# Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study

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## Summary

**Background** CLEOPATRA is a phase 3 study to compare the efficacy and safety of pertuzumab, trastuzumab, and docetaxel with placebo, trastuzumab, and docetaxel in patients with HER2-positive first-line metastatic breast cancer. The results of the primary analysis showed significantly longer median progression-free survival in the pertuzumab group than in the placebo group. Interim analysis of overall survival favoured the pertuzumab group but was not significant. Here, we report results for overall survival after an additional year of follow-up.

**Methods** The study was a double-blind randomised trial undertaken at 204 centres in 25 countries. Patients with HER2-positive metastatic breast cancer who had not received previous chemotherapy or biological treatment for their metastatic disease were randomly assigned to receive either pertuzumab, trastuzumab, and docetaxel (n=402) or the same regimen with a matching placebo replacing pertuzumab (n=406). Randomisation was in a 1:1 ratio, stratified by geographical region and previous treatment status. The primary endpoint was progression-free survival (assessed independently), which has been reported previously; no follow-up data were gathered for the primary endpoint. Secondary endpoints included overall survival, progression-free survival (assessed by investigator), objective response rate, and safety. Median follow-up was 30 months in both groups. Efficacy endpoints were analysed in the intention-to-treat population and safety was analysed by treatment received. The study is completed but safety and survival data continue to be followed up. This trial is registered with ClinicalTrials.gov, number NCT00567190.

**Findings** In the intention-to-treat population, 267 patients died by data cutoff (May 14, 2012), 154 (38%) of 406 in the placebo group and 113 (28%) of 402 in the pertuzumab group. Median overall survival was 37·6 months (95% CI 34·3–NE [not estimable]) in the placebo group but had not been reached (95% CI 42·4–NE) in the pertuzumab group (hazard ratio 0·66, 95% CI 0·52–0·84; p=0·0008). Investigator-assessed median progression-free survival was 12·4 months (95% CI 10·4–13·5) in the placebo group and 18·7 months (16·6–21·6) in the pertuzumab group (hazard ratio 0·69, 95% CI 0·58–0·81). Serious adverse events were reported in 115 (29%) of 396 patients who received placebo, trastuzumab, and docetaxel and 148 (36%) of 408 who received pertuzumab, trastuzumab, and docetaxel, and included febrile neutropenia, neutropenia, diarrhoea, pneumonia, and cellulitis. Overall, adverse events were similar to those reported at the primary analysis with respect to frequency, severity, and specificity.

**Interpretation** Our analysis shows a significant improvement in overall survival with pertuzumab, trastuzumab, and docetaxel in patients with HER2-positive metastatic breast cancer, compared with placebo, trastuzumab, and docetaxel. Since this effect was not achieved at the expense of adverse events, this regimen represents a substantial improvement on the standard of care for this population of patients.

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## Introduction

Breast cancers with very high expression of HER2 on their cell surface (known as HER2-positive) are characterised by a more aggressive phenotype, resulting in adverse disease prognosis.[1] The frequency of HER2-positive breast cancer ranges from about 10% to 30%.[2,3] Trastuzumab, a humanised monoclonal antibody that specifically targets HER2, significantly improves the prognosis of HER2-positive breast cancer.[4–8] However, metastatic breast cancer is incurable, and about 50% of patients have disease progression within 1 year of treatment for advanced disease.[6,9]

Findings of clinical trials in early[10,11] and advanced[12,13] HER2-positive breast cancer showed that targeting of HER2 with more than one agent is better than use of one agent only. Primary results of the Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study[12] led to approval of a regimen combining pertuzumab,

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See Comment page 438

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See Online for appendix

a novel humanised monoclonal antibody that targets HER2, with trastuzumab and docetaxel in HER2-positive first-line metastatic breast cancer. Patients who received pertuzumab, trastuzumab, and docetaxel had significantly prolonged median progression-free survival (assessed independently) compared with individuals who received a regimen in which placebo replaced pertuzumab.[12] The frequencies of diarrhoea, rash, mucosal inflammation, febrile neutropenia, and dry skin were increased in patients treated in the pertuzumab group by more than 5% compared with those treated in the placebo group. Most adverse events were grade 1–2 and arose during concomitant treatment with docetaxel.[14] In an interim analysis of overall survival, which was done at the same time as the primary analysis, pertuzumab, trastuzumab, and docetaxel were favoured strongly; however, those data were immature.

After a formal request by European health authorities, we have done an additional interim analysis of overall survival in the CLEOPATRA study, before the planned final analysis takes place at 385 deaths. Here, we report overall survival data after an additional year of follow-up.

## Methods

### Study design

We have reported full details of this study elsewhere.[12] CLEOPATRA is a randomised, double-blind, placebo-controlled phase 3 trial at 204 sites in 25 countries. Our aim was to compare the efficacy and safety of pertuzumab, trastuzumab, and docetaxel (referred to here as the pertuzumab group) with placebo, trastuzumab, and docetaxel (the placebo group) in patients with HER2-positive metastatic breast cancer who had not received previous chemotherapy or biological treatment for their metastatic disease.

We judged patients eligible for our study if they were aged 18 years or older, had measurable or non-measurable disease, a left-ventricular ejection fraction (LVEF) of at least 50% at baseline, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. We included patients who had received (neo)adjuvant chemotherapy with or without trastuzumab if the interval between completion of treatment and diagnosis of metastatic breast cancer was at least 12 months. We allowed one hormonal treatment for metastatic breast cancer before randomisation. Exclusion criteria included treatment for metastatic

