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Overall survival benefit with pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer in CLEOPATRA, a randomised Phase 3 study

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Summary

Background—Primary results from the randomised, double-blind phase 3 study CLEOPATRA demonstrated significantly improved median progression-free survival (PFS) with pertuzumab plus trastuzumab plus docetaxel versus placebo plus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2 (HER2)-positive first-line metastatic breast cancer (MBC). Overall survival (OS) data at the primary analysis showed a strong trend in favour of the

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Contributors
SMS, JC, AS, GR, and JB were involved in the conception and design of the study. S-BK, JR, VS, MC, J-MF, AS, and MCB contributed to data collection and assembly. SMS, S-BK, JC, ECi, J-MF, AS, AK, ECl, GR, MCB, and JB interpreted and analysed the data. All authors were involved in the writing and reviewing of the manuscript and approved the final version for submission.

Conflicts of interest
SMS discloses an uncompensated consultant/advisory role for Roche/Genentech; her institution has received research funding from Roche/Genentech, Agendia, and Pfizer/PUMA. JC is a consultant for Roche, Celgene, and Novartis and has received honoraria from Roche, Celgene, Novartis, and Eisai. J-MF has received honoraria from Roche, Pfizer, and Sanofi-Aventis. AS is a consultant for Roche and Sanofi-Aventis and has received honoraria from both companies. AK, ECl, and GR are employees of Roche Products Limited. ECl discloses stock ownership from AstraZeneca. GR discloses stock ownership from Roche and GlaxoSmithKline; an immediate family member owns stocks from GlaxoSmithKline. MCB is an employee of Genentech. JB discloses a consultant/advisory role for Roche/Genentech and Sanofi-Aventis. S-BK, JR, VS, MC, and ECi have no conflicts of interest to disclose.

pertuzumab arm but did not reach statistical significance. Here we report confirmatory OS results after one additional year of follow-up.

Methods—Patients were randomly assigned to study treatment. OS and investigator-assessed PFS were analysed using the Kaplan-Meier approach and log-rank tests stratified by geographic region and prior treatment status. This trial is registered with ClinicalTrials.gov, NCT00567190.

Findings—In the intent-to-treat population (808 patients), 267 deaths had occurred at data cut-off (placebo arm: 154 of 406 [37·9%], pertuzumab arm: 113 of 402 [28·1%]). Treatment with pertuzumab plus trastuzumab plus docetaxel resulted in a 34% reduction in the risk of death during the course of the study (HR=0·66; 95% CI 0·52–0·84; p=0·0008). Median OS was 37·6 months in the placebo arm and was not yet reached in the pertuzumab arm. A descriptive follow-up analysis of investigator-assessed PFS showed a median PFS of 12·4 and 18·7 months in the placebo versus pertuzumab arm (HR=0·69; 95% CI 0·58–0·81). No new safety concerns were identified with one additional year of follow-up. Adverse events were similar to those reported at the primary analysis with respect to incidence, severity, and specificity.

Interpretation—This OS analysis demonstrated statistically significant and clinically meaningful survival benefit with pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive MBC. Updated analyses of investigator-assessed PFS and safety were consistent with the results from the primary analysis.

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Introduction

Breast cancers with an abnormally high expression of the human epidermal growth factor receptor 2 (HER2) (known as “HER2-positive”) on their cell surface are characterised by a more aggressive phenotype resulting in adverse disease prognosis.[1] Approximately 20% of breast cancers are HER2-positive.[2] Trastuzumab, a humanised monoclonal antibody that specifically targets HER2, significantly improved the prognosis of HER2-positive breast cancer.[3–7] However, metastatic breast cancer (MBC) is incurable and approximately 50% of patients experience disease progression within 1 year of therapy for their advanced disease.[5;8]

Recent clinical trials in early[9;10] and advanced[11;12] HER2-positive breast cancer demonstrated that the combined targeting of HER2 is superior to the use of one HER2-targeted agent only. Results from the CLEOPATRA study led to approval of the study regimen combining pertuzumab, a novel HER2-targeted humanised monoclonal antibody, with trastuzumab and docetaxel in HER2-positive first-line MBC, first granted by the US Food and Drug Administration in June 2012. Patients in the pertuzumab arm benefited from significantly prolonged median progression-free survival (PFS) compared with patients receiving treatment in the placebo arm.[11] Adverse events were generally balanced between both arms; however, the incidences of diarrhoea, rash, mucosal inflammation, febrile neutropenia, and dry skin were increased in the pertuzumab arm by more than 5%. The majority of adverse events were grade 1–2 and occurred during concomitant treatment with docetaxel.[13] An interim analysis of overall survival, conducted at the same time as the primary analysis of independently assessed PFS, showed a strong trend in favour of

pertuzumab plus trastuzumab plus docetaxel; however, these results were immature. Following a formal request from European health authorities, an additional, second interim analysis of overall survival prior to the planned final analysis at 385 deaths was performed. Here we report confirmatory overall survival results following one additional year of follow-up.

