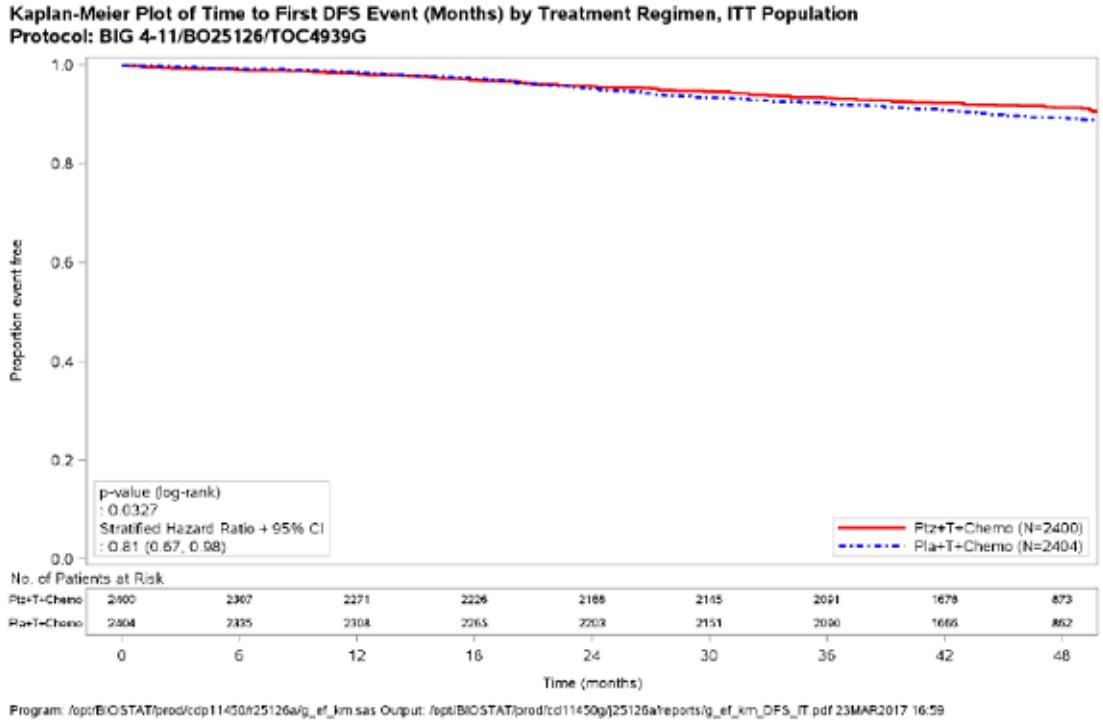
Summary of Time to First DFS Event by Treatment Regimen, Stratified Analysis, ITT Population
Protocol: BIG 4-11/BO25126/TOC4939G

Disease Free Survival	Pertuzumab + Trastuzumab + Chemotherapy (N=2400)		Placebo + Trastuzumab + Chemotherapy (N=2404)
Patients with event (%)	192 (8.0%)		236 (9.8%)
Patients without event (%)	2208 (92.0%)		2168 (90.2%)
Stratified Analysis			
p-value (log-rank)		0.0327	
Hazard Ratio		0.81	
95% CI		(0.67, 0.98)	
3 year duration			
Patients remaining at risk	2091		2090
Event Free Rate (%)	93.42		92.29
95% CI	(92.40, 94.43)		(91.21, 93.38)

Time to DFS Event (months) - Censoring: DFS (1=censored, 0=event).
Strata are: nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen.
Hazard ratios were estimated by Cox regression.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ef_tte.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ef_tte_STR1_DFS_IT.out
23MAR2017 17:11 Page 1 of 1

Figure 13 Kaplan-Meier Plot of Time to First DFS Event (Months) by Treatment Regimen: ITT Population



Overall Survival (OS)

Table 33 Summary of Overall Survival, Stratified Analysis (ITT Population)

Protocol: BIG 4-11/BO25126/TOC4939G

Overall Survival	Pertuzumab + Trastuzumab + Chemotherapy (N=2400)		Placebo + Trastuzumab + Chemotherapy (N=2404)
Patients with event (%)	80 (3.3%)		89 (3.7%)
Patients without event (%)	2320 (96.7%)		2315 (96.3%)
Stratified Analysis			
p-value (log-rank)		0.4673	
Hazard Ratio		0.89	
95% CI		(0.66, 1.21)	
3 year duration			
Patients remaining at risk	2186		2209
Event Free Rate (%)	97.65		97.67
95% CI	(97.03, 98.27)		(97.06, 98.29)

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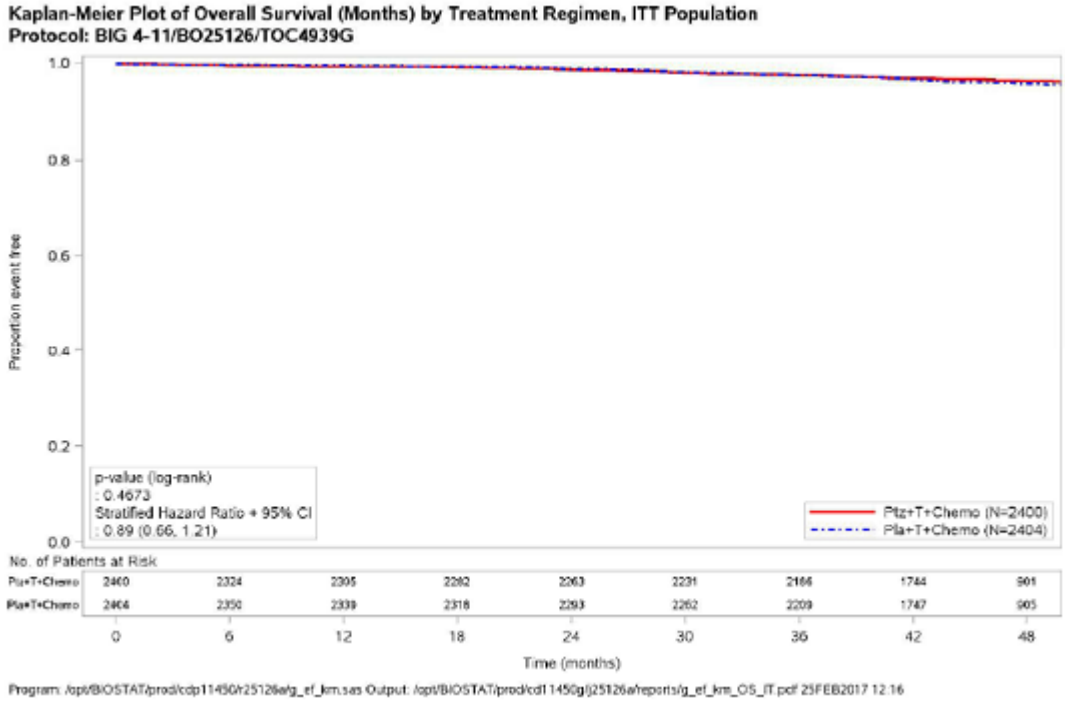
Figure 14 Kaplan-Meier Plot of Overall Survival (ITT Population)



Results of sensitivity analyses

Primary endpoint:

For the patients who were censored (7.1% in Ptz+H+Chemo versus 8.7% in Pla+H+Chemo), the median time to censoring was 45.4 months/45.5 months for patients treated with Ptz+H+Chemo respectively Pla+H+Chemo, i.e. there was no indication of a difference in follow-up time, which is also seen in the Kaplan-Meier time of time to censoring. The hazard ratio for time to censoring was 1.02 (0.96; 1.08). Moreover, the number of assessments appeared to be balanced between the two groups, as was the mean and median time from the previous assessment to the IDFS event.

The analysis of time to censoring showed very similar median times to censoring in the two treatment arms.

Table 34 Time to Censoring for IDFS Events, ITT Population

Summary of Time to Censoring for IDFS Event by Treatment Regimen, ITT Population
Protocol: BIG 4-11/BO25126/TOC4939G

Time to Censoring for IDFS

	Pertuzumab + Trastuzumab + Chemotherapy (N=2400)	Placebo + Trastuzumab + Chemotherapy (N=2404)
Patients with event (%)	2229 (92.9%)	2194 (91.3%)
Patients without event (%)	171 (7.1%)	210 (8.7%)
Time to event (months)		
Median	45.4	45.5
95% CI	(45.2, 45.6)	(45.2, 45.7)
25% and 75%-ile	42.1, 50.2	42.1, 50.2
Range	0 to 59	0 to 59
Hazard Ratio	1.02	
95% CI	(0.96, 1.08)	

Time to censoring for IDFS Event (months) - Censoring: IDFS (1=censored, 0=event).
Range including censored values.
Summaries of time to censoring for IDFS (median, percentiles) are Kaplan-Meier estimates.
95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.

Figure 15

Kaplan-Meier Plot of Time to Censoring of IDFS Event (Months) by Treatment Regimen, ITT Population
Protocol: BIG 4-11/BO25126/TOC4939G

Also, the number of assessments that could detect recurrence was balanced between the two arms (mean [SD]: 14.75 [4.04] vs. 14.79 [3.71]).

Table 35

Summary of Number of Assessments that could detect Recurrence by Treatment Regimen, ITT Population
Protocol: BIG 4-11/BO25126/TOC4939G

	Pertuzumab + Trastuzumab + Chemotherapy (N=2400)	Placebo + Trastuzumab + Chemotherapy (N=2404)
Number of assessments for recurrence: n (%)		
0	0	0
1	23 (1.0%)	16 (0.7%)
2-7	130 (5.4%)	105 (4.4%)
8-14	727 (30.3%)	804 (33.4%)
>14	1520 (63.3%)	1479 (61.5%)
n	2400	2404
Mean (SD)	14.75 (4.04)	14.79 (3.71)
Median	15.00	15.00
Range	1.0 - 36.0	1.0 - 36.0

Assessments refer to physical examination or radiological examination.

Table 36 Overview of Sensitivity Analysis Results for IDFS (ITT Population)

Sensi-tivity Analysis	HR [95% CI]	p-value	Ptz+H+Chemo		Pla+H+Chemo		Analysis Description
			Events	3-year IDFS	Events	3-year IDFS	
ITT	0.81 [0.66, 1.00]	0.0446	171	94.06%	210	93.24%	Strata: nodal status, protocol version, central HR status, adjuvant chemotherapy regimen (eCRF)
1	0.81 [0.65, 0.99]	0.0434	157	94.32%	196	93.46%	Censor at NACT if start date prior to first IDFS event
2	0.94 [0.79, 1.11]	0.4511	253	90.38%	273	90.39%	Count patients as having an event at date of NACT if date prior to first IDFS event
3	0.77 [0.62, 0.96]	0.0183	143	94.92%	184	93.80%	Censor patients who discontinued study follow-up at last assessment known to be recurrence-free (ignores late reported deaths as events)
4	0.93 [0.80, 1.07]	0.2837	371	87.48%	399	87.55%	Patients who discontinued study follow-up without a recurrence are considered to have a recurrence at the date of the next planned assessment, had they continued in the study
5	0.95 [0.82, 1.11]	0.5418	325	92.79%	344	92.35%	Count patients who withdrew from targeted treatment due to toxicity as having an IDFS event 1 day after date last known to be recurrence-free
6	0.89 [0.78, 1.02]	0.1020	410	91.31%	457	90.44%	Count patients who discontinued study follow-up as having an IDFS event 1 day after the last assessment known to be recurrence-free
7	0.82 [0.67, 1.00]	0.0549	171	94.06%	210	93.24%	Unstratified analysis
8	0.80 [0.66, 0.98]	0.0345	171	94.06%	210	93.24%	Adjuvant chemotherapy strata based on regimen actually received
9	0.81 [0.67, 1.00]	0.0467	171	94.06%	210	93.24%	Protocol version excluded from strata
10	0.82 [0.67, 1.00]	0.0471	171	94.06%	210	93.24%	Strata defined according to IxRS

Chemo=chemotherapy; CI=confidence interval; H=trastuzumab; HR=hazard ratio; IDFS=invasive disease-free survival; ITT=Intention-to-Treat; NACT = new anti-cancer therapy; Pla=placebo; Ptz=pertuzumab.

Note: The methodological details of the individual sensitivity analyses are described in Section 3.9.3.4.

Sources: Sens#1 ; Sens#2 (KM-plot Sens#2) ; Sens#3 (KM-plot Sens#3) ; Sens#4 ; Sens#5 (KM-plot Sens#5) ; Sens#6 (KM-plot Sens#6) ; Sens#7 ; Sens#8 ; Sens#9 ; Sens#10.

Secondary endpoints:

Sensitivity analyses were planned but not performed, since the results of the sensitivity analyses of the primary endpoint showed no inconsistencies with the result of the primary analysis.

Exploratory endpoints

Recurrence-Free Interval (RFI)

Table 37 Summary of RFI, Stratified Analysis (ITT Population)

Summary of Recurrence-Free Interval (RFI) by Treatment Regimen, Stratified Analysis, ITT Population
Protocol: BIG 4-11/BO25126/TOC4939G

Recurrence Free Interval

	Pertuzumab + Trastuzumab + Chemotherapy (N=2400)		Placebo + Trastuzumab + Chemotherapy (N=2404)
Patients with event (%)	138 (5.8%)		173 (7.2%)
Patients without event (%)	2262 (94.3%)		2231 (92.8%)
Stratified Analysis			
p-value (log-rank)		0.0430	
Hazard Ratio		0.79	
95% CI		(0.63, 0.99)	
3 year duration			
Patients remaining at risk	2116		2129
Event Free Rate (%)	95.18		94.27
95% CI	(94.30, 96.06)		(93.32, 95.21)

RFI (months) - Censoring: RFI (1=censored, 0=event).
Strata are: nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen.
Hazard ratios were estimated by Cox regression.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ef_tte.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ef_tte_STR1_RFI_IT.out
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Distant Recurrence-Free Interval (DRFI)

Table 38 Summary of DRFI, Stratified Analysis (ITT Population)

Summary of Distant Recurrence-Free Interval (DRFI) by Treatment Regimen, Stratified Analysis, ITT Population
Protocol: BIG 4-11/BO25126/TOC4939G

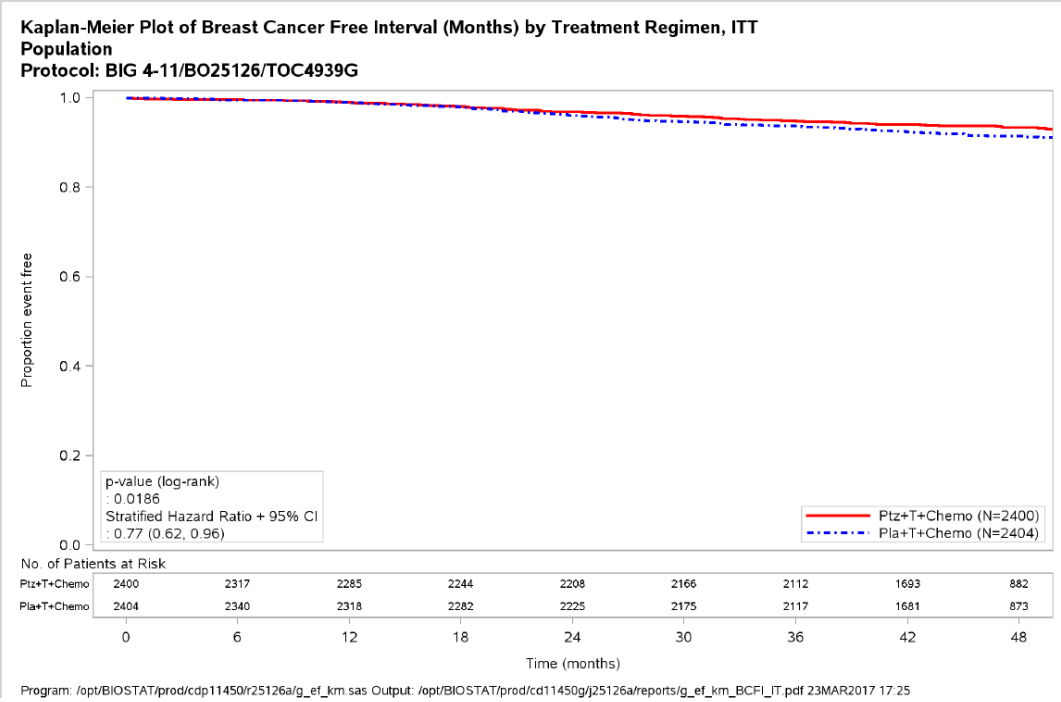
Distant Recurrence Free Interval

	Pertuzumab + Trastuzumab + Chemotherapy (N=2400)		Placebo + Trastuzumab + Chemotherapy (N=2404)
Patients with event (%)	119 (5.0%)		145 (6.0%)
Patients without event (%)	2281 (95.0%)		2259 (94.0%)
Stratified Analysis			
p-value (log-rank)		0.1007	
Hazard Ratio		0.82	
95% CI		(0.64, 1.04)	
3 year duration			
Patients remaining at risk	2126		2145
Event Free Rate (%)	95.70		95.13
95% CI	(94.86, 96.53)		(94.25, 96.00)

DRFI (months) - Censoring: DRFI (1=censored, 0=event).
Strata are: nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen.
Hazard ratios were estimated by Cox regression.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ef_tte.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ef_tte_STR1_DRFI_IT.out
21MAR2017 18:48 Page 1 of 1 ¶

Table 39 Breast Cancer-Free Interval (BCFI)



Patient-reported outcomes

Timing of the chemotherapy PRO assessment was tailored to the patient's treatment regimen, namely the end of anthracycline treatment (only in patients receiving an anthracycline-based regimen), the end of taxane therapy (all patients), and the end of HER2-targeted treatment (all patients). Note that in the PRO outputs, while the time point denoted as "Week 13" corresponds to the end of taxane treatment in all patients, the actual time of this assessment depends on the type of chemotherapy. For patients receiving anthracycline-based chemotherapy, the actual time point was Week 10 or Week 13 of HER2-targeted treatment (depending on the chemotherapy regimen given). For patients receiving non-anthracycline-based chemotherapy (i.e., the Ptz + TCH regimen), this was Week 19 of HER2-targeted treatment.

For the analyses of function, treatment-related symptoms, and global health status/HRQoL, as assessed by the scales of the EORTC QLQ-C30 and the QLQ-BR23 questionnaires, a difference of ≥10 points from the baseline score within a treatment arm is considered a clinically meaningful change.

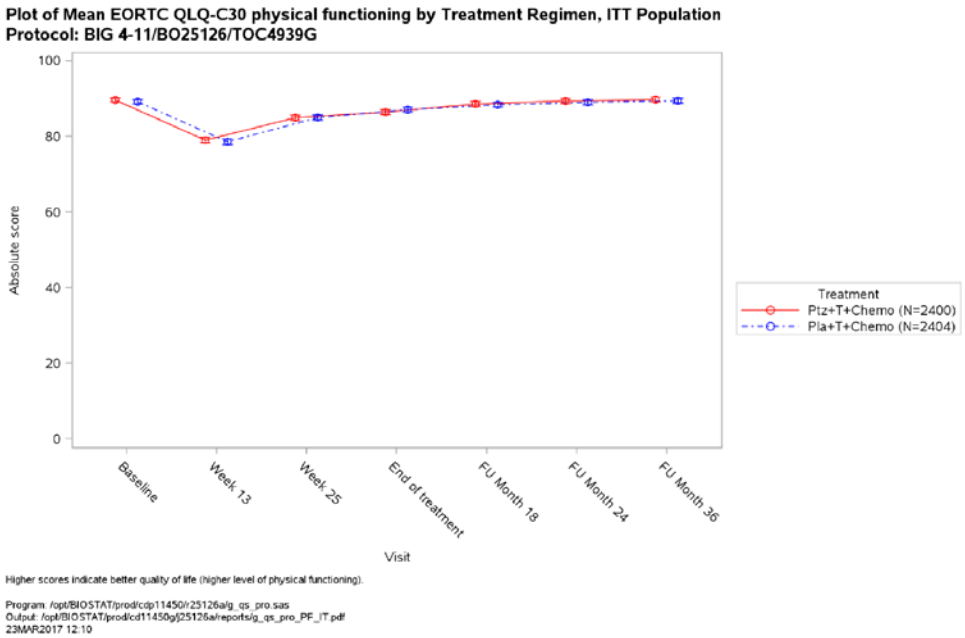
Key results from PRO analyses are provided below.

- Completion rates for all questionnaires were consistently high throughout the study (>85.0%).
- Patients experienced a clinically considerable decline in physical function (Figure 16) and global health status (Figure 17) during chemotherapy (Week 13) similarly in both treatment arms; thereafter, scores improved and returned to baseline levels during HER2-targeted treatment. Patients' ability to conduct daily activities, as assessed by role function (Figure 18), was maintained in both arms over the course of study treatment.
- Diarrhea symptoms scores as measured by EORTC QLQ-C30 were highest (i.e., worst) at the end of taxane treatment (Week 13) in both arms (Figure 19). The scores in both arms remained elevated during the HER2-targeted treatment period, but the difference from baseline was clinically considerable (≥ 10 points) only in the pertuzumab arm at the end of taxane and during the HER2-targeted treatment period. Symptoms of fatigue, dyspnea, body image, and systemic chemotherapy side effects clinically significantly deteriorated at the end of taxane treatment (Week

13) in both arms. Appetite loss showed a clinically considerable deterioration at the end of taxane treatment in the pertuzumab arm only. Of the patients reporting hair loss (only ~300 in each arm), a clinically considerable deterioration was observed in patients' upset by hair loss at the end of taxane treatment and during HER2-targeted treatment in both arms. Around 300 patients in each arm recorded sexual activity. Amongst these patients, the decline in sexual enjoyment scores was clinically considerable for both arms at the end of taxane treatment, but only in the pertuzumab arm during HER2-targeted treatment (after cessation of chemotherapy). Differences in all other symptom scores were not clinically considerable.

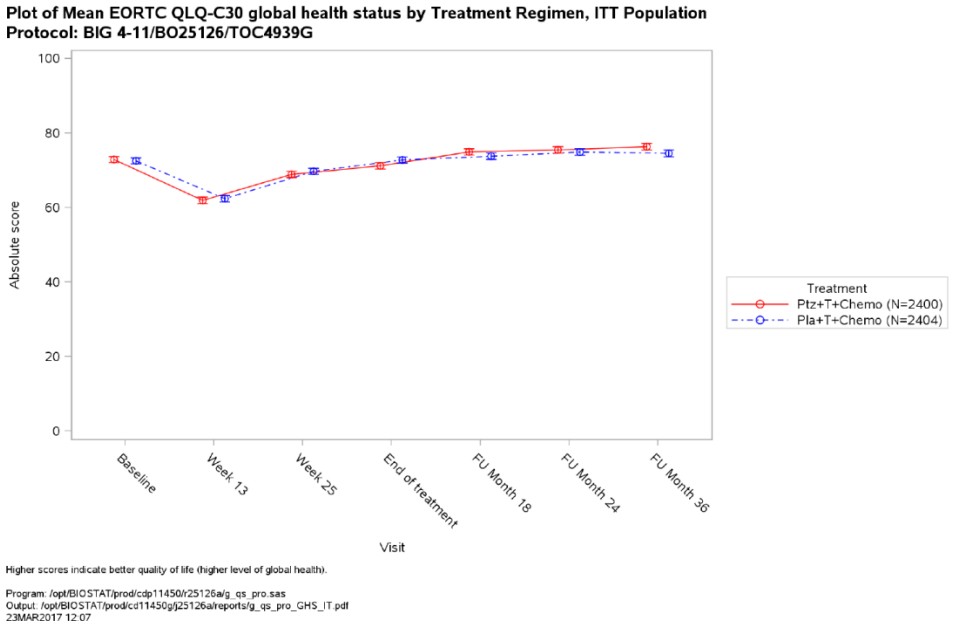
- No clinically considerable differences in patient-reported treatment-related symptoms, all function scales, or global health status were observed in either arm after cessation of HER2-targeted treatment. All returned to or remained at baseline levels during the follow-up period (Months 18, 24, and 36).
- There were no major differences (≥ 5 percentage points) between treatment arms in the five EQ-5D domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).

Figure 16 Mean Scores of EORTC QLQ-C30 Physical Functioning (ITT Population)



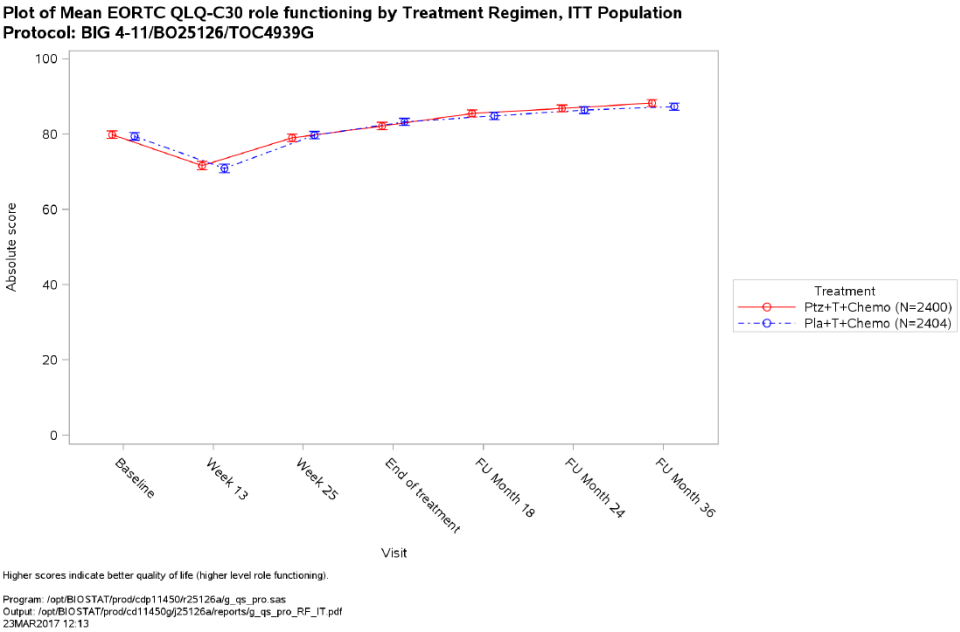
Note: The programmed outputs shift the two curves for greater visual clarity. The time points are the same in both treatment arms.
The time point "Week 13" in this table and the associated programmed outputs corresponds to the end of taxane treatment; the actual time depends on the type of chemotherapy received.

