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Final results from the PERUSE study of first-line pertuzumab plus trastuzumab plus a taxane for HER2-positive locally recurrent or metastatic breast cancer,

(Article begins on next page)

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ORIGINAL ARTICLE

Final results from the PERUSE study of first-line pertuzumab plus trastuzumab plus a taxane for HER2-positive locally recurrent or metastatic breast cancer, with a multivariable approach to guide prognostication

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Background: The phase III CLinical Evaluation Of Pertuzumab And TRAstuzumab (CLEOPATRA) trial established the combination of pertuzumab, trastuzumab and docetaxel as standard first-line therapy for human epidermal growth factor receptor 2 (HER2)-positive locally recurrent/metastatic breast cancer (LR/mBC). The multicentre single-arm PERtUzumab global SafEty (PERUSE) study assessed the safety and efficacy of pertuzumab and trastuzumab combined with investigator-selected taxane in this setting.

Patients and methods: Eligible patients with inoperable HER2-positive LR/mBC and no prior systemic therapy for LR/mBC (except endocrine therapy) received docetaxel, paclitaxel or nab-paclitaxel with trastuzumab and pertuzumab until disease progression or unacceptable toxicity. The primary endpoint was safety. Secondary endpoints included progression-free survival (PFS) and overall survival (OS). Prespecified subgroup analyses included subgroups according to taxane, hormone receptor (HR) status and prior trastuzumab. Exploratory univariable analyses identified potential prognostic factors; those that remained significant in multivariable analysis were used to analyse PFS and OS in subgroups with all, some or none of these factors.

Results: Of 1436 treated patients, 588 (41%) initially received paclitaxel and 918 (64%) had HR-positive disease. The most common grade ≥3 adverse events were neutropenia (10%, mainly with docetaxel) and diarrhoea (8%). At the final analysis (median follow-up: 5.7 years), median PFS was 20.7 [95% confidence interval (CI) 18.9-23.1] months overall and was similar irrespective of HR status or taxane. Median OS was 65.3 (95% CI 60.9-70.9) months overall. OS was similar regardless of taxane backbone but was more favourable in patients with HR-positive than HR-negative LR/mBC. In exploratory analyses, trastuzumab-pretreated patients with visceral disease had the shortest median PFS (13.1 months) and OS (46.3 months).

Conclusions: Mature results from PERUSE show a safety and efficacy profile consistent with results from CLEOPATRA and median OS exceeding 5 years. Results suggest that paclitaxel is a valid alternative to docetaxel as backbone chemotherapy. Exploratory analyses suggest risk factors that could guide future trial design.

Key words: pertuzumab, paclitaxel, HER2 positive, metastatic breast cancer, overall survival, hormone receptor

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INTRODUCTION

In human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer, results from the randomised phase III CLinical Evaluation Of Pertuzumab And TRAstuzumab (CLEOPATRA) trial evaluating the addition of pertuzumab to first-line trastuzumab and docetaxel set a new standard.[1-3] Both progression-free survival (PFS) and overall survival (OS) were significantly improved with dual HER2 blockade compared with a single HER2-directed therapy. Subsequently, several trials have evaluated alternative regimens, including non-taxane-based chemotherapy agents, such as vinorelbine and eribulin,[4-6] or exchanging intravenous trastuzumab for the subcutaneous formulation.[7] PERtUzumab global SafEty (PERUSE), an international single-arm study, assessed the safety and efficacy of three widely used taxanes in combination with dual HER2 targeting as first-line therapy for locally recurrent/metastatic breast cancer (LR/mBC). Preliminary results suggested that the subgroup of patients receiving paclitaxel with pertuzumab and trastuzumab derived similar efficacy but experienced fewer toxicities than those treated with a docetaxel-based regimen.[8] Here we report final safety and efficacy results from the PERUSE study, including prespecified subgroup analyses according to hormone receptor (HR) status and investigator-selected taxane.

PATIENTS AND METHODS

The global, open-label, single-arm phase IIIb PERUSE study (NCT01572038) was designed to evaluate the safety and tolerability of pertuzumab in combination with trastuzumab and a taxane. Eligibility criteria have been described in detail previously.[8] In brief, eligible patients had unresectable HER2-positive LR/mBC, at least one measurable lesion and/or non-measurable disease evaluable according to Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1), Eastern Cooperative Oncology Group (ECOG) performance status ≤2, left ventricular ejection fraction (LVEF) ≥50% and no prior systemic therapy (except ≤2 lines of endocrine therapy, one of which could have been in combination with everolimus) for LR/mBC. Prior anti-HER2 therapy (approved or investigational) other than (neo)adjuvant trastuzumab and/or lapatinib was prohibited. Patients with disease progression during (neo)adjuvant trastuzumab and/or lapatinib therapy were excluded, as were patients with recurrence within 6 months of completing (neo)adjuvant non-hormonal systemic therapy. Patients with central nervous system metastases were eligible if they were stable for ≥3 months preceding screening after receiving local therapy without anti-HER2 therapy.

Choice of taxane agent (docetaxel, paclitaxel or nab-paclitaxel) was at the investigators' discretion. Taxanes were administered weekly or every 3 weeks (q3w) in accordance with recognised guidelines and/or local prescribing information, and given in combination with q3w pertuzumab (Perjeta®, F. Hoffmann-La Roche Ltd, Basel, Switzerland) at a dose of 840 mg in cycle 1 followed by 420 mg in subsequent cycles, and q3w trastuzumab (Herceptin®, F. Hoffmann-La Roche Ltd) at a dose of 8 mg/kg in cycle 1 followed by 6 mg/kg for subsequent cycles. During treatment, patients were permitted to switch to an alternative taxane per protocol. Study treatment was administered until unacceptable toxicity, disease progression, withdrawal of consent or death, whichever occurred first. Approved endocrine maintenance therapies were permitted after discontinuation of chemotherapy.

