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CLINICAL TRIAL

Treatment of older patients with HER2-positive metastatic breast cancer with pertuzumab, trastuzumab, and docetaxel: subgroup analyses from a randomized, double-blind, placebo-controlled phase III trial (CLEOPATRA)

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Abstract Although the incidence of cancer increases with age, older patients are under-represented in cancer treatment trials, resulting in limited data availability in this patient population. Here we present results from pre-defined subgroup analyses conducted by age group (<65 vs ≥65 years) from a randomized, double-blind, placebo-controlled phase III trial in patients with HER2-positive metastatic breast cancer. Patients who had not received previous chemotherapy or biological therapy for HER2-positive locally recurrent, unresectable or metastatic breast cancer were randomly assigned to treatment with placebo, trastuzumab, and docetaxel or with pertuzumab, trastuzumab, and docetaxel. Primary endpoint was independently assessed progression-free survival. We performed pre-specified subgroup analyses of progression-free survival according to age. The study is registered with ClinicalTrials.gov, NCT00567190. 808 patients were enrolled. Of those, 127 patients were 65 years of age or older (placebo arm: 67, pertuzumab arm: 60). Patients in both age groups experienced progression-free survival benefit with treatment in the pertuzumab arm (<65 years: HR: 0.65; 95 % CI 0.53–0.80; ≥65 years: HR: 0.52; 95 % CI 0.31–0.86). Diarrhoea, fatigue, asthenia, decreased appetite, vomiting, and dysgeusia were reported more frequently in patients 65 years of age or older compared with younger patients. Neutropenia and febrile neutropenia were reported less frequently in the older age group. The efficacy and safety data reported in CLEOPATRA suggest that the combined use of pertuzumab, trastuzumab, and docetaxel should not be limited by patient age.

Keywords Elderly · HER2 · Metastatic breast cancer · Older women · Pertuzumab · Trastuzumab

Introduction

Cancer is an age-related disease and the probability of developing breast cancer is highest in women 70 years of

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age or older [1]. Given the changing population demographics, the overall incidence of breast cancer will rise, driven by cancer diagnosed in older patients [2, 3], highlighting the importance of treatment guidelines for this patient population. In a US-based study Hutchins et al. [4] reported that although the estimated proportion of women ≥65 years of age with breast cancer is 49 %, they only represent 9 % of the patients participating in clinical trials. This discrepancy and the resulting scarcity of level I evidence leads to uncertainties about best practice in older patients, especially since older patients generally present with more comorbidities and related medications than younger patients [5–7], increasing the complexity of their management. Although survival rates of patients with breast cancer ≥65 years of age in the US have increased over an observation period from 1977 to 2006 [8], several population-based studies have shown that older patients are frequently not treated according to standard of care [7, 9–11], with adverse consequences on survival outcomes [12, 13]. Results from a prospective, observational US-based study in patients with HER2-positive metastatic breast cancer showed that elderly patients present with higher rates of underlying cardiovascular disease and are less likely to receive cytotoxic anti-cancer therapies compared with younger patients [14]. Trastuzumab-based treatment resulted in a survival benefit in all age groups compared with trastuzumab-free therapy [14]. Similarly, in HER2-positive early breast cancer, trastuzumab-based therapy significantly improved disease-free [15] and overall survival [16] compared with chemotherapy alone. In an exploratory analysis from the same study, age (≤40 vs >40 years) was not significantly associated with disease-free or overall survival, either in the trastuzumab arm or in the observation arm [17]. This analysis was limited by a relatively short median follow-up of 2 years, which was chosen to avoid bias introduced by cross-over to the trastuzumab arm [17].

We performed a randomized, double-blind, placebo-controlled phase III study to investigate the efficacy and safety of pertuzumab, trastuzumab, and docetaxel compared with placebo, trastuzumab, and docetaxel in patients with HER2-positive first-line metastatic breast cancer. Progression-free survival was significantly improved with pertuzumab, trastuzumab, and docetaxel [18], and this combination was first approved in June 2012 by the US FDA for first-line treatment of HER2-positive metastatic breast cancer. After one additional year of follow-up, the overall survival benefit with pertuzumab, trastuzumab, and docetaxel had reached statistical significance, demonstrating a clinically meaningful improvement compared with trastuzumab and docetaxel [19]. In CLEOPATRA, 16 % ($n = 127$) of patients were 65 years of age or older. Here we report efficacy and safety analyses in older patients compared with those in patients <65 years of age.