Figure 17 Mean Scores of EORTC QLQ-C30 Global Health Status (ITT Population)



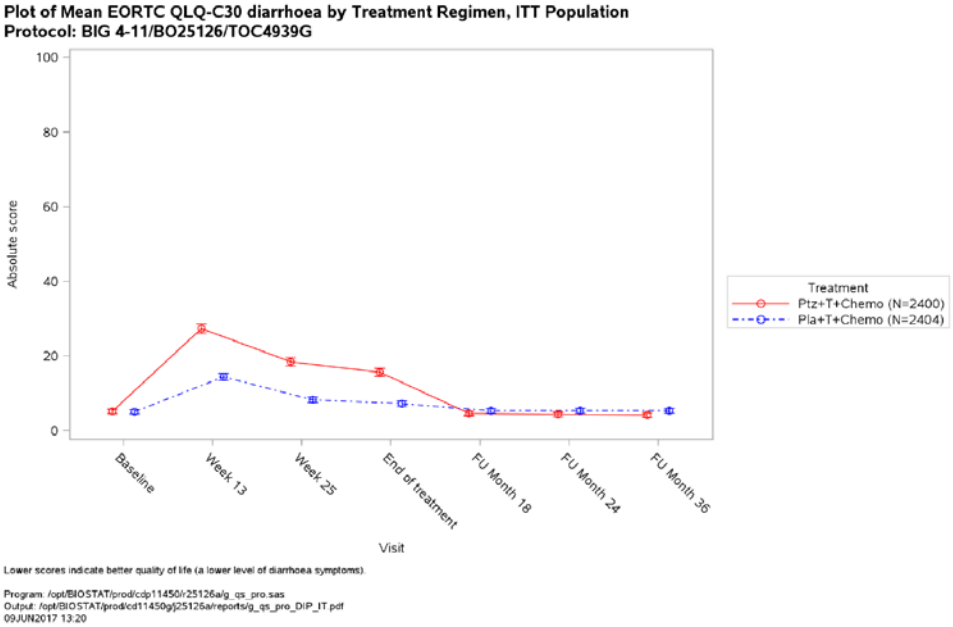
Note: The programmed outputs shift the two curves for greater visual clarity. The time points are the same in both treatment arms. The time point "Week 13" in this table and the associated programmed outputs corresponds to the end of taxane treatment; the actual time depends on the type of chemotherapy received.

Figure 18 Mean Scores of EORTC QLQ-C30 Role Functioning (ITT Population)



Note: The programmed outputs shift the two curves for greater visual clarity. The time points are the same in both treatment arms. The time point "Week 13" in this table and the associated programmed outputs corresponds to the end of taxane treatment; the actual time depends on the type of chemotherapy received.

Figure 19 Mean Scores of EORTC QLQ-C30 Diarrhea (ITT Population)



Note: The programmed outputs shift the two curves for greater visual clarity. The time points are the same in both treatment arms. The time point "Week 13" in this table and the associated programmed outputs corresponds to the end of taxane treatment; the actual time depends on the type of chemotherapy received.

Ancillary analyses

Subgroup analyses

Nodal status

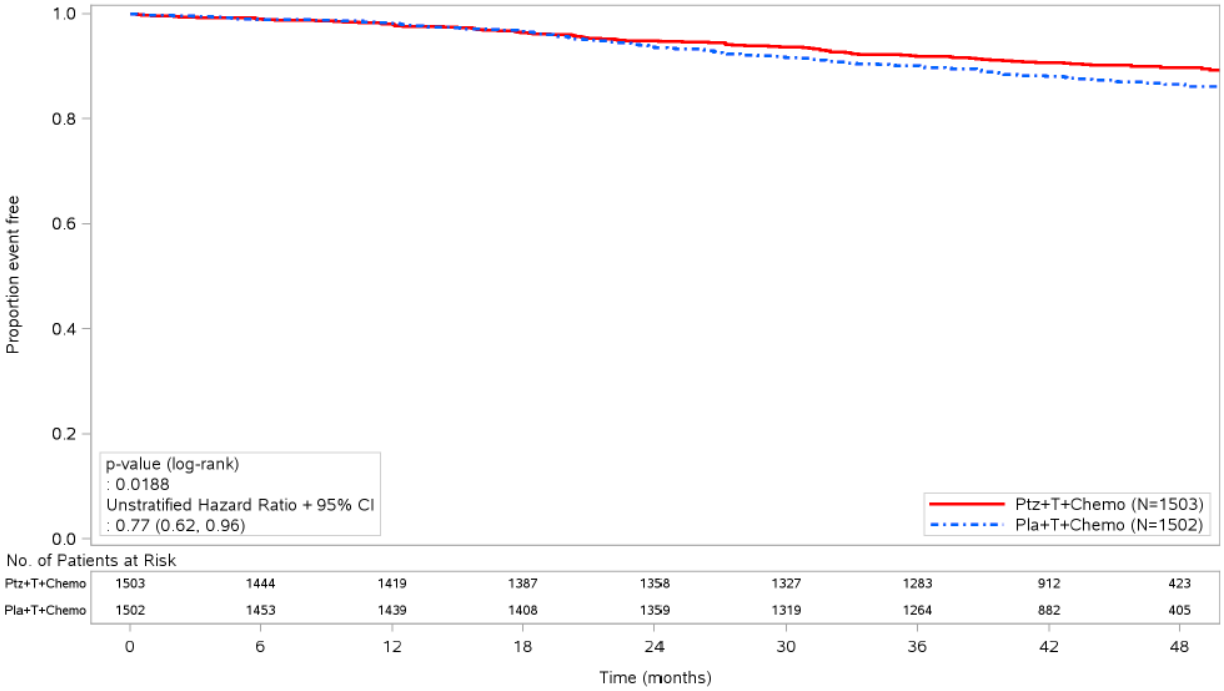
Patients with node-positive disease (a pre-defined subgroup) showed statistically significant benefit with Ptz+H+Chemo treatment with IDFS event-free rates of 91.99% vs. 90.15% at 3 years (HR 0.77, 95%CI 0.62, 0.96) (KM curve below). These results indicate a 23% reduction in risk of recurrence or death in patients randomized to Ptz+H+Chemo; the event-free rates at were 89.88% vs. 86.68%, respectively.

In comparison, the estimated HR for IDFS for the node-negative subgroup (HR 1.13, 95%CI 0.68, 1.86) did not show evidence of treatment benefit at this time; nor did the subgroup of patients with node-negative disease and a tumour > 1cm in diameter (i.e., a subset of the node-negative subgroup; HR 1.23, 95%CI 0.72, 2.10).

Kaplan-Meier curve for Event-free rates for IDFS over Time by Treatment Regimen, Node Positive Cohort, ITT Population:

Figure 20

Kaplan-Meier Plot of Time to First IDFS Event (Months) by Treatment Regimen, Node Positive Cohort, ITT Population
Protocol: BIG 4-11/BO25126/TOC4939G

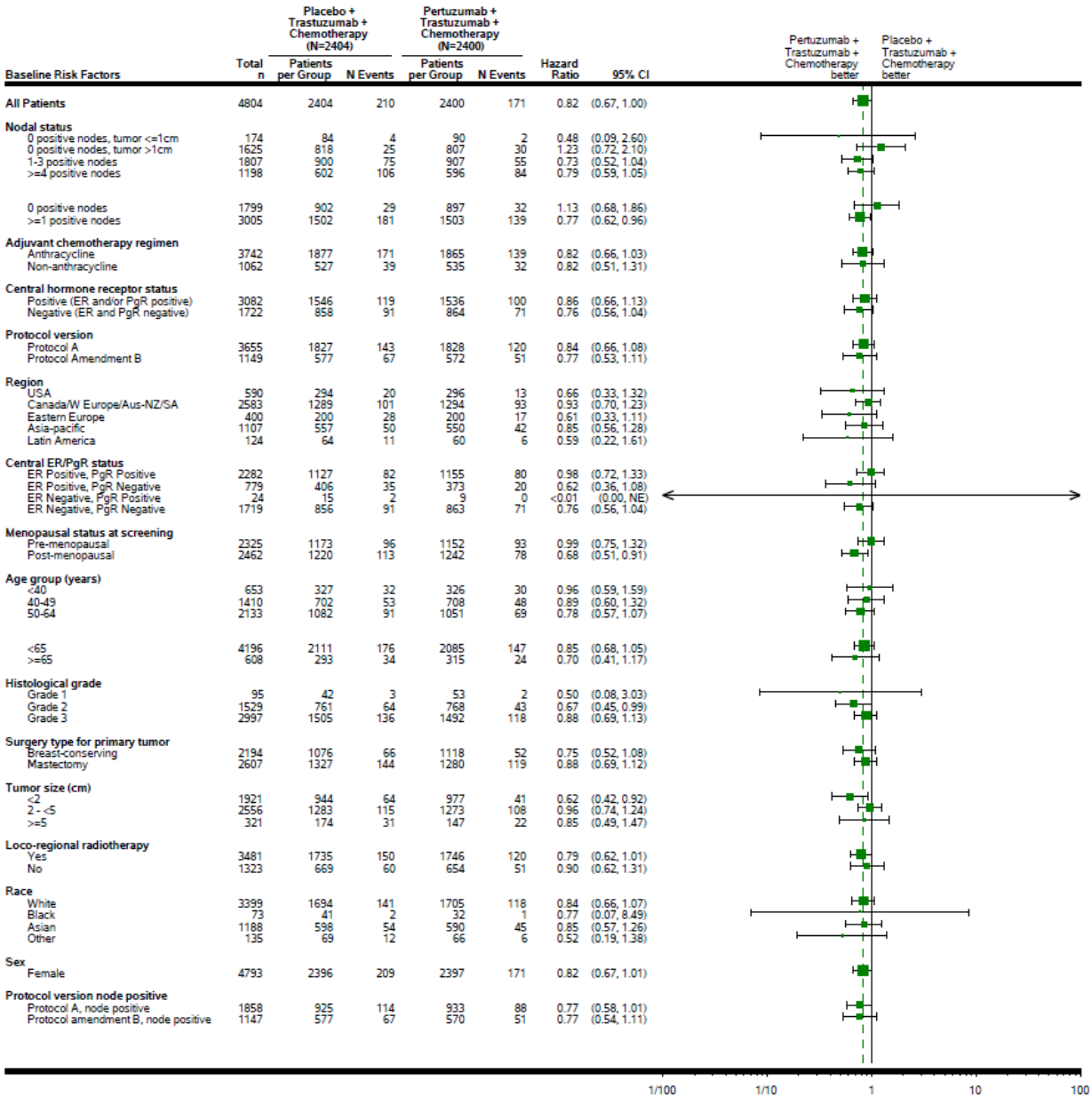


No. of Patients at Risk

Ptz+T+Chemo	1503	1444	1419	1387	1358	1327	1283	912	423
Pla+T+Chemo	1502	1453	1439	1408	1359	1319	1264	882	405
	0	6	12	18	24	30	36	42	48

Time (months)

Figure 21. Forest Plot of Hazard Ratios and 95% Confidence Intervals for IDFS by Subgroup



All Patients refers to the unstratified analysis for the ITT population

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/g_ef_tte_sub.sas Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/g_ef_tte_sub_IDFS_IT.pdf 25FEB2017 12:07

Hormone receptor status

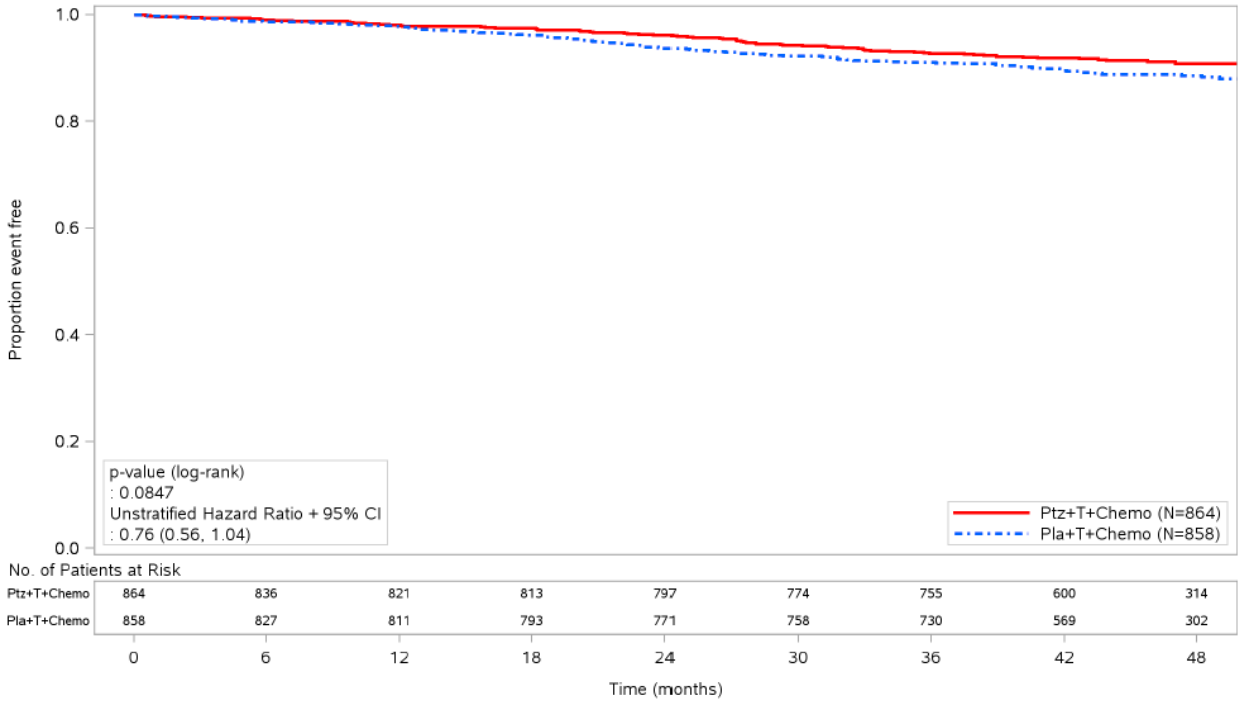
Central hormone receptor status is another pre-specified factor of particular interest. Improved IDFS was observed in patients irrespective of hormone receptor status (see Forest plot). The benefit of adding Perjeta to trastuzumab and chemotherapy was not significantly dependent on hormone receptor status, i.e. for patients with hormone receptor-negative disease the results were HR 0.76 (95%CI 0.56, 1.04) (KM curve below), and for patients with hormone receptor-positive disease the results showed HR 0.86 (95%CI 0.66, 1.13).

The 3-year IDFS event-free rates for the hormone receptor-negative subgroup were 92.77% in the Ptz+H+Chemo arm vs. 91.17% in the Pla+H+Chemo arm. At 4 years, the IDFS event-free rates for this subgroup were 90.96% vs. 88.67%, respectively. For the hormone receptor-positive subgroup, IDFS event-free rates were 94.79% vs. 94.37% at 3 years and 93.03% vs. 91.63% at 4 years.

Kaplan-Meier curve for Event-free rates for IDFS over Time by Treatment Regimen, hormone receptor-negative patients, ITT Population:

Figure 22

Kaplan-Meier Plot of Time to First IDFS Event (Months) by Treatment Regimen, Central Hormone Receptor Negative Patients, ITT Population
Protocol: BIG 4-11/BO25126/TOC4939G



HER2 subgroups

Exploratory analyses were carried out to assess potential relationships between different levels of HER2-overexpression and improvements in IDFS with the addition of Perjeta to H+Chemo in the adjuvant setting. These subgroups were not specified in the SAP, but were documented in a separate, more detailed data analysis plan, finalized prior to database lock.

Table 40

Summary of Time to First IDFS Event (Months) by HER2 IHC and FISH Subgroups and Treatment Regimen: ITT Population
Protocol: BIG 4-11/BO25126/TOC4939G

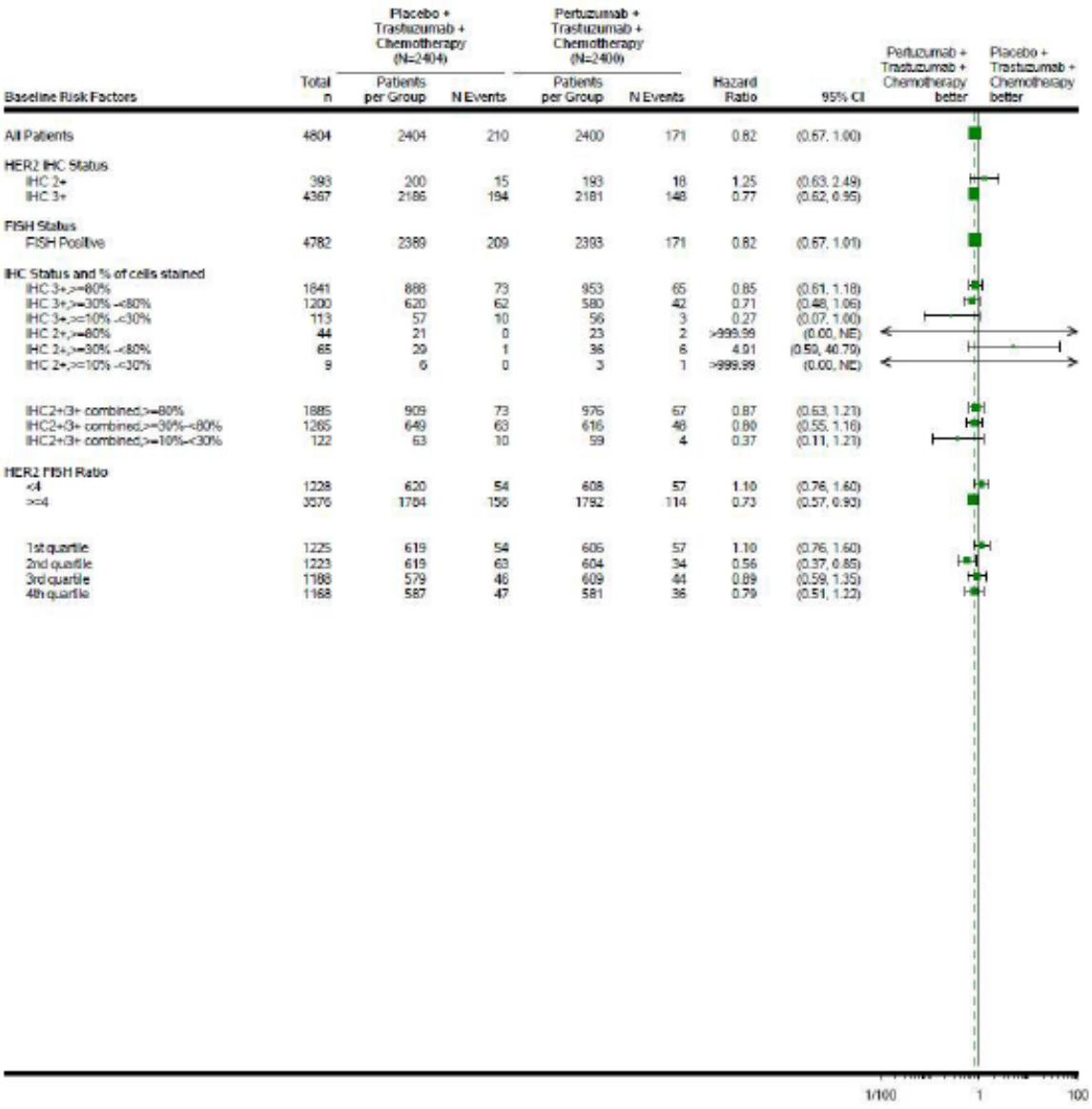
		Pertuzumab + Trastuzumab + Chemotherapy (N=2400)			Placebo + Trastuzumab + Chemotherapy (N=2404)				
		Patients per Group	N Events	3 Year KM	Patients per Group	N Events	3 Year KM	Hazard Ratio	95% CI
All		2400	171	94.1	2404	210	93.2	0.82	(0.67, 1.00)
HER2 IHC Status	IHC 2+	193	18	93.1	200	15	93.7	1.25	(0.63, 2.49)
	IHC 3+	2181	148	94.3	2186	194	93.2	0.77	(0.62, 0.95)
FISH Status	FISH Positive	2393	171	94.0	2389	209	93.2	0.82	(0.67, 1.01)
IHC Status and % of cells stained	IHC 3+, >=80%	953	65	94.3	888	73	93.5	0.85	(0.61, 1.18)
	IHC 3+, >=30% - <80%	580	42	94.0	620	62	92.6	0.71	(0.48, 1.06)
	IHC 3+, >=10% - <30%	56	3	96.2	57	10	87.6	0.27	(0.07, 1.00)
	IHC 2+, >=80%	23	2	95.7	21	0	100.0	>999.99	(0.00, NE)
	IHC 2+, >=30% - <80%	36	6	85.8	29	1	96.4	4.91	(0.59, 40.79)
	IHC 2+, >=10% - <30%	3	1	100.0	6	0	100.0	>999.99	(0.00, NE)
	IHC2+/3+ combined, >=80%	976	67	94.3	909	73	93.7	0.87	(0.63, 1.21)
	IHC2+/3+ combined, >=30% - <80%	616	48	93.5	649	63	92.8	0.80	(0.55, 1.16)
	IHC2+/3+ combined, >=10% - <30%	59	4	96.4	63	10	88.6	0.37	(0.11, 1.21)
HER2 FISH Ratio	<4	608	57	92.0	620	54	94.0	1.10	(0.76, 1.60)
	>=4	1792	114	94.8	1784	156	93.0	0.73	(0.57, 0.93)
	1st quartile	606	57	91.9	619	54	94.0	1.10	(0.76, 1.60)
	2nd quartile	604	34	95.1	619	63	91.5	0.56	(0.37, 0.85)
	3rd quartile	609	44	94.7	579	46	93.3	0.89	(0.59, 1.35)
	4th quartile	581	36	94.5	587	47	94.2	0.79	(0.51, 1.22)

3 year KM represents the Kaplan-Meier estimate for IDFS at 3 years.
Hazard ratio represents the hazard for patients taking pertuzumab + trastuzumab + chemotherapy versus patients on placebo + trastuzumab + chemotherapy.
HER2 data based on central readings.

In order to explore the potential relationship between HER2-related tumor heterogeneity and the IDFS hazard ratio, subgroups were defined by levels of HER2 protein overexpression, using the two main IHC categories (IHC2+ and IHC3+) and the percentage of cells staining positive for HER2 (using pragmatic cut offs of 80%, 30%, and 10%). It is important to note that the great majority of patients had IHC3+ disease; only 8.2% of patients in the study had IHC2+ disease, and there were only 33 IDFS events in this subgroup.

Table 41

Forest Plot of Time to First IDFS Event (Months) by HER2 IHC and FISH Subgroups, ITT Population
Protocol: BIG 4-11/BO25126/TOC4939G



Similar analyses were performed based on HER2 gene amplification. Subgroups were defined using the HER2 FISH ratio (i.e., the number of HER2 gene copies relative to the number of signals for CEP17) with subgroups based on a pragmatic cutoff of 4.0 (<4.0 or ≥4.0) and by quartiles of the HER2 FISH ratio. Again, the majority of patients had a HER2 FISH ratio ≥4.0 with only 25.6% of patients in the subgroup with a HER2 FISH ratio <4.0 (and 111 events in that subgroup).

Considering HER2 protein levels, a lower HR (suggesting greater benefit) was observed for patients with IHC3+ disease (HR 0.77, 95%CI 0.62, 0.95) than for patients with IHC2+ disease (HR 1.25, 95%CI 0.63, 2.49). Similarly, a lower HR (suggesting greater benefit) was observed for patients with greater HER2 gene amplification in their tumor indicated by a FISH ratio ≥4 (HR 0.73, 95%CI 0.57, 0.93) compared with a FISH ratio <4.0 (HR 1.10, 95%CI 0.76, 1.60).

Overall survival – OS subgroups

Due to the immaturity of the OS analysis, which was based on only 80 (3.3%) deaths in the Ptz+H+Chemo arm and 89 (3.7%) deaths in the Pla+H+Chemo arm, representing 26% of the target events for the final OS analysis, no conclusions on the exploratory analyses of OS within subgroups can be drawn.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial APHINITY

Title: APHINITY				
Study identifier	BIG 4-11/BO25126/TOC4939g			
Design	A randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer.			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Not applicable (study is event driven) Not applicable Not applicable	
Hypothesis	Superiority			
Treatments groups	Chemotherapy plus trastuzumab plus placebo		Chemotherapy (A+T 3-4 cycles each or T+C 6 cycles), 1 year of trastuzumab Q3W.	
	Chemotherapy plus trastuzumab plus pertuzumab		Chemotherapy (A+T 3-4 cycles each or T+C 6 cycles), 1 year of trastuzumab Q3W, 1 year pertuzumab Q3W	
Endpoints and definitions	Primary endpoint	IDFS	Invasive disease-free survival	
	Secondary endpoint	IDFS-SPNBC	IDFS including second primary non-breast cancers	
	Other Secondary endpoints	DFS, OS	Disease-Free Survival, Overall Survival	
Database lock	19 December 2016			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (all subjects) at 1st interim analysis			
Descriptive statistics and estimate variability	Treatment group	Ptz + H + Chemo	Pla + H + Chemo	
	Number of subject	2400	2404	
	IDFS (Event-free proportion at 3 years)	94%	93%	
	95%-CI	93.09-95.03	92.21-94.26	
	IDFS-SPNBC (Event-free proportion at 3 years)	93.5 %	92.5 %	
	95%-CI	92.49-94.51	91.43-93.58	
	DFS	93.4 %	92.3 %	

	95%-CI	92.40-94.43	91.21-93.38
Effect estimate per comparison	IDFS ITT population	Comparison groups	Ptz+H+Chemo vs Pla+H+Chemo
		HR	0.81
		95%-CI	0.66-1.00
		P-value	0.0446
	IDFS-SPNBC	Comparison groups	Ptz+H+Chemo vs Pla+H+Chemo
		HR	0.82
		95%-CI	0.68-0.99
		P-value	0.0430
	DFS	Comparison groups	Ptz+H+Chemo vs Pla+H+Chemo
		HR	0.81
		95%-CI	0.67-0.98
		P-value	0.0327
Notes	OS not mature, 26% events		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Not applicable.

Supportive study(ies)

Not applicable.

2.4.3. Discussion on clinical efficacy

Perjeta is already authorised in the European Union (EU) for use in combination with trastuzumab and docetaxel in patients with HER2 positive metastatic breast cancer (MBC), who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease, and for use in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2 -positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.

The proposed new indication (as finally agreed to be restricted) is:

Early Breast Cancer

Perjeta is indicated for use in combination with trastuzumab and chemotherapy in:

- *the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence (see section 5.1)*

The proposed dose of Perjeta is unchanged.

The efficacy of adding Perjeta to standard chemotherapy and trastuzumab is supported by the APHINITY study (pivotal study).