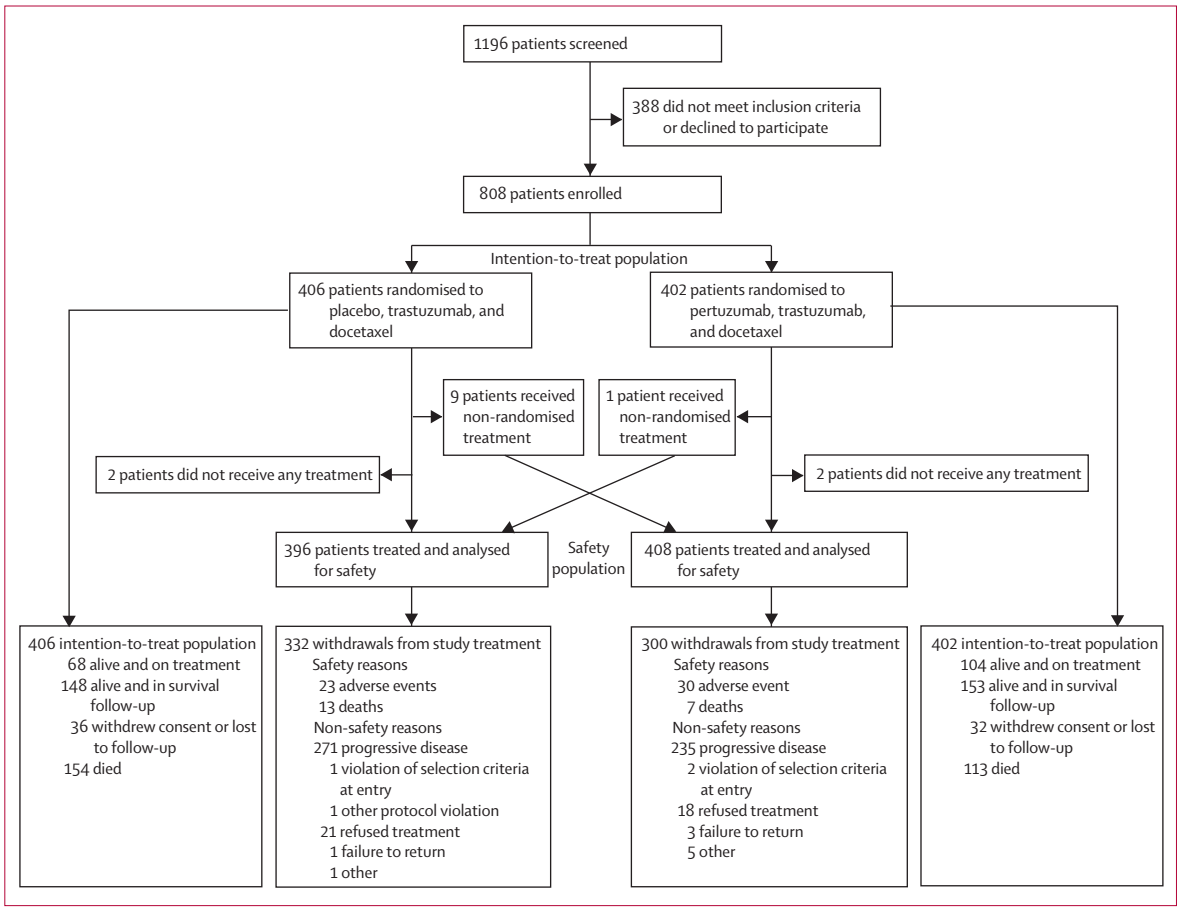


*Figure 1:* **Trial profile**

breast cancer (other than that described), CNS metastases, previous exposure to a cumulative dose of doxorubicin of more than 360 mg/m² (or its equivalent), and a decline in LVEF to less than 50% during or after former trastuzumab treatment.

We did the study in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. We obtained protocol approval from an independent ethics committee for every site. Every patient gave written informed consent.

### Randomisation and masking

An independent group (Roche Randomisation Group) randomly assigned patients in a 1:1 ratio to either the pertuzumab group or the placebo group. To balance treatment assignment, we applied a complete block randomisation scheme (block size of four). We stratified treatment allocation by geographical region (Asia, Europe, North America, and South America) and previous treatment status (neoadjuvant or adjuvant treatment received, or nothing). We used an interactive voice response system to gather screening information for patients and to allocate treatment. We allocated patient identification numbers sequentially, in the order in which patients were enrolled.

Patients and investigators were both unaware of the random assignment. To achieve masking, the placebo was matched by appearance (solution and packaging). We did not allow unmasking of treatment assignment until study end, except for safety reasons. We defined the end of the study, apart from for follow-up analyses of safety and survival, as when any interim analysis of overall survival met predefined criteria for significance, when about 385 deaths had been recorded, or when the trial was terminated by the sponsor, whichever occurred first. Hence, patients were not unmasked after the primary analysis for independently assessed progression-free survival and treatment allocation remained concealed for this interim analysis.

### Procedures

We administered study drugs intravenously every 3 weeks. We gave pertuzumab or matching placebo on day 1 of every cycle, starting at a dose of 840 mg and decreasing to 420 mg in subsequent cycles. We administered trastuzumab on day 2 of the first cycle at a dose of 8 mg/kg, changing to day 1 from cycle two onwards and lowering the dose to 6 mg/kg. We initiated docetaxel at 75 mg/m² on day 2 of the first cycle and day 1 of subsequent cycles, and we escalated the dose to 100 mg/m² if tolerated. To manage toxic effects, we allowed the docetaxel dose to be reduced by 25%. Dose reductions of pertuzumab and trastuzumab were not permitted. We administered pertuzumab and trastuzumab until disease progression happened or unmanageable toxic effects arose. We recommended at least six cycles of docetaxel but allowed fewer cycles in case of disease progression or unmanageable toxic effects and more cycles at the discretion of the treating doctor.

The primary endpoint was progression-free survival, assessed at an independent review facility. This endpoint was reached at a prespecified target of 381 events and is reported elsewhere;[12] further data for the primary endpoint

| | Placebo, trastuzumab, and docetaxel (n=406) | Pertuzumab, trastuzumab, and docetaxel (n=402) |
|---|---|---|
| Women | 404 (100%) | 402 (100%) |
| Age (years) | 54·0 (46·0–61·0) | 54·0 (46·0–60·0) |
| Ethnic origin | | |
| Asian | 133 (33%) | 128 (32%) |
| Black | 20 (5%) | 10 (2%) |
| White | 235 (58%) | 245 (61%) |
| Other* | 18 (4%) | 19 (5%) |
| Region | | |
| Asia | 128 (32%) | 125 (31%) |
| Europe | 152 (37%) | 154 (38%) |
| North America | 68 (17%) | 67 (17%) |
| South America | 58 (14%) | 56 (14%) |
| ECOG performance status | | |
| 0 | 248 (61%) | 274 (68%) |
| 1 | 157 (39%) | 125 (31%) |
| ≥2 | 1 (<1%) | 3 (1%) |
| Disease type at screening | | |
| Non-visceral | 90 (22%) | 88 (22%) |
| Visceral | 316 (78%) | 314 (78%) |
| Oestrogen and progesterone receptor status | | |
| Positive | 199 (49%) | 189 (47%) |
| Negative | 196 (48%) | 212 (53%) |
| Unknown | 11 (3%) | 1 (<1%) |
| HER2 status (immunohistochemistry) | | |
| 0 and 1+ | 2 (<1%) | 4 (1%) |
| 2+ | 32 (8%) | 47 (12%) |
| 3+ | 371 (91%) | 350 (87%) |
| No data | 1 (<1%) | 1 (<1%) |
| HER2 status (FISH) | | |
| Positive | 383 (94%) | 384 (96%) |
| Negative | 4 (1%) | 1 (<1%) |
| No data | 19 (5%) | 17 (4%) |
| Previous (neo)adjuvant chemotherapy | | |
| No | 214 (53%) | 218 (54%) |
| Yes | 192 (47%) | 184 (46%) |
| Components of (neo)adjuvant treatment† | | |
| Anthracycline | 164 (40%) | 150 (37%) |
| Hormone | 97 (24%) | 106 (26%) |
| Taxane | 94 (23%) | 91 (23%) |
| Trastuzumab | 41 (10%) | 47 (12%) |

Data are number of patients (%) or median (IQR). *Includes Native American and Alaska Native populations. †Totals are more than 100% because patients could have received more than one treatment. ECOG=Eastern Cooperative Oncology Group. FISH=fluorescence in-situ hybridisation.