Methods

Study design and treatment

Study details have been published previously [18, 19]. CLEOPATRA was a randomized, double-blind, placebo-controlled phase III trial designed with two treatment arms: placebo, trastuzumab (Herceptin®, F. Hoffmann-La Roche, Basel, Switzerland) and docetaxel (Taxotere®, Sanofi-Aventis, Paris, France) (referred to as placebo arm); and pertuzumab (Perjeta®, F. Hoffmann-La Roche), trastuzumab and docetaxel (referred to as pertuzumab arm). Primary endpoint was progression-free survival, defined as the time from randomization to disease progression, confirmed by an independent review facility according to Response Evaluation Criteria in Solid Tumors (RECIST) [20] or death from any cause within 18 weeks of the patient's last tumour assessment. Secondary endpoints included overall survival, progression-free survival by investigator assessment, objective response rate and safety. All study drugs were administered intravenously during a 3-weekly cycle. Pertuzumab/placebo was given at 840 mg in cycle 1, followed by 420 mg in every subsequent cycle. Trastuzumab loading dose was 8 mg/kg in cycle 1 and 6 mg/kg for subsequent cycles. Dose modifications of pertuzumab and trastuzumab were not permitted. Docetaxel was given at 75 mg/m^2. Docetaxel dose escalation to 100 mg/m^2 was allowed if tolerated; two docetaxel dose reductions by 25 % to 75 or 55 mg/m^2 were allowed in order to manage toxicities. Pertuzumab/placebo and trastuzumab were administered until investigator-assessed disease progression or unmanageable toxicity. At least six cycles of docetaxel were recommended; fewer cycles were allowed in the event of disease progression or unmanageable toxicity, more cycles at the discretion of the treating physician.

The study was conducted according to Good Clinical Practice and the Declaration of Helsinki. Protocol approval was obtained from an independent ethics committee at each participating site. All patients provided written informed consent.

Patients

Patients with HER2-positive (by central confirmation) locally recurrent, unresectable, or metastatic breast cancer who had not received prior chemotherapy or biological therapy for their advanced disease were eligible. Further inclusion criteria were measurable and/or non-measurable disease, a baseline left ventricular ejection fraction (LVEF) of at least 50 %, an Eastern Cooperative Oncology Group (ECOG) performance status [21] of 0 or 1, a disease-free interval of at least 12 months between completion of

systemic treatment (excluding hormonal therapy) and diagnosis of metastatic disease, and a minimum age of 18 years. Exposure to trastuzumab during neoadjuvant and adjuvant therapy was allowed, as well as one hormonal treatment regimen for metastatic breast cancer before randomization. Among the exclusion criteria were treatment for metastatic breast cancer other than that described, metastases to the central nervous system, decline in LVEF to below 50 % during or after prior therapy with trastuzumab, prior exposure to a cumulative dose of doxorubicin (or its equivalent) of more than 360 mg/m^2, and history of congestive heart failure.

Assessments

Tumour assessments were based on RECIST and performed every 9 weeks. Adverse events were monitored continuously and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0. LVEF was assessed by echocardiography or multiple-gated acquisition scanning and the same method was to be used for an individual patient throughout the study. LVEF measurements took place at baseline, every 9 weeks during the treatment period, at the treatment discontinuation visit, every 6 months in the first year of follow-up, then annually for up to 3 years.

Randomization and masking

Patients were randomly assigned treatment in a 1:1 ratio. A complete block randomization scheme was applied in order to balance treatment assignment. Treatment allocation was stratified by geographic region (Asia, Europe, North America, and South America) and prior treatment status (neoadjuvant and/or adjuvant treatment received or not). An interactive voice response system was utilized to collect patient screening information and to allocate treatment. Patient identification numbers were allocated sequentially in the order in which patients were enrolled. The study was double-blinded.