Design and conduct of clinical studies

To support the efficacy of Perjeta in the sought indication, the MAH submitted results from one single study (APHINITY). The APHINITY study is an ongoing phase III, prospective, randomized, double-blind, placebo-controlled, multicenter, two-arm clinical study in HER2-positive operable early breast cancer. The eligibility criteria were generally appropriate, although the number of possible chemotherapy regimens could have been more limited to reduce bias. Patients were randomized 1:1 to standard chemotherapy 6-8 cycles (investigator's choice) plus trastuzumab plus pertuzumab or placebo (2400 patients to the Ptz+H+Chemo arm and 2405 patients to the Pla+H+chemo arm) from 08 November 2011 to 31 August 2013). Trastuzumab and pertuzumab or placebo was given IV 3-weekly for 52 weeks.

The method for randomization is considered adequate. Both nodal status and hormone receptor status are prognostic factors for the primary endpoint, hence the stratification according to these factors is supported. The two different adjuvant chemotherapy regimens corresponds to potentially different time points for initiation of targeted treatment relative to surgery, stratification according to adjuvant chemotherapy regimen is supported.

The study population defined by the inclusion- and exclusion criteria is generally endorsed, as it resembles the patient population, who should receive adjuvant chemotherapy and trastuzumab according to the ESMO guideline. However, due to the relatively high risk of recurrence in the HER2-positive population, even in node-negative patients with tumours <1 cm, ESMO recommends to consider anti-HER2 treatment, particularly in case of ER-negative disease. According to the inclusion criteria of the APHINITY trial, some of these patients are excluded, e.g. patients with tumor size less than 0.5 cm, probably for the purpose of including patients with higher risk of relapse. Since it is considered not to have a significant impact on the trial results, it is acceptable that patients were excluded by this criterion.

Additionally, subjects with prior malignancies within 5 years and previous chemotherapy/anti-HER2 therapy were excluded. This is endorsed, as it ensures a homogenous population with no late effects of previous cancer treatment or increased risk of recurrence or death.

It is noted, however, that following the observation that the proportion of node-negative disease patients enrolled in the first year was nearly twice that expected, the study was amended and the inclusion of patients with node-negative was stopped in order to have a population consistent with Study BCIRG 006, upon which assumptions of the APHINITY Study were based. The MAH acknowledges that stopping recruitment of node-negative patients into the study have resulted in a patient population that may not be entirely representative of all patients with HER2-positive early breast cancer, but this choice was driven by the intention to have a population similar to BCIRG006 study, and focusing on node-positive patients that were at a higher risk of relapse and in a greater need of more effective treatments. Moreover, for these patients the assumptions were based on a more robust evidence and a stronger treatment effect was expected. In light of the new proposed indication, this approach is no longer an issue. Adjuvant radiotherapy and/or endocrine therapy was started after the end of chemotherapy and in accordance with protocol recommendations.

The rather small imbalances recorded in the use of adjuvant radiotherapy and endocrine therapy in the APHINITY study across geographical regions are not considered to pose any major biases on the efficacy results of the study.

A total of 4 analyses of OS are planned. The first and the last of these are event driven, but for the second and third interim analysis, the Applicant has provided the requested details regarding the timing of the analyses.

The primary endpoint was invasive disease-free survival (IDFS). Secondary endpoints included IDFS excluding second non-breast malignancies (IDFS-SPNBC); disease-free survival (DFS); overall survival

(OS); recurrence-free survival (RFI); distant recurrence-free interval (DRFI); safety and quality of life (QOL). The chosen endpoints were assessed clinically relevant and appropriate for an adjuvant breast cancer trial.

The study had 80% power to detect a hazard ratio 0.75 for IDFS with an alpha 5% (two-sided) significance level. A total enrolment of 3806 patients was initially planned (Protocol A). Patients were initially stratified according to nodal status, adjuvant chemotherapy regimen, hormone receptor status, and geographical region. A sample size reassessment was done after approximately 1900 patients had been recruited at a pace more than 50% higher than expected (September 2012); the sample size was increased from 3806 to 4800 patients (Protocol B), and on the basis of available data, the period of enrolment was reduced from 27 to 25 months and the expected time for observing 379 events was estimated to be at 46 months instead of 55 months from the date the last patient was randomized.

Analysis of IDFS stratified according to the original randomization factors of adjuvant chemotherapy, nodal status, central hormone receptor status and geographical region was consistent with the primary result.

Major protocol deviations were balanced between arms, and are not expected to have impacted the results. The analysis methods for the time to event endpoints are appropriate, and a series of relevant sensitivity analyses investigating potential for bias due to potential imbalance in assessments and follow-up time, as well as the robustness of the primary analysis are planned. Requested details have been provided regarding the start of new anti-cancer therapy and there are no considerable impact on the study outcome. The Applicant have clarified that 15.5% (n = 372) of patients in the Perjeta arm vs. 12.6% (n = 304) of patients in the placebo arm discontinued Perjeta/placebo. There are no meaningful imbalances between the two arms, safety being the most common reason for premature discontinuation.

More than 99% of patients in each arm were female, with only 11 male patients enrolled in the study. A quarter of the patients were recruited after protocol amendment B. In order to assess the impact of the changes introduced with Protocol B, demographics and baseline characteristics summarised by Protocol Version were to be provided, as planned. Apart from a higher prevalence of Asian patients due to the differential timings in the approval of clinical trial application, all other differences (e.g. higher rate of mastectomy, larger tumor size) are expected based on the decision to enroll only node-positive patients. The difference in 3-year IDFS appears to be driven by node-positive patients.

Patients received both adjuvant radiotherapy and endocrine therapy according to standard practice, and these may differ between sites, especially the radiotherapy standard practice may vary according to local practices and available equipment. The available endocrine therapies are quite uniform in their efficacy profiles and it is therefore less problematic if there are differences in the use and sequence of e.g. aromatase inhibitors, but the duration of the adjuvant therapy matters. As adjuvant radiotherapy and endocrine therapy prevent both local and distant recurrences, these variations may present important biases. The Applicant has provided additional information about this and after a thorough review, it is agreed that the rather small imbalances recorded in the use of adjuvant radiotherapy and endocrine therapy in the APHINITY study across geographical regions are not considered to pose any major biases on the efficacy results of the study.

Efficacy data and additional analyses

The study met its **primary endpoint** at the time of primary analysis with 4 years of follow-up. Treatment with pertuzumab plus trastuzumab and standard chemotherapy resulted in a statistically significant improvement in IDFS, corresponding to a 19% reduction in the risk of recurrence or death, as compared to placebo plus trastuzumab and standard chemotherapy (HR 0.81, 95%CI 0.66; 1.00, p=0.0446) in the adjuvant setting of early breast cancer. The K-M IDFS curves tend to overlap up to 2 years. Estimates of IDFS event-free rates at 3 years were 94.06% vs. 93.24% in the Ptz+H+Chemo vs. Pla+H+ Chemo arms,

respectively, and at 4 years were 92.28% vs. 90.58%, suggesting a sustained benefit over time after the end of treatment (1-year duration). At this point in time 171 patients (7.1%) in the pertuzumab arm versus 210 patients (8.7%) in the placebo arm have had an event. Of these patients, 112 patients (4.7%) vs. 139 patients (5.8%) had a distant recurrence as the most frequent IDFS event. This reflects the fact that adjuvant treatment of breast cancer is aimed at preventing incurable distant recurrences and these results show that local recurrence is not the major issue with this disease. Most of the distant metastases were located in the CNS, lung, and liver. Hence, a reduction of risk of invasive disease can often be translated into a clinically relevant prevention of incurable disease, only amendable for palliative treatment and ultimately resulting in death. Therefore, considering the low number of events so far, the results are considered clinically meaningful. Moreover, the efficacy of the addition of pertuzumab is expected to be consistent and may be even improved over time as more events occur, because the adding of pertuzumab have shown convincing improvement of efficacy in the neoadjuvant and metastatic setting.

Another issue is the known increased risk of CNS disease in the HER2-positive population, as submitted data show that the incidence of CNS metastases was similar in the two treatment arms (1.8% vs. 1.9%), and although numbers are small, this may reflect poor CNS penetration of the adjuvant treatment including pertuzumab. To our knowledge, there are no conclusive data regarding the efficacy of pertuzumab in the CNS and therefore the activity is expected to be similar to that of trastuzumab in terms of its limited ability to cross the blood-brain barrier. The Applicant provided further knowledge on the CNS efficacy of Perjeta, as requested. It is agreed that it may be difficult, and maybe not possible, to distinguish between the efficacy of trastuzumab and pertuzumab, when given concomitantly. It is considered encouraging that uptake of pertuzumab in CNS metastases have been observed by PET/CT in a study by Ulaner et al. 2017, however, an actual treatment benefit has not yet sufficiently been shown. It is agreed that the suggested additional 5 years of follow-up time in the APHINITY study will provide valuable information on this subject, including the Applicant's hypothesis that Perjeta may delay time to CNS metastases.

The key **secondary endpoints** were invasive disease-free survival including second non-breast malignancies (IDFS-SPNBC), disease-free survival (DFS), and overall survival (OS). Results for IDFS-SPNBC was similar to IDFS, and showed a clinically meaningful and statistical difference favouring the pertuzumab arm (HR 0.82, 95% CI 0.68; 0.99, p=0.0430). DFS also showed a significant benefit with the addition of pertuzumab (HR 0.81, 95% CI 0.67; 0.98, p=0.0327). Overall survival data was immature. As patients with recurrent disease have several treatment options, the overall survival is not expected to be affected before the time of the final analysis (10 years after last patient randomized), occurring in the year 2023. Moreover, it is not considered an issue with regard to the B/R assessment of the present application. Having in mind, that in the HERA trial of adjuvant trastuzumab, OS was not statistically significant until 8 years had passed, the submitted results are considered acceptable and as could be expected at this point in time. Importanty, the available data on OS and other endpoints did not raise any concerns.

The **exploratory endpoints** were recurrence-free interval (RFI), distant recurrence-free interval (DRFI), and breast cancer-free interval (BCFI). RFI showed a clinically significant improvement (HR 0.79, 95% CI 0.63; 0.99, p=0.0430) as well as BCFI (HR 0.77, 95% CI 0.62; 0.96, p=0.0186). The DRFI did not show a statistically significant difference between the arms, probably due to too few events (5% vs. 6%, respectively).

Patient-reported outcome showed a considerable decline in physical function and global health status during chemotherapy and the incidence was similar in both treatment arms. This is considered to be due to the known toxicity profile of chemotherapy and is considered confirmed by the fact that scores improved and returned to baseline levels after chemotherapy had ended and patients only received HER2-targeted treatment. Diarrhoea is a known treatment-related adverse effect of both pertuzumab and taxanes, so the increased incidence of diarrhoea and the effect on PRO was expectable and does seem to be manageable in the short period of time when both therapies were given concomitantly (9 weeks). Overall, it is considered encouraging that all patients returned to or remained at baseline levels during the follow-up period (Months

18, 24, and 36) according to the patient-reported treatment-related symptoms, all function scales, and global health status.

All **sensitivity analyses** were in favour of the pertuzumab arm, but only some were statistically significant. Many of the sensitivity analyses investigated the effect of stratification with results almost identical to the primary analysis. In addition, the effect of discontinuation, withdrawal, and start of new anti-cancer therapy were investigated in the sensitivity analyses. As new anti-cancer therapy was broadly defined, and the reasons have been clarified sufficiently by the Applicant, the previous issues regarding this has now been resolved.

Subgroup analyses were performed for the primary endpoint IDFS, however, they were not powered to detect a statistically significant effect and was considered exploratory by the Applicant. Patients with **node-positive** disease (n=3005) have a high risk of recurrence and not surprisingly, there were a markedly greater benefit in this subgroup (HR 0.77, 95% CI 0.62; 0.96). This may reflect that these high-risk patients get a recurrence earlier in time than other subgroups, and results show a higher number of events in this subgroup (12% vs 9%). Patients with **node-negative** disease (n=1799) have a low risk of recurrence and results for this subgroup was not statistically significant (HR 1.13, 95% CI 0.68; 1.86), however, less than 4% of the patients have had an event and the confidence intervals are wide. This reflects the low risk, although it is expected that over time, this group will probably also obtain significant benefit. As HR-positive disease recur later in time compared to other subgroups, this is what may be reflected by this analysis. **Hormone receptor-negative** patients is another high-risk subgroup (n=1722) and appeared to have a benefit from the addition of pertuzumab, however, the differences were not significant because the confidence intervals were very wide and included 1. The number of events was 11% vs 8%, respectively, indicating immaturity of data. However, it is important to note that in the HERA trial, as well as in BCIRG 006 trial, based on which the assumptions were made, the benefit from the addition of trastuzumab was observed regardless of nodal status. Due to rate of accrual much higher than expected, and subsequent to the amendments introduced to the study design (stop of the enrolment of node-negative subjects, and increase of the sample size based on the inclusion of solely node-positive subjects), the target number of events for the primary IDFS analysis was expected to be reached earlier than initially planned. However, in practice it took longer to reach 379 events than estimated under both protocol A and protocol B. This is especially relevant for the subset of patients at lower risk of recurrence, such as node-negative patients, whose representativeness was also artificially reduced, and that experienced relatively few events compared to node-positive patients. Despite the stop of the enrolment of node-negative patients, introduced with protocol amendment of 20 November 2012 (i.e. 12 months after first patient enrolled), the median follow-up in the node-negative subgroup (48.3 months) was only slightly longer than the overall population (45.4 months), and the node-positive subgroup (44.5 months), and events were observed only in 3.5% of the patients in this subset of patients, with a rate of recurrences in node-positive subjects (10.3%) that was almost three times the one observed in node-negative patients.

In conclusion, the results observed in the overall population could appear to be driven by the node-positive subgroup that has been artificially increased with protocol amendment. It cannot be excluded that with a longer follow-up, a benefit could be shown also for node-negative patients, but this is not self-evident. Even though exploratory analyses of treatment by subgroup interaction effects did not indicate heterogeneity of treatment effect, and there are no biological explanation for assuming a lower activity of pertuzumab in node-negative patients, based on the available data and the observed low-risk of recurrence in this subgroup treated with standard of care chemotherapy + trastuzumab, the need and the benefit of dual anti-HER2 regimen in node-negative subjects may nevertheless be questioned. The Applicant restricted the initially proposed indication to adult patients with HER2-positive early breast cancer "at high risk of recurrence", i.e. to the protocol pre-defined subgroups of node-positive or hormone-receptor negative patients, as the current results are clinically significant at this point in time due to higher risk of recurrence and therefore more events in these subgroups. A reference to section 5.1 was added, with the subgroup

analyses, and a clarification that high-risk patients were defined as those with node-positive or hormone receptor-negative disease.

The rather small imbalances recorded in the use of adjuvant radiotherapy and endocrine therapy in the APHINITY study across geographical regions are not considered to pose any major biases on the efficacy results of the study.

The Applicant proposed to extend the follow-up time by additional 5 years, because it is considered that within this time frame clinically relevant information could be provided. It is considered that the extended follow-up will be very informative both with regard to the number of relapses over time (especially in the CNS) and the extent of late toxicity from the adjuvant treatment.

The data regarding HER2 protein expression levels should be interpreted cautiously due to the small sample size, the nature of an exploratory analysis, and because the analysis was not adjusted for other prognostic factors such as nodal status. However, it is noted that HER2 protein expression levels could be a clinically relevant factor, and the subgroup analysis may become relevant the time of the final analysis.

2.4.4. Conclusions on the clinical efficacy

Based on the results from the primary analysis of the APHINITY study, the efficacy of adding pertuzumab to standard chemotherapy and trastuzumab is not considered demonstrated in the ITT population. The study treatment reduced the risk of relapse or death by 19%, and as the majority of the observed relapses were distant, this translates into prevention of incurable disease, only amendable for palliative treatment and ultimately resulting in death. However, the borderline statistically significant benefit was not considered supported by all secondary endpoints and sensitivity analyses, and seems to be mainly driven by the highest risk subgroups. Hence, the efficacy of adding pertuzumab to standard chemotherapy is considered demonstrated in the high-risk subgroups of patients with node-positive or hormone-receptor-negative disease, where the efficacy has been significantly demonstrated to a clinically relevant extent. In addition, it is considered that results in the adjuvant setting may improve over time as more events occur, in the context of pertuzumab's established efficacy in the neoadjuvant and metastatic setting of breast cancer.

In conclusion, efficacy has been demonstrated in the indication of high-risk patients with node-positive or hormone receptor-negative disease.

2.5. Clinical safety

Introduction

The overall safety profile of Ptz+H+Chemo in the APHINITY study was consistent with the known safety profile of Perjeta in combination with trastuzumab and standard chemotherapy in HER2-positive metastatic or inoperable breast cancer, and no new or unexpected toxicities were reported. The frequency and nature of AEs reported were as expected for this study population, and for the treatment regimens being assessed. The overall incidence of primary cardiac events was < 1% of patients in both arms.

Patient exposure

In total, the APHINITY study provides safety data on 2364 patients exposed to Perjeta plus trastuzumab and standard chemotherapy (Ptz+H+Chemo) in the adjuvant setting. Safety data have previously been submitted for more than 2000 patients treated with Perjeta alone or in combination with a range of Herceptin and/or chemotherapy regimens in registration-directed and supporting clinical trials in the neoadjuvant and

metastatic settings. In addition, it is estimated that more than 160,000 patients have received Perjeta in routine clinical practice based on marketing data, and includes those treated in the EBC and metastatic breast cancer setting.

Patients were further categorized according to chemotherapy regimen received (anthracycline-based or non-anthracycline-based):

- Ptz+H+Chemo (safety population, n=2364)
    - Ptz+H+anthracycline: N=1834
    - Ptz+H+non-anthracycline: N=528
- Pla+H+Chemo (safety population, n=2405)
    - Pla+H+anthracycline: N=1894
    - Pla+H+non-anthracycline: N=510

Note that a total of 2362 patients in the Ptz+H+Chemo arm were categorized as receiving an anthracycline-based regimen (1834 patients) or a non-anthracycline-based regimen (528 patients) but the number of patients in the Ptz+H+Chemo safety population was 2364 (a difference of 2 patients). Similarly, a total of 2404 patients in the Pla+H+Chemo arm were categorized as receiving an anthracycline-based regimen (1894 patients) or a non-anthracycline-based regimen (510 patients), but the number of patients in the Pla+H+Chemo safety population was 2405 (a difference of one patient). The reason for the difference is because a total of three patients did not receive any carboplatin. To be categorized as receiving a non-anthracycline-based regimen, patients had to have received at least one dose of carboplatin, and have no exposure to anthracyclines. Patients who only received a taxane (regardless of whether they received Perjeta, placebo or Herceptin) could not be assigned to either the non-anthracycline or the anthracycline cohorts.

At the time of the clinical cut-off for the primary analysis (19 December 2016), 2028 patients (84.5%) in the Ptz+H+Chemo arm and 2100 patients (87.4%) in the Pla+H+Chemo arm had completed treatment. The remaining patients (372 [15.5%] in the Ptz+H+Chemo arm and 304 [12.6%] in the Pla+H+Chemo arm) did not complete, or never started, Perjeta or placebo treatment.

Overall, the median duration of study treatment (64 weeks), as well as targeted treatment (55 weeks), was the same in both treatment arms (Table 42). Note that the duration of treatment includes 28 days after the last dose of study medication representing the timing of the end of study treatment visit and the reporting period for adverse events during the treatment period.

Table 42 Overview of Treatment Duration by Treatment Regimen (Safety Population)

Overview of Treatment Duration by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Study Treatment Period Duration (weeks)		
n	2364	2405
Median	64	64
Range	4 - 80	4 - 74
Anthracycline Treatment Duration (weeks)		
n	1834	1894
Median	11	13
Range	4 - 26	4 - 18
Taxane + Targeted Treatment Duration (weeks)		
n	2364	2338
Median	55	55
Range	4 - 59	4 - 70
Targeted Treatment Duration (weeks)		
n	2364	2335
Median	55	55
Range	4 - 59	4 - 70

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ex_dur.sas / Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ex_dur_TRT1A_SE.out
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Summary of exposure to Anthracycline-based chemotherapy:

	Ptz + H + Chemo arm (N=1834)	Pla + H + Chemo arm (N=1894)
Completed anthracycline	1818 (99.1%)	1847 (97.5%)
Completed taxane	1650 (90.0%)	1674 (88.4%)
Completed chemo + targeted therapy	1586 (86.5%)	1600 (84.5%)
Completed targeted therapy but not chemotherapy	10 (0.5%)	15 (0.8%)

Chemo=chemotherapy (including both anthracycline and taxane components), H=Herceptin, Pla=placebo, Ptz=pertuzumab.

Summary of exposure to Non-anthracycline-based chemotherapy:

	Ptz + H + Chemo (N=528)	Pla + H + Chemo (N=510)
Completed docetaxel and carboplatin (TC)	448 (84.1%)	469 (91.6%)
Completed TC+ targeted therapy	416 (78.8%)	448 (87.8%)
Completed targeted therapy but not TC	37 (7.0%)	13 (2.5%)
Median treatment duration[a] (range)	55 (4–59)	55 (4–59)

TC= docetaxel+carboplatin.

[a] Duration of docetaxel and carboplatin and + targeted treatment (weeks).

Dose Adjustments/Delays

Perjeta/placebo dose delays or interruptions due to toxicities were permitted in APHINITY. Perjeta/placebo was administered without the need for dose adjustment/delays in 1156 patients (48.9%) vs. 1194 patients (49.6%).

Table 43

Exposure to Pertuzumab/Placebo by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Treatment Duration (weeks)		
n	2364	2335
Median	54	54
Range	3 - 58	3 - 69
Number of Infusions (stat)		
n	2364	2335
Median	18	18
Range	1 - 22	1 - 18
Number of Infusions (cat)		
< 12	182 (7.7%)	145 (6.0%)
12 - 16	144 (6.1%)	148 (6.2%)
17	422 (17.9%)	374 (15.6%)
> 17	1616 (68.4%)	1668 (69.4%)
Number (%) of Patients Completing at Least:		
1 infusion	2364 (100.0%)	2335 (97.1%)
4 infusions	2285 (96.7%)	2281 (94.8%)
6 infusions	2253 (95.3%)	2241 (93.2%)
12 infusions	2182 (92.3%)	2190 (91.1%)
17 infusions	2038 (86.2%)	2042 (84.9%)
Cumulative Dose (mg)		
n	2364	2335
Median	7980	0
Range	420 - 9660	0
Number of Dose Adjustments/Delays (stat)		
n	2364	2335
Median	1	0
Range	0 - 8	0 - 7
Number of Dose Adjustments/Delays (cat)		
0	1156 (48.9%)	1194 (49.6%)
1	699 (29.6%)	664 (27.6%)
2	307 (13.0%)	303 (12.6%)
> 2	202 (8.5%)	174 (7.2%)
Number of Dose Adjustments/Delays due to Adverse Event (stat)		
n	2364	2335
Median	0	0
Range	0 - 6	0 - 5

Treatment duration relates to Pertuzumab/placebo.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ex.sas / Output:
/opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ex_TRT1A_PP_SE.out
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Note: 11 patients in the Ptz + H + Chemo arm received >18 cycles of pertuzumab.

Adverse events

Table 44 Summary of Adverse Events in the APHINITY Study

	Treatment Arm	
	Ptz+H+Chemo (N = 2364)	**Pla+H+Chemo (N = 2405)**
Patients with		
Any AE	99.9%	99.5%
Grade 3 – 5 AE	64.2%	57.3%
Serious AE	29.3%	24.3%
AE leading to treatment withdrawal[a]	13.1%	11.5%
AE leading to Perjeta/placebo withdrawal	7.0%	5.8%
AE leading to any treatment interruption/modification[b]	51.5%	44.2%
AE leading to Perjeta/placebo interruption/modification	30.6%	26.3%
AEs leading to death[c]	0.8%[d]	0.8%[d]
Death due to recurrent disease	2.0%	2.6%
Death due to other causes[e]	0.3%	0.5%
Cardiac Safety		
Primary cardiac event[f]	0.7%	0.3%
Secondary cardiac event[g]	2.7%	2.8%
Other Events to Monitor		
Diarrhea: All Grades	71.3%	45.2%
Grade ≥ 3	9.9%	3.7%
Rash: All Grades	51.9%	41.7%
Grade ≥ 3	2.5%	1.5%
Leukopenia: All Grades	49.8%	48.1%
Grade ≥ 3	37.3%	35.0%
Infusion-Related Reaction: All Grades	54.7%	51.3%
Grade ≥ 3	2.7%	2.1%
Anaphylaxis & Hypersensitivity: All Grades	4.9%	3.6%
Grade ≥ 3	0.8%	0.7%
Interstitial Lung Disease: All Grades	0.8%	0.9%
Grade ≥ 3	0.2%	0.2%
Mucositis: All Grades	57.0%	49.1%
Grade ≥ 3	4.9%	2.3%

AE = adverse event; Chemo = chemotherapy; H = Herceptin; Pla = placebo; Ptz = Perjeta.

[a] Any adverse event leading to discontinuation of one or more study drugs (including chemotherapy).

[b] Any adverse event leading to dose interruption or modification of one or more study drugs (including chemotherapy).

[c] Adverse event with outcome of death (i.e., Grade 5 adverse event) at any time during the study.

[d] Includes secondary primary non-breast cancers that were reported as AEs (9 events in the Ptz+H+Chemo arm, and 8 events in the Pla+H+Chemo arm).

[e] Deaths due to causes other than recurrence of disease and adverse event.

[f] Heart failure (NYHA Class III or IV) and a drop in LVEF of at least 10 ejection fraction points from baseline and to below 50%, or cardiac death

[g] defined as an asymptomatic or mildly symptomatic (NYHA Class II) significant LVEF drop of at least 10 ejection fraction points below baseline and to below 50%.

Source: Table 44 ; Table 55 and Table 58 in the APHNITY Primary CSR.