***Table 1:*** **Baseline characteristics of intention-to-treat population**

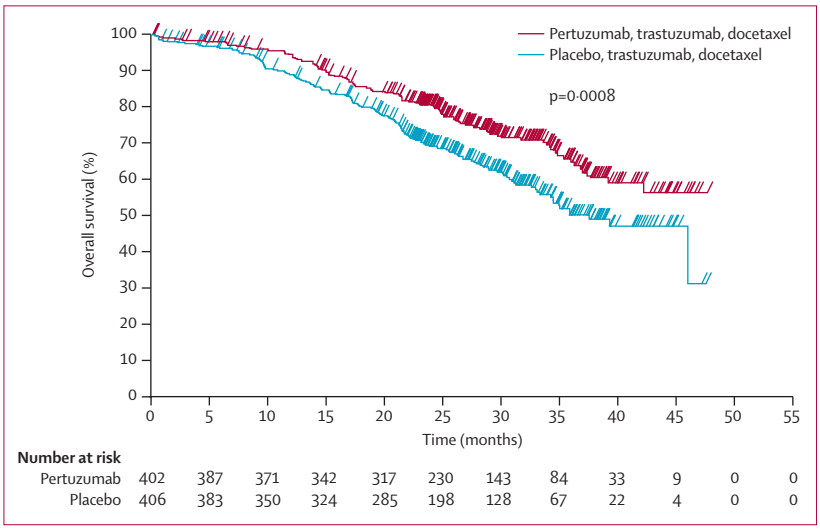


***Figure 2:*** **Kaplan-Meier estimates of overall survival (intention-to-treat population)**
Patients are stratified by previous treatment status and region. Tick marks indicate censoring events.

were not obtained. Secondary endpoints included overall survival, progression-free survival by investigator assessment, objective response rate, and safety.

Tumour assessments for primary and secondary endpoints were based on Response Evaluation Criteria In Solid Tumors (RECIST) and were done every 9 weeks by the investigator and independent reviewer. For the primary endpoint assessment, investigative sites provided the independent review facility with tumour assessment scans and other relevant clinical information until disease progression was detected or until the prespecified target of 381 events was met. Secondary endpoint tumour assessments by the investigator continued until disease progression was detected. We defined overall survival as the time from randomisation to death from any cause. We based treatment decisions on the investigator's assessment of disease progression. We monitored adverse events continuously and graded them according to the National Cancer Institute's Common Terminology Criteria for

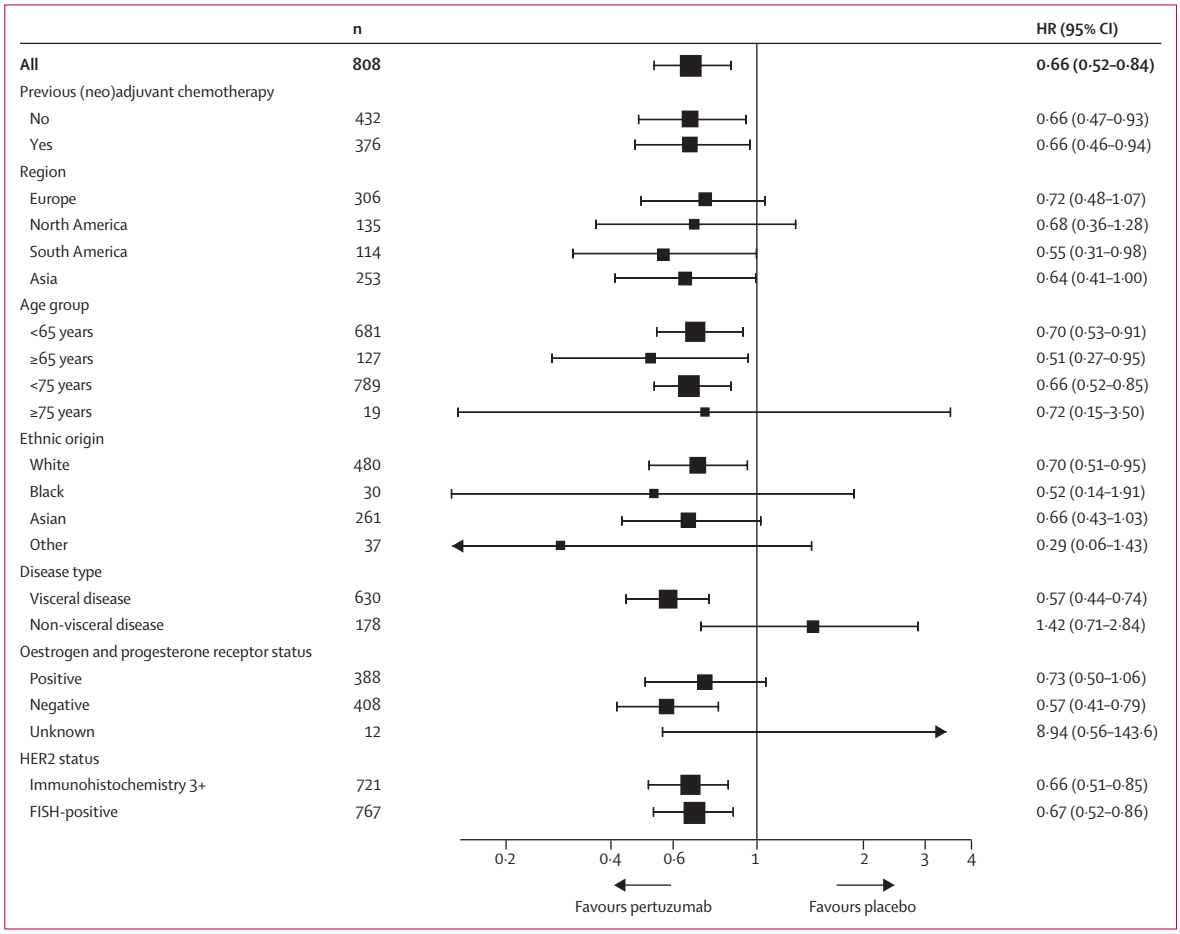


***Figure 3:*** **Forest plot analysis of overall survival**
Hazard ratios (HRs) and 95% CIs are presented for overall survival in all prespecified subgroups, according to baseline characteristics. The number of patients with unknown hormone receptor status was very small (n=12), resulting in wide 95% CIs. Ethnic origin was decided by the investigator. The subcategory "Other" includes Native American and Alaska Native populations. FISH=fluorescence in-situ hybridisation.