Methods

Study design

Full details of this study have been reported previously.[11] Briefly, CLEOPATRA was a randomised, double-blind, placebo-controlled phase 3 trial to evaluate the efficacy and safety of pertuzumab (Perjeta®, F. Hoffmann-La Roche/Genentech Inc.) plus trastuzumab (Herceptin®, F. Hoffmann-La Roche/Genentech Inc.) plus docetaxel (Taxotere®, Sanofi-Aventis) compared with placebo plus trastuzumab plus docetaxel in patients with HER2-positive MBC who had not received previous chemotherapy or biologic therapy for their metastatic disease. Primary endpoint was independently assessed PFS; secondary endpoints included overall survival, PFS by investigator assessment, objective response rate, and safety. Overall survival was defined as the time from randomisation to death from any cause. The study was conducted in accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Protocol approval was obtained from an independent ethics committee for each site and written informed consent was obtained from each participant.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to one of the two treatment arms, with treatment allocation stratified by geographic region (Asia, Europe, North America, and South America) and prior treatment status (neoadjuvant and/or adjuvant therapy received or not). An Interactive Voice Response System was utilised to collect patient screening information and to allocate treatment. A complete block randomisation scheme was applied in order to balance treatment assignment. The patient identification numbers were allocated sequentially in the order in which patients were enrolled. The study was double-blinded. Unblinding of treatment assignment was not permitted until study end except for safety reasons. The end of the study, apart from follow-up analyses of safety and survival, was defined to be reached when any interim analysis of overall survival met the pre-defined criteria for statistical significance, when approximately 385 overall survival events had been reached, or when the trial was terminated by the sponsor; whichever occurred first. Hence patients were not unblinded following the primary analysis of independently assessed PFS and treatment allocation remained concealed prior to the second interim overall survival analysis.

Survival follow-up

After the treatment discontinuation visit, survival information was collected via telephone or clinic visits every 18 weeks (± 1 week) until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor. In order to minimise the chance of a biased overall survival estimate resulting from scheduled survival follow-up every 18 weeks, immediately

prior to the data cut-offs for the primary PFS analysis, and for any overall survival analysis, the investigative sites contacted every patient to confirm their current survival status.

Statistical considerations for overall survival analyses

The data cut-off for the second interim overall survival analysis took place in May 2012, 1 year after the data cut-off for the primary PFS analysis. Patients who were alive or lost to follow-up at the time of the overall survival analysis were censored at the last known alive date. Patients with no post-baseline information were censored at the time of randomisation plus 1 day. With 385 deaths at the final analysis, the study was estimated to have 80% power to detect a 33% improvement in overall survival in the pertuzumab arm (hazard ratio [HR]=0·75). The median overall survival was estimated to be 36 months in the placebo arm and 48 months in the pertuzumab arm, assuming overall survival is exponentially distributed. In order to allow formal statistical interpretation of the second interim overall survival analysis without inflating the overall Type I error, the study protocol and the statistical analysis plan were amended to specify that the Lan-DeMets α-spending function with the O'Brien-Fleming stopping boundary would be applied.

The log-rank test, with stratification according to prior treatment status and region, was used to compare overall survival between arms. The Kaplan-Meier approach was used to estimate the median overall survival in each arm. A Cox proportional-hazard model, with stratification according to prior treatment status and region, was used to estimate the hazard ratio and 95% confidence intervals (CI). Pre-specified subgroup analyses of overall survival were performed to determine the consistency of the treatment effect according to key baseline characteristics.

Role of the funding source

The study was funded and sponsored by F. Hoffmann-La Roche Ltd and Genentech Inc. It was designed by the senior academic authors and representatives of the sponsor. The sponsor provided study drugs, and was involved in protocol development, regulatory and ethics approvals, and safety monitoring. The data were collected by the sponsor and analysed by the sponsor in collaboration with the senior academic authors. None of the authors have received any payment in relation to the writing of this manuscript. All authors had full access to all study data and had final responsibility for the decision to submit for publication.

Results

The cut-off date for data collection was 14 May 2012, 1 year after the cut-off for the primary analysis of independently assessed PFS and 22 months after the last patient had been enrolled. Patient disposition is presented in figure 1.