Table 45 Adverse Events with an Incidence Rate of at least 5% in Either Treatment Arm (Safety Population)

Most Common (>=5%) Adverse Events by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)	
NAUSEA	1632 (69.0%)	1575 (65.5%)	
ALOPECIA	1577 (66.7%)	1610 (66.9%)	
DIARRHOEA	1683 (71.2%)	1086 (45.2%)	
FATIGUE	1154 (48.8%)	1065 (44.3%)	
VOMITING	768 (32.5%)	733 (30.5%)	
ARTHRALGIA	678 (28.7%)	782 (32.5%)	
CONSTIPATION	684 (28.9%)	759 (31.6%)	
MYALGIA	615 (26.0%)	710 (29.5%)	
STOMATITIS	671 (28.4%)	573 (23.8%)	
ANAEMIA	655 (27.7%)	557 (23.2%)	
NEUTROPENIA	587 (24.8%)	562 (23.4%)	
DYSGEUSIA	614 (26.0%)	518 (21.5%)	
RASH	609 (25.8%)	488 (20.3%)	
HEADACHE	531 (22.5%)	563 (23.4%)	
DECREASED APPETITE	565 (23.9%)	478 (19.9%)	
ASTHENIA	505 (21.4%)	500 (20.8%)	
MUCOSAL INFLAMMATION	552 (23.4%)	448 (18.6%)	
HOT FLUSH	482 (20.4%)	509 (21.2%)	
PYREXIA	473 (20.0%)	469 (19.5%)	
OEDEMA PERIPHERAL	405 (17.1%)	483 (20.1%)	
PERIPHERAL SENSORY NEUROPATHY	427 (18.1%)	422 (17.5%)	
INSOMNIA	404 (17.1%)	400 (16.6%)	
EPISTAXIS	430 (18.2%)	326 (13.6%)	
NEUROPATHY PERIPHERAL	366 (15.5%)	369 (15.3%)	
COUGH	374 (15.8%)	351 (14.6%)	
DYSPEPSIA	325 (13.7%)	341 (14.2%)	
NEUTROPHIL COUNT DECREASED	327 (13.8%)	330 (13.7%)	
LACRIMATION INCREASED	310 (13.1%)	322 (13.4%)	
NASOPHARYNGITIS	316 (13.4%)	284 (11.8%)	
DRY SKIN	311 (13.2%)	268 (11.1%)	
NAIL DISORDER	280 (11.8%)	284 (11.8%)	
RADIATION SKIN INJURY	298 (12.6%)	266 (11.1%)	g
DYSPNOEA	281 (11.9%)	277 (11.5%)	
FEBRILE NEUTROPENIA	287 (12.1%)	266 (11.1%)	
ABDOMINAL PAIN	287 (12.1%)	262 (10.9%)	
PRURITUS	331 (14.0%)	217 (9.0%)	
DIZZINESS	270 (11.4%)	275 (11.4%)	
PARAESTHESIA	278 (11.8%)	240 (10.0%)	
PAIN IN EXTREMITY	236 (10.0%)	252 (10.5%)	
BONE PAIN	223 (9.4%)	256 (10.6%)	
ALANINE AMINOTRANSFERASE INCREASED	221 (9.3%)	244 (10.1%)	
ABDOMINAL PAIN UPPER	245 (10.4%)	218 (9.1%)	
ERYTHEMA	235 (9.9%)	214 (8.9%)	
BACK PAIN	207 (8.8%)	238 (9.9%)	
WHITE BLOOD CELL COUNT DECREASED	234 (9.9%)	206 (8.6%)	
LEUKOPENIA	216 (9.1%)	222 (9.2%)	
MUSCULOSKELETAL PAIN	201 (8.5%)	216 (9.0%)	
OROPHARYNGEAL PAIN	216 (9.1%)	175 (7.3%)	
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	217 (9.2%)	158 (6.6%)	
UPPER RESPIRATORY TRACT INFECTION	191 (8.1%)	177 (7.4%)	
NAIL DISCOLOURATION	175 (7.4%)	178 (7.4%)	

MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
URINARY TRACT INFECTION	187 (7.9%)	163 (6.8%)
MUSCLE SPASMS	217 (9.2%)	123 (5.1%)
RHINORRHOEA	191 (8.1%)	135 (5.6%)
PAIN	157 (6.6%)	165 (6.9%)
HAEMORRHOIDS	185 (7.8%)	125 (5.2%)
ASPARTATE AMINOTRANSFERASE INCREASED	145 (6.1%)	162 (6.7%)
LYMPHOEDEMA	134 (5.7%)	161 (6.7%)
OEDEMA	139 (5.9%)	156 (6.5%)
DRY MOUTH	148 (6.3%)	136 (5.7%)
CONJUNCTIVITIS	147 (6.2%)	124 (5.2%)
EJECTION FRACTION DECREASED	124 (5.2%)	147 (6.1%)
WEIGHT DECREASED	192 (8.1%)	76 (3.2%)
ANXIETY	151 (6.4%)	110 (4.6%)
RHINITIS	141 (6.0%)	116 (4.8%)
HYPOKALAEMIA	154 (6.5%)	99 (4.1%)
DRY EYE	140 (5.9%)	112 (4.7%)
INFLUENZA LIKE ILLNESS	127 (5.4%)	120 (5.0%)
GASTROOESOPHAGEAL REFLUX DISEASE	121 (5.1%)	108 (4.5%)
HYPOMAGNESAEMIA	150 (6.3%)	79 (3.3%)
HYPERTENSION	92 (3.9%)	126 (5.2%)
WEIGHT INCREASED	59 (2.5%)	130 (5.4%)

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.

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Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ae_pt_TRT1A_SE.out
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Serious adverse event / deaths / other significant events

Grade 3-5 adverse events

Table 46 Most Common (≥ 5%) NCI-CTCAE Grade 3 - 5 Adverse Events By Treatment Regimen (Safety Population)

Most Common (>=5%) NCI-CTCAE Grade >=3 Adverse Events by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
NEUTROPENIA	385 (16.3%)	377 (15.7%)
FEBRILE NEUTROPENIA	287 (12.1%)	266 (11.1%)
NEUTROPHIL COUNT DECREASED	228 (9.6%)	230 (9.6%)
DIARRHOEA	232 (9.8%)	90 (3.7%)
ANAEMIA	163 (6.9%)	113 (4.7%)

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ae_pt.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ae_pt_TRT1A_CTC3_SE.out
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Adverse events leading to death

The same proportion of patients in each treatment arm died during the study due to AEs, 18 patients (0.8%) vs. 20 patients (0.8%).A total of 39 SAEs in 38 patients resulted in death, of which two (one in each treatment arm) were considered related to study treatment by the investigator, as summarized below (see also Table 47):

- Patient 2438280008 (Ptz+H+Chemo): this 58-year old woman died of a malignant tongue neoplasm on Study Day 685. The onset of this event and the fatal outcome occurred during the post-treatment phase of the study. The SAE was assessed by the investigator as related to HER2-targeted therapy because the patient had no other apparent predisposing factors for this malignancy.
- Patient 2314490002 (Pla+H+Chemo): a 58-year old woman who died suddenly of cardiac failure. She received four cycles of epirubicin (90 mg/m2) and cyclophosphamide, and radiotherapy to the left chest wall from Study Day 201 to Study Day 240. She experienced Grade 3 (NYHA III) cardiac failure starting approximately 2 months after completing placebo and Herceptin but recovered. This event was reported as an SAE of cardiac failure but did not meet the LVEF criteria for a primary or secondary cardiac event. The patient died suddenly of cardiac failure on Study Day 1373 (during the post-treatment phase of the study). The fatal SAE was assessed by the investigator as related to HER2-targeted therapy, and unrelated to chemotherapy. However, the investigator commented, “cardiogenic shock with sudden cardiac death (known chemotherapy induced dilated cardiomyopathy)”.

Table 47 Adverse Events Resulting in Death by Treatment Regimen (Safety Population)

Adverse Events Resulting in Death by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA SOC and Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Total number of deaths	18 (0.8%)	20 (0.8%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) / ACUTE MYELOID LEUKAEMIA	2 (<0.1%)	1 (<0.1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) / LUNG NEOPLASM MALIGNANT	1 (<0.1%)	2 (<0.1%)
INFECTIONS AND INFESTATIONS / SEPSIS	1 (<0.1%)	1 (<0.1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) / ADENOCARCINOMA PANCREAS	0	2 (<0.1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS / FEBRILE NEUTROPENIA	1 (<0.1%)	0
CARDIAC DISORDERS / ACUTE MYOCARDIAL INFARCTION	0	1 (<0.1%)
CARDIAC DISORDERS / CARDIAC ARREST	0	1 (<0.1%)
CARDIAC DISORDERS / CARDIAC FAILURE	0	1 (<0.1%)
CARDIAC DISORDERS / CARDIOGENIC SHOCK	1 (<0.1%)	0
CARDIAC DISORDERS / MITRAL VALVE DISEASE	1 (<0.1%)	0
GASTROINTESTINAL DISORDERS / COLITIS	0	1 (<0.1%)
GASTROINTESTINAL DISORDERS / GASTROINTESTINAL PERFORATION	0	1 (<0.1%)
GASTROINTESTINAL DISORDERS / INTESTINAL ISCHAEMIA	0	1 (<0.1%)
INFECTIONS AND INFESTATIONS / LUNG INFECTION	0	1 (<0.1%)
INFECTIONS AND INFESTATIONS / SEPTIC SHOCK	0	1 (<0.1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS / ROAD TRAFFIC ACCIDENT	1 (<0.1%)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS / SUBARACHNOID HAEMORRHAGE	1 (<0.1%)	0
METABOLISM AND NUTRITION DISORDERS / HYPERKALAEMIA	1 (<0.1%)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) / ADENOCARCINOMA	1 (<0.1%)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) / GASTRIC CANCER	1 (<0.1%)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) / GASTRIC NEOPLASM	0	1 (<0.1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) / GASTROINTESTINAL CARCINOMA	1 (<0.1%)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) / GLIOBLASTOMA	1 (<0.1%)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) / METASTATIC MALIGNANT MELANOMA	1 (<0.1%)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) / MYELOID LEUKAEMIA	0	1 (<0.1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) / SMALL CELL LUNG CANCER	0	1 (<0.1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) / TONGUE NEOPLASM MALIGNANT STAGE UNSPECIFIED	1 (<0.1%)	0
NERVOUS SYSTEM DISORDERS / CEREBRAL HAEMORRHAGE	1 (<0.1%)	0
PSYCHIATRIC DISORDERS / SUICIDE ATTEMPT	0	1 (<0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / INTERSTITIAL LUNG DISEASE	1 (<0.1%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / PNEUMONIA ASPIRATION	1 (<0.1%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / PULMONARY EMBOLISM	0	1 (<0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / PULMONARY FIBROSIS	0	1 (<0.1%)

Investigator text for AEs encoded using MedDRA v19.1 .

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Note: Deaths due to AEs at anytime during the study period, including the post-treatment follow-up period.

Other serious adverse events

The incidence of SAEs was higher in the pertuzumab arm. A total of 692 patients (29.3%) in the pertuzumab arm experienced 1073 SAEs, and 585 patients (24.3%) in the placebo arm experienced 883 SAEs (Table 48).

SAEs were reported most frequently in the following SOCs:

- Blood and Lymphatic System Disorders: 11.0% vs. 10.5%.
- Infections and Infestations: 6.8% vs. 5.8%.
- Gastrointestinal disorders: 5.2% vs. 3.3%.

Table 48 Serious Adverse Events (≥1%) (Safety Population)
Serious Adverse Events by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA System Organ Class MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Total number of patients with at least one adverse event	692 (29.3%)	585 (24.3%)
Overall total number of events	1073	883
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total number of patients with at least one adverse event	259 (11.0%)	252 (10.5%)
FEBRILE NEUTROPENIA	208 (8.8%)	196 (8.1%)
Total number of events	298	286
GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	124 (5.2%)	79 (3.3%)
DIARRHOEA	58 (2.5%)	18 (0.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total number of patients with at least one adverse event	69 (2.9%)	68 (2.8%)
PYREXIA	39 (1.6%)	45 (1.9%)
Total number of events	77	80

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.

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Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ae_TRT1A_SER_SE.out
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Other significant events

Cardiac events

A primary cardiac event was defined as either:

- Heart Failure (NYHA Class III or IV) and a drop in LVEF of at least 10 EF points from baseline AND to below 50%

or

- Cardiac Death

Table 49 Summary of Cardiac Events (Safety Population)

Cardiac Safety Summary by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)		Placebo + Trastuzumab + Chemotherapy (N=2405)
Primary Cardiac Event	17 (0.7%)		8 (0.3%)
Treatment difference (pertuzumab - placebo) 95% CI*		0.4 (0.0, 0.8)	
Heart Failure (NYHA III or IV) and LVEF decline [a]	15 (0.6%)		6 (0.2%)
Cardiac death (definite or probable)	2 (<0.1%)		2 (<0.1%)
Secondary Cardiac Event	64 (2.7%)		67 (2.8%)
Treatment difference (pertuzumab - placebo) 95% CI*		-0.1 (-1.0, 0.9)	
Identified automatically from LVEF assessments	50 (2.1%)		47 (2.0%)
Identified by CAB [b]	14 (0.6%)		20 (0.8%)

Percentages are based on N in the column headings.
Primary cardiac events are counted over the whole study period, including post-treatment follow-up.
Secondary cardiac events are counted up to the date of recurrence or end of post-treatment follow-up, whichever occurs earlier.
Secondary cardiac events are only counted for patients who have not experienced a primary cardiac event.
Significant LVEF decline defined as a decline of >=10% points to a value <50%.
* 95% confidence interval with Hauck-Anderson correction.

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[a] LVEF decline of at least 10 Ejection Fraction points from baseline AND to below 50%.

[b] The CAB were sent cases where a patient experienced an LVEF drop to <50% and where the drop was ≥10% points from baseline but where there was no repeat LVEF assessment within 7 to 35 days or where there was no subsequent LVEF assessment after a significant drop.

¶

A total of 25 patients met the criteria for a primary cardiac event: 17 patients (0.7%) vs. 8 patients (0.3%) (Table 49). Heart failure (NYHA III or IV) with an LVEF decline was reported in 15 patients (0.6%) versus 7 patients (0.3%). Cardiac death (death with a definite or probable cardiac cause) was reported in 4 patients: 2 patients (< 0.1%) vs. 2 patients (< 0.1%).

All cardiac deaths occurred in patients who received anthracycline-based chemotherapy. One cardiac death, which occurred in the placebo arm, was assessed by the investigator as related to HER2-targeted therapy. Cardiac deaths are presented below:

Ptz+H+Chemo arm

Patient 2323350003 experienced two primary cardiac events (one fatal) but no preceding asymptomatic or mildly symptomatic LVEF decline. This 77 year old woman had pre-existing hypertension and mitral valve disease. She received three cycles of fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2) and cyclophosphamide (500 mg/m^2), and radiotherapy to the left breast and supraclavicular area (Study Day 134 to 172). She experienced heart failure on Study Day 186, which resulted in permanent discontinuation of HER2-targeted therapy. She subsequently died on Study Day 1334 (during the post-treatment phase of the study) due to worsening mitral value disease. The fatal SAE was assessed by the investigator as unrelated to HER2-targeted therapy, and related to the patient's medical history of mitral value disease.

Patient 2316620009: This 80 year old woman died from cardiogenic shock on Study Day 453. The patient received four cycles of epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2), and radiotherapy to the left breast, left supraclavicular area, left axilla and left tumor bed (from Study Day 209 to 273). Treatment with HER2-targeted therapy and paclitaxel was permanently discontinued due to the physician's decision, with the last doses administered on Study Day 107 and Study Day 121, respectively. The fatal SAE was assessed by the investigator as unrelated to HER2-targeted therapy, and related to the patient's medical history of mammary cancer. However, on an unspecified date, the patient's electrocardiogram was noted to show acute elevation of myocardial infarction in the region of the rear wall.

Pla+H+Chemo arm:

Patient 2314490002: This 58-year old woman received four cycles of epirubicin (90 mg/m^2) and cyclophosphamide, and radiotherapy to the left chest wall from Study Day 201 to Study Day 240. She experienced Grade 3 (NYHA III) cardiac failure starting approximately 2 months after completing placebo

and Herceptin but recovered. This event was reported as an SAE of cardiac failure but did not meet the LVEF criteria for a primary or secondary cardiac event. The patient died suddenly of cardiac failure on Study Day 1373 (during the post-treatment phase of the study). The fatal SAE was assessed by the investigator as related to HER2-targeted therapy, and unrelated to chemotherapy. However, the investigator commented, “cardiogenic shock with sudden cardiac death (known chemotherapy induced dilated cardiomyopathy)”.

Patient 2324510001: This 66-year old woman died of acute myocardial infarction on Study Day 1636 (during the post-treatment phase of the study). The patient completed HER2-targeted therapy on Study Day 442 (18 cycles). Additionally, the patient received four cycles of doxorubicin (60 mg/m^2 and cyclophosphamide, and radiotherapy to the left breast from Study Day 220 to Study Day 255. The fatal SAE was assessed by the investigator as unrelated to HER2-targeted therapy.

Timing of primary cardiac events

Almost all of the primary cardiac events (16/17 events in the Ptz+H+Chemo arm, and 7/8 events in the Pla+H+Chemo arm) were reported during the first 2 years from randomization. Two events were reported > 2 years from randomization: one event in the Ptz+H+Chemo arm was reported approximately 3.5 years after randomization, and one event in the Pla+H+Chemo arm was reported approximately 4.5 years after randomization.

Importantly, of the 25 primary cardiac events that occurred during the APHINTY study, one occurred during the anthracycline treatment phase (before commencement of HER2-targeted therapy). This patient (Patient 2327600002) was randomized to the Ptz+H+Chemo arm but since she was unable to start Perjeta treatment due to the cardiac event, she was analyzed in the Pla+H+Chemo arm. All of the other patients who experienced primary cardiac events were analyzed in the treatment arm to which they were randomized.

Recovery from primary cardiac events

Table 50 Overview of Recovery from Primary Cardiac Events

Patient No.	Recovery based on LVEF criteria alone [a]	Investigator Reported Outcome
Ptz + H + Chemo		
2316620009 [b]	No	Fatal
2323350003 [c]	No	Fatal
	No	Resolved with sequelae
2089210003	Yes	Not resolved as of CCOD
2316300030	No	Not resolved as of CCOD
2316340006	No	Not resolved as of CCOD
2326770011	No	Not resolved as of CCOD
2333880002	No	Not resolved as of CCOD
2392330008	No	Not resolved as of CCOD
2312870022	No [d]	Resolved with sequelae
2314110015	Yes	Resolved with sequelae
2308140005	Yes	Resolved
2308670010	Yes	Resolved
2318390008	Yes	Resolved
2323420001	Yes	Resolved
2326380006	Yes	Resolved
2326560005	No [e,f]	Resolved
2372890028	No [g]	Resolved
Pla + H + Chemo		
2314490002 [h]	No	Fatal
2324510001	No	Fatal
2320970012	Yes [i]	Not resolved as of CCOD
2327600002 [j]	No	Resolved with sequelae
2102670020	Yes	Resolved
2308040004	Yes	Resolved
2314840001	Yes	Resolved
2439730008	No	Resolved

CCOD=clinical cut-off date, chemo=chemotherapy, H=Herceptin, INV=investigator, LVEF=left ventricular ejection fraction, N/A=not applicable, Ptz = pertuzumab, Pla=placebo. Source: Table 59 in Primary APHINITY CSR.

[a] Defined as two consecutive LVEF assessments > 50%.

[b] PT reported was cardiogenic shock.

[c] Patient had two primary cardiac events: heart failure (resolved with sequelae) but subsequently died due to a second primary cardiac event (worsening of mitral valve disease).

[d] Single drop (Study Day 337), then single recovery (Study Day 771).

[e] Two events of heart failure (one during treatment and one in follow-up; both resolved).

[f] Single drop (Study Day 198), then single recovery (Study Day 1166), then single drop (Study Day 1356), then single recovery (Study Day 1500).

[g] Single drop (Study Day 172), then single recovery (Study Day 259).

[h] Prior to the fatal event, the patient had a serious cardiac event with documented ventricular abnormalities but this did not meet the LVEF criteria for a primary or secondary cardiac event.

[i] Single drop (Study Day 176), then single recovery (Study Day 253), further drop (Study Day 590), single recovery (Study Day 956).

j This patient was randomized to the Ptz + H + Chemo arm, but was analyzed for safety in the Pla + H + Chemo arm because the patient developed an acute myocardial infarction with associated LVEF decline (meeting the criteria for a primary cardiac event) during the anthracycline period and was withdrawn from treatment prior to receiving Perjeta.

Updated data with cut-off date 15 may 2017

Overall, a total of 25 patients met the criteria for a primary cardiac event: 17 patients in the pertuzumab arm and 8 patients in the Placebo arm. At the time of primary data cutoff (19 December 2016), 2 patients in each arm had experienced a fatal cardiac event. Of the remaining 15 patients in the pertuzumab arm and 6 patients in the Placebo arm, 7 and 4 patients, respectively, had achieved LVEF recovery (defined as two consecutive LVEFs ⩾50%). No additional patients had experienced a primary cardiac event and there was no change in the recovery rates, compared to the primary data cutoff. Therefore, 8 patients remained in the pertuzumab arm and 2 patients in the Placebo arm who had not died or recovered at the time of the most recent data cutoff (15 May 2017). Of these 8 patients, no further data is expected for 4 patients: 2 patients have died due to second primary cancers (Patients 23163000030 and 2316340006) and 2 have completely

withdrawn from the study (Patients 2326560005 and 2372890028). Further follow-up data may become available for 4 patients (Patients 2392330008, 2326770011, 2333880002 and 2312870022) in the pertuzumab arm. Of these 4 patients, an additional LVEF assessment (53%) has been reported for Patient 2392330008, which meets the criteria for acute recovery. Of the 2 remaining patients in the Placebo arm who had not recovered at the most recent data cutoff, further follow-up data may become available for one patient (Patient 2439730008). The other patient (Patient 2327600002) has withdrawn from the study and no further follow-up data will be received.

Table 51 Recovery from Cardiac Events (Safety Population)

Acute Recovery from Cardiac Events by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G
Clinical cut-off date: 15MAY2017
Snapshot date: 19JUL2017

	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Number of Patients with a non-death Primary Cardiac Event	15 (0.6%)	6 (0.2%)
Acute recovery achieved[4]		
n	15	6
Yes	7 (46.7%)	4 (66.7%)
No	8 (53.3%)	2 (33.3%)
Time to acute recovery (weeks)		
n	7	4
Median	27.00	16.29
Range	3.1 - 52.4	11.0 - 30.1
Number of Patients with a Secondary Cardiac Event	66 (2.8%)	67 (2.8%)
Acute recovery achieved[4]		
n	70	67
Yes	54 (77.1%)	55 (82.1%)
No	16 (22.9%)	12 (17.9%)
Time to acute recovery (weeks)		
n	54	55
Median	18.07	23.29
Range	4.4 - 129.7	1.7 - 113.9

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Risk factors for primary cardiac events

Pre-defined baseline characteristics considered to be possible risk factors for a primary cardiac event were evaluated in the individual patients who developed a primary cardiac event, and included anthracycline exposure, trastuzumab exposure, radiation exposure, age, smoking status, diabetes mellitus, hypertension and other cardiac conditions or medication. All of the patients who developed a primary cardiac event had at least one of these potential risk factors. Most patients had received anthracyclines or radiotherapy or both. Only one patient (Patient 2372890028) had not received prior anthracyclines or chest radiotherapy. The other identified risk factors in this particular patient were smoking history and coronary artery disease.

Anthracycline exposure

Table 52 Cardiac Safety Summary by Chemotherapy Regimen

	Ptz + H + Anthracycline			Pla + H + Anthracycline			Ptz + H + Non-Anthracycline	Pla + H + Non-Anthracycline
	Total Patients (N = 1834)	Dose Dense (N = 136)	Non-dose dense (N = 1698)	Total Patients (N = 1894)	Dose Dense (N = 124)	Non-dose dense (N = 1770)	Total Patients (N = 528)	Total Patients (N = 510)
Primary cardiac event	15 (0.8%)	1 (0.7%)	14 (0.8%)	7 (0.4%)	1 (0.8%)	6 (0.3%)	2 (0.4%)	1 (0.2%)
Heart failure (NYHA III or IV) and LVEF decline [a]	13 (0.7%)	1 (0.7%)	12 (0.7%)	5 (0.3%)	1 (0.8%)	4 (0.2%)	2 (0.4%)	1 (0.2%)
Cardiac death	2 (0.1%)	0	2 (0.1%)	2 (0.1%)	0	2 (0.1%)	0	0
Secondary cardiac event	55 (3.0%)	8 (5.9%)	47 (2.8%)	60 (3.2%)	6 (4.8%)	54 (3.1%)	9 (1.7%)	7 (1.4%)
Identified from LVEF assessments	46 (2.5%)	8 (5.9%)	38 (2.2%)	44 (2.3%)	4 (3.2%)	40 (2.3%)	4 (0.8%)	3 (0.6%)
Identified by CAB [b]	9 (0.5%)	0	9 (0.5%)	16 (0.8%)	2 (1.6%)	14 (0.8%)	5 (0.9%)	4 (0.8%)

CAB=Cardiac Advisory Board, H = Herceptin, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association=, Pla = placebo, Ptz = Perjeta.

[a] LVEF decline of at least 10 Ejection Fraction points from baseline AND to below 50%.

[b] The CAB were sent cases where a patient experienced an LVEF drop to <50% and where the drop was ≥10% points from baseline but where there was no repeat LVEF assessment within 7 to 35 days or where there was no subsequent LVEF assessment after a significant drop.

Source: t_saf_cs_TRT2A_ANTH_SE, t_saf_cs_TRT3A_DDAN_SE, t_saf_cs_TRT3A_NDDA_SE, t_saf_cs_TRT2A_NACO_SE. ¶

Most of the primary cardiac events were reported in patients who received anthracycline-based treatment (Table 52):

- Of the 17 patients in the Ptz+H+Chemo arm who experienced a primary cardiac event, 15 patients received anthracycline-based chemotherapy (88.2%), and 2 patients received non-anthracycline-based chemotherapy (11.8%).
- Of the 8 patients in the Pla+H+Chemo arm who experienced a primary cardiac event, 7 patients received anthracycline-based chemotherapy (87.5%), and 1 patient received non-anthracycline-based chemotherapy (12.5%).

The great majority of patients who received anthracycline-based chemotherapy did not experience a primary cardiac event (0.8% vs. 0.4%). Although anthracycline exposure appears to be a clear risk factor for a primary cardiac event, the incidence of primary cardiac events was not much greater in absolute terms than that observed in patients treated with non-anthracycline-based chemotherapy (0.4% vs. 0.2%).

Asymptomatic or mildly symptomatic LVEF declines

Eight patients experienced both a primary cardiac event and an asymptomatic or mildly symptomatic LVEF decline, i.e., an event that would have been counted as a secondary cardiac event had the patient not also experienced a primary cardiac event: 6 patients (0.3%] in the Ptz+H+Chemo arm vs. 2 patients (<0.1%] in the Pla+H+Chemo arm. In 5 of these 8 patients (4 patients in the Ptz+H+Chemo arm vs. 1 patient in the Pla+H+Chemo arm), the significant LVEF decline occurred prior to the primary cardiac event. The remaining 3 patients had no such event preceding the primary cardiac event (2 patients in the Ptz+H+Chemo arm and 1 patient in the Pla+H+Chemo arm).