Statistical analyses

A sample size of 800 patients was planned for the study and the primary analysis was defined to take place after 381 independently assessed progression-free survival events had occurred. With this number of events, it was estimated that the study had 80 % power to detect a 33 % improvement in median progression-free survival in the pertuzumab arm (hazard ratio [HR]: 0.75) at a two-sided significance level of 5 %. The log-rank test, with stratification according to prior treatment status and region, was used to compare independently assessed progression-free survival between both treatment arms. The Kaplan–Meier approach was used to estimate the median independently assessed progression-free survival in each arm. A Cox proportional hazards model, with stratification according to prior treatment status and region, was used to estimate the hazard ratio and 95 % confidence intervals (CIs). To analyze the consistency of the treatment effect, pre-specified subgroup analyses of progression-free survival were performed, including age groups (<65, ≥ 65, <75, and ≥ 75 years). Adverse events were reported and analyzed using descriptive methods. The time to first event of left ventricular systolic dysfunction (LVSD) was evaluated by the Kaplan–Meier approach. A Cox regression analysis of time to first LVSD event was performed to investigate pre-defined potential risk factors for cardiac dysfunction, including age. SAS version 8.2 was used for statistical analyses. Efficacy analyses were performed according to treatment allocation (intention-to-treat [ITT] population) and safety analyses were performed as per treatment received.

The trial is registered with ClinicalTrials.gov, NCT00567190.

Results

Study population

In total, 808 patients were enrolled into the study from 204 sites in 25 countries; 406 patients were randomized to the placebo arm, 402 patients were randomized to the pertuzumab arm. In the ITT population, 681 patients (84.3 %) were younger than 65 years (339 in the placebo arm, 342 in the pertuzumab arm). There were 127 patients (15.7 %) 65 years of age or older (67 in the placebo arm, 60 in the pertuzumab arm). Two patients in each arm did not receive any study treatment. Eight patients randomized to the placebo arm received at least one dose of pertuzumab. In the pertuzumab arm, one patient-received treatment allocated to the placebo arm only. The safety population therefore comprised 678 patients <65 years (placebo arm: 332; pertuzumab arm: 346) and 126 patients ≥ 65 years (placebo arm: 65; pertuzumab arm: 61). The data cut-off for the analyses presented here took place in May 2011. Table 1 presents disease characteristics at baseline per age group. In both age groups, a higher proportion of patients randomized to the pertuzumab arm presented with ECOG performance status of 0. In patients ≥ 65 years, a higher proportion of patients randomized to the pertuzumab arm presented with non-visceral disease. In the younger age group, 9.1 % of patients in the placebo arm and 12.6 % of patients in the pertuzumab arm had received neoadjuvant or adjuvant treatment with trastuzumab. For older patients, the proportion of patients with previous exposure to trastuzumab was 14.9 % in the

Table 1 Disease characteristics at baseline per age group

n (%)	<65 years		≥65 years	
	Placebo + trastuzumab + docetaxel (*n* = 339)	Pertuzumab + trastuzumab + docetaxel (*n* = 342)	Placebo + trastuzumab + docetaxel (*n* = 67)	Pertuzumab + trastuzumab + docetaxel (*n* = 60)
Median age (range), years	51 (27–64)	53 (22–64)	68 (65–89)	69 (65–82)
ECOG PS				
0	208 (61.4)	235 (68.7)	40 (59.7)	39 (65.0)
1	130 (38.3)	105 (30.7)	27 (40.3)	20 (33.3)
2[a]	0 (0.0)	2 (0.6)	0 (0.0)	1 (1.7)
3[a]	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Disease type				
Visceral disease	261 (77.0)	269 (78.7)	55 (82.1)	45 (75.0)
Non-visceral disease	78 (23.0)	73 (21.3)	12 (17.9)	15 (25.0)
Median number of lesions (target and non-target)	5.0 (1–19)	5.0 (1–17)	4.0 (1–16)	4.0 (1–17)
Number of patients	339	342	67	59
Median measurable tumour burden (target lesions), mm	79.0 (10–455)	79.0 (10–422)	79.0 (13–365)	82.5 (10–404)
Number of patients	306	310	63	56
Hormone receptor status				
ER- and/or PgR-positive	172 (50.7)	158 (46.2)	27 (40.3)	31 (51.7)
ER- and PgR-negative	159 (46.9)	183 (53.5)	37 (55.2)	29 (48.3)
Unknown	8 (2.4)	1 (0.3)	3 (4.5)	0 (0.0)
HER2 status by IHC				
0 or 1+	2 (0.6)	3 (0.9)	0 (0.0)	1 (1.7)
2+	26 (7.7)	38 (11.1)	6 (9.0)	9 (15.0)
3+	310 (91.4)	300 (87.7)	61 (91.0)	50 (83.3)
Unknown	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
HER2 status by FISH				
Positive	320 (94.4)	326 (95.3)	63 (94.0)	58 (96.7)
Negative	4 (1.2)	1 (0.3)	0 (0.0)	0 (0.0)
Unknown	15 (4.4)	15 (4.4)	4 (6.0)	2 (3.3)
Prior trastuzumab treatment	31 (9.1)	43 (12.6)	10 (14.9)	4 (6.7)
Prior anthracycline treatment	140 (41.3)	135 (39.5)	24 (35.8)	15 (25.0)
Prior radiotherapy	141 (41.6)	146 (42.7)	34 (50.7)	25 (41.7)
Median disease-free interval[b], months	29.0 (0–181)	29.0 (0–186)	28.0 (0–259)	62.0 (18–276)
Number of patients	156	153	31	20

