ORIGINAL ARTICLE

Clinical considerations of the role of palbociclib in the management of advanced breast cancer patients with and without visceral metastases

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Background: This report assesses the efficacy and safety of palbociclib plus endocrine therapy (ET) in women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer (ABC) with or without visceral metastases.

Patients and methods: Pre- and postmenopausal women with disease progression following prior ET (PALOMA-3; $N = 521$) and postmenopausal women untreated for ABC (PALOMA-2; $N = 666$) were randomized 2 : 1 to ET (fulvestrant or letrozole, respectively) plus palbociclib or placebo. Progression-free survival (PFS), safety, and patient-reported quality of life (QoL) were evaluated by prior treatment and visceral involvement.

Results: Visceral metastases incidence was higher in patients with prior resistance to ET (58.3%, PALOMA-3) than in patients naive to ET in the ABC setting (48.6%, PALOMA-2). In patients with prior resistance to ET and visceral metastases, median PFS (mPFS) was 9.2 months with palbociclib plus fulvestrant versus 3.4 months with placebo plus fulvestrant [hazard ratio (HR), 0.47; 95% confidence interval (CI), 0.35–0.61], and objective response rate (ORR) was 28.0% versus 6.7%, respectively. In patients with nonvisceral metastases, mPFS was 16.6 versus 7.3 months, HR 0.53; 95% CI 0.36–0.77. In patients with visceral disease and naive to ET in the advanced disease setting, mPFS was 19.3 months with palbociclib plus letrozole versus 12.9 months with placebo plus letrozole (HR 0.63; 95% CI 0.47–0.85); ORR was 55.1% versus 40.0%; in patients with nonvisceral disease, mPFS was not reached with palbociclib plus letrozole versus 16.8 months with placebo plus letrozole (HR 0.50; 95% CI 0.36–0.70). In patients with prior resistance to ET with visceral metastases, palbociclib plus fulvestrant significantly delayed deterioration of QoL versus placebo plus fulvestrant, whereas patient-reported QoL was maintained with palbociclib plus letrozole in patients naive to endocrine-based therapy for ABC.

Conclusions: Palbociclib plus ET prolonged mPFS in patients with visceral metastases, increased ORRs, and in patients previously treated for ABC, delayed QoL deterioration, presenting a standard treatment option among patients with visceral metastases amenable to endocrine-based therapy.

Clinical trial registration: NCT01942135, NCT01740427

Key words: palbociclib, metastatic breast cancer, advanced breast cancer, visceral disease, visceral metastases

Introduction

Many women with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2−) ABC present with visceral metastases, and their prognosis is generally worse than those without visceral involvement [1]. Endocrine therapy (ET) is an effective strategy to manage HR+/HER2− ABC, and sequential ET is the preferred treatment option for patients without immediately life-threatening diseases or rapidly progressing visceral metastases [2–4]. Chemotherapy should be considered for any symptomatic visceral crisis, but otherwise treatment guidelines recommend three sequential ET regimens until no clinical benefit is evident or symptomatic visceral disease occurs [4], for the purpose of delaying the use of chemotherapy as long as possible. Despite this, many patients with visceral disease who are not in visceral crisis receive chemotherapy as early-line treatment [1, 5], although it may be generally associated with worse tolerability [6] and poorer QoL compared with ET [7].

Significant progress has been made in understanding the molecular signaling pathways that account for endocrine resistance, leading to development of various targeted therapies aimed at preventing or reversing resistance [2]. One such therapy is palbociclib, a first-in-class, selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK 4/6) [8, 9]. Activation of CDK 4/6 promotes cell proliferation, and preclinical studies demonstrated that inhibition of CDK4/6 by palbociclib caused cell-cycle arrest in endocrine-resistant breast cancer cell lines [10]. In addition, combining palbociclib with ET results in synergistic effects [10]. These findings led to the design of clinical studies in which the addition of palbociclib to ET resulted in significantly improved progression-free survival (PFS) in both previously treated (PALOMA-3) and treatment-naive (PALOMA-1 and -2) women with HR+/HER2− ABC [11–14].

When evaluating new therapeutic strategies, it is important to weigh the risk and benefit for high-risk patients, such as those with visceral organ metastases. To this end, we carried out pre-specified analyses in the phase III PALOMA-3 and PALOMA-2 studies and compared the efficacy and safety of palbociclib plus ET in patients with visceral versus nonvisceral metastases. These studies enrolled patients with varying degrees of ET responsiveness: premenopausal and postmenopausal women with resistance to prior ET in PALOMA-3, and postmenopausal women still treatment naive for advanced disease in PALOMA-2. Because the prevalence of visceral involvement is higher in patients who progressed on prior ET compared with patients naive to ET in the ABC setting, we first analyzed the PALOMA-3 data and then carried out the same analyses for PALOMA-2.

Methods

Patients and study designs

This analysis includes data from the phase III PALOMA-2 and PALOMA-3 trials. Patients with symptomatic visceral spread who were at risk of life-threatening complications were excluded from both studies [12, 13]. Patients remained on treatment until disease progression, unacceptable toxicity, or consent withdrawal [12, 13]. Detailed descriptions of study methodology have been described elsewhere [12, 13], and are

highlighted in further detail in supplementary Table S1, available at *Annals of Oncology* online.

Both studies were approved by institutional review boards or ethics committees at participating sites and carried out in accordance with the International Harmonisation Good Clinical Practice guidelines and provisions of the Declaration of Helsinki.

End points

The primary end point was investigator-assessed PFS. Secondary end points for efficacy included objective response rate (ORR; defined as confirmed complete or partial response) [13], and time to response (TTR; time to first documented complete or partial response). Other secondary end points included safety and patient-reported outcomes (PROs).

Assessments

In PALOMA-3, visceral metastases referred to lung, liver, brain, pleural, and peritoneal involvement; in PALOMA-2, visceral referred to any lung (including pleura) and/or liver involvement. Lung involvement in PALOMA-3 is defined as the presence of a measurable lesion in the lung, whereas in PALOMA-2 lung involvement includes nonmeasurable pleura and pleural effusion in addition to a measurable lung lesion; therefore, efficacy data for the lung from only the PALOMA-3 study are reported in this study. During the treatment phase of both studies, efficacy was evaluated via tumor assessments carried out every 12 weeks—except in PALOMA-3, scans were every 8 weeks for the first year—from the date of randomization until radiographic/clinical documentation of progressive disease per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria [13]. Safety was assessed at screening, on day 1 of all treatment cycles, on day 14/15 of cycles 1 and 2, at the end of treatment/withdrawal, and post treatment follow-up by evaluating treatment-emergent adverse events (TEAEs) based on incidence, severity (graded by National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0), and the relationship to study drug. PROs were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) in PALOMA-3 and the Functional Assessment of Cancer Therapy-Breast (FACT-B) in PALOMA-2.