Secondary cardiac events

A secondary cardiac event was defined as:

- Asymptomatic or mildly symptomatic (NYHA Class II) significant drop in LVEF defined as an absolute decrease of at least 10 EF points from baseline AND to below 50%, confirmed by a second LVEF assessment within approximately three weeks of the first significant LVEF assessment or confirmed by the CAB.

A total of 131 patients experienced a secondary cardiac event (see Table 52: 64 patients (2.7%) vs. 67 patients (2.8%).

- 97 patients were identified automatically from LVEF assessments: 50 patients (2.1%) vs. 47 patients (2.0%).

- 34 patients were identified by the CAB: 14 patients (0.6%) vs. 20 patients (0.8%).

Other cardiac events

Other cardiac events are defined as:

- Acute coronary syndrome
- Acute myocardial infarction
- Severe rhythm disturbances requiring treatment

Table 53 Other Cardiac Events by Treatment Regimen (Safety Population)

Other Cardiac Events by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Any other cardiac events	63 (2.7%)	58 (2.4%)
Total number of events	72	65
Acute Coronary Syndrome (PT)	0	2 (<0.1%)
Acute myocardial infarction	4 (0.2%)	4 (0.2%)
Severe rhythm disturbances requiring treatment	60 (2.5%)	52 (2.2%)

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The most frequently reported severe rhythm disturbances requiring treatment included tachycardia (12 patients [0.5%] in the Ptz+H+Chemo arm vs. 14 patients [0.6%] in the Pla+H+Chemo), atrial fibrillation (8 patients [0.3%] vs. 10 patients [0.4%], respectively), syncope (9 patients [0.4%] vs. 3 patients [0.1%], respectively), and palpitations (6 patients [0.3%] vs. 8 patients [0.3%], respectively). The majority of the severe rhythm disturbances requiring treatment occurred in patients treated with an anthracycline-based regimen.

Table 54 Timing of Onset of Syncope

Timing of Syncope Events	Treatment	
	Ptz + H + Chemo	Pla + H + Chemo
Number of Patients	(n = 1834)	(n = 1894)
During Anthracycline Treatment	7 (0.4%)	7 (0.4%)
Number of Patients	(n = 2364)	(n = 2405)
During the Targeted Therapy + Chemotherapy Treatment Period[a]	20 (0.8%)	15 (0.6%)
Number of Patients	(n = 2364)	(n = 2405)
During the Targeted Therapy Post-Chemotherapy Treatment Period[a]	10 (0.4%)	5 (0.2%)

[a] One patient in each treatment arm experienced separate syncope events in both the targeted therapy + chemotherapy period and the targeted therapy post-chemotherapy period
Source: t_ae_TRT2A_AEAN_SE; t_ae_TRT1A_TACH_SE; t_ae_TRT1A _TAPO_SE.

The incidence of syncopal events considered by the Investigator to be related to HER2-targeted treatment was very low in both treatment arms in both treatment arms (see Table 55).

Table 55 Syncope Events Considered Related to HER-2 Targeted Treatment by Investigator

Preferred term	All Grades		≥ Grade 3	
	Ptz + H + Chemo (n = 2364)	Pla + H + Chemo (n = 2405)	Ptz + H + Chemo (n = 2364)	Pla + H + Chemo (n = 2405)
Syncope	4 (0.2%)	3 (0.1%)	3 (0.1%)	3 (0.1%)

Source: t_ae_TRT1A_REL_SEIDM:/Authoring Repository/RO4368451/Clinical/Study BO25126/CSR Documents & Data Outputs/Primary CSR, Study BO25126 (APHINITY), , Data Output/t_ae_TRT1A_REL_SE or page 186 of the full CSR; t_ae_TRT1A_REL3_SE. page 10023 primary

The incidence of all syncope events regardless of requirement for treatment showed a very small difference between arms, even smaller for ≥ Grade 3. Of the patients requiring treatment for syncope, for the majority of patients (8 out of 9 patients) in the pertuzumab arm, the syncopal event appeared to have been associated with intravascular volume depletion (diarrhea, nausea, vomiting, dehydration, hypotension and/or anaemia), and occurred during concomitant chemotherapy. None of the syncope events requiring treatment led to study therapy withdrawal.Withdrawal of any study medication due to other cardiac events occurred in 9 patients in the Ptz+H+Chemo arm (0.4%) vs. 8 patients [0.3%] in the Pla+H+Chemo arm. These figures include 3 patients who withdrew from study medication before commencement of HER2-targeted therapy. Withdrawal of Ptz/Pla due to other cardiac events occurred in 5 patients in each arm, mainly due to myocardial infarction (2 patients in each arm).

Changes in LVEF

Patients had to have an LVEF of at least 55% (measured by ECHO [preferred] or MUGA scan) to enter the study. At baseline, the mean LVEF was 65.2% in the Ptz+H+Chemo arm, and 65.3% in the Pla+H+Chemo arm. Table 56 summarizes the worst on-study LVEF measurements. The worst on-study LVEF was a mean of 7.5% lower than baseline in the Ptz+H+Chemo arm, and 7.6% lower than baseline in the Pla+H+Chemo arm.

LVEF drops to <40% during the study occurred in 34 patients (1.4%) vs. 32 patients (1.3%). The majority of these patients were treated with an anthracycline-based regimen (27 vs. 30 patients). The remaining patients (7 vs. 2 patients) received a non-anthracycline chemotherapy regimen.

A total of 133 patients (5.7%) in the Ptz+H+Chemo arm experienced at least one significant LVEF drop (defined as a drop in LVEF of at least 10 EF points from baseline and to below 50%) during the study compared with 165 patients (7.0%) in Pla+H+Chemo arm.

Table 56 Summary of Maximum Decrease in LVEF Measures by Treatment Regimen (Safety Population)

Summary of Maximum Decrease in LVEF Measures by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Baseline LVEF (%)		
n	2363	2401
Mean (SD)	65.2 (5.9)	65.3 (6.1)
Median	65.0	65.0
Range	51 - 90	50 - 92
Change from Baseline to Worst Value		
n	2348	2351
Mean (SD)	-7.5 (6.6)	-7.6 (6.7)
Median	-7.0	-7.0
Range	-49 - 11	-54 - 14
Treatment difference*	0.1	
95% C.I.	(-0.3, 0.5)	
Worst value <40%		
Yes	34 (1.4%)	32 (1.3%)
No	2330 (98.6%)	2373 (98.7%)

* Treatment difference defined as pertuzumab - placebo.

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Diarrhea

In both treatment arms, the majority of diarrhea events (all Grades) that started during targeted treatment (63.7% vs. 66.2% of events) occurred in the first 3 cycles of treatment. Less than 10% of patients in either treatment arm experienced diarrhea from Cycle 4 onwards, and <3% of patients from Cycle 7 onwards. The majority of Grade ≥ 3 events of diarrhea that started during targeted treatment also occurred in the first three cycles of treatment (84.4% of Grade ≥ 3 events vs. 84.1% of Grade ≥ 3 events).

The median time from first targeted treatment to onset of a diarrhea event was 7 days vs. 10 days. On average, events of diarrhea lasted longer in the pertuzumab arm, median 8 days vs. median 6 days; the median duration of the longest event was 35 days vs. 13 days.

The median time from first targeted treatment to onset of Grade ≥3 diarrhea was 8 days in both treatment arms. On average, Grade ≥3 diarrhea events lasted longer in the Ptz+H+Chemo arm (median 20 days vs. median 8 days); the median duration of the longest event was 22 days vs. 8 days.

Table 57 Summary of Diarrhea Adverse Events (Safety Population)

Summary of Diarrhoea Adverse Events, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA System Organ Class MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Total number of patients with at least one adverse event	1685 (71.3%)	1086 (45.2%)
Overall total number of events	3415	1792
GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	1683 (71.2%)	1086 (45.2%)
DIARRHOEA	1683 (71.2%)	1086 (45.2%)
DIARRHOEA HAEMORRHAGIC	0	1 (<0.1%)
Total number of events	3411	1791
INFECTIONS AND INFESTATIONS		
Total number of patients with at least one adverse event	4 (0.2%)	1 (<0.1%)
DIARRHOEA INFECTIOUS	4 (0.2%)	1 (<0.1%)
Total number of events	4	1

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.
Diarrhoea events identified from the PT 'DIARRHOEA INFECTIOUS', 'DIARRHOEA', 'DIARRHOEA HAEMORRHAGIC', 'DIARRHOEA NEONATAL' or 'POST PROCEDURAL DIARRHOEA'.

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The highest incidence of diarrhea was reported during the TTTC (taxane treatment) period (61.4% of patients vs. 33.8% of patients, respectively), with a decrease observed upon chemotherapy cessation in the PCTT (pertuzumab treatment) period (18.1% vs. 9.2% of patients, respectively). During the anthracycline period, diarrhea was reported in 16.1% vs. 14.7% of patients. The highest incidence of Grade ≥3 diarrhea was also reported during the TTTC period (8.4% vs. 2.5% of patients, respectively), followed by the anthracycline period (1.2% vs. 1.3%, respectively), and the PCTT period (0.5% vs. 0.2% of patients, respectively).

For patients who experienced diarrhea, guidance per the study protocol and Perjeta label recommended early intervention with loperamide as well as fluid and electrolyte replacement. For the treatment of diarrhea AEs, loperamide was administered to 842 patients (35.6%) in the Ptz+H+Chemo arm, and 356 patients (14.8%) in the Pla+H+Chemo arm.

Table 58 Selected Treatments for Diarrhea AEs by Treatment Regimen (0.1%)

Treatment	Ptz + H + Chemo (n = 2364)	Pla + H+Chemo (n = 2405)
Patients treated with Antidiarrhoeals		
Loperamide	842 (35.6%)	356 (14.8%)
Patients treated with Electrolytes		
Sodium Chloride	29 (1.2%)	19 (0.8%)
Fluid Replacement	23 (1.0%)	10 (0.4%)
Potassium Chloride	6 (0.3%)	5 (0.2%)
Glucose/Sodium Chloride	6 (0.3%)	2 (< 0.1%)
Electrolytes	5 (0.2%)	3 (0.1%)
Potassium Chloride/Sodium Chloride	4 (0.2%)	0 4 (< 0.1%)
Other Fluid Replacement	4 (0.2%)	2 (< 0.1%)
Citric Acid/Glucose/Potassium Chloride/Sodium Bicarbonate/Sodium Chloride/Sodium Citrate Acid	1 (< 0.1%)	3 (0.1%)

Source: t_cm_DIA_SE.link to page 10 of the Primary CSR Part B

Rash

Table 59 Summary of Rash (AEGT) Adverse Events (Safety Population)
Summary of Rash (AEGT) Adverse Events, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA System Organ Class MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Total number of patients with at least one adverse event	1226 (51.9%)	1002 (41.7%)
Overall total number of events	2008	1588
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total number of patients with at least one adverse event	1199 (50.7%)	978 (40.7%)
RASH	609 (25.8%)	488 (20.3%)
ERYTHEMA	235 (9.9%)	214 (8.9%)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	217 (9.2%)	158 (6.6%)
DERMATITIS	108 (4.6%)	92 (3.8%)
RASH MACULO-PAPULAR	81 (3.4%)	57 (2.4%)
DERMATITIS ACNEIFORM	88 (3.7%)	49 (2.0%)
SKIN EXFOLIATION	43 (1.8%)	32 (1.3%)
ECZEMA	43 (1.8%)	25 (1.0%)
ACNE	32 (1.4%)	30 (1.2%)
SKIN TOXICITY	21 (0.9%)	19 (0.8%)
RASH PRURITIC	17 (0.7%)	21 (0.9%)
SKIN ULCER	21 (0.9%)	11 (0.5%)
DERMATITIS ALLERGIC	14 (0.6%)	13 (0.5%)
RASH MACULAR	16 (0.7%)	11 (0.5%)
RASH PAPULAR	9 (0.4%)	6 (0.2%)
DERMATITIS BULLOUS	6 (0.3%)	8 (0.3%)
RASH ERYTHEMATOUS	6 (0.3%)	6 (0.2%)
DERMATITIS EXFOLIATIVE	7 (0.3%)	4 (0.2%)
DRUG ERUPTION	6 (0.3%)	5 (0.2%)
RASH GENERALISED	7 (0.3%)	4 (0.2%)
ERYTHEMA MULTIFORME	4 (0.2%)	2 (<0.1%)
EXFOLIATIVE RASH	5 (0.2%)	1 (<0.1%)
TOXIC SKIN ERUPTION	2 (<0.1%)	2 (<0.1%)
GENERALISED ERYTHEMA	2 (<0.1%)	1 (<0.1%)
SEBORRHOEIC DERMATITIS	2 (<0.1%)	1 (<0.1%)
RASH FOLLICULAR	0	2 (<0.1%)
RASH VESICULAR	1 (<0.1%)	1 (<0.1%)
BUTTERFLY RASH	0	1 (<0.1%)
NODULAR RASH	0	1 (<0.1%)
TOXIC EPIDERMAL NECROLYSIS	1 (<0.1%)	0
Total number of events	1912	1524
INFECTIONS AND INFESTATIONS		
Total number of patients with at least one adverse event	81 (3.4%)	57 (2.4%)
FOLLICULITIS	39 (1.6%)	21 (0.9%)
RASH PUSTULAR	33 (1.4%)	20 (0.8%)
FURUNCLE	8 (0.3%)	13 (0.5%)
DERMATITIS INFECTED	1 (<0.1%)	1 (<0.1%)
ACNE PUSTULAR	0	1 (<0.1%)
EYELID FOLLICULITIS	0	1 (<0.1%)
Total number of events	93	63
EYE DISORDERS		
Total number of patients with at least one adverse event	3 (0.1%)	1 (<0.1%)
ERYTHEMA OF EYELID	3 (0.1%)	0
EYELID RASH	0	1 (<0.1%)

Total number of events	3	1

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.
Rash events identified from the Roche Standard AEGT 'EGFR Associated rash'.

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Leucopenia

Table 60 Summary of Leukopenia (SMQ) Adverse Events (Safety Population)

Summary of Leukopenia (SMQ) Adverse Events, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA System Organ Class MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Total number of patients with at least one adverse event	1178 (49.8%)	1158 (48.1%)
Overall total number of events	3149	3008
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total number of patients with at least one adverse event	871 (36.8%)	853 (35.5%)
NEUTROPENIA	587 (24.8%)	562 (23.4%)
FEBRILE NEUTROPENIA	287 (12.1%)	266 (11.1%)
LEUKOPENIA	216 (9.1%)	222 (9.2%)
GRANULOCYTOPENIA	19 (0.8%)	23 (1.0%)
LYMPHOPENIA	13 (0.5%)	14 (0.6%)
AGRANULOCYTOSIS	3 (0.1%)	3 (0.1%)
Total number of events	1843	1806
INVESTIGATIONS		
Total number of patients with at least one adverse event	433 (18.3%)	428 (17.8%)
NEUTROPHIL COUNT DECREASED	327 (13.8%)	330 (13.7%)
WHITE BLOOD CELL COUNT DECREASED	234 (9.9%)	206 (8.6%)
LYMPHOCYTE COUNT DECREASED	20 (0.8%)	10 (0.4%)
METAMYELOCYTE COUNT DECREASED	1 (<0.1%)	0
Total number of events	1294	1196
INFECTIONS AND INFESTATIONS		
Total number of patients with at least one adverse event	11 (0.5%)	6 (0.2%)
NEUTROPENIC SEPSIS	10 (0.4%)	4 (0.2%)
NEUTROPENIC INFECTION	1 (<0.1%)	2 (<0.1%)
Total number of events	12	6

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.
Leukopenia events identified from the SMQ (narrow) 'Haematopoietic Leukopenia'.

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Infusion-related reactions (IRR)

Overall, IRRs were experienced in 1293 patients (54.7%) vs. 1199 patients (51.3%). Grade 1–2 IRRs were reported in 53.1% vs 50.1% of the patients and grade ≥ 3 events were reported in 65 patients (2.7%) vs. 49 patients (2.1%); there were no fatal events. The most common (≥5%) IRRs starting on the day of Perjeta/placebo infusion were fatigue (218 patients [9.2%] vs. 194 patients [8.3%], respectively), followed by arthralgia (182 patients [7.7%] vs. 213 patients [9.1%]), hot flush (157 patients [6.6%] vs. 148 patients [6.3%]), myalgia (120 patients [5.1%] vs. 144 patients [6.2%]), and dysgeusia (119 patients [5.0%] vs. 100 patients [4.3%]).

In Cycle 1, the incidence of IRRs (all Grades) starting on the day of Perjeta/placebo infusion was similar between the treatment arms (495 patients [20.9%] vs. 420 patients [18.0%]). Grade ≥ 3 events were

reported in 1.2% vs. 0.7%. In Cycle 2, the incidence of IRRs (all Grades) starting on the day of Perjeta/placebo infusion was lower and also similar between the treatment arms, 13.3% vs. 12.6%. Grade ≥ 3 events were reported in 0.3% vs. 0.4% of the patients, respectively. Serious IRR events were reported in 3 patients (0.1%) in the Ptz+H+Chemo arm, and 1 patient (< 0.1%) in the Pla+H+Chemo arm.

Anaphylaxis and hypersensitivity

The most common events were hypersensitivity (3.4% vs. 2.9%) followed by drug hypersensitivity (1.3% vs. 0.5%). The majority of events were Grade 1 or 2 in severity. Grade ≥ 3 events were reported in 18 patients (0.8%) vs. 17 patients (0.7%); there were no fatal events. The highest incidence of anaphylaxis and hypersensitivity AEs was reported during the TTTC period, i.e. hypersensitivity (62 patients [2.6%] vs. 50 patients [2.1%]), followed by drug hypersensitivity (22 patients [0.9%] vs. 8 patients [0.3%]).

Serious events were reported in 15 patients (0.6%) vs. 8 patients (0.3%) and most frequently reported was hypersensitivity (11 patients [0.5%] vs. 3 patients [0.1%]).

Table 61 Summary of Anaphylaxis & Hypersensitivity (AEGT) Adverse Events (Safety Population)

Summary of Anaphylaxis & Hypersensitivity(AEGT) Adverse Events, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA System Organ Class MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Total number of patients with at least one adverse event	116 (4.9%)	86 (3.6%)
Overall total number of events	138	118
IMMUNE SYSTEM DISORDERS		
Total number of patients with at least one adverse event	113 (4.8%)	86 (3.6%)
HYPERSENSITIVITY	80 (3.4%)	70 (2.9%)
DRUG HYPERSENSITIVITY	30 (1.3%)	12 (0.5%)
ANAPHYLACTIC REACTION	2 (<0.1%)	5 (0.2%)
ANAPHYLACTIC SHOCK	1 (<0.1%)	2 (<0.1%)
Total number of events	135	118
VASCULAR DISORDERS		
Total number of patients with at least one adverse event	2 (<0.1%)	0
CIRCULATORY COLLAPSE	2 (<0.1%)	0
Total number of events	2	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total number of patients with at least one adverse event	1 (<0.1%)	0
INJECTION SITE HYPERSENSITIVITY	1 (<0.1%)	0
Total number of events	1	0

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.
Anaphylaxis and hypersensitivity events identified from the Roche Standard AEGT 'Anaphylaxis and Hypersensitivity'.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ae.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ae_TRT1A_ANHY_SE.out
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Interstitial lung disease

The most commonly reported AEs were pneumonitis and radiation pneumonitis (both 0.3% vs. 0.2%, respectively). Grade ≥ 3 events were reported in 5 patients (0.2%) vs. 4 patients (0.2%).

AEs were reported most frequently during the PCTT period (when radiotherapy was given, if indicated): radiation pneumonitis (7 patients [0.3%] vs. 5 patients [0.2%]), and pneumonitis (2 patients [<0.1%] vs. 1 patient [<0.1%], respectively).

There were 13 SAEs reported (4 SAEs vs. 9 SAEs); two SAEs resulted in death. The most frequently reported were pneumonitis (2 patients [<0.1%] vs. 4 patients [0.2%], respectively), followed by ILD (1 patient [<0.1%] vs. 2 patients [<0.1%], respectively).

Table 62 Summary of Interstitial Lung Disease AEs (Safety Population)

Summary of Interstitial Lung Disease (SMQ) Adverse Events, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA System Organ Class MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Total number of patients with at least one adverse event	19 (0.8%)	22 (0.9%)
Overall total number of events	19	22
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total number of patients with at least one adverse event	11 (0.5%)	11 (0.5%)
PNEUMONITIS	8 (0.3%)	6 (0.2%)
INTERSTITIAL LUNG DISEASE	2 (<0.1%)	3 (0.1%)
PULMONARY FIBROSIS	1 (<0.1%)	1 (<0.1%)
LUNG INFILTRATION	0	1 (<0.1%)
Total number of events	11	11
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total number of patients with at least one adverse event	7 (0.3%)	10 (0.4%)
RADIATION PNEUMONITIS	7 (0.3%)	5 (0.2%)
PULMONARY RADIATION INJURY	0	5 (0.2%)
Total number of events	7	10
INFECTIONS AND INFESTATIONS		
Total number of patients with at least one adverse event	1 (<0.1%)	1 (<0.1%)
BRONCHIOLITIS	1 (<0.1%)	1 (<0.1%)
Total number of events	1	1

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.
ILD events identified from the SMQ (narrow) 'Interstitial Lung Disease'.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ae.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ae_TRT1A_ILD_SE.out
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Mucositis

The most frequently reported events were stomatitis (28.4% vs. 23.8%), mucosal inflammation (23.4% vs. 18.6%), pharyngitis (4.2% vs. 3.5%), and mouth ulceration (2.9% vs. 3.1%). Grade ≥ 3 events were reported in 115 patients (4.9%) vs. 55 patients (2.3%). None of the events had a fatal outcome.

AEs of mucositis were more frequently reported during the TTTC period (stomatitis: 17.3% vs. 13.1%; mucosal inflammation: 14.8% vs. 10.9%), followed by the anthracycline treatment period (stomatitis: 17.3% vs. 15.9%; mucosal inflammation: 13.1% vs. 11.0%, respectively). During the PCTT period the incidence of stomatitis had fallen to approximately 2% in each arm. In the post-treatment follow-up period, only one event of stomatitis was reported in the placebo arm.

Mucositis AEs which led to withdrawal from any study treatment included stomatitis (6 patients [0.3%] vs. 1 patient (<0.1%)), followed by mucosal inflammation (2 patients [<0.1%] vs. 1 patients [<0.1%]. Stomatitis led to withdrawal from Perjeta in 2 patients (<0.1%) in the pertuzumab arm only.

The most frequently reported mucositis SAEs were gastroenteritis (8 patients [0.3%] vs. 3 patient [0.1%]), stomatitis (7 patients [0.3%] vs. 1 patient [<0.1%], respectively), and mucosal inflammation (4 patients [0.2%] vs. 1 patient [<0.1%], respectively). None of the SAEs resulted in death.

Table 63 Summary of Mucositis AEs (Safety Population)
Summary of Mucositis (AEGT) Adverse Events, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA System Organ Class MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Total number of patients with at least one adverse event	1348 (57.0%)	1180 (49.1%)
Overall total number of events	2328	1917
GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	848 (35.9%)	732 (30.4%)
STOMATITIS	671 (28.4%)	573 (23.8%)
MOUTH ULCERATION	69 (2.9%)	75 (3.1%)
GASTRITIS	58 (2.5%)	46 (1.9%)
APHTHOUS ULCER	35 (1.5%)	23 (1.0%)
OESOPHAGITIS	30 (1.3%)	23 (1.0%)
GLOSSITIS	8 (0.3%)	14 (0.6%)
ANAL INFLAMMATION	13 (0.5%)	8 (0.3%)
COLITIS	9 (0.4%)	10 (0.4%)
CHEILITIS	6 (0.3%)	9 (0.4%)
PROCTITIS	10 (0.4%)	5 (0.2%)
GINGIVAL ULCERATION	5 (0.2%)	9 (0.4%)
CHRONIC GASTRITIS	5 (0.2%)	2 (<0.1%)
GASTRITIS EROSIVE	3 (0.1%)	2 (<0.1%)
ENTEROCOLITIS	2 (<0.1%)	1 (<0.1%)
GASTROINTESTINAL INFLAMMATION	3 (0.1%)	0
DUODENITIS	1 (<0.1%)	1 (<0.1%)
COLITIS ULCERATIVE	1 (<0.1%)	0
DIARRHOEA HAEMORRHAGIC	0	1 (<0.1%)
NONINFECTIVE GINGIVITIS	1 (<0.1%)	0
Total number of events	1313	1080
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total number of patients with at least one adverse event	554 (23.4%)	449 (18.7%)
MUCOSAL INFLAMMATION	552 (23.4%)	448 (18.6%)
MUCOSAL HAEMORRHAGE	1 (<0.1%)	0
MUCOSAL PAIN	0	1 (<0.1%)
MUCOSAL TOXICITY	1 (<0.1%)	0
MUCOSAL ULCERATION	1 (<0.1%)	0
Total number of events	751	588
INFECTIONS AND INFESTATIONS		
Total number of patients with at least one adverse event	209 (8.8%)	205 (8.5%)
PHARYNGITIS	99 (4.2%)	85 (3.5%)
GASTROENTERITIS	41 (1.7%)	47 (2.0%)
GINGIVITIS	38 (1.6%)	38 (1.6%)
ANGULAR CHEILITIS	26 (1.1%)	20 (0.8%)
LARYNGITIS	19 (0.8%)	26 (1.1%)
Total number of events	258	246
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total number of patients with at least one adverse event	6 (0.3%)	3 (0.1%)
PHARYNGEAL INFLAMMATION	6 (0.3%)	3 (0.1%)
Total number of events	6	3

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.
Mucositis events identified from the Roche Standard AEGT 'Mucositis of the Gastro-Intestinal Tract'.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ae.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ae_TRT1A_MUCO_SE.out
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Pregnancies

Up to the primary clinical cutoff date, 33 pregnancies were reported in 29 patients (19 pregnancies reported in 16 patients in the pertuzumab arm, and 14 pregnancies reported in 13 patients in the placebo arm). One pregnancy occurred during study treatment, and 32 pregnancies occurred during the post-treatment period (of these, 4 occurred within 7 months [210 days] of the last dose of study medication). Five pregnancies resulted in spontaneous abortions, and 4 pregnancies ended with therapeutic abortions. Nine pregnancies were ongoing at the time of the clinical cutoff, and 15 pregnancies resulted in live births. Of the 5 pregnancies that occurred during or within 7 months of the last dose of study medication, two were

terminated, two resulted in healthy live singleton births, and one resulted in premature delivery of twins who subsequently died. Of the 15 live births, 5 were premature – two of these were twin births. No reports of pre-natal or post-natal complications attributable to Perjeta or Herceptin were received. The incidence of premature delivery (5/20 [23.8%]) was higher than expected based on the general population (approximately 8% [NHS Choices 2017]), and there was also a relatively high incidence of spontaneous abortion (5/20 [23.8%], expected rate 15-20% [FDA Guidance 2014]). However, there was no major difference in incidence between treatment arms.