At the second interim overall survival analysis 267 deaths representing 69% (267 of 385) of the pre-specified total number of events for the final analysis had occurred. The median follow-up was 30 months in both arms. The O'Brien-Fleming stopping boundary for the second interim overall survival analysis was determined based on the number of deaths that had occurred at the first and second interim overall survival analyses as a proportion of the

number of deaths planned for the final analysis. The stopping boundary at this second interim overall survival analysis was defined as p≤0·0138 and HR≤0·739. More deaths occurred in the placebo than in the pertuzumab arm (154 of 406 [37·9%] *vs* 113 of 402 [28·1%]). The hazard ratio was 0·66 (95% CI 0·52–0·84; p=0·0008) (figure 2A) and crossed the pre-specified O'Brien-Fleming stopping boundary of the Lan-DeMets α-spending function. The overall survival result therefore demonstrates a statistically significant survival benefit for patients receiving treatment in the pertuzumab arm compared with patients in the placebo arm. Median overall survival was 37·6 months for patients in the placebo arm and has not yet been reached for the pertuzumab arm. The Kaplan-Meier curves showed an early separation that continued over time. The estimated Kaplan-Meier survival rates at 1, 2, and 3 years in the placebo *vs* the pertuzumab arm were 89·0% *vs* 94·4%, 69·4% *vs* 80·7%, and 50·4% *vs* 65·8%, respectively. The analysis of overall survival in pre-defined subgroups was consistent with the analysis in the whole intent-to-treat (ITT) population, indicating a consistent survival benefit with pertuzumab plus trastuzumab plus docetaxel in all but one subgroup analysed (figure 2B). An exploratory subgroup analysis was performed for patients who had received prior neoadjuvant or adjuvant therapy with trastuzumab (88 of 808). The observed hazard ratio of 0·68 (95% CI 0·30–1·55) indicates overall survival benefit in the pertuzumab arm for this subpopulation.

Due to the pre-specified fixed-sequence testing hierarchy (independently assessed PFS first, followed by overall survival, then objective response rate), and to the statistical significance being reached in this second interim overall survival analysis, the difference in objective response rate of 10·8% points (95% CI 4·2–17·5; p=0·0011) between treatment arms is now considered statistically significant.

At the time of data cut-off, 296 of 406 (72·9%) patients in the placebo arm and 257 of 402 (63·9%) patients in the pertuzumab arm had experienced a PFS event according to the investigator. The hazard ratio was 0·69 (95% CI 0·58–0·81) and the median PFS was 12·4 months in the placebo arm versus 18·7 months in the pertuzumab arm (figure 3A), consistent with results at the primary analysis.[11] This descriptive follow-up analysis of investigator-assessed PFS demonstrated that the PFS benefit observed at the primary analysis was maintained after an additional year of follow-up. Updated exploratory subgroup analyses were performed for pre-specified baseline characteristics (figure 3B). The benefit associated with pertuzumab-based treatment was maintained in all subgroups investigated.

In the ITT population, 338 of 406 patients in the placebo arm and 298 of 402 patients in the pertuzumab arm had discontinued study treatment at data cut-off. The proportion of patients receiving subsequent therapy for breast cancer after discontinuation of study treatment was similar in both arms (placebo arm: 260 of 338 [76·9%] patients; pertuzumab arm: 225 of 298 [75·5%] patients) (table 1). Treatment allocation remained blinded at discontinuation of study treatment and pertuzumab was not allowed as subsequent breast cancer therapy. Within the patient group receiving subsequent breast cancer therapy, treatments were generally balanced between both arms, with 68·5% of patients (178 of 260) in the placebo arm and 71·1% of patients (160 of 225) in the pertuzumab arm receiving any HER2-targeted therapy. Treatment with trastuzumab was continued in 40·4% (105 of 260) and 47·1% (106 of 225) of patients in the placebo and pertuzumab arms, respectively, following

discontinuation of study treatment. The pattern of subsequent use of cytotoxic agents was also similar in both arms.

The median time on treatment was longer for patients in the pertuzumab arm compared with patients in the placebo arm, consistent with a longer median PFS by investigator assessment in the pertuzumab arm. The exposure to docetaxel was comparable between both arms (table 2). Granulocyte colony-stimulating factors were used for the treatment of adverse events in 26·4% (107 of 406) and 28·1% (113 of 402) of patients in the placebo and pertuzumab arms, respectively.