Data analysis

Data cut-off dates were 23 October 2015 for PALOMA-3 (later than 5 December 2014 cut-off date for interim analysis reported by Turner et al. [12]) and 26 February 2016 for PALOMA-2. For efficacy, safety, and PROs, the data were analyzed by baseline metastatic site (visceral and nonvisceral) and treatment arm. Baseline characteristics and efficacy results were reported for patients in the intent-to-treat populations. Median PFS (mPFS) was estimated using the Kaplan–Meier (KM) method. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated using Cox proportional hazard model. In this report, the nominal *P* values for efficacy are presented without adjusting for multiplicity. Odds ratios and their 95% CIs were calculated for confirmed ORRs. A subpopulation treatment effect pattern plot (STEPP) analysis [15] was conducted to graph the treatment effect for PFS (HR) across a continuum of baseline treatment-free intervals (TFIs) of various subgroups in PALOMA-2; TFI was defined as the time from the end of (neo)-adjuvant treatment to disease recurrence. TEAEs were reported in the as-treated population using descriptive statistics. Time to deterioration in QoL was analyzed using the KM method and *P* values were calculated using a one-sided unstratified log-rank test. Overall changes from baseline scores were compared using a repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

These studies are still on-going to collect survival data.

Results

Patients

The prevalence of visceral metastases was higher in the 304/521 (58.3%) patients with resistance to prior ET in PALOMA-3 than in the 324/666 (48.6%) patients in the PALOMA-2 study naive to ET in the advanced disease setting (Table 1). In PALOMA-3, the most common site for visceral metastases was the liver, 62.5% and 76.9% in the palbociclib plus fulvestrant and placebo plus fulvestrant groups, respectively (Table 1), and 50% and 41% of patients had lung involvement. In PALOMA-2, liver metastases were present in 35.0% and 41.8% of patients in the palbociclib- and placebo-containing treatment arms, respectively. Among patients with nonvisceral disease, 124/217 (57.1%) in PALOMA-3 and 151/342 (44.2%) in PALOMA-2 had bone-only disease. More than 70% of patients in PALOMA-3 with visceral or nonvisceral metastases had received previous chemotherapy for their primary diagnosis (Table 1). Of those patients, more than 30% with visceral metastases and ∼30% with nonvisceral metastases received previous chemotherapy in the advanced setting.

In PALOMA-2, approximately half of the patients with visceral or nonvisceral metastases had received chemotherapy previously (Table 1). The majority of patients in both studies had normal liver enzymes at baseline (i.e. aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase; Table 1). Less than 2% of patients in both studies had ALT/AST >3 times the upper limit of normal.

Efficacy

PALOMA-3. At data cut-off (23 October 2015), mPFS was significantly longer in patients treated with palbociclib plus fulvestrant than with placebo plus fulvestrant in the presence of visceral metastases (9.2 months, 95% CI 7.5–11.1 versus 3.4 months, 1.9–5.1, respectively; HR 0.47; 95% CI 0.35–0.61) and in the absence of visceral metastases (16.6 months, 13.2–NE versus 7.3 months, 4.8–10.9; HR 0.53; 0.36–0.77) (Figure 1A and B; Table 2). In patients with liver metastases, mPFS was significantly longer in the palbociclib plus fulvestrant group versus the placebo plus fulvestrant group (Table 2). In patients with lung metastases, mPFS was significantly longer in the palbociclib plus fulvestrant group versus the placebo plus fulvestrant group (11.1 months, 95% CI 9.3–12.0 versus 3.6 months 2.1–7.2, respectively, HR 0.45 (95% CI 0.29–0.68). In patients with bone-only disease, mPFS was longer with palbociclib plus fulvestrant compared with placebo plus fulvestrant (14.3 months, 95% CI 11.2–NE versus 9.2 months, 4.8–20.0, respectively; HR 0.63; 95% CI 0.38–1.06) (Figure 1C).

The ORR was significantly higher in patients with visceral metastases treated with palbociclib plus fulvestrant versus placebo plus fulvestrant (28.0% versus 6.7%, respectively, Table 2). ORRs were significantly higher in patients with liver metastases (27.2% versus 3.8%) (Table 2) and numerically higher in patients with lung metastases (25.0% versus 11.6%) in the palbociclib plus fulvestrant group compared with the placebo plus fulvestrant group. For patients with liver metastases, median TTR (mTTR) was also shorter with palbociclib plus fulvestrant treatment than with placebo plus fulvestrant (3.8 versus 5.6 months)

(Table 2) and the mTTR in lung tumoral lesions was 3.9 and 3.6 months, respectively.

PALOMA-2. At data cut-off (26 February 2016), mPFS for patients with visceral metastases was significantly longer in those treated with palbociclib plus letrozole compared with placebo plus letrozole (19.3 months, 95% CI 16.4–22.2 versus 12.9 months, 8.4–16.6, respectively; HR 0.63; 95% CI 0.47–0.85) (Figure 1D). In patients without visceral metastases, mPFS was also significantly longer in patients treated with palbociclib plus letrozole versus those treated with placebo plus letrozole with the mPFS not yet reached for patients in the palbociclib plus letrozole group (Figure 1E). In patients with liver metastases, mPFS was significantly longer in patients treated with palbociclib plus letrozole compared with placebo plus letrozole (13.7 months, 95% CI 10.9–16.6 versus 8.4 months, 5.5–12.9, respectively; HR 0.62; 95% CI 0.41–0.95). For patients with bone-only disease, mPFS was significantly prolonged with palbociclib plus letrozole compared with placebo plus letrozole (not reached, 95% CI 24.8–NE versus 11.2 months, 8.2–22.0, respectively; HR 0.36; 95% CI 0.22–0.59) (Figure 1F).

The ORR was significantly higher in patients with visceral metastases treated with palbociclib plus letrozole compared with placebo plus letrozole (55.1% versus 40.0%, respectively; Table 2). The ORR and mTTR were similar between palbociclib plus letrozole and placebo plus letrozole treatment groups in patients with liver metastases (ORR: 41.3% versus 37.0%, respectively; mTTR: 3.0 and 2.9 months; Table 2).

The exploratory STEPP analysis carried out on PALOMA-2 baseline TFI data revealed that the treatment effect on PFS (in terms of HR) remained relatively constant across study subpopulations regardless of the length of baseline TFI (Figure 2).

Patient-reported outcomes

In PALOMA-3, a statistically significantly greater delay in time to deterioration in global QoL was observed in the subgroup with visceral metastases, who were treated with palbociclib plus fulvestrant compared with placebo plus fulvestrant (HR 0.54; *P* < 0.001; Figure 3A). A similar trend was observed between treatments in patients without visceral metastases but it was not statistically significant (Figure 3B). In patients with visceral metastases, the overall change in QLQ-C30 scales from baseline scores favored the palbociclib plus fulvestrant group for global health/QoL, emotional functioning, role functioning (supplementary Figure S1, available at *Annals of Oncology* online) and symptoms like pain, nausea and vomiting, and insomnia (all *P* < 0.05). No significant differences were observed between treatment arms in the nonvisceral metastases group. In PALOMA-2, patient-reported QoL, as assessed by the FACT-B total score, was maintained with the addition of palbociclib to letrozole; no significant differences were observed between treatment groups in the visceral and nonvisceral metastases subgroups (Figure 3C and D). No significant difference in time to deterioration in QoL was observed between treatment arms in the patients with and without visceral metastases.