Adverse Events (version 3.0). We defined serious adverse events as: fatal; life-threatening; needing admission or leading to prolongation of an existing hospital stay; resulting in persistent or substantial disability; a congenital anomaly; or medically significant or requiring intervention to prevent any of the aforementioned outcomes.

During the screening period, for every patient, we obtained demographic data and a complete medical history, did a full physical examination, and assessed vital signs. On day 1 of every treatment cycle, and at the treatment discontinuation visit, we did a symptoms-directed physical examination and assessed vital signs. We assessed ECOG performance status at screening, on day 1 of every cycle, at the treatment discontinuation visit, and every 9 weeks at the time of tumour assessment if study treatment had been discontinued before disease progression was detected. We measured LVEF at screening, every 9 weeks during the treatment period, at the treatment discontinuation visit, then every 6 months in the first year of follow-up and annually for up to 3 years. We took blood samples for laboratory tests during the screening period, during every treatment cycle, and at the treatment discontinuation visit.

After the treatment discontinuation visit, we gathered survival information by telephone or at clinic visits every 18 weeks (SD 1 week) until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor. To minimise the chance of a biased overall survival estimate resulting from scheduled survival follow-up every 18 weeks, immediately before the data cutoffs for the primary progression-free survival analysis, and for any overall survival analysis, investigative sites contacted every patient to confirm their current survival status.

## Statistical analysis

After the primary analysis of independently assessed progression-free survival, which included an interim analysis of overall survival,[12] European health authorities formally requested we undertake an additional interim analysis of overall survival. This second interim analysis of overall survival was done with a data cutoff in May, 2012, 1 year after the data cutoff for the primary analysis of progression-free survival. We censored patients who were alive or lost to follow-up at the last known date they were alive. For individuals with no information available after baseline, we censored them at the time of randomisation plus 1 day. With 385 deaths required for the final analysis, we estimated that the study had 80% power to detect a 33% improvement in overall survival in the pertuzumab group (hazard ratio 0·75). Assuming that overall survival is distributed exponentially, we estimated median overall survival as 36 months in the placebo group and 48 months in the pertuzumab group.

To allow formal statistical interpretation of the second interim analysis of overall survival without inflating the overall type I error, we amended the study protocol and the statistical analysis plan to specify that the Lan-DeMets α spending function with the O'Brien-Fleming stopping boundary would be applied in the same manner as defined for the first interim analysis.[15] We established the O'Brien-Fleming stopping boundary for every interim analysis on the basis of the exact 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 analysis was defined as a p value of 0·0138 or less and a hazard ratio of 0·739 or less.

We used the log-rank test, with stratification by previous treatment status and geographical region, to compare overall survival between treatment groups and the Kaplan-Meier approach to estimate median overall survival in each group. We estimated hazard ratios and 95% CIs with a Cox proportional-hazards model, with stratification by previous treatment status and region. To ascertain the consistency of the treatment effect, we did prespecified subgroup analyses of overall survival according to stratification factors (previous treatment status and region), key demographic characteristics (age group and ethnic origin), and important breast cancer characteristics (visceral *vs* non-visceral disease, hormone receptor status, and HER2 status). We used SAS version 8.2 for statistical analyses.

This trial is registered with ClinicalTrials.gov, number NCT00567190.

## Role of the funding source

The study was funded and sponsored by F Hoffmann-La Roche and Genentech. The sponsor designed the study (in collaboration with SMS and JB), provided study

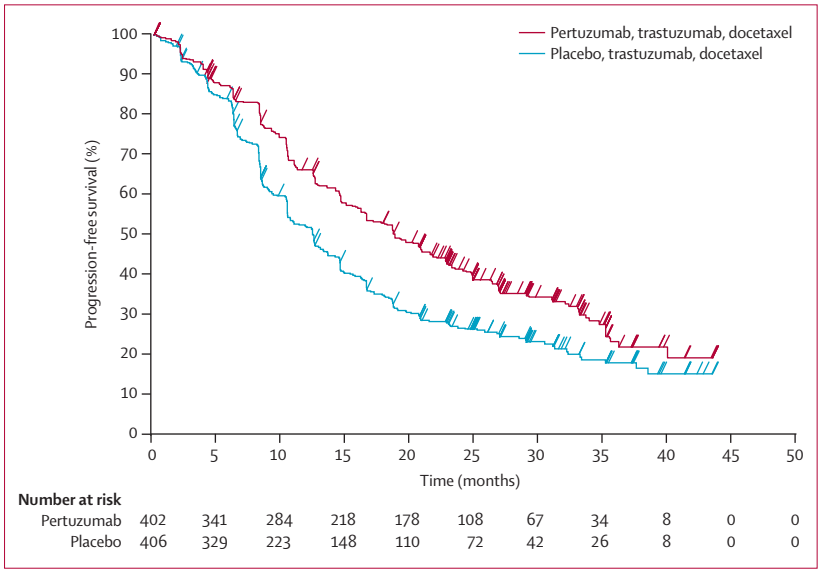


*Figure 4:* **Kaplan-Meier estimates of progression-free survival (intention-to-treat population)**
Patients are stratified by previous treatment status and region. Tick marks indicate censoring events.

drugs, and played a part in protocol development, regulatory and ethics approval, and safety monitoring. Data were gathered and statistical analyses were done by the sponsor. All authors had full access to all study data and interpreted and analysed the data. No authors received any payment in relation to writing of this report. All authors had final responsibility for the decision to submit for publication.

## Results

The cutoff date for data collection was May 14, 2012, 1 year after the cutoff for the primary analysis of independently assessed progression-free survival and 22 months after the last patient had been enrolled. Figure 1 shows the trial profile and table 1 presents patients' baseline characteristics.