Hepatic dysfunction

A total of 340 patients (14.4%) vs. 368 patients (15.3%) had hepatic-related AEs. The most commonly reported PTs were ALT increased (9.3% vs. 10.1%, respectively) and AST increased (6.1% vs. 6.7%, respectively). The majority of these reported events were Grade 1 or 2 in severity; Grade ≥3 events of ALT increased was reported in 0.9% vs. 1.0% of patients respectively and AST increased was reported in 12 patients (0.5%) in each arm.

Table 64 Drug-Related Hepatic Disorder (Safety Population)

Summary of Drug-Related Hepatic Disorder (SMQ) Adverse Events, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA System Organ Class MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Total number of patients with at least one adverse event	340 (14.4%)	368 (15.3%)
Overall total number of events	666	764
INVESTIGATIONS		
Total number of patients with at least one adverse event	290 (12.3%)	317 (13.2%)
ALANINE AMINOTRANSFERASE INCREASED	221 (9.3%)	244 (10.1%)
ASPARTATE AMINOTRANSFERASE INCREASED	145 (6.1%)	162 (6.7%)
BLOOD ALKALINE PHOSPHATASE INCREASED	41 (1.7%)	50 (2.1%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	21 (0.9%)	39 (1.6%)
TRANSAMINASES INCREASED	22 (0.9%)	19 (0.8%)
BLOOD BILIRUBIN INCREASED	16 (0.7%)	14 (0.6%)
LIVER FUNCTION TEST INCREASED	7 (0.3%)	3 (0.1%)
HEPATIC ENZYME INCREASED	2 (<0.1%)	6 (0.2%)
BILIRUBIN CONJUGATED INCREASED	2 (<0.1%)	1 (<0.1%)
HEPATIC ENZYME ABNORMAL	0	2 (<0.1%)
BLOOD BILIRUBIN UNCONJUGATED INCREASED	1 (<0.1%)	0
LIVER FUNCTION TEST ABNORMAL	1 (<0.1%)	0
Total number of events	593	692
HEPATOBILIARY DISORDERS		
Total number of patients with at least one adverse event	53 (2.2%)	57 (2.4%)
HEPATIC FUNCTION ABNORMAL	13 (0.5%)	23 (1.0%)
HEPATIC STEATOSIS	11 (0.5%)	10 (0.4%)
LIVER INJURY	5 (0.2%)	5 (0.2%)
HEPATIC CYST	5 (0.2%)	4 (0.2%)
HEPATOCELLULAR INJURY	3 (0.1%)	6 (0.2%)
HEPATOBILIARY DISEASE	6 (0.3%)	2 (<0.1%)
HEPATOTOXICITY	4 (0.2%)	3 (0.1%)
DRUG-INDUCED LIVER INJURY	3 (0.1%)	0
HEPATIC PAIN	1 (<0.1%)	2 (<0.1%)
HYPERBILIRUBINAEMIA	3 (0.1%)	0
CHOLESTASIS	2 (<0.1%)	0
HEPATIC FAILURE	1 (<0.1%)	1 (<0.1%)
HEPATITIS	0	2 (<0.1%)
HEPATITIS ACUTE	0	1 (<0.1%)
HEPATITIS TOXIC	1 (<0.1%)	0
HYPERTRANSAMINASAEMIA	0	1 (<0.1%)
LIVER DISORDER	1 (<0.1%)	0
OCULAR ICTERUS	0	1 (<0.1%)
Total number of events	61	65
METABOLISM AND NUTRITION DISORDERS		
Total number of patients with at least one adverse event	10 (0.4%)	5 (0.2%)
HYPOALBUMINAEMIA	10 (0.4%)	5 (0.2%)
Total number of events	10	5
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total number of patients with at least one adverse event	1 (<0.1%)	1 (<0.1%)
SPIDER NAEVUS	1 (<0.1%)	0
YELLOW SKIN	0	1 (<0.1%)
Total number of events	1	1
GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	0	1 (<0.1%)
ASCITES	0	1 (<0.1%)
Total number of events	0	1
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Total number of patients with at least one adverse event	1 (<0.1%)	0
HAEMANGIOMA OF LIVER	1 (<0.1%)	0
Total number of events	1	0

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.
Drug-related hepatic disorder events identified from the SMQ 'Drug-Related Hepatic Disorder - Comprehensive Search'.

Hy's Law Definition of Drug-Induced Liver Injury

For this study, potential cases of drug-induced liver injury were detected using the following criteria for Hy's law, as defined in the Data Analysis Plan (DAP): AST and/or ALT > 3 x baseline and total bilirubin ≥ 2 x ULN at the same visit/date. Hy's Law criteria for drug-induced liver injury require there to be no alternative cause for hepatic dysfunction (such as coexistent liver disease) or confounding factors such as administration of a known hepatotoxic agent. In the APHINITY study, all patients were scheduled to receive other potentially hepatotoxic agents (notably anthracyclines and/or taxanes) so only laboratory criteria were used.

Five patients fulfilled the liver enzyme criteria for Hy's Law according to these laboratory criteria (3 patients vs. 2 patients).

All 5 patients had confounding factors, as summarized below, and in none of the patients was Perjeta considered a likely causal factor.

With regard to the patients in the experimental arm, in one case (Patient 2316340014) the event occurred 203 days after last dose of study treatment and the patient was receiving concomitant treatment with glatiramer acetate for multiple sclerosis. In Patient 2332850008 Grade 3 drug-induced hepatitis was assessed as unrelated to Perjeta, Herceptin and paclitaxel, and related to simvastatin which was a concomitant medication at study entry. The patient's ALT and AST returned to normal despite continued treatment with Perjeta, Herceptin and paclitaxel. Patient 2351340011 was identified as having laboratory test results meeting the DAP-defined Hy's Law criteria. The narrative relating to this patient (who does not appear in the listing of liver laboratory test results meeting Hy's Law) is included below:

- Patient 2351340011: this 53-year old woman started treatment with docetaxel, carboplatin, Perjeta and Herceptin on Study Day 1 (Cycle 1). On Study Day 6, she was found to have a raised AST of 112 U/L (3.6 x ULN), ALT of 83 U/L (2.4 x ULN), alkaline phosphatase of 341 U/L (3.3 x ULN), and bilirubin of 82.08 umol/L (3.9 x ULN; Grade 3). On Study Day 9, a bone marrow biopsy was conducted and a diagnosis of hemophagocytic lymphohistiocytosis was made. The investigator assessed this as related to pre-existing/underlying disease (unspecified). Treatment with Perjeta, Herceptin, docetaxel and carboplatin was permanently discontinued. By Week 4 (Study Day 38), only the alkaline phosphatase remained elevated at 142 U/L (1.4 x ULN). This returned to the normal range by Study Day 61. The patient went on to receive non-study adjuvant treatment with etoposide from Study Day 11 to Study Day 20 (one cycle), paclitaxel from Study Day 63 to Study Day 141 (12 cycles), and trastuzumab from Study Day 42 to Study Day 463 (28 cycles).

<u>Adverse events starting during a Perjeta/placebo infusion</u>

Overall, AEs started during a Perjeta/placebo infusion more frequently in the Ptz+H+Chemo arm compared to the Pla+H+Chemo arm (240 patients [10.2%] vs. 181 patients [7.8%], respectively). The majority of AEs reported were Grade 1 or 2 in severity (9.6% vs. 7.3%). However, 19 patients (0.8%) and 14 patients (0.6%) experienced Grade ≥3 events, respectively. No fatal events were reported.

AEs started more frequently during the first Perjeta infusion than during the first placebo infusion (139 patients [5.9%] vs. 71 patients [3.0%]). The majority of AEs were Grade 1 or 2 in severity (129 patients [5.5%] vs. 68 patients [2.9%]).

The frequency of AEs that started during a second Perjeta infusion was similar to the frequency during the second placebo infusion (2.2% vs. 1.8%).

<u>Adverse events during Anthracycline treatment</u>

As per protocol, HER2-targeted therapy did not commence until completion of anthracycline-based chemotherapy. Thus, during the anthracycline treatment period, patients in the Ptz+H+Chemo arm received exactly the same treatment (chemotherapy only) as patients in the Pla+H+Chemo arm.

Of the 95,985 AEs reported during the APHINITY study, 28.7% of AEs were reported in the Ptz+H+Chemo arm versus 31.7% of AEs in the Pla+H+Chemo arm during the anthracycline treatment period.

A similar proportion of patients experienced at least one AE during the anthracycline treatment period. During the anthracycline treatment period, a similar proportion of patients experienced Grade ≥ 3 AEs in both arms (39.0% vs. 39.5%). The majority of Grade ≥ 3 AEs were in the Blood and Lymphatic System Disorders SOC (neutropenia: 13.1% vs. 12.7%).

Adverse events during targeted therapy + taxane (TTTC) period

Of the 95,985 AEs reported during the APHINITY study, 45.5% of AEs were reported in the Ptz+H+Chemo arm versus 43.6% of AEs in the Pla+H+Chemo arm during the TTTC period.

The most common AEs (≥10% of patients) reported during the TTTC period were diarrhea (61.4% vs. 33.8%), nausea (24.4% vs. 21.0%), fatigue (24.2% vs. 20.7%), anemia (18.4% vs. 14.0%), myalgia (18.1% vs. 21.5%), arthralgia (13.3% vs. 17.8%), dysgeusia (17.3% vs. 13.4%), stomatitis (17.3% vs. 13.1%), rash (15.9% vs. 13.2%), vomiting (15.7% vs. 11.6%), epistaxis (15.0% vs. 11.3%), alopecia (14.6% vs. 15.3%), mucosal inflammation (14.8% vs. 10.9%), decreased appetite (13.8% vs. 8.9%), peripheral sensory neuropathy (13.4% vs. 13.7%), neutropenia (11.5% vs. 11.3%), oedema peripheral (11.0% vs. 13.1%), pyrexia (12.2% vs. 11.4%), neuropathy peripheral (11.7% vs. 11.8%), asthenia (11.5% vs. 11.1%), and constipation (10.4% vs. 13.8%).

During the TTTC period, a higher proportion of patients experienced Grade ≥ 3 AEs (42.0% vs. 33.5%), and the Grade ≥ 3 AEs commonly reported were febrile neutropenia (7.7% vs. 6.9%), neutropenia (7.1% vs. 7.4%), anaemia (5.2% vs. 3.2%), and diarrhea (8.4% vs. 2.5%).

Adverse events during the post-chemotherapy targeted therapy (PCTT) period

Of the 95,985 AEs reported during the APHINITY study, 25.5% of AEs were reported in the Ptz+H+Chemo arm versus 24.6% of AEs in the Pla+H+Chemo arm during the PCTT period.

The most common AEs (≥10%) reported were diarrhea (18.1% vs. 9.2%), arthralgia (15.3% vs. 16.5%), and pruritus (10.0% vs. 5.8%).

A similar proportion of patients experienced Grade ≥ 3 AEs (13.0% vs. 11.1%), most frequently ejection fraction decreased (1.4% vs. 1.1%), hypertension (0.8% vs. 0.7%), neutropenia (0.5% vs. 0.4%), diarrhea (0.5% vs. 0.2%), and neutrophil count decreased (0.4% vs. 0.2%). The incidence of Grade ≥ 3 diarrhea events was 0.5% vs. 0.2% during the period of targeted treatment alone.

The proportion of patients who experienced at least one AE that led to the withdrawal of Perjeta or placebo during the PCTT period was similar in the two treatment arms (125 patients [5.3%] vs. 110 patients [4.6%]).

Adverse events post-treatment follow-up period

Table 65

Adverse Events During Post-Treatment Period by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA System Organ Class MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Total number of patients with at least one adverse event	100 (4.2%)	116 (4.8%)
Overall total number of events	118	135
INVESTIGATIONS		
Total number of patients with at least one adverse event	40 (1.7%)	51 (2.1%)
EJECTION FRACTION DECREASED	39 (1.6%)	51 (2.1%)
ELECTROCARDIOGRAM QT PROLONGED	1 (<0.1%)	0
HEART RATE INCREASED	1 (<0.1%)	0
Total number of events	42	56

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Table includes AEs with date of onset > 28 days after last dose of study treatment.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ae.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ae_TRT1A_POST_SE.out
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Adverse events by chemotherapy type

Table 66

Safety Summary by Treatment Regimen and Chemotherapy Type, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

	Pertuzumab + Trastuzumab + Anthracycline (N=1834)	Pertuzumab + Trastuzumab + Non-Anthracycline (N=528)	Placebo + Trastuzumab + Anthracycline (N=1894)	Placebo + Trastuzumab + Non-Anthracycline (N=510)
Total number of patients with at least one event (AE/death)*	1833 (>99.9%)	526 (99.6%)	1882 (99.4%)	510 (100.0%)
Total number of events (AE/death)*	38501	11463	35724	10263
Total number of deaths	55 (3.0%)	18 (3.4%)	79 (4.2%)	16 (3.1%)
Total number of patients with at least one				
AE with fatal outcome	6 (0.3%)	4 (0.8%)	11 (0.6%)	3 (0.6%)
Serious AE	512 (27.9%)	180 (34.1%)	444 (23.4%)	141 (27.6%)
AE leading to withdrawal from pertuzumab/placebo treatment	131 (7.1%)	35 (6.6%)	113 (6.0%)	26 (5.1%)
AE leading to withdrawal from any treatment	235 (12.8%)	74 (14.0%)	237 (12.5%)	40 (7.8%)
AE leading to dose modification/interruption of pertuzumab/placebo	516 (28.1%)	207 (39.2%)	482 (25.4%)	150 (29.4%)
AE leading to dose modification/interruption of any study treatment	919 (50.1%)	297 (56.3%)	840 (44.4%)	224 (43.9%)
Related (HER2-targeted) AE	1165 (63.5%)	372 (70.5%)	1048 (55.3%)	320 (62.7%)
NCI-CTCAE Grade >=3 AE	1133 (61.8%)	384 (72.7%)	1080 (57.0%)	299 (58.6%)
AE during pertuzumab/placebo infusion	194 (10.6%)	46 (8.7%)	150 (7.9%)	31 (6.1%)
Cardiac Safety				
Symptomatic Cardiac Dysfunction (Primary Cardiac Event)	15 (0.8%)	2 (0.4%)	7 (0.4%)	1 (0.2%)
Heart failure (NYHA III or IV) and significant LVEF decline	13 (0.7%)	2 (0.4%)	5 (0.3%)	1 (0.2%)
Cardiac death (definite or probable)	2 (0.1%)	0	2 (0.1%)	0
Secondary cardiac endpoint	55 (3.0%)	9 (1.7%)	60 (3.2%)	7 (1.4%)

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
* Includes deaths for patients that had no adverse events; 1 patient had a death without any AE in the Placebo arm.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately.
Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.
Total number of deaths are counted over the whole study period, including post-treatment follow-up.
Significant LVEF decline defined as a decline of >=10% points to a value <50%.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_saf_sum.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_saf_sum_TRT2A_SE.out
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Safety Summary by Treatment Regimen and Chemotherapy Type, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

	Pertuzumab + Trastuzumab + Anthracycline (N=1834)	Pertuzumab + Trastuzumab + Non-Anthracycline (N=528)	Placebo + Trastuzumab + Anthracycline (N=1894)	Placebo + Trastuzumab + Non-Anthracycline (N=510)
Medical concepts: patients with				
Diarrhoea	1237 (67.4%)	447 (84.7%)	772 (40.8%)	314 (61.6%)
NCI-CTCAE Grade >=3	138 (7.5%)	95 (18.0%)	59 (3.1%)	31 (6.1%)
Rash	968 (52.8%)	258 (48.9%)	789 (41.7%)	213 (41.8%)
NCI-CTCAE Grade >=3	54 (2.9%)	5 (0.9%)	30 (1.6%)	6 (1.2%)
Leukopenia	941 (51.3%)	236 (44.7%)	921 (48.6%)	237 (46.5%)
NCI-CTCAE Grade >=3	713 (38.9%)	167 (31.6%)	673 (35.5%)	168 (32.9%)
Febrile neutropenia	235 (12.8%)	51 (9.7%)	204 (10.8%)	62 (12.2%)
NCI-CTCAE Grade >=3	235 (12.8%)	51 (9.7%)	204 (10.8%)	62 (12.2%)
Anaphylaxis and hypersensitivity	76 (4.1%)	40 (7.6%)	61 (3.2%)	25 (4.9%)
NCI-CTCAE Grade >=3	11 (0.6%)	7 (1.3%)	9 (0.5%)	8 (1.6%)
Mucositis	1085 (59.2%)	262 (49.6%)	948 (50.1%)	232 (45.5%)
NCI-CTCAE Grade >=3	91 (5.0%)	24 (4.5%)	44 (2.3%)	11 (2.2%)
Interstitial lung disease	17 (0.9%)	2 (0.4%)	20 (1.1%)	2 (0.4%)
NCI-CTCAE Grade >=3	3 (0.2%)	2 (0.4%)	3 (0.2%)	1 (0.2%)

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
* Includes deaths for patients that had no adverse events; 1 patient had a death without any AE in the Placebo arm.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately.
Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.
Total number of deaths are counted over the whole study period, including post-treatment follow-up.
Significant LVEF decline defined as a decline of >=10% points to a value <50%.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_saf_sum.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_saf_sum_TRT2A_SE.out
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Laboratory findings

Table 67 Laboratory Test Results with Highest NCI CTCAE Grade Post-Baseline by Treatment Regimen: Safety Population

Laboratory Test Results with Highest NCI CTCAE Grade Post-Baseline by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

Laboratory Test Direction of Abnormality	Highest CTC Grade	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Hemoglobin			
	n	2363	2395
Low	1	1083 (45.8%)	1164 (48.6%)
	2	876 (37.1%)	835 (34.9%)
	3	197 (8.3%)	141 (5.9%)
	Any	2156 (91.2%)	2140 (89.4%)
High	1	79 (3.3%)	93 (3.9%)
	2	1 (<0.1%)	3 (0.1%)
	3	4 (0.2%)	3 (0.1%)
	Any	84 (3.6%)	99 (4.1%)
Leukocytes			
	n	2327	2352
Low	1	421 (18.1%)	469 (19.9%)
	2	572 (24.6%)	538 (22.9%)
	3	424 (18.2%)	411 (17.5%)
	4	278 (11.9%)	274 (11.6%)
	Any	1695 (72.8%)	1692 (71.9%)
High	3	1 (<0.1%)	10 (0.4%)
	Any	1 (<0.1%)	10 (0.4%)
Neutrophils			
	n	2321	2351
Low	1	210 (9.0%)	206 (8.8%)
	2	362 (15.6%)	382 (16.2%)
	3	285 (12.3%)	296 (12.6%)
	4	657 (28.3%)	623 (26.5%)
	Any	1514 (65.2%)	1507 (64.1%)
Platelets			
	n	2354	2383

Low	1	484 (20.6%)	464 (19.5%)
	2	57 (2.4%)	50 (2.1%)
	3	39 (1.7%)	38 (1.6%)
	4	114 (4.8%)	112 (4.7%)
	Any	694 (29.5%)	664 (27.9%)
Creatinine			
	n	2363	2394
High	1	1872 (79.2%)	1974 (82.5%)
	2	300 (12.7%)	241 (10.1%)
	3	44 (1.9%)	38 (1.6%)
	4	1 (<0.1%)	1 (<0.1%)
	Any	2217 (93.8%)	2254 (94.2%)
Phosphate			
	n	2335	2359
Low	1	127 (5.4%)	114 (4.8%)
	2	430 (18.4%)	405 (17.2%)
	3	84 (3.6%)	61 (2.6%)
	4	41 (1.8%)	41 (1.7%)
	Any	682 (29.2%)	621 (26.3%)

Laboratory Test Results with Highest NCI CTCAE Grade Post-Baseline by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

Laboratory Test Direction of Abnormality	Highest CTC Grade	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Calcium			
	n	2363	2390
Low	1	486 (20.6%)	457 (19.1%)
	2	104 (4.4%)	70 (2.9%)
	3	25 (1.1%)	14 (0.6%)
	4	86 (3.6%)	80 (3.3%)
	Any	701 (29.7%)	621 (26.0%)
High	1	325 (13.8%)	360 (15.1%)
	2	6 (0.3%)	3 (0.1%)
	3	2 (<0.1%)	3 (0.1%)
	4	22 (0.9%)	17 (0.7%)
	Any	355 (15.0%)	383 (16.0%)
Magnesium			
	n	2355	2383
Low	1	610 (25.9%)	558 (23.4%)
	2	104 (4.4%)	57 (2.4%)
	3	30 (1.3%)	13 (0.5%)
	4	54 (2.3%)	28 (1.2%)
	Any	798 (33.9%)	656 (27.5%)
High	1	147 (6.2%)	146 (6.1%)
	3	55 (2.3%)	41 (1.7%)
	4	2 (<0.1%)	3 (0.1%)
	Any	204 (8.7%)	190 (8.0%)
Sodium			
	n	2363	2392
Low	1	395 (16.7%)	441 (18.4%)
	3	33 (1.4%)	33 (1.4%)
	4	46 (1.9%)	53 (2.2%)
	Any	474 (20.1%)	527 (22.0%)
High	1	291 (12.3%)	278 (11.6%)
	2	24 (1.0%)	30 (1.3%)
	3	2 (<0.1%)	1 (<0.1%)
	4	11 (0.5%)	7 (0.3%)
	Any	328 (13.9%)	316 (13.2%)
Potassium			
	n	2362	2393
Low	2	530 (22.4%)	434 (18.1%)
	3	88 (3.7%)	50 (2.1%)
	4	53 (2.2%)	53 (2.2%)
	Any	671 (28.4%)	537 (22.4%)
High	1	291 (12.3%)	281 (11.7%)
	2	53 (2.2%)	53 (2.2%)
	3	30 (1.3%)	23 (1.0%)
	4	11 (0.5%)	10 (0.4%)
	Any	385 (16.3%)	367 (15.3%)

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
'n' denotes the number of patients with a post-baseline lab value within this time interval. For a patient with multiple post-baseline lab abnormalities, the highest (worst) grade of these abnormalities for the given lab test is reported. 'Any' is the number of patients with a post-baseline abnormality of any grade for the specified lab test.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_lb_nci.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_lb_nci_PBASE_SE.out

Table 67 Laboratory Test Results with Highest NCI CTCAE Grade Post-Baseline by Treatment Regimen: Safety Population (cont.)

Laboratory Test Results with Highest NCI CTCAE Grade Post-Baseline by Treatment Regimen,
Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

Laboratory Test Direction of Abnormality	Highest CTC Grade	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Alkaline Phosphatase			
	n	2363	2394
High	1	599 (25.3%)	638 (26.6%)
	2	16 (0.7%)	14 (0.6%)
	3	1 (<0.1%)	1 (<0.1%)
	Any	616 (26.1%)	653 (27.3%)
AST			
	n	2358	2392
High	1	950 (40.3%)	934 (39.0%)
	2	46 (2.0%)	45 (1.9%)
	3	24 (1.0%)	16 (0.7%)
	4	1 (<0.1%)	1 (<0.1%)
	Any	1021 (43.3%)	996 (41.6%)
ALT			
	n	2362	2394
High	1	1211 (51.3%)	1167 (48.7%)
	2	105 (4.4%)	109 (4.6%)
	3	53 (2.2%)	40 (1.7%)
	4	2 (<0.1%)	6 (0.3%)
	Any	1371 (58.0%)	1322 (55.2%)
Total Bilirubin			
	n	2359	2393
High	1	130 (5.5%)	142 (5.9%)
	2	34 (1.4%)	45 (1.9%)
	3	9 (0.4%)	12 (0.5%)
	4	2 (<0.1%)	2 (<0.1%)
	Any	175 (7.4%)	201 (8.4%)

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
'n' denotes the number of patients with a post-baseline lab value within this time interval. For a patient with multiple post-baseline lab abnormalities, the highest (worst) grade of these abnormalities for the given lab test is reported. 'Any' is the number of patients with a post-baseline abnormality of any grade for the specified lab test.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_lb_nci.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_lb_nci_PBASE_SE.out
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Shifts from baseline in haematological parameters

At baseline, patients' laboratory values were generally within normal ranges for all laboratory parameters tested (as required by the protocol). Shifts from baseline were most common with hematological parameters, in particular, hemoglobin and leukocytes. Table 68 summarizes the number of patients whose hematology values worsened during treatment, shifting to Grade ≥ 3.

Table 68 Summary of Newly Occurring Grade ≥ 3 Hematology Values During Treatment (Safety Population)

	Ptz+H+Chemo arm N = 2364		Pla+H+Chemo arm N = 2405	
	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
↓ Hemoglobin	178 (7.5%)	-	115 (4.8%)	-
↓ Leukocytes	424 (17.9%)	261 (11.0%)	410 (17.0%)	255 (10.6%)
↓ Platelets	39 (1.6%)	105 (4.4%)	38 (1.6%)	98 (4.1%)
↓ Neutrophils	285 (12.1%)	640 (27.1%)	295 (12.3%)	604 (25.1%)

Source:.Table 77 in Primary APHINITY CSR.

Table 69 shows the number of patients whose biochemistry values worsened during treatment, shifting to Grade≥3. Grade 4 shifts occurred in <1% of patients, apart from potassium (low), sodium (low), magnesium (low), calcium (low), and phosphate (low). Grade ≥3 shifts occurred in <3% of patients, apart from potassium (low) and phosphate (low).

Table 69 Summary of Newly Occurring Grade ≥3 Biochemistry Values During Treatment (Safety Population)

	Ptz+H+Chemo N = 2364		Pla+H+Chemo N = 2405	
	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
↑ AST	24 (1.0%)	1 (<0.1%)	16 (0.7%)	1 (<0.1%)
↑ Alkaline Phosphatase	1 (<0.1%)	-	1 (<0.1%)	-
↑ ALT	53 (2.2%)	2 (<0.1%)	40 (1.7%)	6 (0.2%)
↑ Total Bilirubin	9 (0.4%)	2 (<0.1%)	13 (0.5%)	2 (<0.1%)
↑ Serum Creatinine	44 (1.9%)	1 (<0.1%)	38 (1.6%)	2 (<0.1%)
↓ Potassium	88 (3.7%)	41 (1.7%)	50 (2.1%)	46 (1.9%)
↑ Potassium	30 (1.3%)	13 (0.5%)	23 (1.0%)	12 (0.5%)
↓ Sodium	32 (1.4%)	33 (1.4%)	33 (1.4%)	44 (1.8%)
↓ Magnesium	29 (1.2%)	43 (1.8%)	13 (0.5%)	19 (0.8%)
↑ Magnesium	53 (2.2%)	1 (<0.1%)	40 (1.7%)	2 (<0.1%)
↓ Calcium	25 (1.1%)	41 (1.7%)	14 (0.6%)	39 (1.6%)
↑ Calcium	2 (<0.1%)	18 (0.8%)	3 (0.1%)	14 (0.6%)
↓ Phosphate	81 (3.4%)	33 (1.4%)	59 (2.5%)	30 (1.2%)

Source: Table 78 in Primary APHINITY CSR.