Adverse events (AEs) were coded according to Medical Dictionary for Regulatory Activities (version 21.0) and severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). LVEF assessment has been described previously.[8]

The primary objective of PERUSE was to evaluate the safety and tolerability of pertuzumab in combination with trastuzumab and a taxane. Secondary endpoints included PFS, OS, overall response rate (ORR), clinical benefit rate (defined as a best response of partial or complete response, or disease stabilisation maintained for ≥6 months), duration of response, time to response and patient-reported outcomes, assessed using the Functional Assessment of Cancer Therapy—Breast (FACT-B) questionnaire.

Investigators assessed tumour response using computed tomography or magnetic resonance imaging scans (and isotope bone scan if indicated) according to RECIST (version 1.1). Objective responses were confirmed ≥4 weeks after initial documentation. Tumour assessments were carried out every three cycles for the first 3 years, and every six cycles thereafter in patients who remained progression free.

Safety analyses were based on the safety population, comprising all enrolled patients who received at least one dose of study treatment. PFS and OS were estimated using the Kaplan—Meier method in the intention-to-treat (ITT) population, defined as all enrolled patients, and medians were estimated with 95% confidence intervals (CIs). PFS was defined as the interval between enrolment and first radiographically documented disease progression according to RECIST (excluding progression recorded only as 'clinical progression') or death, whichever occurred first. Patients with no post-baseline tumour assessments were censored on day 1; those who were alive and progression free or lost to follow-up were censored at the date of last evaluable tumour assessment. Patients with two or more missed RECIST scan visits (19 weeks) were censored at the last evaluable visit before the missed visits. ORR analysis was based on the best (confirmed) overall response as assessed by investigators in all enrolled patients with measurable disease at baseline.

All analyses were descriptive. No formal statistical hypothesis testing was carried out. Prespecified subgroup analyses of efficacy included subgroups defined by HR status, selected taxane, age (<65 versus ≥65 years), ECOG performance status (0/1 versus 2), visceral disease at baseline, prior (neo)adjuvant chemotherapy and prior trastuzumab. For subgroup analyses by taxane, patients were analysed according to the first taxane they received during study therapy. There were no adjustments for multiplicity of endpoints or comparisons within subgroups. Post

hoc exploratory multivariable Cox regression analyses explored the impact of key clinical factors on PFS. Factors demonstrating prognostic value were used to identify subgroups with all, some or none of the risk factors and explore PFS and OS outcomes between subgroups.

The study was carried out in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki, and all patients provided written informed consent. The protocol and all accompanying materials provided to patients were approved by independent ethics committees at the participating institutions.

RESULTS

Patient population

Between 11 May 2012 and 16 September 2014, 1436 patients were enrolled from sites in Europe, Asia, North and South America, Africa and Australia and began treatment with pertuzumab. One patient discontinued therapy immediately after the first pertuzumab administration and therefore received neither trastuzumab nor taxane, and seven additional patients discontinued all study treatments before receiving their first taxane dose. The initial taxane selected by the investigator was docetaxel in 775 patients (54%), paclitaxel in 588 patients (41%) and nab-paclitaxel in 65 patients (5%). Baseline characteristics and prior therapy (overall and in key subgroups) are summarised in Table 1.

Treatment exposure

At the final data cut-off (26 August 2019), the median duration of follow-up was 68.7 months (95% CI 67.5-69.3 months; range 0.0-87.3 months), corresponding to 5.7 years. The median duration of anti-HER2 therapy was

24 cycles (range 1-126 cycles) (corresponding to 16.1 months). The median duration of taxane exposure was 6 cycles (range 1-94 cycles), corresponding to 4.2 months (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.06.024). Median treatment exposure was longer in patients aged ≤65 than >65 years (17.5 versus 11.1 months, respectively) and longer in patients who were trastuzumab naïve than trastuzumab pretreated (17.9 versus 13.2 months, respectively). All but one patient had discontinued study treatment by the final analysis. The majority of patients (62%) discontinued pertuzumab and trastuzumab because of disease progression (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.06.024). In contrast, taxane therapy was often discontinued for reasons other than progression: in 35% of patients, the primary reason for stopping taxane was 'completed regimen' and a further 30% stopped at the investigator's decision. A total of 295 patients (21%) received maintenance endocrine therapy, most commonly with an aromatase inhibitor (13%) or antiestrogen (6%).

Safety

The most common AEs were gastrointestinal and skin/subcutaneous events (Figure 1 and Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.06.024). Grade ≥3 AEs occurred in 61% of patients and were considered related to pertuzumab in 20% of patients, to trastuzumab in 17% and to taxane in 36%. The most common grade ≥3 AEs were neutropenia (10%) and diarrhoea (8%). Consistent with the preliminary safety report,[8] docetaxel was associated with higher incidences of grade ≥3 neutropenia (15% compared with 5% and 2% in patients treated with paclitaxel and nab-paclitaxel, respectively) and grade ≥3