Overall, adverse events reported at the first data cut-off in May 2011 and after one additional year of follow-up were similar with respect to incidence, severity, and specificity. No new safety concerns were identified with longer follow-up. In summary, higher incidences of at least 5% were reported for diarrhoea, rash, mucosal inflammation, pruritus, febrile neutropenia, and dry skin (all grades) in patients receiving treatment in the pertuzumab arm (table 3). The incidences of grade ≥3 neutropenia, febrile neutropenia, and diarrhoea were higher in the pertuzumab arm compared with the placebo arm by at least 2% (table 4). Mucosal inflammation of grade ≥3 was reported in 1·0% of patients (4 of 396) in the placebo arm and in 1·5% of patients (6 of 408) in the pertuzumab arm. Following discontinuation of docetaxel, the incidence of all adverse events decreased considerably; adverse events of grade ≥3 were rare (tables 3 and 4). However, the frequencies of diarrhoea, rash, and pruritus remained noticeably elevated in the pertuzumab arm; no episodes of febrile neutropenia were reported in either arm following discontinuation of docetaxel. Treatment with pertuzumab plus trastuzumab plus docetaxel did not increase the rate of left ventricular systolic dysfunction (LVSD) compared with treatment with placebo plus trastuzumab plus docetaxel (table 5).

In the safety population, 152 of 396 (38·4%) patients in the placebo arm died versus 113 of 408 (27·7%) patients in the pertuzumab arm. The majority of deaths were attributed to disease progression, with 34·3% (136 of 396 patients) in the placebo arm and 24·5% (100 of 408 patients) in the pertuzumab arm. A similar number of patients in both arms died as a result of adverse events (placebo arm: 12 of 396 [3·0%] patients; pertuzumab arm: eight of 408 [2·0%] patients). Febrile neutropenia or infections were the most common cause of death due to an adverse event (placebo arm: five of 396 [1·3%] patients; pertuzumab arm: five of 408 [1·2%] patients).

Discussion

This overall survival analysis crossed the pre-specified stopping boundary for statistical significance, demonstrating that treatment with pertuzumab plus trastuzumab plus docetaxel significantly improved overall survival compared with placebo plus trastuzumab plus docetaxel and it is therefore considered the confirmatory analysis (HR=0·66; 95% CI 0·52–0·84; p=0·0008). Median overall survival was 37·6 months for patients in the placebo arm and had not yet been reached in the pertuzumab arm. The final analysis, planned after 385 overall survival events have been reached, will be a descriptive follow-up analysis only. Prior to the confirmatory analysis of overall survival the trial remained blinded and cross-

over was not allowed. At the time of data cut-off, 68 of 406 patients in the placebo arm and 104 of 402 patients in the pertuzumab arm were still alive and on study treatment. As a consequence of the statistically significant survival benefit, cross-over to the pertuzumab arm has been offered to patients still receiving study treatment in the placebo arm. Subgroup analyses of overall survival were consistent with the analysis in the whole ITT population. Patients with non-visceral disease were the only subgroup in which treatment benefit with pertuzumab plus trastuzumab plus docetaxel was not demonstrated. It should be noted that the number of overall survival events was very low in this subgroup. In the placebo arm, 14 of 90 patients died versus 19 of 88 patients in the pertuzumab arm. A thorough investigation of baseline characteristics for patients with visceral or non-visceral disease showed that, by chance, some baseline characteristics, such as median treatment-free interval, bone-only disease, tumour burden, hormone receptor status, HER2 expression status (immunohistochemistry 3+ *vs* 2+), and prior neoadjuvant or adjuvant treatment with trastuzumab, were imbalanced in the non-visceral disease group and, as a consequence, patients receiving treatment in the placebo arm more often presented with characteristics linked to a favourable disease prognosis. This observation could explain the inconclusive result for patients with non-visceral disease. Overall, the confirmatory results for overall survival were consistent with the first interim overall survival analysis and with the primary analysis of independently assessed PFS.[11] Among patients receiving subsequent anti-breast cancer therapy, the type of drugs used was generally balanced between both arms, suggesting that the type of later-line therapy did not influence the overall survival results given that the same therapy was equally effective in both arms. Adverse events reported here with one additional year of follow-up were generally similar to those reported at the primary analysis in terms of incidence, severity, and specificity. At this point, there is no evidence of cumulative or late toxicity associated with pertuzumab. Diarrhoea, rash, mucosal inflammation, pruritus, febrile neutropenia, and dry skin (all grades) were reported more frequently by at least 5% in the pertuzumab than in the placebo arm. As reported previously,[11;14] combination therapy with pertuzumab did not increase the incidence of cardiac dysfunction compared with treatment in the placebo arm. The number of cardiac adverse events reported at the primary analysis and with one more year of follow-up was similar, suggesting no late cardiac toxicity with trastuzumab and pertuzumab.