At this second interim analysis of overall survival, 267 deaths had occurred, representing 69% (267 of 385) of the prespecified total number of events for the final analysis. Median follow-up was 30·1 months (IQR 23·9–36·4) in the placebo group and 29·7 months (24·6–36·9) in the pertuzumab group. The number of deaths among patients assigned to the placebo group was higher than that among individuals allocated to the pertuzumab group (154 [38%] of 406 *vs* 113 [28%] of 402; hazard ratio 0·66, 95% CI 0·52–0·84; p=0·0008; figure 2). The hazard ratio crossed the prespecified O'Brien-Fleming stopping boundary of the Lan-DeMets α spending function. Therefore, a significant survival benefit is seen for patients allocated treatment in the pertuzumab group compared with individuals assigned to the placebo group. Median overall survival was 37·6 months (95% CI 34·3–NE [not estimable]) for patients allocated to the placebo group and it had not been reached (95% CI 42·4–NE) for individuals assigned to the pertuzumab group. Kaplan-Meier curves showed an early separation between treatment regimens that continued over time. Estimated Kaplan-Meier overall survival at 1 year, 2 years, and 3 years in the placebo group, compared with the pertuzumab group, was 89·0% (95% CI 85·9–92·1) versus 94·4% (91·8–96·5), 69·4% (64·7–74·1) versus

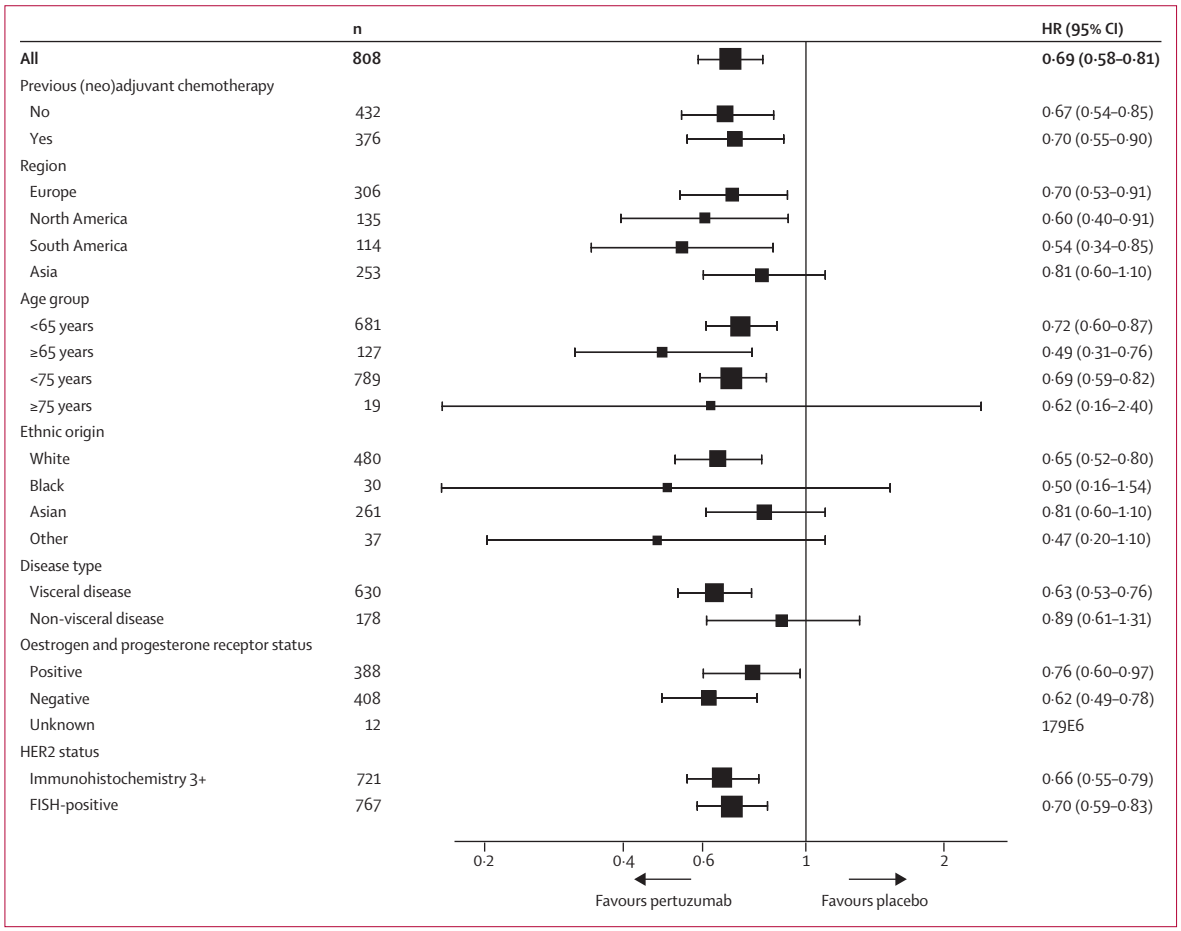


***Figure 5:*** **Forest plot analysis of progression-free survival**

Hazard ratios (HRs) and 95% CIs are presented for progression-free survival in all prespecified subgroups, according to baseline characteristics. The HR for unknown hormone receptor status was not quantifiable because of the few patients in this subgroup. Ethnic origin was decided by the investigator. The subcategory "Other" includes Native American and Alaska Native populations. FISH=fluorescence in-situ hybridisation.

| | Placebo, trastuzumab, and docetaxel (n=260)* | Pertuzumab, trastuzumab, and docetaxel (n=225)* |
|---|---|---|
| Any HER2-targeted treatment† | 178 (68%) | 160 (71%) |
| Trastuzumab | 104 (40%) | 106 (47%) |
| Lapatinib | 114 (44%) | 93 (41%) |
| Trastuzumab emtansine | 26 (10%) | 21 (9%) |
| Capecitabine | 140 (54%) | 113 (50%) |
| Vinorelbine | 70 (27%) | 51 (23%) |
| Cyclophosphamide | 43 (17%) | 30 (13%) |
| Doxorubicin | 46 (18%) | 29 (13%) |
| Paclitaxel | 32 (12%) | 21 (9%) |
| Docetaxel | 11 (4%) | 13 (6%) |

Data are number of patients (%). *Number of patients who received any additional treatments. †Excluding pertuzumab.

***Table 2:*** **Breast cancer treatments received by patients who discontinued study treatment**

| | Placebo, trastuzumab, and docetaxel (n=396) | Pertuzumab, trastuzumab, and docetaxel (n=408) |
|---|---|---|
| **Study treatment** | | |
| Number of cycles | 15 (9–29) | 24 (11–38) |
| Time on treatment (months) | 11·4 (6·8–21·0) | 17·4 (8·5–26·3) |
| **Docetaxel** | | |
| Number of cycles | 8 (6–10) | 8 (6–10) |
| Dose intensity (mg/m² per week) | 24·8 (23·0–25·5) | 24·6 (22·9–25·2) |
| Dose escalation to 100 mg/m² | 60 (15%) | 49 (12%) |
| Dose reduction to <75 mg/m² | 90 (23%) | 104 (25%) |
| Proportion of cycles delayed, interrupted, discontinued, or infusion rate reduced | 12% | 13% |

Data are number of patients (%) or median (IQR), unless otherwise stated.