Table 1. Baseline characteristics overall and by taxane, HR and prior trastuzumab subgroup								
Characteristic	All patients (n = 1436)	Taxane[a]			HR[b]		Prior trastuzumab	
		Docetaxel (n = 775)	Paclitaxel (n = 588)	Nab-paclitaxel (n = 65)	Positive (n = 918)	Negative (n = 512)	Yes (n = 400)	No (n = 1036)
Age, years								
Median (range)	54 (23-87)	53 (23-82)	56 (26-87)	53 (31-81)	54 (26-83)	55 (23-87)	53 (27-82)	55 (23-87)
>65, n (%)	269 (19)	120 (15)	134 (23)	12 (18)	174 (19)	95 (19)	59 (15)	210 (20)
ECOG PS,[c] n (%)								
0 or 1	1371 (95)	754 (97)	547 (93)	64 (98)	873 (95)	492 (96)	382 (96)	989 (95)
2	63 (4)	20 (3)	40 (7)	1 (2)	44 (5)	19 (4)	18 (5)	45 (4)
Sex, n (%)								
Female	1429 (100)	772 (100)	586 (100)	63 (97)	911 (99)	512 (100)	397 (99)	1032 (100)
Male	7 (<1)	3 (<1)	2 (<1)	2 (3)	7 (1)	0	3 (1)	4 (<1)
Race, n (%)								
White	1032 (72)	577 (74)	398 (68)	51 (78)	673 (73)	355 (69)	289 (72)	743 (72)
Asian	88 (6)	48 (6)	34 (6)	5 (8)	52 (6)	34 (7)	14 (4)	74 (7)
Native American	28 (2)	3 (<1)	24 (4)	0	11 (1)	17 (3)	6 (2)	22 (2)
Black	9 (1)	4 (1)	5 (1)	0	7 (1)	2 (<1)	2 (1)	7 (1)
Other	57 (4)	37 (5)	18 (3)	2 (3)	32 (3)	25 (5)	12 (3)	45 (4)
Not collected per local regulations	222 (15)	106 (14)	109 (19)	7 (11)	143 (16)	79 (15)	77 (19)	145 (14)
Visceral disease, n (%)	992 (69)	547 (71)	397 (68)	42 (65)	614 (67)	374 (73)	262 (66)	730 (70)

ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hormone receptor.
[a] Eight patients discontinued all study treatment before receiving taxane.
[b] Unknown in 6 patients.
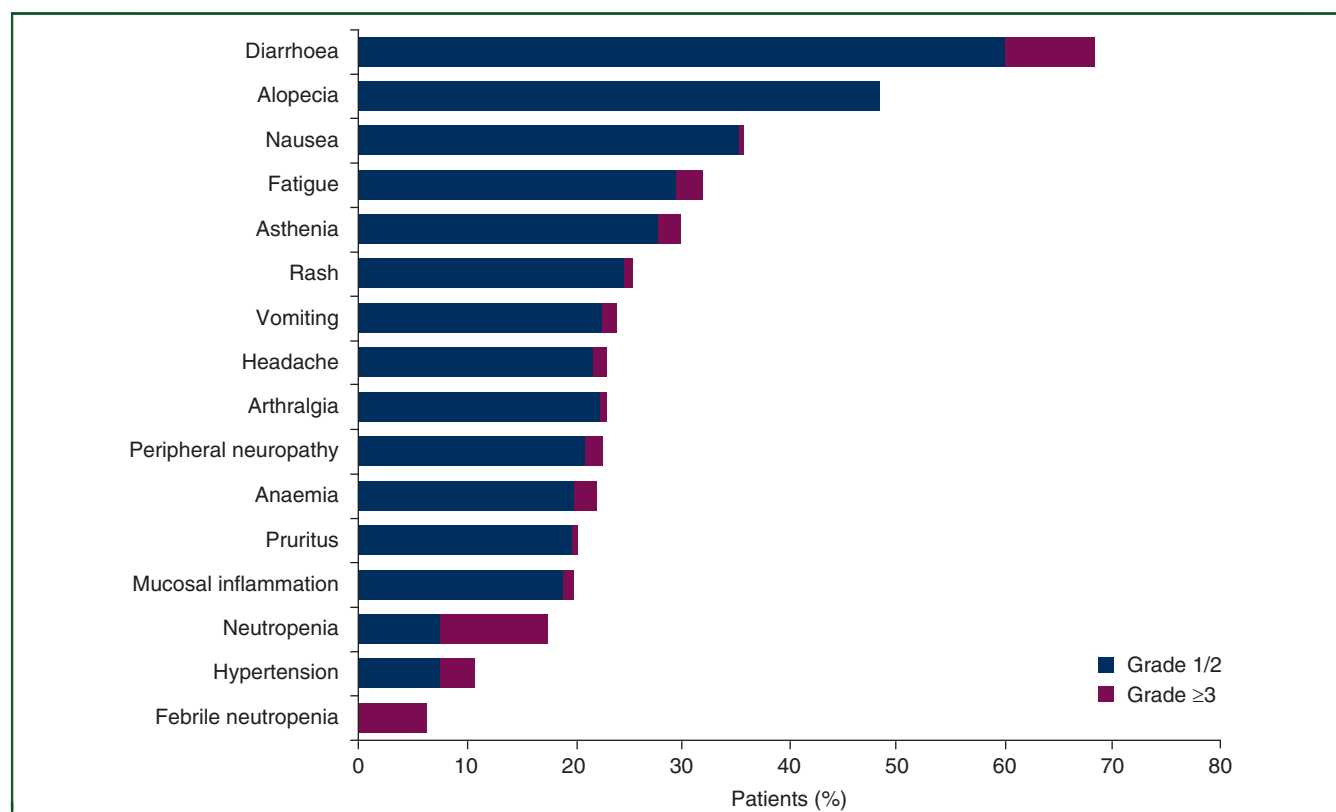[c] Missing in 2 patients.