The positive results from CLEOPATRA are encouraging with regards to the efficacy and safety of a pertuzumab plus trastuzumab plus chemotherapy regimen in HER2-positive early breast cancer, currently studied in the APHINITY trial.[15] CLEOPATRA, together with recent clinical trials with drugs specifically targeting pro-survival cellular signalling pathways, has shown promising improvements of therapy outcomes. EMILIA, a trial in patients with HER2-positive MBC, most of whom received treatment in second or later line, has demonstrated significant improvement of PFS and overall survival together with a favourable safety profile with trastuzumab emtansine (T-DM1) compared with capecitabine and lapatinib.[16] Based on these findings, results of the combination of pertuzumab and T-DM1 in HER2-positive first-line MBC, investigated in the MARIANNE study (NCT01120184), are awaited with interest. In addition to combined HER2 targeting, inhibition of HER2 in conjunction with inhibition of other components of the intracellular signalling cascade is under investigation. The combination of everolimus, an inhibitor of

mammalian target of rapamycin (mTOR), with trastuzumab and chemotherapy in HER2-positive MBC is being investigated in two phase 3 studies (NCT00876395, NCT01007942). Combining anti-HER2 therapy with agents targeting intracellular proteins involved in the pro-survival signalling cascade may be an option that merits further investigation.

In summary, the overall survival benefit reported in CLEOPATRA was statistically significant and clinically meaningful, further supporting the positive benefit–risk ratio of treatment with pertuzumab, trastuzumab, and docetaxel in patients with HER2-positive MBC. Consistent with findings in other clinical trials,[9;10;12] CLEOPATRA provides evidence that combined targeting of HER2 is a more effective anti-cancer treatment approach than the use of one HER2-targeted agent only.

Research in context

Systematic review

Anti-cancer therapies for MBC can delay disease progression and can prolong survival but metastatic disease remains incurable and will progress eventually. In order to put the overall survival results reported in CLEOPATRA into context with data from previous phase 2 and 3 studies in which trastuzumab plus chemotherapy combinations were given for HER2-positive MBC, we performed a PubMed search using the search terms “overall survival”, “trastuzumab”, “HER2”, and “metastatic breast cancer”. We restricted the review period to the past 20 years and included original reports of prospective clinical trials only. The median overall survival for trastuzumab plus chemotherapy ranged from 15[17] to 48[18] months (a list of all publications used in this systematic review is provided in the Appendix). It should be noted that treatment was given for different lines of HER2-positive MBC and that in some studies two cytotoxic agents were used plus trastuzumab. Amongst these studies, we identified three phase 3 studies of trastuzumab–chemotherapy combinations for HER2-positive first-line MBC with median overall survival of 25·1,[4] 35·7 and 38·8,[8] and 37·1 and 37·4 months,[19] respectively.

Interpretation

Due to the heterogeneity of the study populations and differences in study design, comparisons across different trials are controversial and should be considered with caution. However, this review suggests that the median overall survival of 37·6 months with trastuzumab plus docetaxel observed in the placebo arm of CLEOPATRA is consistent with results from previous studies in HER2-positive first-line MBC. The survival rates at 1, 2, and 3 years and the 34% reduction in the risk of death during the course of the study demonstrate durable clinical benefit for patients given pertuzumab plus trastuzumab plus docetaxel; this is a significant improvement compared with the current standard of care.

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Appendix

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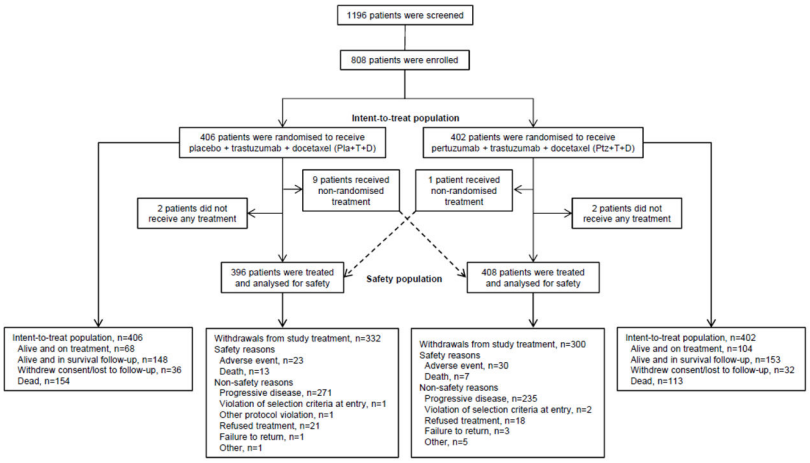