ECOG PS Eastern Cooperative Oncology Group performance status, *ER* estrogen receptor, *FISH* fluorescence in situ hybridization, *IHC* immunohistochemistry, *PgR* progesterone receptor

[a] Protocol violation

[b] Defined as the period between completion of systemic treatment (excluding hormonal therapy) and diagnosis of metastatic disease

placebo arm and 6.7 % in the pertuzumab arm. A longer median disease-free interval, defined as the period between completion of systemic treatment (excluding hormonal therapy) and diagnosis of metastatic disease, was reported for patients ≥65 years in the pertuzumab arm (62 months) compared with all other subgroups (28 or 29 months). In the study population, a higher proportion of older compared with younger patients reported previous (36.2 vs 28.2 %) and current (85.8 vs 66.7 %) diseases other than breast cancer at baseline (Online Resource 1).

Efficacy

The analysis of independently assessed progression-free survival in the whole ITT population demonstrated a median progression-free survival of 12.4 months in the placebo arm and 18.5 months in the pertuzumab arm (HR: 0.62; 95 % CI 0.51–0.75; $P < 0.0001$) [18]. Exploratory analyses of independently assessed progression-free survival by age group (<65, ≥65, <75, and ≥75 years) were pre-defined per protocol. The hazard ratios observed in all age groups were comparable to the hazard ratio in the whole ITT population, suggesting that the treatment benefit observed with pertuzumab is consistent in all analyzed age groups (Fig. 1a). The wide confidence intervals for the group of patients ≥75 years are a consequence of the small sample size ($n = 19$). In a post hoc analysis, Kaplan–Meier estimates for median independently assessed progression-free survival in patients <65 years and patients ≥65 years were calculated (Fig. 1b). In patients younger than 65 years, the median progression-free survival was 12.5 months in the placebo arm and 17.2 months in the pertuzumab arm (HR: 0.65; 95 % CI 0.53–0.80). In patients 65 years of age or older, median progression-free survival was 10.4 months in the placebo arm and 21.6 months in the pertuzumab arm (HR, 0.52; 95 % CI 0.31–0.86) (Table 2).

The objective response rate (complete response plus partial response), assessed in patients with independently confirmed measurable disease at baseline, favored treatment in the pertuzumab arm in all age groups (Table 3). The difference in response rates was 10.8 % points in the whole ITT population, 11.5 % points in patients <65 years and 8.1 % points in patients ≥65 years. The analysis of objective response rate per age group was exploratory only.

Exposure to docetaxel

In all subgroups, at least 90 % of patients who permanently discontinued docetaxel completed the recommended number of at least six cycles of docetaxel (Table 4). The proportion of patients who discontinued docetaxel due to an adverse event was generally balanced across subgroups, although a smaller proportion of patients ≥65 years in the pertuzumab arm discontinued docetaxel due to an adverse event. The median number of docetaxel cycles was comparable between treatment arms but lower in older patients (6.5 and 6.0) compared with the subgroup of younger patients (8.0 in both arms). Docetaxel dose reductions below 75 mg/m^2 occurred more often in patients 65 years of age or older than in younger patients, though this did not impact on median docetaxel dose intensity.