Figure 1. **Most common adverse events (any grade in ≥20% of patients, grade ≥3 in ≥2%).**

febrile neutropenia (11% compared with 1% and 0% with paclitaxel and nab-paclitaxel, respectively). Grade ≥3 diarrhoea occurred at a similar incidence with the three taxanes (8%, 9% and 8%, respectively). Fatal AEs were reported in 31 patients (2%). The only fatal AEs reported in more than one patient were pneumonia ($n = 4$), sepsis ($n = 3$) and cardiac arrest ($n = 2$).

AEs led to discontinuation of pertuzumab in 10% of patients, trastuzumab in 9% of patients and taxane in 20% of patients. The AEs most commonly leading to treatment discontinuation were ejection fraction decreased (3%) and cardiac failure (0.7%) leading to discontinuation of pertuzumab and trastuzumab, and peripheral neuropathy (4%), peripheral sensory neuropathy (2%), paraesthesia (2%), diarrhoea (1%), fatigue (1%), asthenia (0.9%) and onycholysis (0.6%) leading to taxane discontinuation.

Focusing on AEs of special interest (those previously associated with pertuzumab), 1 patient (0.1%) had fatal hepatic failure and 90 patients (6%) experienced an LVEF decline, comprising ejection fraction decreased in 75 patients (5%), left ventricular dysfunction in 8 patients (0.6%), cardiac failure in 7 patients (0.5%) and congestive cardiac failure in 1 patient (0.1%).

Efficacy

A confirmed response was recorded in 952 of the 1198 patients with measurable disease, giving an ORR of 79% (95% CI 77-82%). The clinical benefit rate was 86% (95%

CI 84-88%). In the 952 responding patients, the median time to response was 2.5 months (95% CI 2.4-2.5 months) and the median duration of response was 20.0 months (95% CI 18.2-22.2 months).

By the final data cut-off, 872 of 1436 patients (61%) had experienced disease progression or death. This number is lower than that reported at the interim analysis[8] because of a change before the final analysis to use stricter criteria for defining disease progression to align with the CLEOPATRA trial. Median PFS was 20.7 months (95% CI 18.9-23.1 months) in the ITT population (Figure 2A). Subgroup analyses showed similar PFS irrespective of HR status (Figure 2B) or taxane backbone (Figure 2C) but favoured the subgroup with no prior trastuzumab (Figure 2D).

At the data cut-off, deaths had been recorded in 658 patients (46%), of which 581 (88% of 658) were from progressive disease. Median OS was 65.3 months (95% CI 60.9-70.9 months) in the ITT population (Figure 3A). OS was similar in the subgroups defined by taxane backbone and the Kaplan—Meier curves for docetaxel and paclitaxel were overlapping (Figure 3C). However, OS was more favourable in patients with HR-positive disease than HR-negative disease (Figure 3B), and in those with no prior trastuzumab than prior trastuzumab (Figure 3D). Efficacy in additional subgroups is summarised in Table 2.

In *post hoc* multivariable Cox regression analyses, visceral disease and prior therapy (trastuzumab or other) were associated with worse PFS [hazard ratio 1.47 (95% CI 1.26-1.72) for visceral disease; hazard ratio 1.64 (95% CI
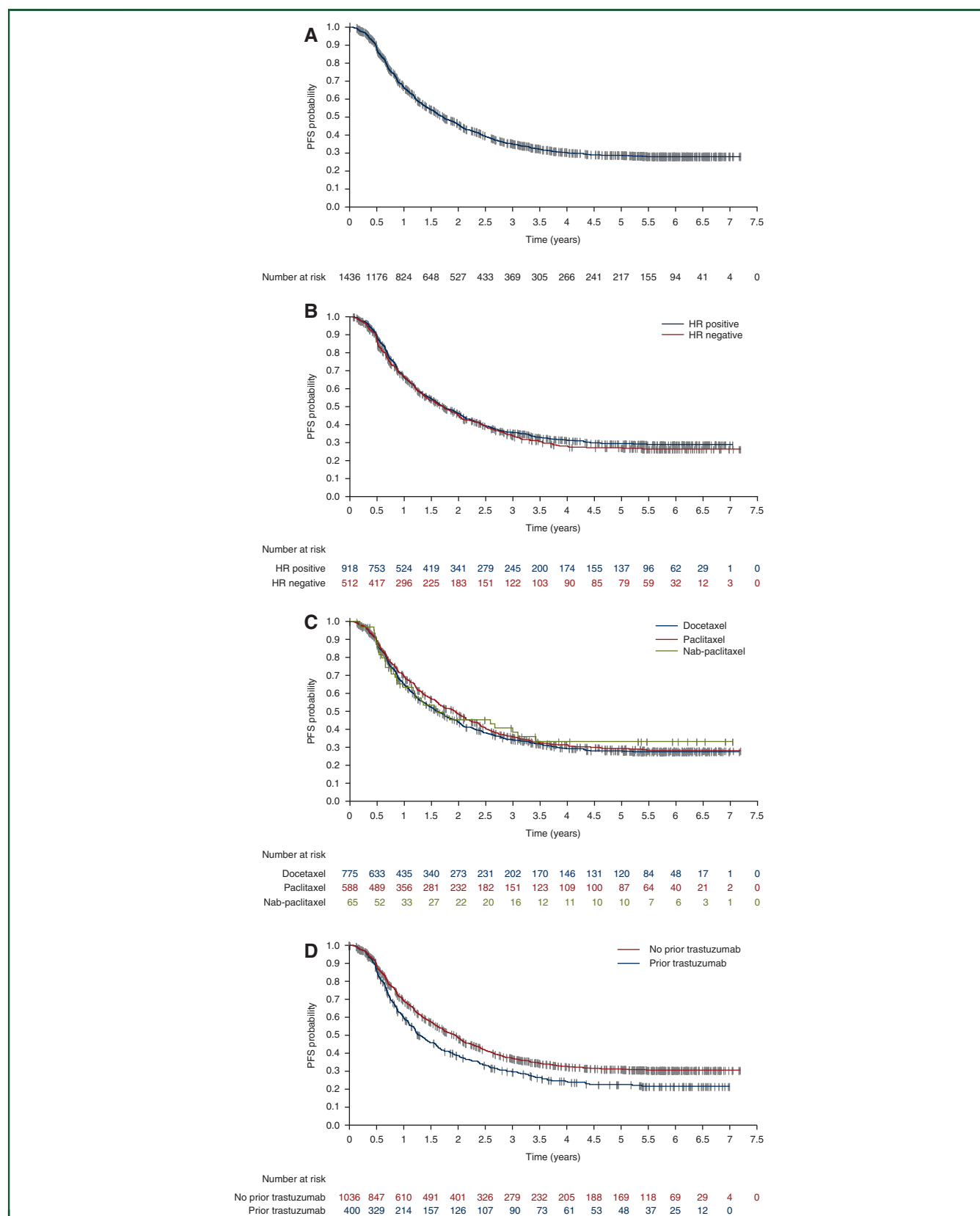
Figure 2. PFS: (A) overall, (B) by HR status, (C) by initially selected taxane, (D) by prior trastuzumab.
HR, hormone receptor; PFS, progression-free survival.