Figure 1.
CONSORT diagram

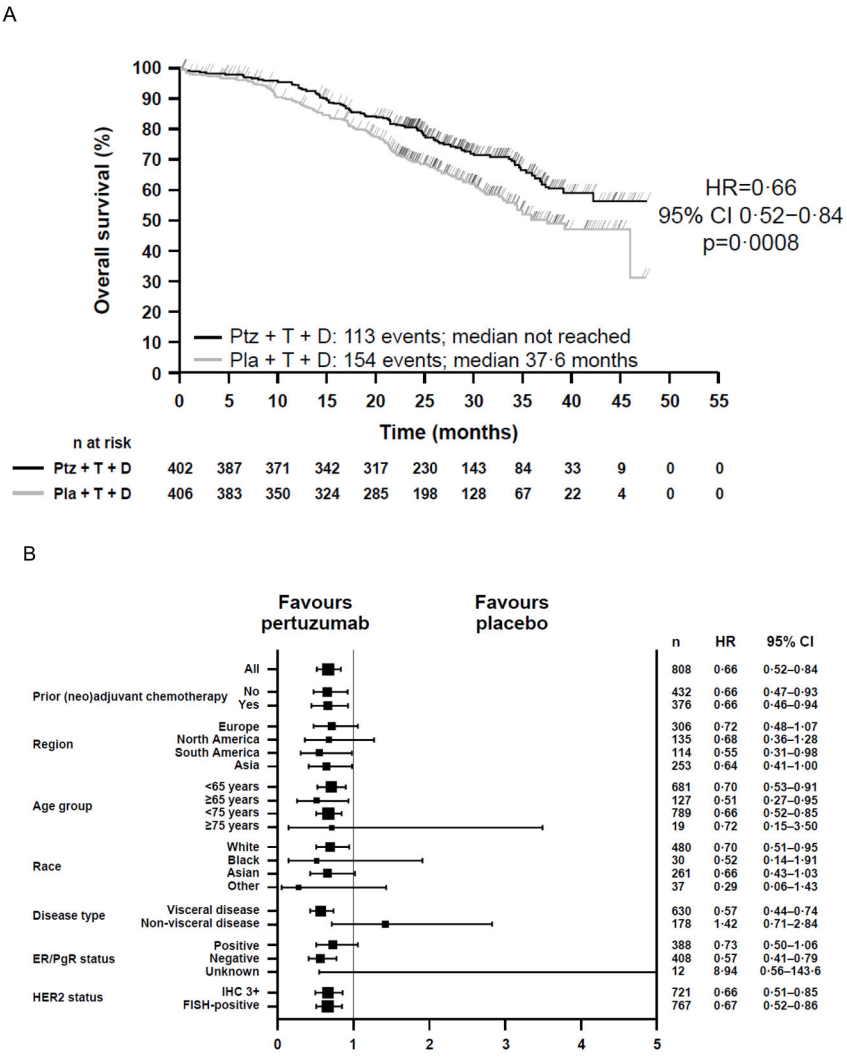

Figure 2. Confirmatory analysis of overall survival

Figure 2A shows Kaplan-Meier estimates of overall survival in patients in the intent-to-treat population, stratified by prior treatment status and region. The tick marks indicate censoring events.

Figure 2B shows hazard ratios and 95% confidence intervals for overall survival in all pre-specified subgroups according to baseline characteristics. It should be noted that the number of patients with unknown hormone receptor status was very small (n=12) resulting in very wide 95% confidence intervals.

CI, confidence interval; D, docetaxel; ER, oestrogen receptor; FISH, fluorescence *in situ* hybridisation; HER2, human epidermal growth factor receptor; HR, hazard ratio; IHC, immunohistochemistry; PgR, progesterone receptor; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

Race was determined by the investigator. The category of “Other” includes American Indian and Alaska Native.