***Table 3:*** **Exposure to study treatment in safety population**

| | Placebo, trastuzumab, and docetaxel (n=396) | | | Pertuzumab, trastuzumab, and docetaxel (n=408) | | |
|---|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3–4 | Grade 5 | Grade 1–2 | Grade 3–4 | Grade 5 |
| Diarrhoea | 171 (43%) | 20 (5%) | 0 | 241 (59%) | 37 (9%) | 0 |
| Alopecia* | 236 (60%) | 1 (<1%) | 0 | 244 (60%) | 0 | 0 |
| Neutropenia | 15 (4%) | 182 (46%) | 0 | 16 (4%) | 200 (49%) | 0 |
| Nausea | 166 (42%) | 2 (1%) | 0 | 174 (43%) | 5 (1%) | 0 |
| Fatigue† | 134 (34%) | 13 (3%) | 0 | 144 (35%) | 9 (2%) | 0 |
| Rash‡ | 91 (23%) | 3 (1%) | 0 | 146 (36%) | 3 (1%) | 0 |
| Decreased appetite | 99 (25%) | 6 (2%) | 0 | 114 (28%) | 7 (2%) | 0 |
| Mucosal inflammation | 75 (19%) | 4 (1%) | 0 | 106 (26%) | 6 (1%) | 0 |
| Asthenia | 114 (29%) | 7 (2%) | 0 | 100 (25%) | 10 (2%) | 0 |
| Vomiting | 91 (23%) | 6 (2%) | 0 | 98 (24%) | 6 (1%) | 0 |
| Peripheral oedema§ | 116 (29%) | 3 (1%) | 0 | 97 (24%) | 2 (<1%) | 0 |
| Pruritus† | 39 (10%) | 0 | 0 | 66 (16%) | 0 | 0 |
| Constipation | 97 (24%) | 4 (1%) | 0 | 63 (15%) | 0 | 0 |
| Febrile neutropenia | 0 | 29 (7%) | 1 (<1%) | 0 | 53 (13%) | 3 (1%) |
| Dry skin¶ | 18 (5%) | 0 | 0 | 43 (11%) | 0 | 0 |

Data are number of patients (%). Adverse events shown here have a frequency of 25% or higher or at least a 5% difference between treatment groups overall. *Data missing for three patients treated with placebo and four treated with pertuzumab. †Data missing for one patient treated with placebo and two treated with pertuzumab. ‡Data missing for one patient treated with placebo. §Data missing for three patients treated with placebo and two treated with pertuzumab. ¶Data missing for five patients treated with placebo and one treated with pertuzumab.

***Table 4:*** **Adverse events (safety population)**

80·7% (76·7–84·6), and 50·4% (43·8–57·1) versus 65·8% (59·8–71·7), respectively. The proportionality of hazards assumption for overall survival was verified by two methods (appendix).

The analysis of overall survival in predefined subgroups accorded with the analysis in the whole intention-to-treat population, indicating a consistent effect on survival with pertuzumab, trastuzumab, and docetaxel compared with placebo, trastuzumab, and docetaxel for all patients except those with non-visceral disease (figure 3). A post-hoc, exploratory subgroup analysis was done for patients who had received previous neoadjuvant or adjuvant treatment with trastuzumab (88 of 808). The observed hazard ratio of 0·68 (95% CI 0·30–1·55) was similar to that for the whole intention-to-treat population.

Owing to the prespecified fixed-sequence testing hierarchy (independently assessed progression-free survival first, followed by overall survival, then objective response rate), and because significance was reached in this second interim analysis of overall survival, the difference in objective response rate of 10·8 percentage points (95% CI 4·2–17·5; p=0·0011)[12] between treatment groups is now judged significant.

At the time of data cutoff, 296 (73%) of 406 patients allocated to the placebo group and 257 (64%) of 402 who were assigned to the pertuzumab group had had a progression-free survival event, according to the investigator (hazard ratio 0·69, 95% CI 0·58–0·81). Median progression-free survival was 12·4 months (95% CI 10·4–13·5) in the placebo group versus 18·7 months (16·6–21·6) in the pertuzumab group (figure 4), which accords with results at the primary analysis.[12] This descriptive follow-up analysis of investigator-assessed progression-free survival showed that the effect seen at the primary analysis was maintained after an additional year of follow-up. Updated exploratory subgroup analyses were done for prespecified baseline characteristics (figure 5), and the effect associated with pertuzumab-based treatment was maintained in all subgroups investigated.

In the intention-to-treat population, 338 (83%) of 406 patients assigned to the placebo group and 298 (74%) of 402 who were allocated to the pertuzumab group had discontinued study treatment at data cutoff. The proportion of patients (in the intention-to-treat population) receiving subsequent treatment for breast cancer after discontinuation of the study regimen was similar in the placebo and pertuzumab groups (77% [260 of 338] *vs* 76% [225 of 298]; table 2). Patients and investigators remained unaware of treatment allocation at discontinuation, and pertuzumab was not allowed as a

| | Placebo, trastuzumab, and docetaxel (n=260) | | Pertuzumab, trastuzumab, and docetaxel (n=303) | |
|---|---|---|---|---|
| | Grade 1–2 | Grade 3–4 | Grade 1–2 | Grade 3–4 |
| Diarrhoea | 35 (13%) | 0 | 71 (23%) | 7 (2%) |
| Alopecia | 6 (2%) | 0 | 4 (1%) | 0 |
| Neutropenia | 8 (3%) | 4 (2%) | 8 (3%) | 0 |
| Nausea* | 29 (11%) | 0 | 29 (10%) | 1 (<1%) |
| Fatigue | 22 (8%) | 3 (1%) | 38 (13%) | 2 (1%) |
| Rash* | 18 (7%) | 1 (<1%) | 48 (16%) | 1 (<1%) |
| Decreased appetite† | 9 (3%) | 1 (<1%) | 22 (7%) | 0 |
| Mucosal inflammation | 4 (2%) | 0 | 10 (3%) | 0 |
| Asthenia‡ | 21 (8%) | 1 (<1%) | 36 (12%) | 2 (1%) |
| Vomiting | 17 (7%) | 0 | 26 (9%) | 0 |
| Peripheral oedema§ | 31 (12%) | 0 | 27 (9%) | 0 |
| Pruritus¶ | 14 (5%) | 0 | 34 (11%) | 0 |
| Constipation | 17 (7%) | 1 (<1%) | 14 (5%) | 0 |
| Febrile neutropenia | 0 | 0 | 0 | 0 |
| Dry skin‖ | 5 (2%) | 0 | 8 (3%) | 0 |

Data are number of patients (%). No grade 5 events arose. *Data missing for one patient in each group. †Data missing for two patients treated with placebo. ‡Data missing for one patient treated with placebo. §Data missing for one patient treated with placebo and two treated with pertuzumab. ¶Data missing for one patient treated with placebo and three treated with pertuzumab. ‖Data missing for four patients treated with placebo.