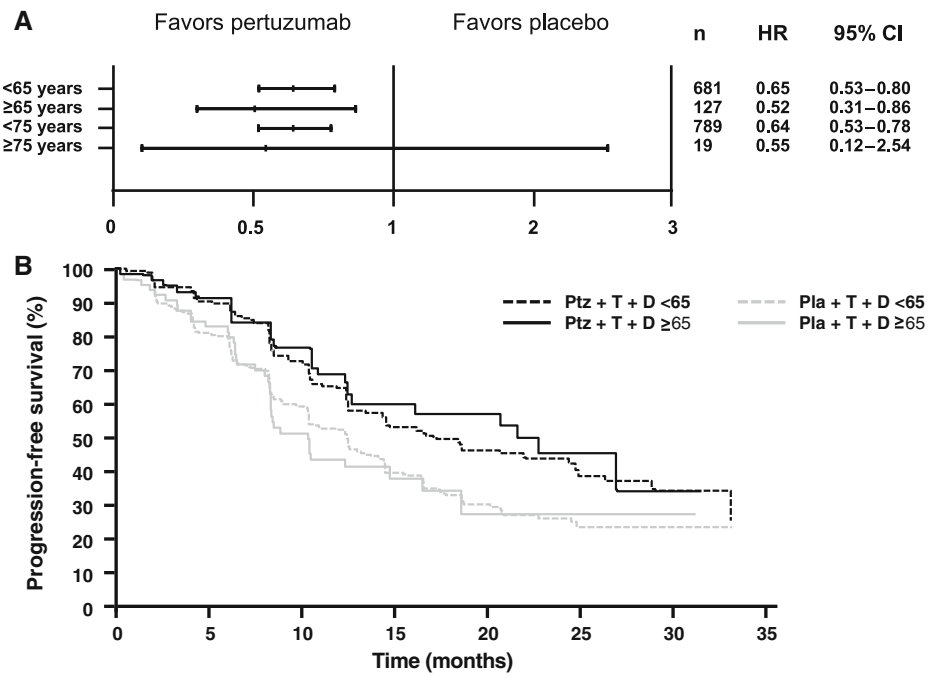

Fig. 1 Independently assessed progression-free survival per age group. **a** Hazard ratios and 95 % confidence intervals for independently assessed progression-free survival in pre-specified subgroups according to age. **b** Kaplan–Meier estimates of independently assessed progression-free survival in patients <65 years and patients ≥65 years randomized to receive placebo, trastuzumab, and docetaxel or pertuzumab, trastuzumab, and docetaxel. *CI* confidence interval, *HR* hazard ratio, *D* docetaxel, *Pla* placebo, *Ptz* pertuzumab, *T* trastuzumab

Table 2 Independently assessed progression-free survival in the whole study population and per age group

	Placebo + trastuzumab + docetaxel	Pertuzumab + trastuzumab + docetaxel
Whole study population, *n*	406	402
Median PFS, months	12.4	18.5
HR (95 % CI)	0.62 (0.51–0.75)	
Patients <65 years, *n*	339	342
Median PFS, months	12.5	17.2
HR (95 % CI)	0.65 (0.53–0.80)	
Patients ≥65 years, *n*	67	60
Median PFS, months	10.4	21.6
HR (95 % CI)	0.52 (0.31–0.86)	

CI confidence interval, *HR* hazard ratio, *PFS* progression-free survival

Table 3 Independently assessed objective response rate in patients with measurable disease at baseline

	Placebo + trastuzumab + docetaxel	Pertuzumab + trastuzumab + docetaxel
Whole study population, *n*	336	343
ORR, *n* (%)	233 (69.3)	275 (80.2)
	$P = 0.0011$	
Patients <65 years, *n*	278	293
ORR, *n* (%)	189 (68.0)	233 (79.5)
Patients ≥65 years, *n*	58	50
ORR, *n* (%)	44 (75.9)	42 (84.0)

ORR objective response rate

Adverse events

In both age groups, the incidences of diarrhoea, neutropenia, and dysgeusia (all grades) were higher in the pertuzumab arm compared with the placebo arm (Table 5). Following the discontinuation of docetaxel, the incidence of adverse events fell considerably, with the exception of LVSD. In both age groups, diarrhoea, fatigue, and rash were reported more frequently in the pertuzumab arm than in the placebo arm following docetaxel discontinuation (Table 5). No episodes of febrile neutropenia were reported in any arm or age group after discontinuation of docetaxel. In patients 65 years of age or older, diarrhoea, fatigue, asthenia, decreased appetite, vomiting, and dysgeusia (all grades) were reported more frequently in both treatment arms compared with younger patients. Neutropenia, on the other hand, was reported less frequently in the older subgroup of patients.