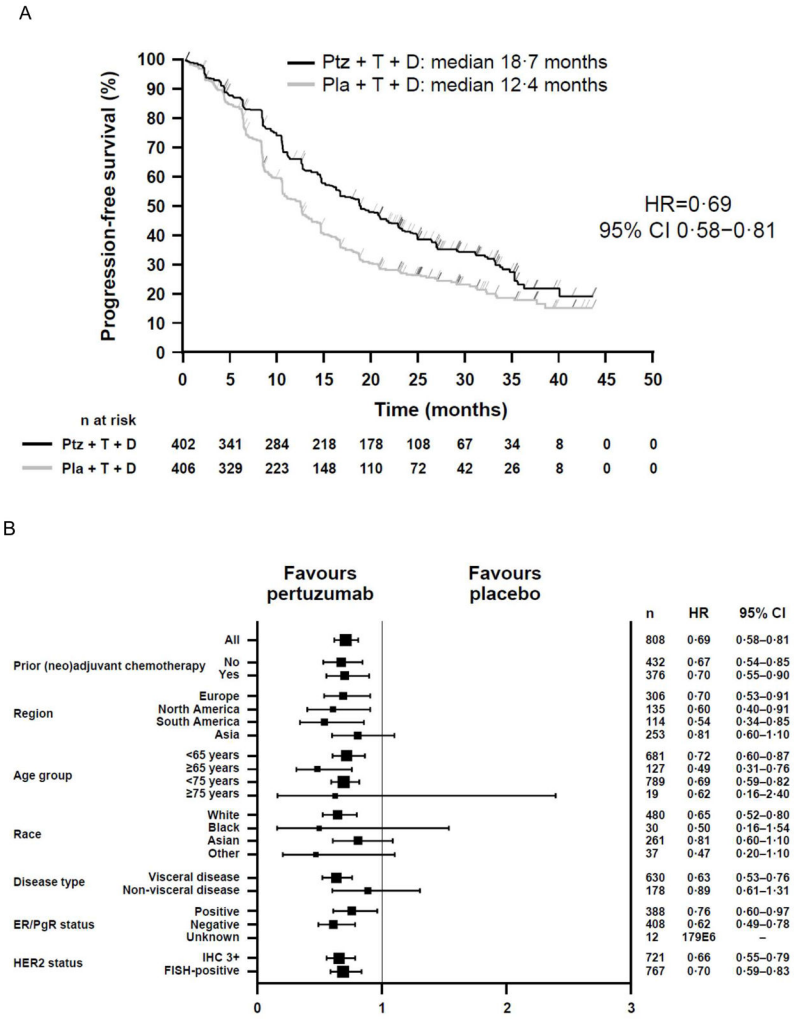

Figure 3. Investigator-assessed progression-free survival

Figure 3A shows Kaplan-Meier estimates of PFS in the intent-to-treat population, stratified by prior treatment status and region. The tick marks indicate censoring events.

Figure 3B shows hazard ratios and 95% confidence intervals for PFS in all pre-specified subgroups according to baseline characteristics. The hazard ratio for the category of unknown hormone receptor status was not quantifiable due to the small number of patients in this group.

CI, confidence interval; D, docetaxel; ER, oestrogen receptor; FISH, fluorescence *in situ* hybridisation; HER2, human epidermal growth factor receptor; HR, hazard ratio; IHC, immunohistochemistry; PgR, progesterone receptor; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

Race was determined by the investigator. The category of “Other” includes American Indian and Alaska Native.

Table 1

Breast cancer therapies following discontinuation of study treatment in patients who had withdrawn from study treatment

n (%)	Placebo + trastuzumab + docetaxel (n=338)	Pertuzumab + trastuzumab + docetaxel (n=298)
Any	260 (76·9)	225 (75·5)
In patients receiving subsequent breast cancer treatment		
	n=260	n=225
Any HER2-targeted therapy*	178 (68·5)	160 (71·1)
Trastuzumab	104 (40·0)	106 (47·1)
Lapatinib	114 (43·8)	93 (41·3)
Trastuzumab emtansine	26 (10·0)	21 (9·3)
Capecitabine	140 (53·8)	113 (50·2)
Vinorelbine	70 (26·9)	51 (22·7)
Cyclophosphamide	43 (16·5)	30 (13·3)
Doxorubicin	46 (17·7)	29 (12·9)
Paclitaxel	32 (12·3)	21 (9·3)
Docetaxel	11 (4·2)	13 (5·8)

* Excluding pertuzumab

Table 2

Exposure to study treatment

	Placebo + trastuzumab + docetaxel (n=396)	Pertuzumab + trastuzumab + docetaxel (n=408)
Study treatment		
Median number of cycles (range)	15 (1–62)	24 (1–66)
Median time on treatment, months	11·4	17·4
Docetaxel		
Median number of cycles (range)	8 (1–41)	8 (1–42)
Median dose intensity, mg/m^2/week	24·8	24·6
Dose escalation to 100 mg/m^2, n (%)	60 (15·2)	49 (12·0)
Dose reduction to <75 mg/m^2, n (%)	90 (22·7)	104 (25·5)
Percentage of cycles delayed, interrupted, discontinued, or infusion rate reduced (%)	12·1	13·1