Table 1. Demographic and baseline characteristics by treatment group for patients with and without visceral metastases

Characteristics	PALOMA-3[a,b]				PALOMA-2[a,b]			
	PAL + FUL		PBO + FUL		PAL + LET		PBO + LET	
	Visceral ($n = 200$)	Nonvisceral ($n = 147$)	Visceral ($n = 104$)	Nonvisceral ($n = 70$)	Visceral ($n = 214$)	Nonvisceral ($n = 230$)	Visceral ($n = 110$)	Nonvisceral ($n = 112$)
Median (range) age, years	57.0 (30.0–88.0)	57.0 (33.0–82.0)	58.5 (35.0–80.0)	54.0 (29.0–74.0)	62.0 (30.0–88.0)	62.0 (36.0–89.0)	61.0 (28.0–88.0)	62.0 (32.0–88.0)
Involved disease sites[c]								
Liver	125 (62.5)	–	80 (76.9)	–	75 (35.0)	–	46 (41.8)	–
Lymph node	97 (48.5)	41 (27.9)	39 (37.5)	24 (34.3)	125 (58.4)	87 (37.8)	65 (59.1)	45 (40.2)
Bone	136 (68.0)	128 (87.1)	76 (73.1)	54 (77.1)	126 (58.9)	199 (86.5)	73 (66.4)	89 (79.5)
Peritoneum	1 (<1)	–	0	–	4 (1.9)	–	0	–
Number of metastatic organ sites[c]								
1	17 (8.5)	94 (63.9)	11 (10.6)	49 (70.0)	17 (7.9)	121 (52.6)	6 (5.5)	60 (53.6)
2	63 (31.5)	32 (21.8)	37 (35.6)	14 (20.0)	63 (29.4)	54 (23.5)	26 (23.6)	26 (23.2)
3	58 (29.0)	15 (10.2)	27 (26.0)	6 (8.6)	66 (30.8)	46 (20.0)	41 (37.3)	20 (17.9)
4	43 (21.5)	3 (2.0)	20 (19.2)	0	45 (21.0)	7 (3.0)	23 (20.9)	6 (5.4)
>4	18 (9.0)	2 (1.4)	9 (8.7)	0	23 (10.7)	2 (<1.0)	14 (12.7)	0
ECOG performance status								
0	114 (57.0)	92 (62.6)	66 (63.5)	50 (71.4)	113 (52.8)	144 (62.6)	51 (46.4)	51 (45.5)
1	86 (43.0)	55 (37.4)	38 (36.5)	20 (28.6)	97 (45.3)	81 (35.2)	59 (53.6)	58 (51.8)
2	–	–	–	–	4 (1.9)	5 (2.2)	0	3 (2.7)
Prior endocrine therapy[d]								
Tamoxifen only	4 (2.0)	1 (<1.0)	3 (2.9)	1 (1.4)	72 (33.6)	59 (25.7)	40 (36.4)	33 (29.5)
Aromatase inhibitor	23 (11.5)	21 (14.3)	9 (8.7)	7 (10.0)	14 (6.5)	19 (8.3)	8 (7.3)	20 (17.9)
Both tamoxifen and aromatase inhibitor	96 (48.0)	63 (42.9)	50 (48.1)	31 (44.3)	38 (17.8)	40 (17.4)	15 (13.6)	10 (8.9)
Prior chemotherapy[e]	149 (74.5)	103 (70.1)	81 (77.9)	56 (80.0)	106 (49.5)	107 (46.5)	60 (54.5)	49 (43.8)
Neoadjuvant	40 (20.0)	26 (17.7)	20 (19.2)	13 (18.6)	33 (15.4)	21 (9.1)	15 (13.6)	17 (15.2)
Adjuvant	85 (42.5)	66 (44.9)	47 (45.2)	41 (58.6)	88 (41.1)	92 (40.0)	51 (46.4)	38 (33.9)
Advanced/metastatic setting	68 (34.0)	39 (26.5)	41 (39.4)	21 (30.0)	–	–	–	–
Liver function tests								
AST								
≤ULN	143 (71.5)	124 (84.4)	69 (66.3)	60 (85.7)	171 (79.9)	197 (85.7)	92 (83.6)	103 (92.0)
>1× and ≤2× ULN	47 (23.5)	20 (13.6)	24 (23.1)	4 (5.7)	35 (16.4)	31 (13.5)	15 (13.6)	9 (8.0)
>2× and ≤3× ULN	6 (3.0)	3 (2.0)	5 (4.8)	2 (2.9)	6 (2.8)	2 (0.9)	3 (2.7)	0
>3× ULN	4 (2.0)	0	4 (3.8)	0	2 (0.9)	0	0	0
ALT								
≤ULN	170 (85.0)	131 (89.1)	79 (76.0)	63 (90.0)	180 (84.1)	202 (87.8)	97 (88.2)	103 (92.0)
>1× and ≤2× ULN	21 (10.5)	14 (9.5)	20 (19.2)	2 (2.9)	33 (15.4)	27 (11.7)	12 (10.9)	6 (5.4)
>2× and ≤3× ULN	7 (3.5)	1 (0.7)	3 (2.9)	3 (4.3)	1 (0.5)	1 (0.4)	1 (0.9)	2 (1.8)
>3× ULN	2 (1.0)	0	2 (1.9)	0	0	0	0	1 (0.9)
Alkaline phosphatase								
≤ULN	152 (76.0)	124 (84.4)	77 (74.0)	58 (82.9)	165 (77.1)	174 (75.7)	86 (78.2)	92 (82.1)
>1× and ≤2× ULN	35 (17.5)	19 (12.9)	21 (20.2)	6 (8.6)	37 (17.3)	47 (20.4)	22 (20.0)	18 (16.1)
>2× and ≤3× ULN	9 (4.5)	1 (0.7)	4 (3.8)	2 (2.9)	7 (3.3)	5 (2.2)	2 (1.8)	0
>3× ULN	2 (1.0)	3 (2.0)	2 (1.9)	0	5 (2.3)	4 (1.7)	0	2 (1.8)