***Table 5:*** **Adverse events after discontinuation of docetaxel**

| | Placebo, trastuzumab, and docetaxel | | Pertuzumab, trastuzumab, and docetaxel | |
|---|---|---|---|---|
| | May, 2011 (n=397) | May, 2012 (n=396) | May, 2011 (n=407) | May, 2012 (n=408) |
| LVSD (all grades) | 33 (8%) | 34 (9%) | 18 (4%) | 22 (5%) |
| Symptomatic LVSD | 7 (2%)* | 7 (2%)† | 4 (1%)‡ | 5 (1%) |
| LVEF decline to <50% and by ≥10% points from baseline§ | 25/379 (7%) | 28/378 (7%) | 15/393 (4%) | 18/394 (5%) |
| LVEF recovery to ≥50%§ | 18/25 (72%) | 25/28 (89%) | 13/15 (87%) | 16/18 (89%) |

Data are number of patients (%). *Four patients had LVSD grade 3 that was not judged symptomatic by the investigator. †Six patients had LVSD grade 3 that was not judged symptomatic by the investigator. ‡One patient had LVSD grade 3 that was not judged symptomatic by the investigator. §In patients with post-baseline LVEF assessment. LVEF=left-ventricular ejection fraction. LVSD=left-ventricular systolic dysfunction.

***Table 6:*** **Cardiac tolerability, by data cutoff date (safety population)**

subsequent breast cancer treatment. Treatments received after discontinuation were generally balanced between both groups, as was the pattern of use of cytotoxic agents.

In the safety population, the median time on treatment was longer for patients who received pertuzumab, trastuzumab, and docetaxel compared with individuals who were given placebo instead of pertuzumab (table 3), which accords with a finding of prolonged median progression-free survival by investigator assessment in the pertuzumab group. Exposure to docetaxel was comparable between both treatment groups (table 3).

Overall, adverse events reported at the first data cutoff in May, 2011, and after an additional year of follow-up were similar with respect to frequency, severity, and specificity. No new safety concerns were identified during the extended follow-up period. Higher frequencies of at least 5% were reported for diarrhoea, rash, mucosal inflammation, pruritus, febrile neutropenia, and dry skin (all grades) in patients receiving pertuzumab, trastuzumab, and docetaxel, compared with individuals who received placebo instead of pertuzumab (data obtained by the May, 2012, cutoff). The prevalence of neutropenia, febrile neutropenia, and diarrhoea (grade 3 or higher) was increased by at least 2% in patients who received pertuzumab, trastuzumab, and docetaxel, compared with those who were given placebo instead of pertuzumab (table 4). After discontinuation of docetaxel, the frequency of all adverse events fell considerably; adverse events of grade 3 or higher were rare (table 5). However, diarrhoea, rash, and pruritus were increased in patients who received pertuzumab and trastuzumab, compared with those treated with placebo and trastuzumab, after discontinuation of docetaxel. No episodes of febrile neutropenia were reported in either treatment group after discontinuation of docetaxel. Granulocyte colony-stimulating factor was used to treat adverse events in 26% (107 of 406) and 28% (113 of 402) of patients in the placebo and pertuzumab groups, respectively. Treatment with pertuzumab, trastuzumab, and docetaxel did not increase the rate of left-ventricular systolic dysfunction compared with placebo, trastuzumab, and docetaxel (table 6). Serious adverse events were reported in 115 (29%) of 396 patients who received placebo, trastuzumab, and docetaxel and 148 (36%) of 408 who received pertuzumab, trastuzumab, and docetaxel, and included febrile neutropenia, neutropenia, diarrhoea, pneumonia, and cellulitis.

In the safety population, 38% (152 of 396) of patients who received placebo, trastuzumab, and docetaxel died, compared with 28% (113 of 408) of those who received pertuzumab in place of placebo. Most deaths were attributed to disease progression (34% [136 of 396] *vs* 25% [100 of 408], respectively). A similar proportion in both treatment groups died as a result of adverse events (3% [12 of 396] *vs* 2% [eight of 408], respectively). Febrile neutropenia or infections were the most frequent causes of death attributable to an adverse event (1% [five of 396] *vs* 1% [five of 408], respectively).

## Discussion

The findings of our interim analysis show that treatment with pertuzumab, trastuzumab, and docetaxel significantly prolongs overall survival compared with placebo, trastuzumab, and docetaxel; therefore, we regard this analysis as confirmatory for overall survival. Of patients receiving subsequent treatment for breast cancer, the types of drugs used were generally balanced between both groups, suggesting that later-line treatment did not affect the overall survival results. The final analysis, planned after 385 deaths have been recorded, will be a descriptive follow-up analysis only. Before we did this

interim analysis of overall survival, patients and investigators remained unaware of treatment allocation, and crossover was not allowed. At the time of data cutoff, 68 of 406 patients allocated to the placebo group and 104 of 402 assigned to the pertuzumab group were alive and on study treatment. Because of the significant effect on survival, crossover to the pertuzumab-containing regimen has been offered to individuals still receiving study treatment in the placebo group.

Results from exploratory subgroup analyses in general indicate a trend in favour of pertuzumab, but because of the small number of patients and absence of statistical power, interpretation is limited. Subgroup analyses of overall survival accord with those in the whole intention-to-treat population, except for patients with non-visceral disease (hazard ratio 1·42, 95% CI 0·71–2·84). The number of deaths was low in this subgroup: in individuals who received placebo, 14 of 90 (16%) died versus 19 of 88 (22%) who were given pertuzumab. Variation around the point estimate can be explained by sample size and chance. In a post-hoc analysis, the hazard ratio for overall survival for patients who received trastuzumab as part of neoadjuvant or adjuvant treatment was similar to that for the whole intention-to-treat population; the wide CIs are attributable to the few patients in this subgroup. This low number of patients is based on the availability of trastuzumab in the adjuvant setting, the standard treatment period of 1 year for adjuvant trastuzumab, patients' eligibility, and the recruitment period. Trastuzumab became available as an adjuvant treatment in 2006. The first patient was enrolled into CLEOPATRA in February, 2008, with the requirement for a disease-free interval of at least 12 months from completion of systemic breast cancer treatment to diagnosis of metastatic disease. The limited use of trastuzumab as an adjuvant treatment 2 years before recruitment into CLEOPATRA began explains the low number of patients with previous exposure to trastuzumab in our study.