Table 3

Adverse events (all grades) overall (≥25% incidence or ≥5% difference between arms) and after discontinuation of docetaxel

	Placebo + trastuzumab + docetaxel		Pertuzumab + trastuzumab + docetaxel	
Adverse event, n (%)	**Overall (n=396)**	**Post docetaxel (n=260)**	**Overall (n=408)**	**Post docetaxel (n=303)**
Diarrhoea	191 (48·2)	35 (13·5)	278 (68·1)	78 (25·7)
Alopecia	240 (60·6)	6 (2·3)	248 (60·8)	4 (1·3)
Neutropenia	197 (49·7)	12 (4·6)	216 (52·9)	8 (2·6)
Nausea	168 (42·4)	30 (11·5)	179 (43·9)	31 (10·2)
Fatigue	148 (37·4)	25 (9·6)	155 (38·0)	40 (13·2)
Rash	95 (24·0)	20 (7·7)	149 (36·5)	50 (16·5)
Decreased appetite	105 (26·5)	12 (4·6)	121 (29·7)	22 (7·3)
Mucosal inflammation	79 (19·9)	4 (1·5)	112 (27·5)	10 (3·3)
Asthenia	121 (30·6)	23 (8·8)	110 (27·0)	38 (12·5)
Vomiting	97 (24·5)	17 (6·5)	104 (25·5)	26 (8·6)
Peripheral oedema	122 (30·8)	32 (12·3)	101 (24·8)	29 (9·6)
Pruritus	40 (10·1)	15 (5·8)	68 (16·7)	37 (12·2)
Constipation	101 (25·5)	18 (6·9)	63 (15·4)	14 (4·6)
Febrile neutropenia	30 (7·6)	0 (0·0)	56 (13·7)	0 (0·0)
Dry skin	23 (5·8)	9 (3·5)	44 (10·8)	8 (2·6)

Table 4

Adverse events (grade ≥3) overall (≥2% incidence) and after discontinuation of docetaxel

	Placebo + trastuzumab + docetaxel		Pertuzumab + trastuzumab + docetaxel	
Adverse event, n (%)	**Overall (n=396)**	**Post docetaxel (n=260)**	**Overall (n=408)**	**Post docetaxel (n=303)**
Neutropenia	182 (46·0)	4 (1·5)	200 (49·0)	0 (0·0)
Febrile neutropenia	30 (7·6)	0 (0·0)	56 (13·7)	0 (0·0)
Leukopenia	59 (14·9)	1 (0·4)	50 (12·3)	0 (0·0)
Diarrhoea	20 (5·1)	0 (0·0)	37 (9·1)	7 (2·3)
Peripheral neuropathy	7 (1·8)	1 (0·4)	11 (2·7)	1 (0·3)
Anaemia	14 (3·5)	1 (0·4)	10 (2·5)	2 (0·7)
Asthenia	7 (1·8)	1 (0·4)	10 (2·5)	2 (0·7)
Fatigue	13 (3·3)	3 (1·2)	9 (2·2)	2 (0·7)
Hypertension	7 (1·8)	4 (1·5)	8 (2·0)	6 (2·0)
Granulocytopenia	9 (2·3)	0 (0·0)	6 (1·5)	0 (0·0)
LVSD	13 (3·3)	7 (2·7)	5 (1·2)	2 (0·7)
Pneumonia	8 (2·0)	3 (1·2)	4 (1·0)	0 (0·0)
Dyspnoea	8 (2·0)	2 (0·8)	4 (1·0)	1 (0·3)

LVSD, left ventricular systolic dysfunction

Table 5

Cardiac tolerability

n (%)	Placebo + trastuzumab + docetaxel		Pertuzumab + trastuzumab + docetaxel	
Data cut-off date	**May 2011 (n=397)**	**May 2012 (n=396)**	**May 2011 (n=407)**	**May 2012 (n=408)**
LVSD (all grades)	33 (8·3)	34 (8·6)	18 (4·4)	22 (5·4)
Symptomatic LVSD	7 (1·8)	7 (1·8)†	4 (1·0)	5 (1·2)
LVEF decline to <50% and by ≥10% points from baseline*	25/379 (6·6)	28/378 (7·4)	15/393 (3·8)	18/394 (4·6)
LVEF recovery to ≥50%*	18/25 (72·0)	25/28 (89·3)	13/15 (86·7)	16/18 (88·9)

LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction

*In patients with post-baseline LVEF assessment

†There were six patients in the placebo arm with LVSD grade ≥3 that was not considered symptomatic by the investigator