[a]Values are *n* (%) unless stated otherwise.
[b]Patients with visceral metastases were defined as those reported in the case report forms by the Principle Investigators, not those reported in the IMPALA randomization system. Involved sites include both target and nontarget sites; sites with multiple lesions are counted once.
[c]Patients in PALOMA-2 were treatment-naive for advanced breast cancer.
[d]Data represent prior endocrine therapy for primary diagnosis.
[e]Data represent previous chemotherapy regimen for primary diagnosis.
–, no data; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECOG, Eastern Cooperative Oncology Group; FUL, fulvestrant; LET, letrozole; PAL, palbociclib; PBO, placebo; ULN, upper limit of normal.
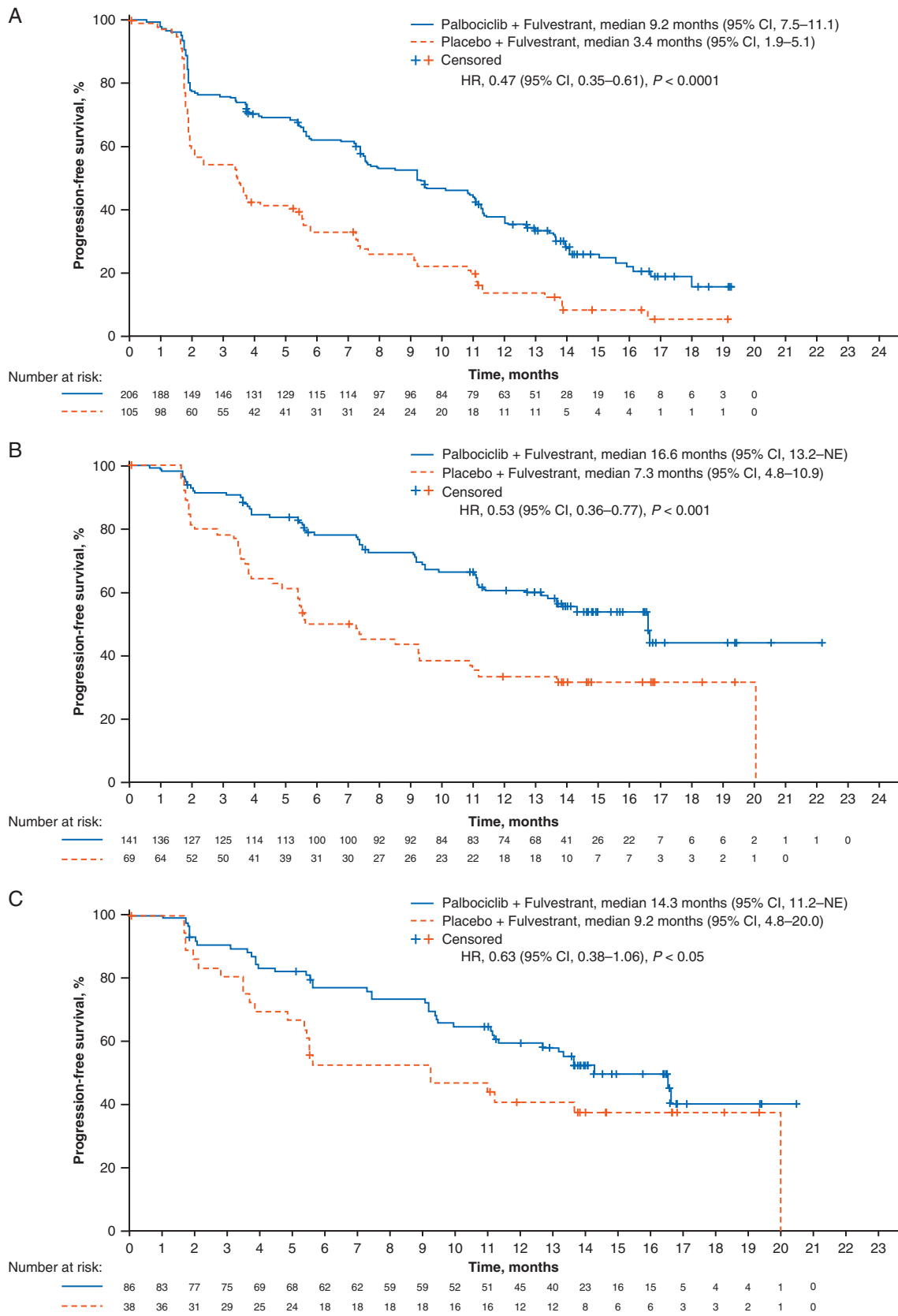
Figure 1. Kaplan–Meier plots of progression-free survival in patients in the PALOMA-3 study with visceral metastases (A), nonvisceral metastases (B), and bone-only disease (C), as well as in patients in the PALOMA-2 study with visceral metastases (D), nonvisceral metastases (E), and bone-only disease (F). HR, hazard ratio; NE, not estimable; NR, not reached.
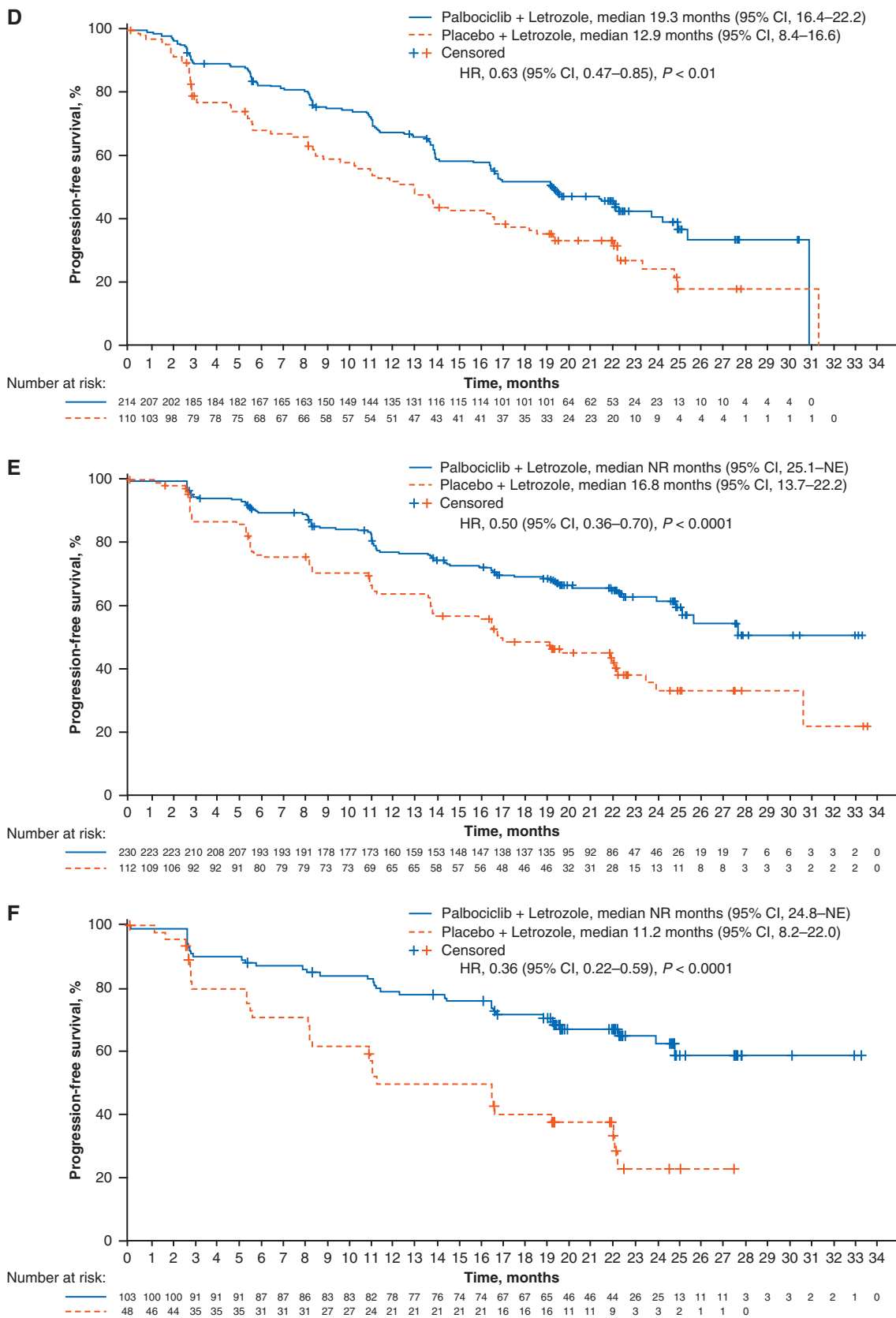
Figure 1. Continued.