Adverse events of grade ≥3 reported more frequently in the pertuzumab arm in both age groups were febrile neutropenia (especially in the younger subgroup) and diarrhoea (especially in older patients) (Table 6). Although peripheral neuropathy (grade ≥3) was reported with similar incidence for both arms in patients <65 years (six patients in each arm), its incidence was higher in patients ≥65 years receiving treatment in the pertuzumab arm (five patients versus one patient). The incidences of diarrhoea and fatigue (grade ≥3) were higher in older patients in both treatment arms compared with younger patients. In contrast, grade ≥3 neutropenia, leukopenia, and febrile neutropenia were reported less frequently in older patients compared with the younger subgroup.

The proportion of patients who received medication with granulocyte-colony-stimulating factors (G-CSFs) was lower in the older subgroup compared with the younger subgroup. In patients less than 65 years of age, 114/332 (34.3 %) patients in the placebo arm and 135/346 (39.0 %) patients in the pertuzumab arm-received G-CSFs. For patients 65 years of age or older, 19/65 (29.2 %) patients received medication with G-CSFs in the placebo arm and 12/61 (19.7 %) patients received G-CSFs in the pertuzumab arm.

In a univariate Cox regression analysis, age had no statistically significant association with the development of asymptomatic or symptomatic LVSD (≥65 years vs <65 years: HR: 1.25; 95 % CI 0.61–2.56; $P = 0.5502$; ≥75 years versus <75 years: HR: 2.25; 95 % CI 0.55–9.29; $P = 0.2606$). Due to the low number of LVSD events overall ($n = 51$; Table 5), the analysis has limited sensitivity to detect differences in time to event by age group.

Discussion

We evaluated efficacy and safety of pertuzumab, trastuzumab, and docetaxel or placebo, trastuzumab, and docetaxel as first-line therapy for HER2-positive metastatic

Table 4 Exposure to docetaxel treatment

	<65 years		≥65 years	
	Placebo + trastuzumab + docetaxel ($n = 332$)	Pertuzumab + trastuzumab + docetaxel ($n = 346$)	Placebo + trastuzumab + docetaxel ($n = 65$)	Pertuzumab + trastuzumab + docetaxel ($n = 61$)
Median number of cycles administered (range)	8.0 (1–41)	8.0 (1–35)	6.5 (1–26)	6.0 (1–16)
Median dose intensity, mg/m^2/week	24.8	24.5	24.8	24.8
Dose escalation to 100 mg/m^2, *n* (%)	53 (16.0)	41 (11.8)	8 (12.3)	7 (11.5)
Dose reduction to <75 mg/m^2, *n* (%)	72 (21.7)	85 (24.6)	17 (26.2)	19 (31.1)
Docetaxel permanently discontinued				
No, *n* (%)	117 (35.2)	97 (28.0)	25 (38.5)	12 (19.7)
Yes, *n* (%)	215 (64.8)	249 (72.0)	40 (61.5)	49 (80.3)
≥6 cycles of docetaxel completed, *n*/*N* (%)	209/215 (97.2)	238/249 (95.6)	36/40 (90.0)	47/49 (95.9)
Reason for discontinuation, *n*/*N* (%)				
Standard practice	127/215 (59.1)	140/249 (56.2)	22/40 (55.0)	37/49 (75.5)
Adverse event	75/215 (34.9)	85/249 (34.1)	15/40 (37.5)	12/49 (24.5)
Refused treatment	6/215 (2.8)	12/249 (4.8)	1/40 (2.5)	0/49 (0.0)
Other	7/215 (3.3)	12/249 (4.8)	2/40 (5.0)	0/49 (0.0)