1.29-2.07) for prior trastuzumab; hazard ratio 1.41 (95% CI 1.10-1.80) for prior therapy other than trastuzumab] (Table 3). Further exploratory analyses defining subgroups with both, one or neither of these risk factors revealed considerably worse PFS [median 13.1 months (95% CI 10.6-15.0)] and OS [median 46.3 months (95% CI 38.3-51.9)] in
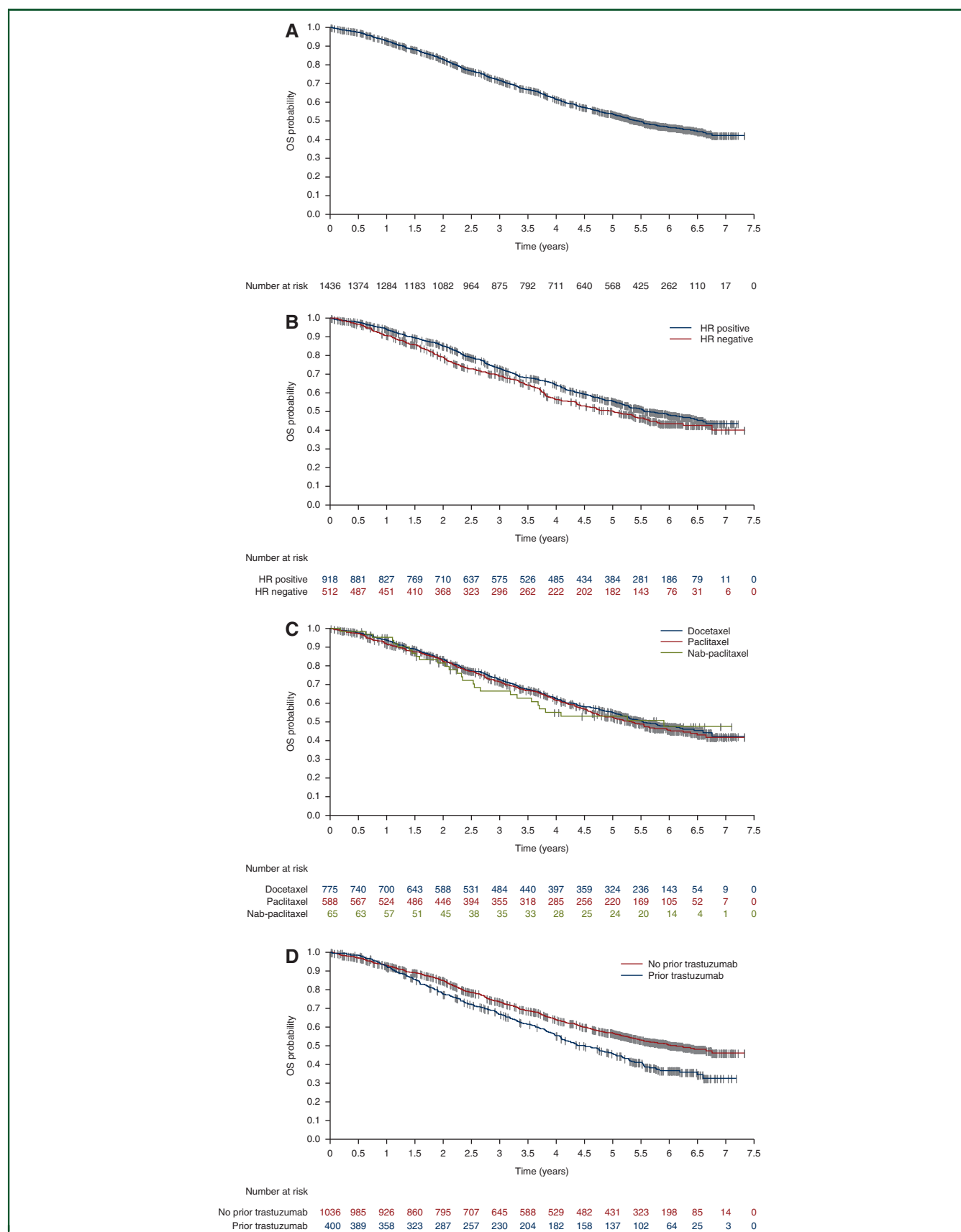
Figure 3. OS: (A) overall, (B) by HR status, (C) by initially selected taxane, (D) by prior trastuzumab.
HR, hormone receptor; OS, overall survival.