Table 2. Median PFS, ORR, and TTR by treatment group for patients with and without visceral metastases				
	PALOMA-3		PALOMA-2	
	(N = 521)		(N = 666)	
	Visceral PAL + FUL versus PBO + FUL	Nonvisceral PAL + FUL versus PBO + FUL	Visceral PAL + LET versus PBO + LET	Nonvisceral PAL + LET versus PBO + LET
ITT population, n	200 versus 104	147 versus 70	214 versus 110	230 versus 112
mPFS, months	9.2 versus 3.4	16.6 versus 7.3	19.3 versus 12.9	NR versus 16.8
HR (95% CI)	0.47 (0.35–0.61)	0.53 (0.36–0.77)	0.63 (0.47–0.85)	0.50 (0.36–0.70)
ORR, %	28.0 versus 6.7	11.6 versus 11.4	55.1 versus 40.0	30.0 versus 29.5
OR (95% CI)	5.39 (2.31–14.55)	1.01 (0.39–2.87)	1.84 (1.13–3.03)	1.03 (0.61–1.74)
mTTR, months	3.8 and 3.6	3.7 and 3.6	4.3 and 5.3	2.9 and 5.4
Patients with liver metastases, n	125 versus 80	–	75 versus 46	–
mPFS, months	7.5 versus 2.4	–	13.7 versus 8.4	–
HR (95% CI)	0.49 (0.36–0.68)	–	0.62 (0.41–0.95)	–
ORR, %	27.2 versus 3.8	–	41.3 versus 37.0	–
mTTR, months	3.8 and 5.6	–	3.0 and 2.9	–
Patients without visceral metastases and excluding bone-only, n		61 versus 32		128 versus 64
mPFS, months	–	16.6 versus 5.6	–	27.6 versus 21.9
HR (95% CI)	–	0.43 (0.24–0.76)	–	0.65 (0.42–1.03)
Patients with visceral metastases and ECOG performance status 0, n	114 versus 66	–	113 versus 51	–
mPFS, months	9.4 versus 3.6	–	19.4 versus 16.4	–
HR (95% CI)	0.52 (0.37–0.74)	–	0.89 (0.56–1.40)	–
ORR, %	32.5 versus 10.6	–	54.0 versus 47.1	–
Patients with visceral metastases and ECOG performance status 1 or 2, n	86 versus 38	–	101 versus 59	–
mPFS, months	9.2 versus 2.0	–	16.8 versus 11.0	–
HR (95% CI)	0.37 (0.24–0.57)	–	0.48 (0.32–0.71)	–
ORR, %	22.1 versus 0	–	56.4 versus 33.9	–

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FUL, fulvestrant; HR, hazard ratio; ITT, intent-to-treat; LET, letrozole; m, median; NR, not reached, not estimable; OR, odds ratio; ORR, overall response rate; PAL, palbociclib; PBO, placebo; PFS, progression-free survival; TTR, time to response.

Safety

In both PALOMA studies, most patients experienced ≥1 TEAE regardless of visceral metastatic status and treatment group (supplementary Table S2, available at *Annals of Oncology* online), and the rates of TEAEs leading to palbociclib or placebo permanent discontinuation were similarly low between patients with and without visceral metastases (PALOMA-3, all patients ≤6.2%; PALOMA-2, all ≤7%, except 11.3% in nonvisceral patients receiving palbociclib plus letrozole). For palbociclib plus ET, the rate of grade 3 TEAEs >5%, as well as the rates of TEAEs leading to temporary treatment discontinuations or dose reductions in PALOMA-3 and -2 were comparable across groups, despite the presence or absence of visceral metastases (supplementary Tables S2 and S3, available at *Annals of Oncology* online). Permanent discontinuations due to AEs among all subgroups of patients were low, particularly in relation to reports of neutropenia and regardless of the presence or absence of visceral disease. Among patients with visceral metastases, the most commonly reported grade 3