Vital signs and other observations

Performance status

The majority of patients' ECOG status remained unchanged during treatment. The proportion of patients whose ECOG status worsened at any time point during treatment was 818 patients [34.6%] vs. 751 patients [31.2%]. At the end of treatment, the ECOG performance status was worse than at baseline in a small proportion of patients in both treatment arms: 319 patients (13.5%) and 261 patients (10.9%), respectively.

Vital signs

Based on a manual review of the data, there were no major differences between the treatment arms in any vital sign parameters (Blood pressure, heart rate, and weight).

Safety in special populations

Intrinsic factors

Adverse events by sex

Table 70 Comparison of Key Events by Sex

	% of patients experiencing an event			
	Male Patients		Female Patients	
	Ptz+H+Chemo N = 3 (0.1%) [a]	Pla+H+Chemo N = 8 (0.3%) [b]	Ptz+H+Chemo N = 2361 (99.9%)	Pla+H+Chemo N = 2397 (99.7%)
Overall Total events	39	110	49949	45890
Total number of patients with at least one AE	3 (100%)	8 (100%)	2358 (99.9%)	2384 (99.5%)
Total number of patients with Grade ≥ 3 AEs	2 (66.7%)	7 (87.5%)	1516 (64.2%)	1372 (57.2%)
Total number of patients with Grade 5 (fatal) AEs	-	1 (12.5%)	10 (0.4%)	13 (0.5%)
Total number of patients with SAEs	1 (33.3%)	4 (50.0%)	691 (29.3%)	581 (24.2%)
Blood and Lymphatic System Disorder (SOC)	-	7 (87.5%)	1252 (53.0%)	1169 (48.8%)
Neutropenia (PT)	-	3 (37.5%)	587 (24.9%)	559 (23.3%)
Anemia (PT)	-	1 (12.5%)	655 (27.7%)	556 (23.2%)
Febrile Neutropenia (PT)	-	2 (25.0%)	287 (12.2%)	264 (11.0%)
Gastrointestinal (SOC)	3 (100%)	7 (87.5%)	2229 (94.4%)	2150 (89.7%)
Nausea	1 (33.3%)	3 (37.5%)	1631 (69.1%)	1572 (65.6%)
Diarrhea (PT)	2 (66.7%)	2 (25.0%)	1681 (71.2%)	1084 (45.2%)
Stomatitis (PT)	2 (66.7%)	2 (25.0%)	669 (28.3%)	571 (23.8%)
Skin and Subcutaneous tissue (SOC)	2 (66.7%)	6 (75.0%)	2063 (87.4%)	2002 (83.5%)
Alopecia (PT)	1 (33.3%)	3 (37.5%)	1576 (66.8%)	1607 (67.0%)
Rash (PT)	1 (33.3%)	2 (25.0%)	608 (25.8%)	486 (20.3%)
Cardiac disorders (SOC)	-	-	269 (11.4%)	254 (10.6%)

AE=adverse event, Pla=placebo, PT=preferred term, Ptz=pertuzumab, SOC=system organ Class.

[a] Patients: 2308140003, 2312640002, 2325820005.

[b] Patients: 2102690010, 2308770003, 2312640004, 2312640019, 2312850028, 2312930002, 2314360017, 2323320002.

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Adverse events by age

Table 71 Comparison of Key Events by Age

% of Patients Experiencing an Event						
Age (years)	**<40**		**40-64**		**≥ 65**	
SOC PT	**Ptz+H+Chemo N = 325**	**Pla+H+Chemo N = 324**	**Ptz+H+Chemo N = 1737**	**Pla+H+Chemo N = 1788**	**Ptz+H+Chemo N = 302**	**Pla+H+Chemo N = 293**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	58.2%	48.5%	51.8%	47.5%	54.3%	58.0%
Neutropenia	32.0%	26.9%	23.7%	22.7%	23.5%	23.9%
Anemia	27.1%	21.0%	26.5%	21.6%	35.4%	35.2%
Febrile Neutropenia	12.0%	13.3%	11.9%	9.7%	13.9%	16.7%
GASTROINTESTINAL DISORDERS	94.2%	91.4%	94.2%	89.0%	96.0%	91.8%
Nausea	74.2%	74.1%	67.8%	65.9%	70.9%	53.6%
Diarrhea	68.3%	44.4%	70.7%	44.5%	77.2%	49.8%
Stomatitis	28.9%	24.7%	28.3%	23.9%	28.1%	22.5%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	90.5%	84.3%	87.4%	83.7%	83.8%	81.2%
Alopecia	70.5%	68.2%	67.0%	67.7%	60.9%	61.1%
Rash	26.5%	18.8%	25.9%	21.1%	24.2%	16.7%
CARDIAC DISORDERS	11.4%	10.5%	11.0%	10.5%	13.6%	11.3%

H = Herceptin; Pla = placebo, PT = Preferred term, Ptz = Perjeta, SOC = System Organ Class.

Source: t_ae_TRT1A_AL40_SE, t_ae_TRT1A_A4064_SE, t_ae_TRT1A_AL65_SE, t_ae_TRT1A_AGE65_SE.

Adverse events by race

Table 72 Key Adverse Events by Race

SOC PT	% of patients experiencing an event							
	White		**Asian**		**Black**		**Other**	
	Ptz+H+Chemo N = 1680	**Pla+H+Chemo N = 1691**	**Ptz+H+Chemo N = 580**	**Pla+H+Chemo N = 605**	**Ptz+H+Chemo N = 32**	**Pla+H+Chemo N = 39**	**Ptz+H+Chemo N = 66**	**Pla+H+Chemo N = 68**
Overall Total events	34581	31833	13488	12442	690	953	1105	737
Total no. of patients with at least one Grade ≥ 3 AEs	63.0%	57.4%	68.6%	57.2%	81.3%	61.5%	50.0%	55.9%
Total no. of patients with at least one Grade 5 (fatal) AEs	0.5%	0.8%	1.4%	0.8%	-	-	1.5%	1.5%
Total no. of patients with at least one SAE	31.0%	26.0%	25.0%	19.5%	34.4%	33.3%	24.2%	20.6%
BLOOD & LYMPHATIC SYSTEM DISORDERS	50.7%	47.4%	57.9%	51.4%	62.5%	59.0%	63.6%	57.4%
Anemia	26.1%	22.7%	30.5%	21.8%	40.6%	46.2%	36.4%	32.4%
Neutropenia	23.3%	22.2%	26.9%	25.6%	37.5%	25.6%	37.9%	30.9%
Febrile neutropenia	11.1%	11.6%	15.9%	9.9%	3.1%	5.1%	10.6%	10.3%
GASTROINTESTINAL DISORDERS	94.5%	90.7%	94.8%	90.1%	100%	82.1%	86.4%	66.2%
Nausea	70.2%	67.2%	66.9%	63.8%	84.4%	66.7%	50.0%	36.8%
Diarrhea	73.4%	46.8%	63.8%	41.0%	87.5%	48.7%	71.2%	36.8%
Stomatitis	24.9%	20.6%	38.8%	34.4%	40.6%	23.1%	19.7%	11.8%
SKIN & SUBCUTANEOUS TISSUE DISORDERS	89.0%	85.2%	85.2%	82.6%	84.4%	79.5%	63.6%	50.0%
Alopecia	64.8%	65.2%	76.0%	75.2%	50.0%	56.4%	39.4%	41.2%
Rash	25.1%	19.5%	30.5%	24.5%	15.6%	15.4%	6.1%	5.9%
CARDIAC DISORDERS	12.2%	11.2%	9.3%	8.1%	12.5%	25.6%	9.1%	7.4%

Pla=placebo, PT = Preferred term, Ptz=Perjeta, SAEs=Serious Adverse Events, SOC = System Organ Class

Source: White, Asian, Black, Other, l_ae_fatal_AP, l_ae_SER_AP.

Adverse events by nodal status and hormone receptor status

Key safety results in subgroups based on nodal status and central hormone receptor status were provided. The safety profile of Ptz/Pla+H+Chemo in patients with node-positive, node-negative, hormone receptor-positive and hormone receptor-negative disease was similar to that seen in the overall patient population.

Extrinsic factors

There was no new information submitted with this application.

Safety related to drug-drug interactions and other interactions

No PK drug-drug interaction was observed between pertuzumab and carboplatin, or pertuzumab and paclitaxel when given in combination with Herceptin.

Discontinuation due to adverse events

Adverse events that led to withdrawal

Table 73

Adverse Events Leading to Discontinuation of Pertuzumab/Placebo by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA System Organ Class MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Total number of patients with at least one adverse event	166 (7.0%)	139 (5.8%)
Overall total number of events	203	171
INVESTIGATIONS		
Total number of patients with at least one adverse event	45 (1.9%)	66 (2.7%)
EJECTION FRACTION DECREASED	43 (1.8%)	60 (2.5%)
ALANINE AMINOTRANSFERASE INCREASED	0	2 (<0.1%)
ASPARTATE AMINOTRANSFERASE INCREASED	0	2 (<0.1%)
PLATELET COUNT DECREASED	1 (<0.1%)	1 (<0.1%)
WEIGHT DECREASED	1 (<0.1%)	1 (<0.1%)
BLOOD ALKALINE PHOSPHATASE INCREASED	0	1 (<0.1%)
BLOOD CREATININE INCREASED	0	1 (<0.1%)
BLOOD LACTATE DEHYDROGENASE INCREASED	0	1 (<0.1%)
TRANSAMINASES INCREASED	0	1 (<0.1%)
Total number of events	45	70
CARDIAC DISORDERS		
Total number of patients with at least one adverse event	35 (1.5%)	25 (1.0%)
CARDIAC FAILURE	28 (1.2%)	15 (0.6%)
MYOCARDIAL INFARCTION	2 (<0.1%)	2 (<0.1%)
PERICARDIAL EFFUSION	1 (<0.1%)	1 (<0.1%)
ACUTE CORONARY SYNDROME	0	1 (<0.1%)
ANGINA PECTORIS	0	1 (<0.1%)
ATRIAL FIBRILLATION	0	1 (<0.1%)
BUNDLE BRANCH BLOCK LEFT	1 (<0.1%)	0
CARDIAC FAILURE CONGESTIVE	0	1 (<0.1%)
CARDIAC VALVE DISEASE	0	1 (<0.1%)
DIASTOLIC DYSFUNCTION	0	1 (<0.1%)
MITRAL VALVE INCOMPETENCE	0	1 (<0.1%)
MYOCARDIAL ISCHAEMIA	1 (<0.1%)	0
PALPITATIONS	1 (<0.1%)	0
STRESS CARDIOMYOPATHY	0	1 (<0.1%)
SUPRAVENTRICULAR TACHYCARDIA	1 (<0.1%)	0
VENTRICULAR ARRHYTHMIA	1 (<0.1%)	0
Total number of events	36	26

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ae.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ae_TRT1A_DSCPP_SE.out
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Adverse Events Leading to Discontinuation of Pertuzumab/Placebo by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA System Organ Class MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	26 (1.1%)	5 (0.2%)
DIARRHOEA	20 (0.8%)	2 (<0.1%)
VOMITING	4 (0.2%)	0
COLITIS	2 (<0.1%)	1 (<0.1%)
NAUSEA	2 (<0.1%)	0
STOMATITIS	2 (<0.1%)	0
ABDOMINAL PAIN	0	1 (<0.1%)
ANAL INFLAMMATION	1 (<0.1%)	0
APHTHOUS ULCER	1 (<0.1%)	0
GASTROINTESTINAL PAIN	1 (<0.1%)	0
INTUSSUSCEPTION	0	1 (<0.1%)
PROCTITIS	1 (<0.1%)	0
SMALL INTESTINAL OBSTRUCTION	1 (<0.1%)	0
TOOTHACHE	0	1 (<0.1%)
Total number of events	35	6
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total number of patients with at least one adverse event	16 (0.7%)	5 (0.2%)
RASH	8 (0.3%)	1 (<0.1%)
PRURITUS	4 (0.2%)	1 (<0.1%)
ANGIOEDEMA	0	1 (<0.1%)
DRY SKIN	1 (<0.1%)	0
ERYTHEMA	0	1 (<0.1%)
EXFOLIATIVE RASH	0	1 (<0.1%)
NAIL TOXICITY	1 (<0.1%)	0
ONYCHOCLASIS	1 (<0.1%)	0
PSORIASIS	1 (<0.1%)	0
PURPURA	1 (<0.1%)	0
RASH PRURITIC	1 (<0.1%)	0
SKIN FISSURES	1 (<0.1%)	0
URTICARIA	1 (<0.1%)	0
Total number of events	20	5
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total number of patients with at least one adverse event	9 (0.4%)	10 (0.4%)
PYREXIA	1 (<0.1%)	4 (0.2%)
ASTHENIA	2 (<0.1%)	1 (<0.1%)
FATIGUE	0	3 (0.1%)
GENERAL PHYSICAL HEALTH DETERIORATION	1 (<0.1%)	2 (<0.1%)
CHEST PAIN	1 (<0.1%)	1 (<0.1%)
GENERALISED OEDEMA	2 (<0.1%)	0
CHILLS	0	1 (<0.1%)
FACE OEDEMA	1 (<0.1%)	0
MUCOSAL INFLAMMATION	1 (<0.1%)	0
PERFORMANCE STATUS DECREASED	0	1 (<0.1%)
Total number of events	9	13

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ae.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ae_TRT1A_DSCPP_SE.out
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AEs that led to the withdrawal of patients from **Perjeta or placebo** occurred most commonly in the following SOCs:

- Investigations, mainly attributable to ejection fraction decreased (43 patients [1.8%] vs. 60 patients [2.5%], respectively).
- Cardiac Disorders, mainly attributable to cardiac failure (28 patients [1.2%] vs. 15 patients [0.6%], respectively).

- Gastrointestinal Disorders, mainly attributable to diarrhea (20 patients [0.8%] vs. 2 patients [<0.1%], respectively).

The proportion of patients who experienced at least one AE that led to the withdrawal of **any study medication** was similar between the arms (309 patients [13.1%] vs. 277 patients [11.5%], respectively).The most common AEs were in the following SOCs:

- Nervous System Disorders (63 patients [2.7%] vs. 54 patients [2.2%]), mainly attributable to peripheral sensory neuropathy (17 patients [0.7%] vs. 21 patients [0.9%], respectively), and neuropathy peripheral (19 patients [0.8%] vs. 18 patients [0.7%], respectively).
- Gastrointestinal Disorders (59 patients [2.5%] vs. 21 patients [0.9%]), mainly attributable to diarrhea (38 patients [1.6%] vs. 7 patients [0.3%], respectively).
- Investigations (57 patients [2.4%] vs. 84 patients [3.5%]), mainly attributable to ejection fraction decreased (43 patients [1.8%] vs. 60 patients [2.5%], respectively).
- Cardiac Disorders (38 patients [1.6%] vs. 30 patients [1.2%]), mainly attributable to cardiac failure (28 patients [1.2%] vs. 15 patients [0.6%], respectively).

Adverse events that led to dose modifications

Table 74

Adverse Events Leading to Dose Modification (Dose Interruption or Dose Delay) of Pertuzumab/ Placebo by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA System Organ Class MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Total number of patients with at least one adverse event	723 (30.6%)	632 (26.3%)
Overall total number of events	1247	1050
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total number of patients with at least one adverse event	204 (8.6%)	196 (8.1%)
NEUTROPENIA	123 (5.2%)	109 (4.5%)
ANAEMIA	49 (2.1%)	34 (1.4%)
THROMBOCYTOPENIA	32 (1.4%)	29 (1.2%)
LEUKOPENIA	16 (0.7%)	23 (1.0%)
FEBRILE NEUTROPENIA	21 (0.9%)	16 (0.7%)
BONE MARROW FAILURE	2 (<0.1%)	2 (<0.1%)
GRANULOCYTOPENIA	1 (<0.1%)	2 (<0.1%)
LEUKOCYTOSIS	2 (<0.1%)	0
BLOOD DISORDER	1 (<0.1%)	0
HAEMATOTOXICITY	0	1 (<0.1%)
PANCYTOPENIA	0	1 (<0.1%)
Total number of events	295	254

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.

Program: /opt/BIOSTAT/prod/cdp11450/r25126a/t_ae.sas
Output: /opt/BIOSTAT/prod/cd11450g/j25126a/reports/t_ae_TRT1A_DSMPP_SE.out
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Adverse Events Leading to Dose Modification (Dose Interruption or Dose Delay) of Pertuzumab/ Placebo by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA System Organ Class MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
INVESTIGATIONS		
Total number of patients with at least one adverse event	186 (7.9%)	187 (7.8%)
NEUTROPHIL COUNT DECREASED	72 (3.0%)	59 (2.5%)
EJECTION FRACTION DECREASED	50 (2.1%)	50 (2.1%)
ALANINE AMINOTRANSFERASE INCREASED	32 (1.4%)	41 (1.7%)
ASPARTATE AMINOTRANSFERASE INCREASED	15 (0.6%)	25 (1.0%)
PLATELET COUNT DECREASED	19 (0.8%)	18 (0.7%)
WHITE BLOOD CELL COUNT DECREASED	20 (0.8%)	13 (0.5%)
BLOOD ALKALINE PHOSPHATASE INCREASED	1 (<0.1%)	5 (0.2%)
TRANSAMINASES INCREASED	0	4 (0.2%)
WEIGHT DECREASED	3 (0.1%)	1 (<0.1%)
BLOOD BILIRUBIN INCREASED	2 (<0.1%)	1 (<0.1%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	0	3 (0.1%)
BLOOD CREATININE INCREASED	1 (<0.1%)	1 (<0.1%)
C-REACTIVE PROTEIN INCREASED	1 (<0.1%)	1 (<0.1%)
HAEMOGLOBIN DECREASED	1 (<0.1%)	1 (<0.1%)
NEUTROPHIL COUNT	1 (<0.1%)	1 (<0.1%)
PLATELET COUNT	0	2 (<0.1%)
WHITE BLOOD CELL COUNT	1 (<0.1%)	1 (<0.1%)
ALANINE AMINOTRANSFERASE	1 (<0.1%)	0
BODY TEMPERATURE INCREASED	1 (<0.1%)	0
CLOSTRIDIUM TEST POSITIVE	1 (<0.1%)	0
CREATININE RENAL CLEARANCE DECREASED	0	1 (<0.1%)
ELECTROCARDIOGRAM T WAVE INVERSION	0	1 (<0.1%)
HAEMOGLOBIN	0	1 (<0.1%)
HAPTOGLOBIN DECREASED	0	1 (<0.1%)
HEPATIC ENZYME INCREASED	0	1 (<0.1%)
LIVER FUNCTION TEST INCREASED	0	1 (<0.1%)
TROPONIN INCREASED	1 (<0.1%)	0
TROPONIN T INCREASED	0	1 (<0.1%)
WEIGHT INCREASED	1 (<0.1%)	0
WHITE BLOOD CELL COUNT INCREASED	1 (<0.1%)	0
Total number of events	246	264
INFECTIONS AND INFESTATIONS		
Total number of patients with at least one adverse event	185 (7.8%)	156 (6.5%)
NASOPHARYNGITIS	22 (0.9%)	21 (0.9%)
INFLUENZA	15 (0.6%)	18 (0.7%)
UPPER RESPIRATORY TRACT INFECTION	14 (0.6%)	11 (0.5%)
BRONCHITIS	7 (0.3%)	10 (0.4%)
HERPES ZOSTER	6 (0.3%)	9 (0.4%)
RESPIRATORY TRACT INFECTION VIRAL	9 (0.4%)	5 (0.2%)
URINARY TRACT INFECTION	5 (0.2%)	9 (0.4%)
PNEUMONIA	5 (0.2%)	8 (0.3%)
CELLULITIS	6 (0.3%)	5 (0.2%)
GASTROENTERITIS	7 (0.3%)	4 (0.2%)
INFECTION	5 (0.2%)	5 (0.2%)
DEVICE RELATED INFECTION	5 (0.2%)	4 (0.2%)

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.

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Output: /opt/BIOSTAT/prod/cdl1450g/j25126a/reports/t_ae_TRT1A_DSMPP_SE.out
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Adverse Events Leading to Dose Modification (Dose Interruption or Dose Delay) of Pertuzumab/ Placebo by Treatment Regimen, Safety Evaluated Population
Protocol: BIG 4-11/BO25126/TOC4939G

MedDRA System Organ Class MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	109 (4.6%)	45 (1.9%)
DIARRHOEA	69 (2.9%)	18 (0.7%)
VOMITING	12 (0.5%)	13 (0.5%)
NAUSEA	7 (0.3%)	7 (0.3%)
STOMATITIS	10 (0.4%)	3 (0.1%)
ABDOMINAL PAIN	5 (0.2%)	1 (<0.1%)
ABDOMINAL PAIN UPPER	4 (0.2%)	1 (<0.1%)
COLITIS	1 (<0.1%)	2 (<0.1%)
GASTROOESOPHAGEAL REFLUX DISEASE	2 (<0.1%)	1 (<0.1%)
DENTAL CARIES	1 (<0.1%)	1 (<0.1%)
DUODENAL ULCER	2 (<0.1%)	0
GASTRIC ULCER	2 (<0.1%)	0
GASTRIC ULCER HAEMORRHAGE	2 (<0.1%)	0
HAEMATOCHEZIA	1 (<0.1%)	1 (<0.1%)
HAEMORRHOIDAL HAEMORRHAGE	1 (<0.1%)	1 (<0.1%)
ILEUS	1 (<0.1%)	1 (<0.1%)
ODYNOPHAGIA	1 (<0.1%)	1 (<0.1%)
PERIODONTAL DISEASE	0	2 (<0.1%)
TOOTHACHE	2 (<0.1%)	0
ABDOMINAL DISTENSION	1 (<0.1%)	0
ABDOMINAL HERNIA	0	1 (<0.1%)
ANAL FISSURE	1 (<0.1%)	0
CONSTIPATION	0	1 (<0.1%)
DIVERTICULAR PERFORATION	0	1 (<0.1%)
DUODENAL PERFORATION	0	1 (<0.1%)
DUODENAL ULCER PERFORATION	0	1 (<0.1%)
DYSPEPSIA	1 (<0.1%)	0
GASTROINTESTINAL DISORDER	1 (<0.1%)	0
GASTROINTESTINAL HAEMORRHAGE	0	1 (<0.1%)
GLOSSODYNIA	1 (<0.1%)	0
HAEMORRHOIDS	1 (<0.1%)	0
INTESTINAL HAEMORRHAGE	1 (<0.1%)	0
LIP OEDEMA	0	1 (<0.1%)
LOWER GASTROINTESTINAL HAEMORRHAGE	1 (<0.1%)	0
MOUTH ULCERATION	0	1 (<0.1%)
OEDEMA MOUTH	1 (<0.1%)	0
PANCREATITIS ACUTE	1 (<0.1%)	0
Total number of events	137	63

Investigator text for AEs encoded using MedDRA v19.1 .
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.

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A total of 723 patients (30.6%) vs. 632 patients (26.3%) experienced an AE leading to a dose modification of **Perjeta or placebo** (i.e., dose interruption or dose delay). The SOCs were as follows:

- Blood and Lymphatic Systems Disorders: 204 patients (8.6%) compared to 196 patients (8.1%), mainly attributable to neutropenia (123 patients [5.2%] vs. 109 patients [4.5%]).
- Investigations: 186 patients (7.9%) compared to 187 patients (7.8%), mainly attributable to neutrophil count decreased (72 patients [3.0%] vs. 59 patients [2.5%]), and ejection fraction decreased (50 patients [2.1%] vs. 50 patients [2.1%]).
- Gastrointestinal Disorders: 109 patients (4.6%) compared to 45 patients (1.9%), mainly attributable to diarrhea (69 patients [2.9%] vs. 18 patients [0.7%]).

The incidence of AEs leading to **any study drug** modifications (i.e., including dose interruptions, dose delays, and dose reductions) were1217 patients (51.5%) vs. 1064 patients (44.2%). The higher incidence was mainly due to neutropenia (230 patients [9.7%] vs. 209 patients [8.7%]).

Additional SOCs were:

- Investigations: 288 patients (12.2%) compared to 297 patients (12.3%), the higher incidence mainly attributable to neutrophil count decreased (121 patients [5.1%] vs. 116 patients [4.8%]).
- Gastrointestinal Disorders: 315 patients (13.3%) compared to 160 patients (6.7%), the higher incidence mainly attributable to diarrhea (210 patients [8.9%] vs. 74 patients [3.1%].

Post marketing experience

As of 30 March 2017 (the Data Lock Point [DLP] for the Perjeta EU License renewal), an estimated cumulative total of 160,282 patients have received Perjeta in the marketing experience.

In line with ICH-E2D guideline, for marketed medicinal products, spontaneously reported AEs usually imply at least a suspicion of causality by the reporter and are considered to be suspected adverse reactions for regulatory reporting purposes. A summary of the SOCs under which AEs were most frequently reported from post-authorization sources, is presented in Table 75.

Table 75 SOCs of the Most Frequently Reported AEs from Post-authorization Sources (from 8 June 2012 [IBD] to 30 March 2017 [DLP])*

SOC	Spontaneous, including health authority (worldwide) and literature		Non-interventional post-marketing study and reports from other solicited sources**
	Serious	Non-Serious	Serious
General Disorders and Administration Site Conditions	491	1487	667
Gastrointestinal Disorders	539	1177	257
Skin and Subcutaneous Tissue Disorders	250	1149	23

Source: Appendix 6 of EU License Renewal (available upon request): cumulative summary tabulations of serious and non-serious adverse reactions from post-marketing data sources

*Non-interventional studies (including post-authorization safety studies), reports from other solicited sources, and spontaneous Individual Case Safety Reports (i.e., reports from healthcare professionals, consumers, health authorities [worldwide], and scientific literature)

** This does not include interventional clinical trials

DLP = data lock point, IBD = international birth date, SOC = system organ class

The cumulative post-marketing data is consistent with the data submitted in previous Periodic Benefit-Risk Evaluation Reports (PBRERs), including the data that became available since the last Perjeta PBRER was submitted (Report 1069305 [reporting period 8 December 2015 to 7 June 2016]). No new safety concerns were identified.