Table 2. Summary of efficacy by subgroup

Subgroup	PFS		OS	
	Events, n (%)	Median (95% CI), months	Events, n (%)	Median (95% CI), months
All patients (n = 1436)	872 (61)	20.7 (18.9-23.1)	658 (46)	65.3 (60.9-70.9)
HR positive (n = 918)[a]	550 (60)	20.6 (18.5-23.8)	411 (45)	66.7 (62.4-77.3)
HR negative (n = 512)[a]	318 (62)	20.7 (17.1-23.8)	245 (48)	60.2 (52.3-67.7)
Docetaxel (n = 775)	479 (62)	19.4 (16.9-22.1)	351 (45)	66.5 (61.7-77.3)
Paclitaxel (n = 588)	356 (61)	23.2 (19.6-25.6)	273 (46)	64.0 (56.6-72.2)
Nab-paclitaxel (n = 65)	35 (54)	19.2 (11.7-37.1)	28 (43)	70.9 (39.7-NE)
Visceral disease (n = 992)	644 (65)	18.2 (16.1-20.6)	486 (49)	57.1 (52.4-63.4)
Non-visceral disease (n = 444)	228 (51)	27.2 (23.8-34.4)	172 (39)	81.1 (71.7-NE)
Age ≤65 years (n = 1167)	715 (61)	22.0 (19.6-24.2)	509 (44)	70.0 (64.3-81.1)
Age >65 years (n = 269)	157 (58)	14.7 (12.2-19.5)	149 (55)	50.1 (41.3-54.0)
Prior trastuzumab (n = 400)	274 (69)	15.4 (13.7-19.0)	219 (55)	54.1 (48.7-60.7)
No prior trastuzumab (n = 1036)	598 (58)	23.4 (20.7-25.0)	439 (42)	73.5 (65.6-NE)

CI, confidence interval; HR, hormone receptor; NE, not estimable; OS, overall survival; PFS, progression-free survival.
[a] HR status unknown in 6 patients.

262 patients with both visceral disease and prior trastuzumab therapy (Figure 4).

Subsequent therapy

By the final data cut-off, post-study anticancer therapy had been reported in 679 patients (47%). The most commonly administered anti-HER2 agents were trastuzumab (25%), trastuzumab emtansine (19%), lapatinib (16%) and pertuzumab (7%). The most commonly administered chemotherapy agents were capecitabine (20%), vinorelbine (10%) and taxane (6%). The most commonly administered endocrine therapies were aromatase inhibitors (8%) and antiestrogens (6%).

Patient-reported outcomes

At baseline, at least one subscale of the FACT-B questionnaires was completed by 1335 (93%) of 1429 female patients. Mean (standard deviation) baseline scores at baseline were 99.9 (20.5) for total FACT-B score, 21.0 (6.0)

for physical well-being, 22.2 (5.0) for social well-being, 15.1 (5.0) for emotional well-being, 16.7 (6.1) for functional well-being and 25.0 (6.3) for breast cancer subscale score. As shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2021.06.024, there was almost no change from baseline across all timepoints with >10% of patients completing questionnaires for total FACT-B score or any of the subscales, and mean changes did not exceed meaningful thresholds.

DISCUSSION

The final analysis of PERUSE represents a mature dataset (median follow-up approaching 6 years) in a large global population of patients representative of routine oncology practice in a wide range of health care settings. The patient population was generally similar to that enrolled in the randomised phase III CLEOPATRA trial, except for a smaller proportion of patients with visceral disease (69% versus 88% in CLEOPATRA) and a larger proportion previously treated with trastuzumab (28% versus 12% in CLEOPATRA).[1] The safety profile of first-line pertuzumab combined with trastuzumab and standard taxane therapy for HER2-positive LR/mBC in PERUSE was consistent with the known safety profile of the individual agents and the results from the phase III CLEOPATRA trial.[1,2] Safety results in the final analysis of PERUSE were consistent with the preliminary report, in which AEs were reported according to taxane partner.[8] No cumulative toxicities emerged with longer follow-up and no new safety signals were identified with alternative taxane backbones.