TEAEs of >5% incidence were neutropenia (54.8%) and leukopenia (43.2%) in patients treated with palbociclib plus fulvestrant in PALOMA-3 and neutropenia (57.5%) and leukopenia (22.4%) in patients treated with palbociclib plus letrozole in PALOMA-2 (supplementary Table S3, available at *Annals of Oncology* online). The incidence of infections of any grade was similar between visceral and nonvisceral palbociclib-treated patients across both studies in PALOMA-3 (42.2% and 46.6%, respectively) and PALOMA-2 (56.1% and 63.0%) (supplementary Table S3, available at *Annals of Oncology* online). Infections of any grade in patients who received placebo plus fulvestrant were lower in patients with visceral metastases (28.8%) due to the very short duration of treatment than with nonvisceral metastases (35.3%), and similar to the pattern reported in patients who received placebo plus letrozole (38.2% and 46.4%, respectively) (supplementary Table S3, available at *Annals of Oncology* online). Within PALOMA-3 and -2, grade 3 and 4 AEs of >5% incidence were similar between patients receiving palbociclib and ET. Serious AEs of >1% incidence for any grade and grades 3 and 4
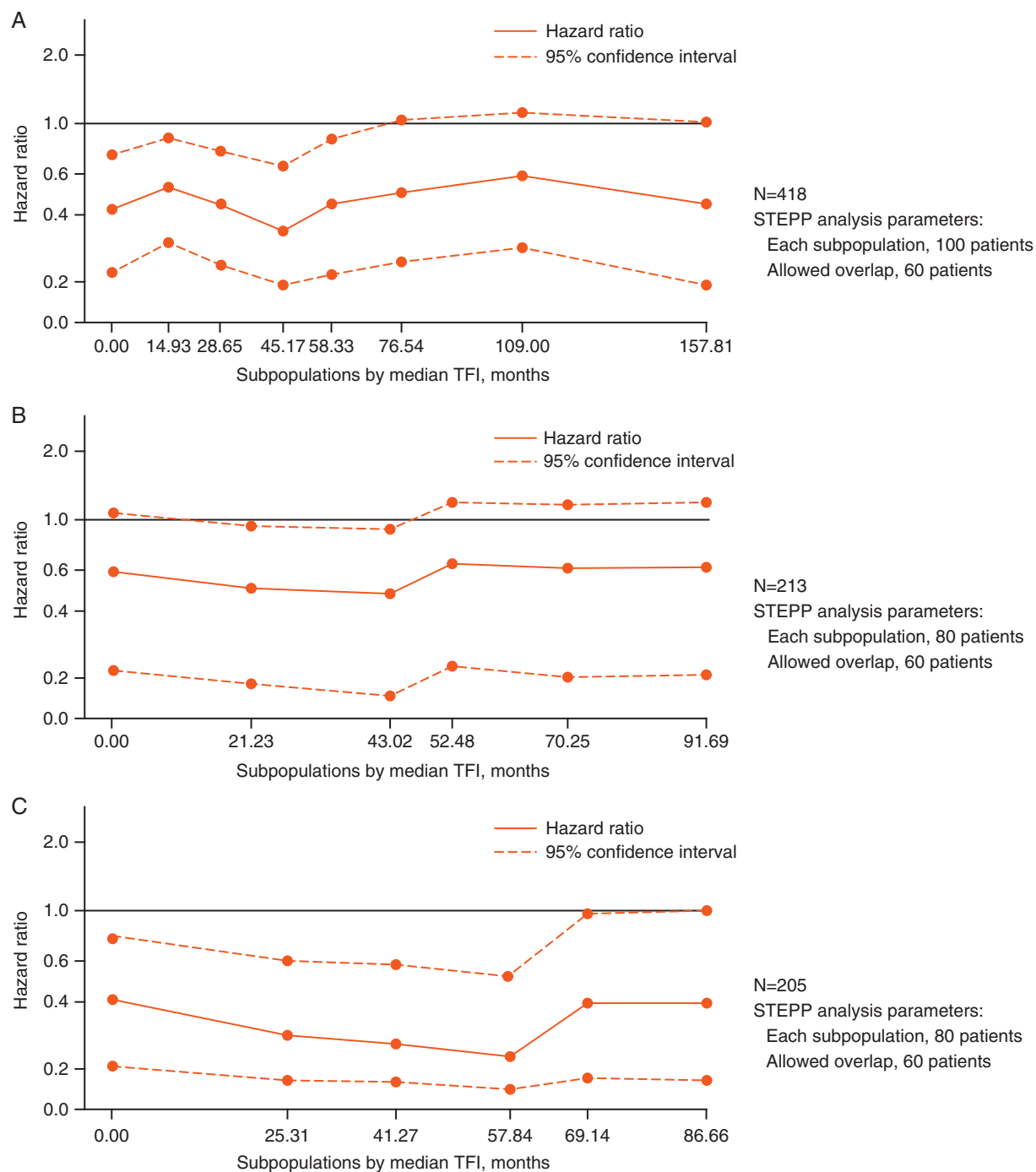
Figure 2. STEPP analysis results of the PFS treatment effect and baseline TFI in subpopulations of patients in the PALOMA-2 study who received adjuvant therapy (A), patients who received adjuvant therapy and had visceral metastases (B), and patients who received adjuvant therapy and had nonvisceral metastases (C). TFI, treatment-free interval (for the purposes of this study, TFI was considered equivalent to disease-free interval [prespecified] in the PALOMA-2 study and was defined as the time from the end of [neo]adjuvant treatment to disease recurrence); PFS, progression-free survival; STEPP, subpopulation treatment effect pattern plot.

(palbociclib- or placebo-related) were low in patients receiving palbociclib and ET regardless of visceral metastases, and similarly low between patients treated with placebo plus ET, regardless of visceral metastases (supplementary Table S3, available at *Annals of Oncology* online).

Discussion

Patients with HR+/HER2– ABC with visceral metastases represent a clinical challenge as their prognosis is generally worse than that of patients without visceral involvement [1]. In this
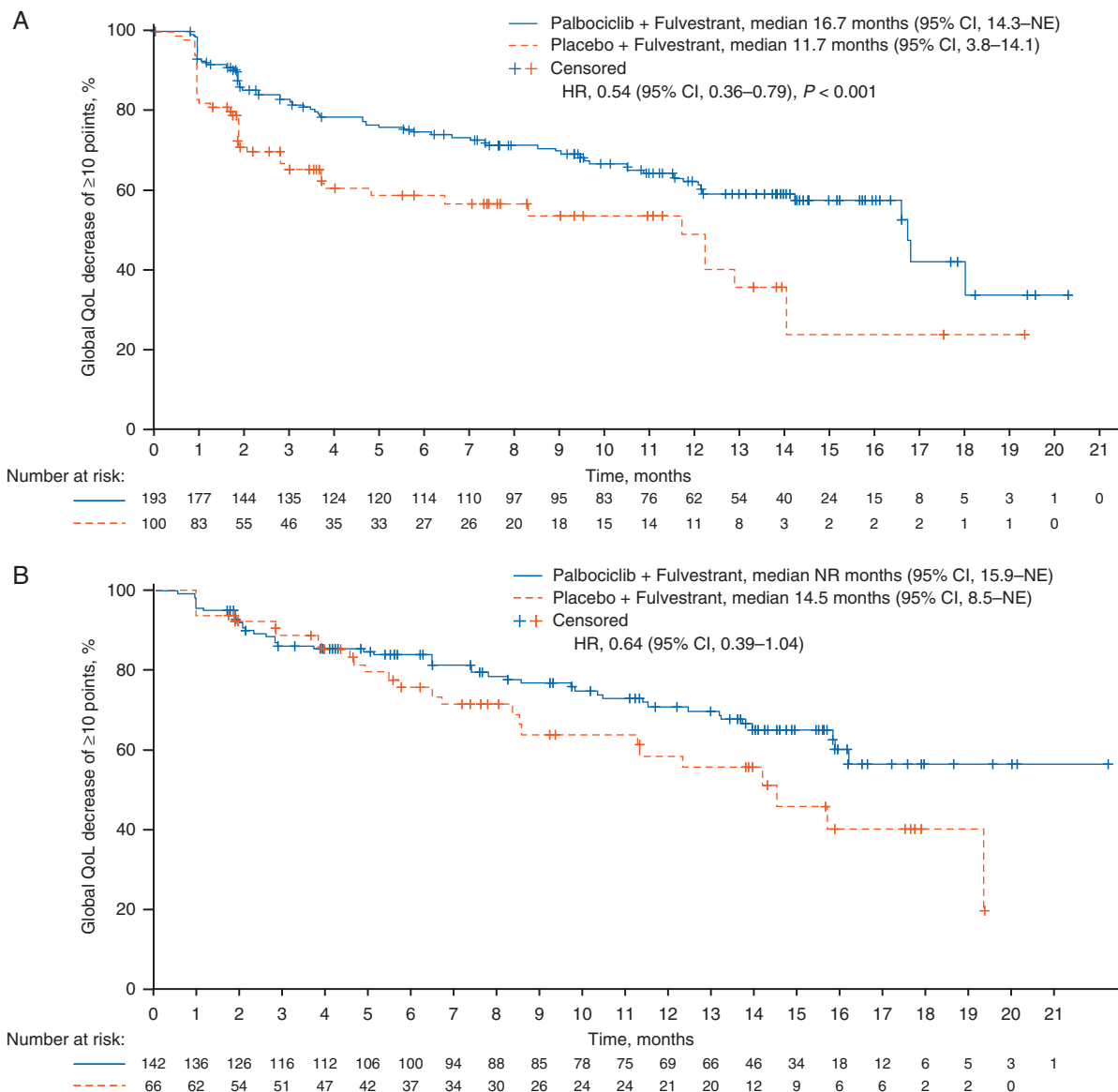
Figure 3. Kaplan–Meier plots of time to deterioration of QoL based on the EORTC QLQ-C30 in patients with visceral metastases (A) and in patients without visceral metastases (B) in the PALOMA-3 study and time to deterioration of FACT-B total score in patients with visceral metastases (C) and without visceral metastases (D) in the PALOMA-2 study. EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; QoL, health-related quality of life; NE, not estimable; NR, not reached; QLQ-C30, EORTC quality-of-life questionnaire.