breast cancer in patients ≥65 years compared with patients <65 years. Treatment with pertuzumab, trastuzumab, and docetaxel resulted in superior progression-free survival in both age groups compared with the placebo arm. The long-median progression-free survival of 21.6 months reported in patients ≥65 years in the pertuzumab arm may be based on some favourable disease characteristics observed in this subgroup, such as a lower proportion of patients with previous exposure to trastuzumab, a higher proportion of patients with non-visceral disease and a longer median disease-free interval, characteristics that suggest more indolent disease in these patients. However, the small sample size limits the interpretation of these observations. A higher incidence of grade ≥3 diarrhoea was reported in older patients treated in the pertuzumab arm, and so patients receiving this regimen should be closely monitored in clinical practice. The dose of docetaxel was reduced more frequently and the median number of docetaxel cycles was lower (6.5 and 6.0 cycles per arm) in older patients, which probably explains the lower incidence of neutropenia and febrile neutropenia, as well as less frequent use of G-CSFs. These observations suggest that toxicities were more often managed by docetaxel dose adjustments in patients ≥65 years than in younger patients. Nevertheless, the median number of docetaxel cycles administered in older patients complies with the per-protocol recommendation of at least six cycles, and ≥90 % of patients who permanently discontinued docetaxel had received at least six cycles of docetaxel. It is interesting to note that, despite more frequent docetaxel dose reductions and a lower median number of docetaxel cycles, the overall efficacy outcomes of older patients were similar to those of younger patients, which raises the question about the optimal duration of chemotherapy when it is combined with HER2-targeted treatment.

The combination of pertuzumab with trastuzumab in CLEOPATRA did not increase the risk of cardiac dysfunction associated with trastuzumab [22], and there was no

Table 5 Ten most common adverse events and adverse events of special interest overall and after discontinuation of docetaxel (all grades)

n (%)	<65 years				≥65 years			
	Placebo + trastuzumab + docetaxel		Pertuzumab + trastuzumab + docetaxel		Placebo + trastuzumab + docetaxel		Pertuzumab + trastuzumab + docetaxel	
	Overall ($n = 332$)	Post-D ($n = 215$)	Overall ($n = 346$)	Post-D ($n = 249$)	Overall ($n = 65$)	Post-D ($n = 40$)	Overall ($n = 61$)	Post-D ($n = 49$)
Total number of patients with at least 1 adverse event	327 (98.5)	173 (80.5)	345 (99.7)	204 (81.9)	64 (98.5)	29 (72.5)	61 (100.0)	45 (91.8)
Blood and lymphatic system disorders	215 (64.8)	18 (8.4)	241 (69.7)	18 (7.2)	34 (52.3)	2 (5.0)	40 (65.6)	4 (8.2)
Alopecia	201 (60.5)	4 (1.9)	216 (62.4)	1 (0.4)	39 (60.0)	0 (0.0)	32 (52.5)	1 (2.0)
Diarrhoea	149 (44.9)	18 (8.4)	229 (66.2)	41 (16.5)	35 (53.8)	5 (12.5)	43 (70.5)	16 (32.7)
Neutropenia	170 (51.2)	8 (3.7)	188 (54.3)	5 (2.0)	27 (41.5)	1 (2.5)	27 (44.3)	0 (0.0)
Nausea	140 (42.2)	23 (10.7)	144 (41.6)	16 (6.4)	25 (38.5)	2 (5.0)	28 (45.9)	6 (12.2)
Fatigue	120 (36.1)	17 (7.9)	125 (36.1)	25 (10.0)	26 (40.0)	5 (12.5)	28 (45.9)	8 (16.3)
Rash	76 (22.9)	13 (6.0)	120 (34.7)	27 (10.8)	20 (30.8)	3 (7.5)	17 (27.9)	8 (16.3)
Asthenia	97 (29.2)	17 (7.9)	89 (25.7)	27 (10.8)	23 (35.4)	3 (7.5)	17 (27.9)	2 (4.1)
Decreased appetite	82 (24.7)	6 (2.8)	99 (28.6)	18 (7.2)	23 (35.4)	1 (2.5)	20 (32.8)	1 (2.0)
Peripheral oedema	97 (29.2)	24 (11.2)	84 (24.3)	18 (7.2)	22 (33.8)	2 (5.0)	10 (16.4)	4 (8.2)
Vomiting	74 (22.3)	13 (6.0)	82 (23.7)	16 (6.4)	21 (32.3)	1 (2.5)	16 (26.2)	2 (4.1)
Dysgeusia	49 (14.8)	2 (0.9)	58 (16.8)	2 (0.8)	13 (20.0)	0 (0.0)	17 (27.9)	2 (4.1)
Febrile neutropenia	26 (7.8)	0 (0.0)	51 (14.7)	0 (0.0)	4 (6.2)	0 (0.0)	5 (8.2)	0 (0.0)
LVSD	26 (7.8)	11 (5.1)	16 (4.6)	10 (4.0)	7 (10.8)	6 (15.0)	2 (3.3)	2 (4.1)