The final efficacy results provide reassuring evidence of the effectiveness of pertuzumab, trastuzumab and investigator-selected taxane. While recognising the limitations of cross-trial comparisons, clinical outcomes with all three regimens are in line with those reported from CLEOPATRA (median PFS of 19.2-23.2 months with the three taxane regimens in PERUSE versus 18.7 months with pertuzumab, trastuzumab and docetaxel in CLEOPATRA;[1] median OS of 64.0-70.9 months in PERUSE versus 57.1 months in CLEOPATRA after >8 years of follow-up at the end-of-study analysis[3]). The results also compare

Table 3. Multivariable Cox regression analysis on PFS

Variable	Hazard ratio (95% CI)	P value[a]
Age (>65 versus ≤65 years)	1.18 (0.98-1.43)	0.08
Child-bearing potential (yes versus no)	0.95 (0.81-1.11)	0.51
Visceral disease at baseline (yes versus no)	1.47 (1.26-1.72)	<0.0001
Prior therapy		0.0003
Trastuzumab versus none	1.64 (1.29-2.07)	
Other versus none	1.41 (1.10-1.80)	
Stage at diagnosis		0.30
II versus I	1.18 (0.89-1.56)	
III versus I	1.30 (0.98-1.72)	
IV versus I	1.28 (0.92-1.79)	
Time since primary diagnosis (years)	0.98 (0.95-1.00)	0.08
HR status		0.73
Positive versus negative	0.94 (0.82-1.09)	
Unknown versus negative	0.92 (0.34-2.47)	
Disease status at diagnosis (locally recurrent versus metastatic)	1.05 (0.78-1.42)	0.75
Time since diagnosis of metastatic disease (months)	1.01 (1.00-1.02)	0.15

CI, confidence interval; HR, hormone receptor; PFS, progression-free survival.
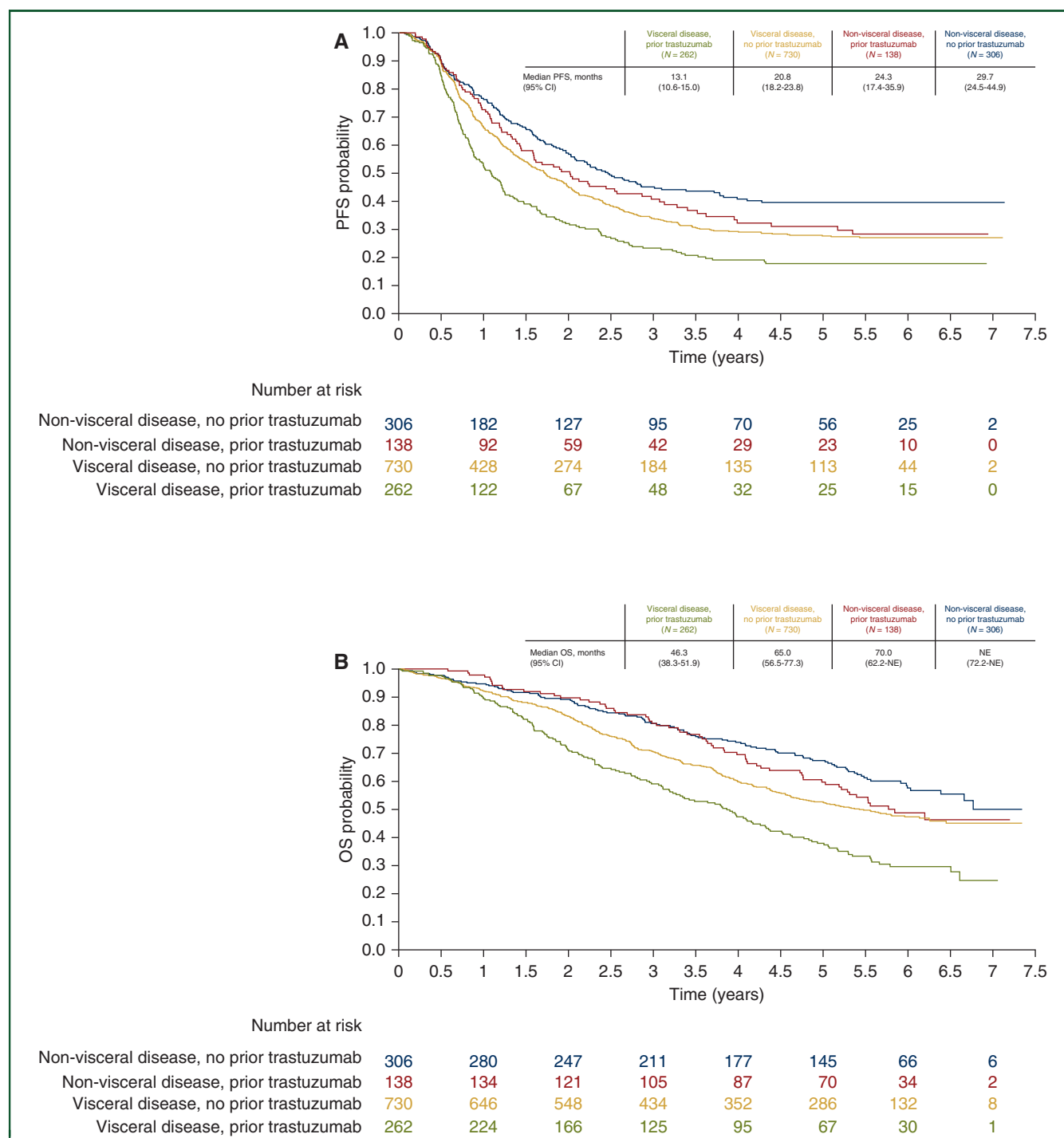[a] Chi-squared test for the effect.

Figure 4. Clinical outcomes according to risk factors identified in multivariable analysis: (A) PFS and (B) OS.
CI, confidence interval; PFS, progression-free survival; OS, overall survival.

favourably with recently published PFS results from the PUFFIN randomised trial evaluating the CLEOPATRA regimen in Chinese patients (median PFS of 14.5 months, OS results immature).[9] Comparison with the first randomised trial of trastuzumab in HER2-positive LR/mBC[10] highlights the remarkable improvements in the treatment of this disease since the introduction of HER2-targeted therapy, notwithstanding the obvious caveats of comparing trials with different designs in different populations and separated temporally by two decades. For

example, a higher proportion of patients included in the trial reported by Slamon et al.[10] than in PERUSE had received endocrine therapy in the adjuvant or metastatic setting before receiving anti-HER2 study therapy with paclitaxel [48/89 (55%)[10] versus 181/589 (31%)[8] patients in H0648g versus PERUSE, respectively].