subgroup analysis of patients from PALOMA-3 and PALOMA-2, mPFS was significantly prolonged in patients with and without visceral metastases at baseline when they were treated with palbociclib plus fulvestrant or letrozole compared with placebo plus fulvestrant or letrozole. These results are consistent with the smaller randomized phase II PALOMA-1 study [16]. The percentage of patients with visceral metastases was higher in PALOMA-3 than in PALOMA-2, which is consistent with evidence from clinical practice in which patients receiving later lines of therapy and/or with prior endocrine resistance were more likely to have visceral metastases compared with patients with *de novo* metastatic disease.

In the PALOMA-2 study, a STEPP analysis did not identify an interaction between the PFS treatment effect and baseline TFI in patients who had received adjuvant therapy and in

subgroups based on visceral or nonvisceral metastases. This is in contrast to the results from the double-blind, randomized, phase III MONARCH 3 study, which compared the addition of abemaciclib or placebo with a nonsteroidal aromatase inhibitor to evaluate investigator-assessed PFS, the primary study end point, in postmenopausal women with HR+/HER2− ABC [17]. In the overall population in MONARCH 3, PFS HRs were lower in subpopulations with a baseline TFI <36 months (an adverse prognostic factor) and increased in subpopulations with TFIs >36 months (a more favorable prognostic factor) [18]. In MONARCH 3, TFI, defined as the time from the end of adjuvant ET until informed consent [17], is similar to the definition for TFI in our analysis of PALOMA-2. However, the median follow-up duration was shorter in the MONARCH 3 study than in PALOMA-2, with few progression events in
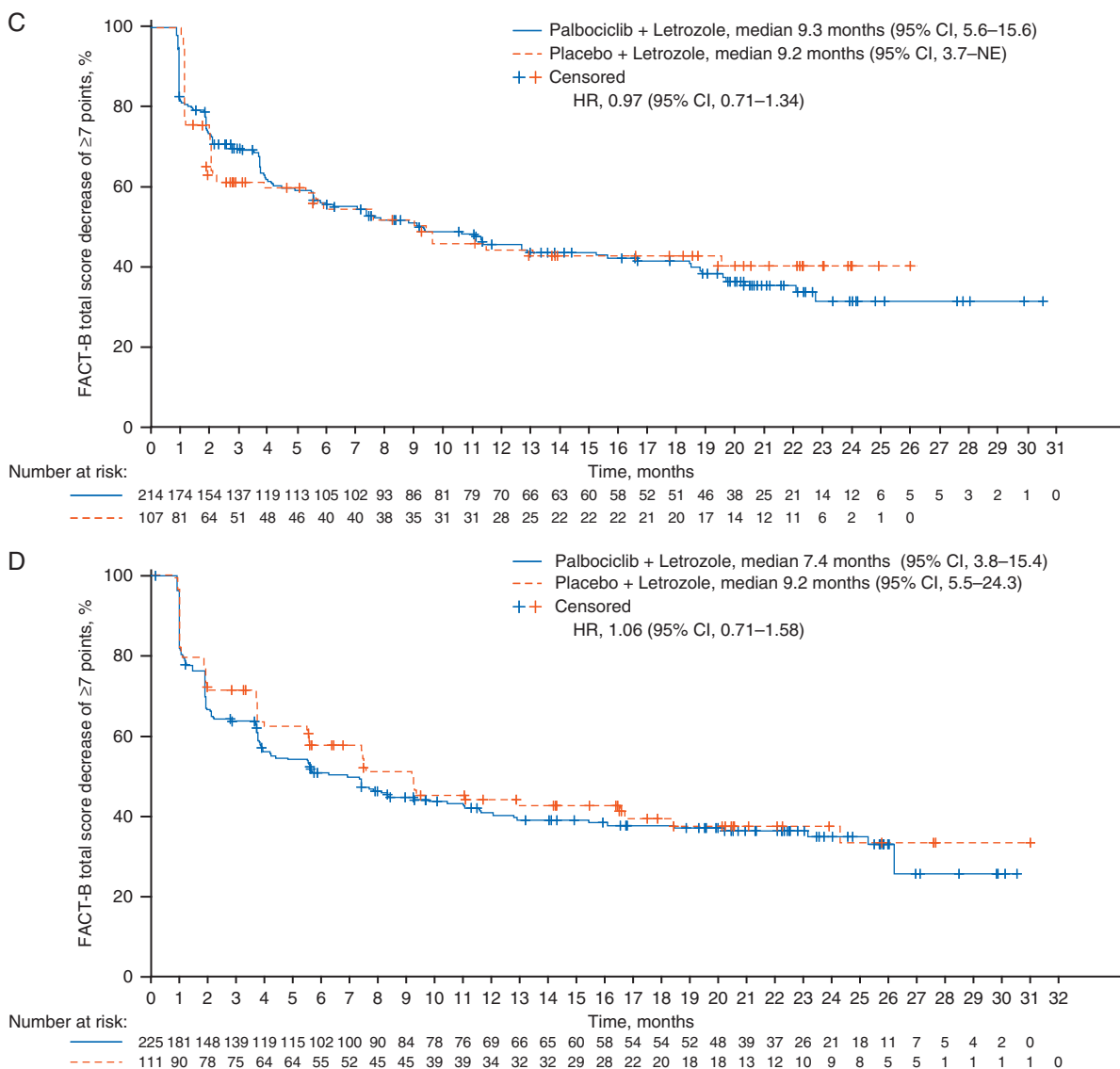
C

Palbociclib + Letrozole, median 9.3 months (95% CI, 5.6–15.6)
Placebo + Letrozole, median 9.2 months (95% CI, 3.7–NE)
Censored
HR, 0.97 (95% CI, 0.71–1.34)

Number at risk:

214 174 154 137 119 113 105 102 93 86 81 79 70 66 63 60 58 52 51 46 38 25 21 14 12 6 5 5 3 2 1 0
107 81 64 51 48 46 40 40 38 35 31 31 28 25 22 22 22 21 20 17 14 12 11 6 2 1 0

D

Palbociclib + Letrozole, median 7.4 months (95% CI, 3.8–15.4)
Placebo + Letrozole, median 9.2 months (95% CI, 5.5–24.3)
Censored
HR, 1.06 (95% CI, 0.71–1.58)

Number at risk:

225 181 148 139 119 115 102 100 90 84 78 76 69 66 65 60 58 54 54 52 48 39 37 26 21 18 11 7 5 4 2 0
111 90 78 75 64 64 55 52 45 45 39 39 34 32 32 29 28 22 20 18 18 13 12 10 9 8 5 5 1 1 1 1 0

Figure 3. Continued.

patients with TFI $\geq$36 months [13, 17]; the difference in findings between the studies is potentially explained by the different durations of follow-up.