D docetaxel, *LVSD* left ventricular systolic dysfunction

Table 6 Ten most common grade ≥3 adverse events overall

n (%)	<65 years		≥65 years	
	Placebo + trastuzumab + docetaxel ($n = 332$)	Pertuzumab + trastuzumab + docetaxel ($n = 346$)	Placebo + trastuzumab + docetaxel ($n = 65$)	Pertuzumab + trastuzumab + docetaxel ($n = 61$)
Total number of patients with at least one grade ≥ 3 adverse event	241 (72.6)	255 (73.7)	48 (73.8)	47 (77.0)
Blood and lymphatic system disorders	184 (55.4)	210 (60.7)	31 (47.7)	30 (49.2)
Neutropenia	156 (47.0)	174 (50.3)	26 (40.0)	25 (41.0)
Leukopenia	51 (15.4)	44 (12.7)	7 (10.8)	6 (9.8)
Febrile neutropenia	26 (7.8)	51 (14.7)	4 (6.2)	5 (8.2)
Diarrhoea	16 (4.8)	23 (6.6)	4 (6.2)	9 (14.8)
Anaemia	9 (2.7)	10 (2.9)	5 (7.7)	0 (0.0)
Fatigue	9 (2.7)	7 (2.0)	4 (6.2)	2 (3.3)
Peripheral neuropathy	6 (1.8)	6 (1.7)	1 (1.5)	5 (8.2)
LVSD	8 (2.4)	4 (1.2)	3 (4.6)	1 (1.6)
Asthenia	4 (1.2)	10 (2.9)	2 (3.1)	0 (0.0)
Granulocytopenia	9 (2.7)	4 (1.2)	0 (0.0)	2 (3.3)

LVSD left ventricular systolic dysfunction

evidence of late or cumulative cardiac toxicity after an additional year of follow-up [19]. Although older patients are at increased risk of congestive heart failure, we could not find a significant correlation of age with the development of asymptomatic or symptomatic LVSD. Nevertheless, routine monitoring of cardiac function in patients receiving trastuzumab and pertuzumab is recommended.

Due to the increase in life expectancy, the number of older patients with breast cancer will rise and treatment decisions should be based on an acceptable benefit–risk ratio. According to data from 2011 in the US, women aged 65–69 and 70–74 years have a life expectancy of about 20 and 16 years, respectively [23]. Underestimation of a patient's life expectancy and of their general physical ability may result in erroneous decisions to treat less aggressively, exposing the patient to an unnecessary risk of breast cancer-related death. However, the higher frequency of co-morbidities, mainly hypertension, arthritis, and heart diseases [7], in older patients with breast cancer is an equally important consideration for disease management. Studies have shown that older patients derive a similar benefit from chemotherapy to younger patients [24–26], but that they are more vulnerable to chemotherapy-related toxicities [24, 27, 28]. In their updated recommendations for the management of elderly patients with breast cancer the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) emphasize that chronological age alone should not be a determinant for the treatment of breast cancer [29]. Decisions regarding treatment should rather be based on physiological age (fitness), estimated life expectancy, risks, benefits, treatment tolerance, patient preference, and potential treatment barriers [29]. In addition, an (abbreviated) comprehensive geriatric assessment may help guide informed treatment decisions for older patients with breast cancer [29].

Based on the efficacy benefit and the adverse events profile observed in CLEOPATRA, we suggest that the use of pertuzumab, trastuzumab, and docetaxel should not be limited by age, though proactive management of toxicities and regular cardiac monitoring should clearly be undertaken. At present, population-based data with the combination of pertuzumab and trastuzumab are limited due to its very recent approval. More evidence on the tolerability and efficacy of pertuzumab and trastuzumab in HER2-positive metastatic breast cancer in combination with different chemotherapy partners and aromatase inhibitors in patients with hormone receptor-positive disease will be obtained in several clinical trials currently ongoing (NCT01572038, NCT01026142, NCT01565083, NCT01491737).

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