In PERUSE, patients with HR-positive disease appeared to have similar PFS but longer OS than those with HR-negative disease, as would be expected given the natural history of disease. Unlike CLEOPATRA, patients in PERUSE could

receive maintenance endocrine therapy, which is relatively widespread in routine practice.[11,12] The maintenance endocrine therapy approach is also similar in some respects to the chemotherapy cohort of the randomised PERtuzumab and Trastuzumab plus Aromatase INhibitor (PERTAIN) trial, showing a median PFS of 16.9 months, although in PERTAIN, taxane therapy was continued for a maximum of 24 weeks before switching to an aromatase inhibitor in combination with pertuzumab plus trastuzumab.[13]

Subgroup analyses according to prior trastuzumab exposure showed a median PFS of 15.4 months in patients previously treated with trastuzumab, and a median OS of 54.1 months (consistent with a median OS of 53.8 months in 47 trastuzumab-pretreated patients in CLEOPATRA[2,3]). Median PFS and OS were longer in trastuzumab-naïve patients, but the lack of prior chemotherapy in a substantial proportion of this subgroup hints at a population enriched with *de novo* metastatic disease, associated with a better prognosis.[11] Reports in the literature from registry-based studies provide differing conclusions on the impact of prior trastuzumab on outcomes with first-line pertuzumab plus trastuzumab regimens;[14-16] these studies are limited by their retrospective nature and relatively small sample sizes. In an analysis of individual patient data from the CLEOPATRA trial, number of metastatic sites and lactate dehydrogenase level were identified as pretreatment prognostic markers, but not prior trastuzumab.[17] However, in PERUSE, *post hoc* multivariable analyses suggested that the presence of both visceral disease and prior trastuzumab identified a population with notably worse PFS and OS outcome (median PFS 13.1 months, median OS 46.3 months) compared with patients with only one or neither of these risk factors (median PFS 29.7 months, median OS not reached in patients with no visceral disease and no prior trastuzumab). This finding should be taken into consideration when selecting stratification factors for future trials, and may help to identify a population in which investigational therapies may be of particular interest.

Final results from PERUSE complement the pivotal CLEOPATRA phase III trial results, demonstrating the generalisability of the findings to a routine clinical practice setting and the broader applicability of the results to alternative taxane backbones, particularly paclitaxel. They also provide important insight into long-term outcomes in patients with HR-positive disease who may have switched from taxane chemotherapy to endocrine maintenance therapy in combination with pertuzumab and trastuzumab. Median OS exceeding 5.5 years in these patients is noteworthy. Although the study was not designed specifically to evaluate this strategy, the large sample size, prospective nature of the study, rigorous data collection and robust tumour assessment suggest that this is a reasonable approach for patients with HR-positive disease. Likewise, findings in the subgroup of patients treated with paclitaxel, including a median OS of 64 months (5.3 years), lend support to the use of this more tolerable chemotherapy partner in combination with first-line pertuzumab and trastuzumab in patients for whom docetaxel may not be considered optimal or appropriate.

In conclusion, final results from the PERUSE study after a median follow-up of almost 6 years support the use of a first-line combination of pertuzumab, trastuzumab and taxane therapy for HER2-positive LR/mBC, and suggest that paclitaxel is a valid alternative to docetaxel as backbone chemotherapy. These results add to the existing body of evidence and reinforce the role of dual HER2 blockade with pertuzumab and trastuzumab in combination with a taxane as the standard-of-care first-line regimen for HER2-positive LR/mBC. Exploratory analyses suggest risk factors that could guide future trial design.

DISCLOSURE

DM has received honoraria for advisory boards from Roche/Genentech, Genomic Health and Eisai, and has been an invited speaker for Roche/Genentech and Genomic Health. EC has received consultancy fees from Roche, Lilly, Novartis and Pfizer, and has received honoraria for speaker engagements from Celgene, Roche, Novartis and Pfizer. AS has received honoraria for scientific talks from Roche, Celgene, AstraZeneca, Pfizer and Novartis, and travel support from Roche and Celgene. FP reports consultant/advisory roles for Amgen, AstraZeneca, Daichii-Sankyo, Eli Lilly, Ipsen, MSD, Novartis, Pierre Fabre, Pfizer and Roche, and research funding from AstraZeneca, Eisai and Roche. TP-Y has received honoraria for advisory boards and lectures from F. Hoffmann-La Roche, Pfizer, Neopharm, MSD, AstraZeneca, Janssen, Teva, Screen Cell, Medison, AbbVie and Takeda, and has received travel support from F. Hoffmann-La Roche, Bristol-Myers Squibb, AstraZeneca and Janssen. MC reports participation in advisory boards for AstraZeneca, Novartis, AbbVie, Sanofi, Pfizer, Sandoz, ACCORD and Lilly GT1 group, consultancy roles for Pierre Fabre Oncology, Sanofi, Novartis, Servier and Sanofi, speaker bureau/expert testimony for Novartis and travel/accommodation/expenses from Pfizer, Novartis, Roche and AstraZeneca. IB and his institution have received an investigator fee from Roche for the PERUSE study. ZN has received travel/accommodation/expenses

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