In the PALOMA-3 and PALOMA-2 studies, the improvement in PFS with palbociclib plus ET was consistent in patients with bone-only disease at baseline versus placebo plus ET, with substantial absolute benefit from the addition of palbociclib most evident in PALOMA-2 (Figure 1). The addition of abemaciclib to ET also likely provided PFS benefit over endocrine monotherapy in patients with bone-only disease at baseline in the MONARCH 3 study (HR 0.58, 95% CI 0.27–1.25) [17], although the statistical analysis of this result may be affected by the shorter duration of follow-up time.

In the phase III, randomized, double-blind, MONARCH 2 study, 373 out of the 669 (55.8%) women of any menopausal status with HR+/HER2− ABC who had progressed on (neo)adjuvant ET within 12 months from the end of adjuvant ET, or while receiving front-line treatment of metastatic disease, had visceral disease at baseline [19]. The patients in this study were treated with either abemaciclib (150 mg twice daily, on a continuous schedule) plus fulvestrant (500 mg) or placebo plus fulvestrant. Although the patient population in MONARCH 2 had not received prior chemotherapy and were less heavily pretreated than patients in PALOMA-3, investigator-assessed PFS (primary end point) in patients with visceral disease was significantly more favorable following treatment with abemaciclib plus fulvestrant than with ET alone (HR 0.481; 95% CI 0.369–0.627), demonstrating the favorable effect of CDK 4/6 inhibitors across a spectrum of patients [19]. The time to deterioration in global QoL was significantly delayed in patients with visceral metastases who were treated with palbociclib plus fulvestrant compared with the placebo arm.

Chemotherapy is often used in patients with visceral metastases who are not in visceral crisis, despite worse clinical outcomes [20]. A network meta-analysis comparing palbociclib treatment with chemotherapy agents for the treatment of HR+/HER2− ABC showed that palbociclib plus fulvestrant and palbociclib plus letrozole demonstrate a trend in incremental efficacy

compared with chemotherapy agents for the first-line and previously treated patients [21]. However, a head-to-head comparison between ET combined with a CDK4/6 inhibitor versus chemotherapy is currently lacking and as such the results of the network meta-analysis reported by Wilson et al. should be interpreted with caution [21]. Our findings highlight the benefit of palbociclib-containing combination therapy for patients with visceral metastases without the cytotoxic effects of chemotherapy. Furthermore, no new safety findings were observed relative to the AE profiles reported in the primary PALOMA-3 and PALOMA-2 studies [12, 13]. Of importance is the analysis of patients with liver metastases. Our studies do not suggest that liver metastases should be treated differently, despite the fact that overall outcomes for such patients may be inferior with respect to the whole study population.

Comparisons with other studies should be interpreted with caution. In the recent phase III FALCON study in endocrine-naive patients with HR+ ABC, patients with visceral metastases treated with fulvestrant had a mPFS that was similar to patients treated with anastrozole (13.8 versus 15.9 months, respectively) [22]. A strategy to improve clinical outcomes in endocrine-naive patients is related to the introduction of targeted therapies, as was evident in PALOMA-2, in which mPFS was significantly prolonged with palbociclib plus letrozole in patients with visceral metastases versus placebo plus letrozole treatment (19.3 versus 12.9 months, respectively). In patients with nonvisceral disease in the FALCON study, mPFS was significantly longer in patients treated with fulvestrant (22.3 months) compared with anastrozole (13.8 months); however, the number of patients with locally advanced stage IIIb or IIIc disease included in that study was not reported [22]. In PALOMA-2, the mPFS of palbociclib plus letrozole has not yet been reached in patients without visceral metastases after a median follow-up of 23 months.

Although the comparisons between patients with and without visceral metastases were prespecified analyses in PALOMA-3 and PALOMA-2, patients with advanced visceral metastases (i.e. patients with symptomatic visceral spread who were at risk of life-threatening complications) were excluded from both studies [12, 13]. Therefore, our findings should not be extrapolated to this subpopulation. Guidelines limit the use of ET to patients without life-threatening visceral metastases; however, our findings lend further support to recommendations for use of ET for the management of HR+/HER2– ABC as initial or salvage therapy, even in the presence of visceral metastases [2–4].

Conclusions

The findings of this prespecified subgroup analysis demonstrate the clinical benefit of palbociclib in combination with ET in patients with HR+/HER2– ABC with visceral metastases. Median PFS and response rate compare favorably with that seen with chemotherapy. The deterioration in symptoms for global QoL assessment were delayed in patients with prior resistance to ET and visceral disease and maintained by the addition of palbociclib to ET in patients with visceral disease who were previously untreated with systemic ET for ABC.

Disclosure

S-AI received honoraria from Novartis and has a consulting/advisory role with Novartis, Hanmi, and Spectrum. MCo received honoraria from Novartis and has a consulting/advisory role with AstraZeneca, Celldex, OBI Pharma, Pfizer, Pierre Fabre, and Puma Biotechnology. MCr received honoraria from Pfizer, Agendia, Celgene, Dompé Farmaceutici, and Pfizer and has a consulting/advisory role with Cynvenio Biosystems, Dompé Farmaceutici, Newomics, and Vortex Biosciences. AD received honoraria from Pfizer and AD's institution has received research funding from Bayer, Calithera Biosciences, Genentech, GlaxoSmithKline, Incyte, Millennium, Pfizer, Veridex, and Wyeth; JE received honoraria from Pfizer, Novartis, and Roche, has a consulting/advisory role with Pfizer and Novartis Pharma KK, and has served on a speakers' bureau for Pfizer, Novartis, Roche, and Celgene. KAG has a consulting/advisory role with Pfizer, Novartis, AstraZeneca, NanoString Technologies, and Merck. NCT received honoraria from Pfizer and has a consulting/advisory role with Pfizer and his institution has received research funding from Servier, Pfizer, Lily, Roche, and AstraZeneca. RSF received honoraria and his institution has received funding from Bayer, Pfizer, Bristol-Myers Squibb, Novartis, and Eisai. SM has received honoraria and accommodation and travel expenses from Novartis; SM's institution has received research funding from Oncothyreon, Pfizer, Novartis, Genentech, Takeda, and Bayer. VD has a consulting/advisory role with Genentech, Lilly, Pfizer, AbbVie, Novartis Pharma KK, and Roche-Peru and has served on a speakers' bureau for Pfizer, Novartis Pharma KK, and Roche-Peru. OL has nothing to disclose. AM, CHB, CG, DRL, and SI are employees of and own stock in Pfizer.

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