Overall, the interim analysis of overall survival presented here accords with findings from the first interim analysis and the primary analysis of independently assessed progression-free survival,[12] an observation that could be attributable to sustained double-blinding of the study and the absence of any crossover before this analysis of overall survival. However, consistency between improvement in progression-free survival and overall survival has been reported in previous studies of trastuzumab in HER2-positive metastatic breast cancer in the first-line setting, despite crossover.[5,6]

Adverse events reported here with the additional year of follow-up were generally similar to those reported at the primary analysis in terms of frequency, severity, and specificity. At this point, no evidence suggests cumulative or late toxic effects associated with pertuzumab. Diarrhoea, rash, mucosal inflammation, pruritus, febrile neutropenia, and dry skin (all grades) were reported by at least 5% of patients more frequently in the pertuzumab group than in the placebo group. Also, combination treatment with pertuzumab does not increase the prevalence of cardiac dysfunction over a regimen containing a placebo.[12,16] The number of cardiac adverse events reported at the primary analysis was similar to that noted in this interim analysis with an additional year of follow-up, suggesting no late cardiac toxic effects with trastuzumab and pertuzumab.

The positive results from CLEOPATRA are encouraging with respect to further investigations of pertuzumab and trastuzumab in HER2-positive breast cancer. The efficacy and safety of a regimen containing pertuzumab, trastuzumab, and chemotherapy in HER2-positive early breast cancer is currently under study in the APHINITY trial.[17] In APHINITY, and in several trials ongoing in HER2-positive metastatic breast cancer, pertuzumab and trastuzumab are combined with different chemotherapy partners based on previous findings that trastuzumab is efficacious with various different chemotherapeutic agents.

Findings of our study, and those of other clinical trials targeting signalling pathways in breast cancer,[18,19] indicate promising improvements in treatment outcomes. In the EMILIA trial in patients with HER2-positive metastatic breast cancer,[18] trastuzumab emtansine was compared with capecitabine and lapatinib (mostly second or later line treatment) and significant increases were noted in progression-free and overall survival, together with a favourable safety profile. On the basis of these findings, results of the MARIANNE study (NCT01120184), of the combination of pertuzumab and trastuzumab emtansine in HER2-positive first-line metastatic breast cancer, are awaited with interest.

In addition to combined HER2 targeting, inhibition of other components of the intracellular signalling cascade is being studied. The combination of everolimus, an inhibitor of mTOR, with trastuzumab and chemotherapy in HER2-positive metastatic breast cancer is under investigation in two phase 3 studies (NCT00876395, NCT01007942). A regimen of anti-HER2 treatment combined with agents targeting intracellular proteins with a role in the pro-survival signalling cascade could be an option that merits further investigation.

The underlying mechanism to the improvement in efficacy when trastuzumab and pertuzumab are combined is possibly due to their complementary mode of action. Although both antibodies bind to the extracellular part of HER2 they target different epitopes. Whereas trastuzumab binds to subdomain IV,[20] thus disrupting ligand-independent mitogenic signalling,[21] activating antibody-dependent cellular cytotoxicity,[22] and inhibiting HER2 cleavage,[23] pertuzumab binds to the dimerisation domain of HER2,[24] therefore preventing ligand-induced heterodimerisation of HER2[25] and activating antibody-dependent cellular cytotoxicity.[22] Preclinical study findings show that, together, trastuzumab and pertuzumab act synergistically.[26] This work supports the idea

### *Panel:* Research in context

#### Systematic review

Treatments for metastatic breast cancer can delay disease progression and prolong survival, but metastatic disease remains incurable and will progress eventually. To put the findings of CLEOPATRA (with respect to overall survival) into context with those from previous phase 2 and 3 studies of trastuzumab and chemotherapy combinations for HER2-positive metastatic breast cancer, we searched PubMed with the 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 (appendix). We selected English language publications only. Median overall survival for trastuzumab plus chemotherapy ranged from 15 months[27] to 48 months[28] (a list of all publications used in this systematic review is provided in the appendix). Treatment was given for different lines of HER2-positive metastatic breast cancer and, in some studies, two cytotoxic agents were used in addition to trastuzumab. Of these studies, we identified three phase 3 studies of trastuzumab and chemotherapy combinations for HER2-positive first-line metastatic breast cancer, with median overall survival of 25·1 months,[5] 35·7 months and 38·8 months,[9] and 37·1 months and 37·4 months.[29]

#### Interpretation

Because of the heterogeneity of study populations and differences in study design, comparisons across different trials are controversial and should be judged with caution. However, our review suggests that the median overall survival of 37·6 months noted with trastuzumab and docetaxel in the placebo group of CLEOPATRA is consistent with results from previous studies in HER2-positive first-line metastatic breast cancer. Survival at 1 year, 2 years, and 3 years, and the reduction in risk of death during the course of the study, show durable clinical benefit for patients given pertuzumab, trastuzumab, and docetaxel. This finding is a substantial improvement on the current standard of care.

that the combination of trastuzumab and pertuzumab comprehensively targets HER2-overexpressing cancer cells, resulting in more effective HER2 blockade than with trastuzumab alone.

In conclusion, the improvement in overall survival with pertuzumab, trastuzumab, and docetaxel, relative to placebo, trastuzumab, and docetaxel, was significant and clinically meaningful. Therefore, our findings lend further support to the positive benefit:risk ratio of treatment with pertuzumab, trastuzumab, and docetaxel in patients with HER2-positive metastatic breast cancer (panel).

#### Contributors

SMS, JC, AS, GR, and JB had the idea for and designed the study. S-BK, JR, VS, MC, J-MF, AS, and MCB contributed to data collection and assembly. SMS, S-BK, JC, EvC, J-MF, AS, AK, EmC, GR, MCB, and JB interpreted and analysed data. All authors wrote and reviewed the report and approved the final version for submission.

#### Conflicts of interest

SMS has been an uncompensated consultant for Roche and Genentech. Her institution has received research funding from Roche, Genentech, Agendia, Pfizer, and PUMA. JC is a consultant for Roche, Celgene, and Novartis and has received honoraria from Roche, Celgene, Novartis, and Eisai. JR has been a consultant for GlaxoSmithKline and Pfizer and has received research funding from GlaxoSmithKline. MC is a consultant for Novartis and Servier. J-MF has received honoraria from Roche, Pfizer, and Sanofi-Aventis. AS is a consultant for and has received honoraria from Roche and Sanofi-Aventis. AK, EmC, and GR are employees of Roche. EmC discloses stock ownership from AstraZeneca. GR discloses stock ownership from Roche and GlaxoSmithKline; an immediate family member owns stocks in GlaxoSmithKline. MCB is an employee of Genentech. JB is a consultant for Roche, Genentech, and Sanofi-Aventis. S-BK, VS, and EvC declare that they have no conflicts of interest.

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