2.5.1. Discussion on clinical safety

The APHINITY study included patients with operable HER2-positive early breast cancer, and the study provides safety data on 2364 patients exposed to Perjeta plus trastuzumab and standard chemotherapy (Ptz+H+Chemo) in the adjuvant setting. In addition, safety data have previously been submitted for more

than 2000 patients treated with Perjeta alone or in combination with a range of trastuzumab and/or chemotherapy regimens in registration-directed and supporting clinical trials in the neoadjuvant and metastatic settings. Due to the relatively short follow-up, follow-up safety data from the APHINITY study will allow to further characterise the safety profile..

At the time of the clinical cut-off for the primary analysis (19 December 2016), 2028 patients (84.5%) in the pertuzumab arm and 2100 patients (87.4%) in the Placebo arm had completed treatment. Thereof 372 [15.5%] and 304 [12.6%], respectively, did not complete, or never started, Perjeta or placebo treatment. The median duration of study treatment was 64 weeks (targeted treatment 55 weeks), which was the same in both treatment arms. The median cumulative dose of pertuzumab received by patients in the Ptz+H+Chemo arm was 7980 mg (range: 420-9660 mg). The median follow-up is approximately 45 months. The Applicant has prolonged the follow-up time by additional 5 years, and the obtained knowledge will be very informative both with regard to the number of relapses over time (especially in the CNS) and the extent of late toxicity from the adjuvant treatment given in the APHINITY trial.

In the pertuzumab arm, the incidence of any **treatment-emergent AE** was 99.9%, and the incidence of any grade ≥ 3 AE was 64.2%. The most common AEs were diarrhea (71.2% vs. 45.2%), nausea (69.0% vs. 65.5%), alopecia (66.7% vs. 66.9%), fatigue (48.8% vs. 44.3%), vomiting (32.5% vs. 30.5%), arthralgia (28.7% vs. 32.5%), and constipation (28.9% vs. 31.6%). Overall, most of the common adverse effects are assessed to be chemotherapy toxicities, as they are similar between the treatment arms.

The incidence of **grade ≥3 AEs** was overall higher in the pertuzumab arm (1518 patients [64.2%] vs. 1379 patients [57.3%], respectively), and consisted mainly of neutropenia, febrile neutropenia, and anemia, as well as diarrhea, and neutrophil count decreased. The higher incidence in the pertuzumab arm was mainly driven by **diarrhea** (9.8% vs. 3.7% in the placebo arm) was significant as >grade 3 diarrhoea translate into more than 7 stools per day and hospitalization as indicated. It was evident that the adverse event of diarrhoea was earlier onset, worse in grade, and had longer duration in the pertuzumab arm. Even though reasonable measures were taken, such as early intervention with loperamide as well as fluid and electrolyte replacement, it is noted that the median duration of diarrhea was 8 days vs 6 days between the arms and that the event was coupled especially to the administration of docetaxel. In addition, loperamide was administered to more than double as many patients in the pertuzumab arm (35.6% vs 14.8%). The Applicant has sufficiently changed the SmPC to be more informative on the risk of diarrhea during taxane chemotherapy and in elderly patients, and proposed reasonable management and handling of this safety issue.

A higher incidence of febrile neutropenia was observed among Perjeta-treated Asian patients compared with other races in the APHINITY trial (15.9% of Perjeta-treated patients and 9.9% of placebo-treated patients).The number of **deaths** due to AEs were comparable between the treatment arms.

The most frequent treatment-related SAEs excluding diarrhoea were cardiac events. A total of 25 patients had a **primary cardiac event**: 17 patients (0.7%) vs. 8 patients (0.3%). Heart failure (NYHA III or IV) with an LVEF decline was reported in 15 patients (0.6%) vs. 7 patients (0.3%). The timing of the primary cardiac events was mostly within 2 years, reversible and the number of events was relatively small, so overall the rate is considered acceptable and expectable. Most of the cardiac events occurred in patients who received anthracycline-based treatment. In particular, all cardiac deaths occurred in patients who received anthracycline-based chemotherapy. Radiotherapy on chest wall, smoking history, and coronary artery disease were other identified risk factors. All these factors are already well known to increase the risk of cardiac events with anti-HER2 therapies. At the time of data cut-off, LVEF recovery was achieved only in 7/15 patients (46.7%) experiencing a non-fatal primary cardiac event in the Pertuzumab arm versus 4/6 patients (66.7%) in the placebo arm of patients experiencing a non-fatal primary cardiac event in that treatment arm). The median time to LVEF recovery was much longer in the pertuzumab arm (27.0 weeks, range 3.1-52.4 weeks) compared to the placebo arm (16.3 weeks, range 11.0-30.1 weeks). The updated

incidence for recovery by the new data cut-off 15 May 2017 was 8/15 (53.3%) and 4/7 (57.1%) for pertuzumab and placebo respectively. As no further data can be expected from the majority of the remaining patients, due to 2 deaths and several patient withdrawals from study, it may be concluded that approximately 50% of the patients will recover from a primary cardiac event within a reasonable timeframe.

The majority of patients who experienced a **secondary cardiac event**, experienced the event in the first year after randomization (48 patients [75.0%] vs. 51 patients [76.1%]). LVEF recovery was achieved in 79.4% vs. 80.6% and the median time to acute recovery was comparable between treatment arms. Therefore, secondary cardiac events were considered rare and within an acceptable range considering the study treatments toxicity profiles. However, it is important to get more long-term safety data regarding cardiac safety (see RMP).

Other relevant AEs included **rash** or similar skin adverse events; **leukopenia** and neutropenia, including febrile neutropenia, and **infusion-related reactions**. These adverse events were manageable and considered primarily related to chemotherapy.

Patients with at least one AE in both treatment arms was also comparable across age groups <40 years, 40-64 years, and ≥65 years. In addition, the safety profile in patients regarding **nodal status** and **hormone-receptor status** was similar to that seen in the overall patient population. The number of patients aged 75 years or older was quite small (56 patients [1.2%]), and the MAH decided not to include as a separate group in the analyses to investigate the safety profile of study treatment by age. Requested data from the Applicant show that diarrhea, vomiting, anaemia, decreased appetite and weight decreased were higher in this age-group compared to all patients.

The most common AE's that led to **withdrawal** of Perjeta or placebo were EF decreased, cardiac failure, and diarrhea. Generally, the incidences were small (<3%) and the toxicities were well known and within an acceptable range. The most common AE's that led to withdrawal of any study medication were peripheral sensory neuropathy, neuropathy peripheral, diarrhea, EF decreased, and cardiac failure. The peripheral neuropathy is a known adverse event to taxanes and the events were few, so this is of no major concern. More patients stopped any treatment due to diarrhea, which was expected due to pertuzumab' s and the taxanes toxicity profiles, however the number is considered within an acceptable range, and mostly a problem while both pertuzumab and taxanes were given concomitantly, which is only for approximately 9-12 weeks. The incidences of decreased EF and cardiac failures are within the known range with these treatments, and although double as many patients discontinued treatment due to cardiac failure in the pertuzumab arm, the overall incidence is low (1.2% vs 0.6%).

The AE's that led to a **dose modification** of Perjeta or placebo were mainly neutropenia, neutrophil count decreased, EF decreased, and diarrhea. Dose modifications were more common in the pertuzumab arm (30.6% vs. 26.3%). The AEs that led to any study medication modifications were mainly neutrophil count decreased and diarrhea, and were overall more common in the pertuzumab arm (51.5% vs. 44.2%).

2.5.2. Conclusions on clinical safety

The addition of pertuzumab to standard chemotherapy is well-tolerated, but is associated with increased incidence of diarrhea, cardiac events, mucositis, and infusion-related reactions. Especially, the risk of primary cardiac events tended to increase, particularly heart failure, apparently with a lower chance and longer time to recovery. However, in the updated set the chance of recovery appeared similar. Diarrhoea was observed much more frequently with Perjeta, and was among the main AEs leading to treatment withdrawal or dose modifications. Most toxicities appear manageable and related to chemotherapy, however, it is evident that many of the toxicities are more pronounced in elderly patients, and this is reflected in the SmPC. The high frequency and severity of diarrhoea related to Perjeta, are likely to affect quality of life.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP endorsed the Risk Management Plan version 10.2 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Infusion-related reactions, Hypersensitivity reactions / anaphylaxis Congestive heart failure / Left ventricular dysfunction Grade ≥ 3 Diarrhea
Important potential risks	Oligohydramnios* Risk in fertility in humans Risk in patients aged 75 years or older Lack of efficacy due to immunogenicity
Missing information	Risk in patients with cardiovascular impairment Risk in pregnant or lactating women

Pharmacovigilance plan

Study **Status**	**Summary of Objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
PERUSE study (MO28047) A Phase IIIb study to evaluate the safety and tolerability of pertuzumab in combination with trastuzumab and a taxane Ongoing	The study will mainly evaluate the safety and tolerability of Perjeta in combination with Herceptin and a taxane. Additionally, it will evaluate pertuzumab in combination with trastuzumab and a taxane with respect to PFS, OS, ORR, CBR, Duration of response, Time to response, Quality of life (FACT-B questionnaire for female patients only).	Congestive heart failure / Left ventricular dysfunction Risk in patients with cardiovascular impairment	Final CSR submission	Sept 2020

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
NA	NA	NA	NA	NA
Category 3 - Required additional pharmacovigilance activities				
Study H4621g (MotHER) An observational study of pregnancy and pregnancy outcomes in women with breast cancer treated with Herceptin or Perjeta in combination with Herceptin during pregnancy or within 6 months prior to conception Ongoing	The objective of this study is to describe adverse pregnancy complications (e.g., oligohydramnios), delayed renal development) pregnancy outcomes (i.e., live births, stillbirths, and abortions), fetal/infant outcomes (e.g., major malformations, deformations, and disruptions), and fetal or infant functional deficits among women with breast cancer treated with Herceptin (either in combination with chemotherapies, or as a single agent),and the subset of women treated with Perjeta plus Herceptin during pregnancy or within 6 months prior to conception.	Oligohydramnios	Submission of annual reports with PSUR	Ongoing
			Final report	2022

CBR = Clinical benefit rate, CSR = Clinical study report, FACT-B = Functional Assessment of Cancer Therapy-Breast, HER2 = human epidermal growth factor receptor 2, ORR = Overall response rate, OS = Overall survival, PFS = Progression-free survival, PSUR = Periodic Safety Update Report.

Risk minimisation measures

Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
Infusion-related reactions, Hypersensitivity reactions/anaphylaxis	Sections 4.4 and 4.8 of the EU SmPC: **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None
Congestive heart failure / Left ventricular dysfunction	Sections 4.2; 4.4; 4.8 of the EU SmPC: **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** PERUSE study (MO28047)
Grade ≥ 3 Diarrhea	Sections 4.4 and 4.8 of the EU SmPC:	**Routine pharmacovigilance activities beyond adverse**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: None	**reactions reporting and signal detection:** *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None
Oligohydramnios	Section 4.6 of the EU SmPC: **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Global Enhanced PV Pregnancy Program **Additional pharmacovigilance activities:** Study H4621g (MotHER)
Risk in fertility in humans	Sections 4.6 of the EU SmPC: **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Global Enhanced PV Pregnancy Program *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None
Risk in patients aged ≥ 75 years	**Routine risk communication:** Section 4.2 and 4.4 of the EU SmPC	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in

Safety concern	Risk minimization measures	Pharmacovigilance activities
		PSURs **Additional pharmacovigilance activities:** None
Risk of lack of efficacy due to immunogenicity	Section 5.1 of the EU SmPC	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None
Risk in patients with cardiovascular impairment	Sections 4.2 and 4.4 of the EU SmPC: **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** PERUSE study (MO28047)
Risk in pregnant or lactating women	Section 4.6 of the EU SmPC **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Global Enhanced PV Pregnancy Program *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs

Safety concern	Risk minimization measures	Pharmacovigilance activities
		Additional pharmacovigilance activities: None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This extension of indication is for the use of Perjeta in the adjuvant setting, in combination with trastuzumab and chemotherapy, for the treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.

3.1.2. Available therapies and unmet medical need

Patients with early breast cancer are treated with 6-8 cycles of chemotherapy in addition to 1 year of trastuzumab.

Despite the current available adjuvant treatment (chemotherapy and trastuzumab), up to 1 in 4 women with HER2-positive early breast cancer will experience recurrence or death within 10 – 11 years of diagnosis. As the median age of patients presenting with HER2-positive breast cancer is in the mid-50s, around five years younger than the general breast cancer population, the median loss of life-years per patient is around two decades for patients dying of HER2-positive breast cancer.

Of the patients diagnosed with HER2-positive metastatic breast cancer, approximately 67% initially present with early disease and subsequently relapse, while the remaining patients present with metastases at first diagnosis (“de novo” metastatic breast cancer) (Yardley et al, 2014). Patients who relapse with metastatic or unresectable disease are generally incurable, whereas the few patients with resectable loco-regional recurrence may still be cured with salvage therapy. In the case of metastatic disease, life expectancy is a median OS of 56.5 months (Swain et al, 2015), so more than 50% of the patients die within 5 years.

There is an unmet medical need for reducing the risk of frequent relapses, despite current available adjuvant treatments, and thereby decrease the risk of early death for the majority of the patients who relapse.

3.1.3. Main clinical studies

The pivotal and only study in this application is the APHINITY study. The APHINITY study is an ongoing, randomized, double-blind, two-arm, phase III study of adjuvant trastuzumab and standard chemotherapy plus Perjeta or placebo, in patients with primary operable breast cancer. For each patient, investigators chose from pre-specified adjuvant chemotherapy regimens, including standard anthracycline-and/or taxane-based chemotherapy. In total, 4804 patients were randomized 1:1 to Perjeta plus trastuzumab and standard chemotherapy (Ptz+H+Chemo) or placebo plus trastuzumab and standard chemotherapy (Pla+H+Chemo) in the adjuvant setting from 08 November 2011 to 31 August 2013.

The primary endpoint was invasive disease-free survival (IDFS) and secondary endpoints included IDFS-including second primary non-breast cancer (IDFS-SPNBC), disease-free survival (DFS), overall survial (OS), recurrence-free interval (RFI), and distant recurrence-free interval (DRFI). Exploratory endpoints included breast cancer-free interval (BCFI), and patient-reported outcomes.

3.2. Favourable effects

The study met its primary endpoint at the time of primary analysis. A statistically relevant improvement in IDFS, corresponding to a 19% reduction in the risk of recurrence or death, HR 0.81 (95%CI 0.66; 1.00, p=0.446) was demonstrated. The K-M IDFS curves tend to overlap up to 2 years. Estimates of IDFS event-free rates at 3 years were 94.06% vs. 93.24% in the pertuzumab arm vs. the placebo arm, respectively, and at 4 years were 92.28% vs. 90.58%, suggesting a sustained benefit over time after the end of treatment (1-year duration). As expected, distant recurrence was the most frequent IDFS event.

Key secondary endpoints were invasive disease-free survival excluding second non-breast malignancies (IDFS-SPNBC), disease-free survival (DFS), and overall survival (OS). Results for IDFS-SPNBC was similar to IDFS, and also showed a statistical difference favouring the pertuzumab arm. DFS also showed a significant benefit with the addition of pertuzumab.

Overall survival data was immature, with only 3.3% and 3.7% events in each arm.

The exploratory endpoints were recurrence-free interval (RFI), distant recurrence-free interval (DRFI), and breast cancer-free interval (BCFI). RFI showed a statistically significant improvement as well as BCFI, however DRFI was not different between the arms, probably due to too few events at the present time (5% vs. 6%, respectively).

Patients with node-positive disease showed statistically significant benefit with Ptz+H+Chemo treatment with IDFS event-free rates of 91.99% vs. 90.15% at 3 years (HR 0.77, 95%CI 0.62, 0.96) (KM curve below). These results indicate a 23% reduction in risk of recurrence or death in patients randomized to Ptz+H+Chemo; the event-free rates at 4 years were 89.88% vs. 86.68%, respectively. For patients with hormone receptor-negative disease the results were HR 0.76 (95%CI 0.56, 1.04). At 4 years, the IDFS event-free rates for this subgroup were 90.96% vs. 88.67%, respectively.

3.3. Uncertainties and limitations about favourable effects

The results from the primary analysis of the APHINITY study were after only 4 years of follow-up and this is a relatively short time for an adjuvant study of early breast cancer. Consistently, there were rather few

events at this point in time, as 171 patients (7.1%) in the pertuzumab arm and 210 patients (8.7%) in the placebo arm have had an IDFS event so far. Especially, limited conclusions can be drawn regarding OS and many of the secondary endpoints due to the low number of events so far. This is, however, expected, and is not considered an issue with regard to the B/R assessment of the present application. Furthermore, based on the available data there was no reason to expect a detrimental effect in the long term. Further data are expected.

3.4. Unfavourable effects

The addition of pertuzumab to standard chemotherapy is associated with increased incidence of diarrhea, cardiac events, mucositis, and infusion-related reactions. Among the most common treatment-emergent AEs, the highest difference between the two arms was observed for diarrhea (71.2% vs. 45.2%, grade ≥ 3 9.8% vs 3.7%). This is reflected in the results of PROs, showing an imbalance between the two arms only for diarrhoea, with a clinically meaningful worsening observed in the experimental arm that persisted until the end of treatment. Most toxicities appear manageable and related to chemotherapy, however, it is evident that many of the toxicities are more pronounced in elderly patients, and this is now reflected in the SmPC.

The most common AE's that led to withdrawal of Perjeta or placebo were EF decreased, cardiac failure, and diarrhoea. Generally, the incidences were small (<3%) and the toxicities were well known with the given therapies. The most common AE's that led to withdrawal of any study medication were peripheral sensory neuropathy, neuropathy peripheral, diarrhoea, EF decreased, and cardiac failure. The peripheral neuropathy is a known adverse event to taxanes and the events were few. More patients stopped any treatment due to diarrhoea, which was expected due to the toxicity profile of pertuzumab and taxane. Heart failure (NYHA III or IV) with LVEF decline of at least 10 Ejection Fraction points from baseline AND to below 50% was reported in 15 patients in the Ptz+H+Chemo arm (0.6%) versus 7 patients in the Pla+H+Chemo arm (0.3%). The incidences of decreased EF and cardiac failures are within the known range with these treatments, and although double as many patients discontinued treatment due to cardiac failure in the pertuzumab arm, the overall incidence was low (1.2% vs 0.6%).

The AE's that led to a dose modification of Perjeta or placebo were mainly neutropenia, neutrophil count decreased, EF decreased, and diarrhoea. Dose modifications were more common in the pertuzumab arm (30.6% vs. 26.3%). The AEs that led to any study medication modifications were mainly neutrophil count decreased and diarrhoea, and were overall more common in the pertuzumab arm (51.5% vs. 44.2%).

3.5. Uncertainties and limitations about unfavourable effects

The median follow-up time in the submitted primary analysis is 4 years, so there are no long-term safety data. Perjeta has been used for longer periods in the metastatic setting, but due to the median survival time in this patient group, there are no long-term data from this population. In the neoadjuvant setting, pertuzumab has been used for 18-24 weeks prior to operation, but this is a shorter time than what is applicable for this application i.e. exposure of approximately 1 year. Long-term follow-up is considered especially relevant regarding cardiac toxicity, in order to allow a better assessment of the long-term outcome (see RMP). Currently, available data show apparent longer time to recovery with Perjeta compared to placebo. Regarding the long-term outcome of cardiac toxicity, the Applicant will also assess this at the time of the next planned IA.

3.6. Effects Table

Effects Table for addition of pertuzumab to standard chemotherapy and trastuzumab in adjuvant treatment of adult patients with HER2-positive early breast cancer (data cut-off: 19 Dec 2016).

Effect	Short description	Unit	Treatment Ptz+H+ Chemo N=2400	Control Pla+H+ Chemo N=2404	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint						
IDFS	Patients with event	N (%)	171 (7.1)	210 (8.7)	HR 0.81 (95%CI: 0.66; 1.00) p=0.0446	
Secondary endpoints						
IDFS-SPNBC	Patients with event	N (%)	189 (7.9)	230 (9.6)	HR 0.82 (95%CI: 0.68; 0.99) p=0.0430	
DFS	Patients with event	N (%)	192 (8.0)	236 (9.8)	HR 0.81 (95%CI: 0.67; 0.98) p=0.0327	
OS	Patients with event	N (%)	80 (3.3)	89 (3.7)	HR 0.89 (95%CI: 0.66; 1.21) p=0.4673 Data are immature	
Exploratory endpoints						
RFI	Patients with event	N (%)	138 (5.8)	173 (7.2)	HR 0.79 (95%CI: 0.63; 0.99) p=0.0430	
DRFI	Patients with event	N (%)	119 (5.0)	145 (6.0)	HR 0.82 (95%CI: 0.64; 1.04) p=0.1007	
BCFI	Patients with event	N (%)	147 (6.1)	190 (7.9)	HR 0.77 (95%CI: 0.62; 0.96) p=0.0186	
Unfavourable Effects						
AE grade 3-5		%	64.2	57.3		
SAE		%	29.3	24.3		
AE leading to interruption/modification of any treatment		%	51.5	44.2		
AE leading to interruption/modification of Perjeta/ placebo		%	30.6	26.3		
AE leading to treatment withdrawal		%	13.1	11.5		
AE leading to withdrawal of Perjeta/ placebo		%	7.0	5.8		
AEs leading to death		%	0.8	0.8		
Death due to recurrent disease		%	2.0	2.6		

Effect	Short description	Unit	Treatment Ptz+H+ Chemo N=2400	Control Pla+H+ Chemo N=2404	Uncertainties / Strength of evidence	References
Death due to other causes		%	0.3	0.5		
Cardiac safety						
Primary cardiac event		%	0.7	0.3	Lack of long-term data	
Secondary cardiac event		%	2.7	2.8		

Abbreviations: IDFS=Invasive disease-free survival; IDFS-SPNBC=Invasive disease-free survival incl. second primary non-breast cancer; DFS=Disease-free survival; OS=Overall survival; RFI=Recurrence-free survival; DRFI=Distant recurrence-free interval; BCFI=Breast cancer-free interval.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The target population of patients with HER2-positive early breast cancer still have an unmet medical need, since the risk of recurrence is high with available adjuvant treatment, as up to 1 in 4 women will experience recurrence or death within 10 – 11 years of diagnosis. Because the median age of patients presenting with HER2-positive breast cancer is in the mid-50s, around five years younger than the general breast cancer population, the median loss of life-years per patient is around two decades for patients dying of HER2-positive breast cancer. In the case of metastatic disease, life expectancy is a median OS of 56.5 months, so more than 50% of the patients die within 5 years.

Whereas the availability of a new treatment option to be added to the present therapeutic armamentarium in the adjuvant setting is considered clinically relevant, as a proportion of patients still relapses, the magnitude of benefit is not considered outstanding in the ITT population; however, the treatment effect seems to be sustained over time (4 years observation period), which is encouraging considering that OS data, as expected, are largely immature. Importantly, the treatment effect seems to be driven by the subgroup of patients with node-positive disease, who represent also the largest proportion of recruited patients.

It cannot be excluded that with a longer follow-up, a benefit could be shown also for node-negative patients, but this is for the time being not self-evident.

Conversely, the efficacy outcome of a 19% reduction in recurrence or death (IDFS HR 0.81 (95%CI: 0.66; 1.00), p=0.0446) is comparable with the improved efficacy outcomes in other adjuvant breast cancer studies, such as docetaxel (HR 0.72); epirubicin (HR~0.77); exemestane (HR 0.68); letrozole (HR 0.81) and anastrozole (HR 0.87). In addition, it is noted that the control arm of the APHINITY study performed better than anticipated, which is in line with other recent adjuvant breast cancer trials (BETH, ALTTO), and may be due to better staging and treatment over the years.

Results from 11 years of follow up shows an improvement of adding trastuzumab compared to observation was within the same range (HR 0.76, 95%CI 0.68; 0.86) (Cameron et al. Lancet 2017).

The safety profile does not raise major concerns. The unfavourable effect of most significance is the high incidence of diarrhoea (71.2%), with an incidence of more than grade 3 of 9.8% in the pertuzumab arm. Although no fatal events, diarrhoea led to dose modifications and discontinuations, however, within an acceptable range. The event was more pronounced and affected PRO during chemotherapy.

Other common toxicities that may affect quality of life, such as nausea, alopecia, fatigue, vomiting, mucositis, neutropenia and anaemia were almost exclusively related to the chemotherapy treatment, although mucositis seem worsened by pertuzumab. There were also an increased number of infusion-related

reactions, but this is known with pertuzumab and manageable. However, a slight increase in the incidence of heart failure (NYHA III or IV) with LVEF decline of at least 10 Ejection Fraction points from baseline AND to below 50% associated with Perjeta is noted, together with tendency to a lower rate of recovery from the event, and a much longer median time to LVEF recovery.

Deaths due to AEs were uncommon and no imbalances were observed.

3.7.2. Balance of benefits and risks

Overall, patients with HER2-positive early breast cancer have a quite good prognosis thanks to development of good treatments over the last decades. Thus, the results seen in the APHINITY study reflects this situation. Nonetheless, there is a statistically significant difference between the two arms in the ITT population, reflecting a risk reduction of 19% for relapse or death in the target population. However, available data do not allow to conclude for a positive B/R in the overall population at this point in time. It is considered that benefit is clearly shown in the high-risk population therefore supporting an indication of adjuvant Perjeta in the high-risk subgroups of HR-negative, node-positive patients.

The risks of adding pertuzumab to standard chemotherapy are most importantly diarrhoea and increased cardiotoxicity. Other common unfavourable effects are manageable and affect PRO primarily during chemotherapy.

Therefore, the B/R balance in the finally agreed restricted indication is considered favourable.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Perjeta in the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence is established to be positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for Perjeta, in combination with trastuzumab and chemotherapy, for the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence. The submission is based on the primary analysis of efficacy and safety data from the pivotal Phase III study

BIG-4-11/BO25126/TOC4939g (APHINITY). Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated to reflect the study results. The Package Leaflet and RMP version 10.2 have been updated accordingly.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
MO28047 (PERUSE) A multicenter, open-label, single-arm study of pertuzumab in combination with trastuzumab and a taxane in first line treatment of patients with HER2- positive advanced (metastatic or locally recurrent) breast cancer	September 2020

These conditions do reflect the advice received from the PRAC.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers, that the new therapeutic indication brings

significant clinical benefit in the absence of existing therapies (see appendix 1).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication for Perjeta, in combination with trastuzumab and chemotherapy, for the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence. The submission is based on the primary analysis of efficacy and safety data from the pivotal Phase III study BIG-4-11/BO25126/TOC4939g (APHINITY). Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated to reflect the study results. The Package Leaflet and RMP version 10.2 have been updated accordingly.

Summary

Please refer to the published Assessment Report Perjeta H-2547 -II-34-AR.