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Overall Survival With Palbociclib Plus Letrozole in Advanced Breast Cancer

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ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned coprimary or secondary analyses are not yet available. Clinical trial updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

PALOMA-2 demonstrated statistically and clinically significant improvement in progression-free survival with palbociclib plus letrozole versus placebo plus letrozole in estrogen receptor–positive/human epidermal growth factor receptor 2–negative (ER+/HER2–) advanced breast cancer (ABC). Here, we report results for the secondary end point overall survival (OS). Postmenopausal women (N = 666) with ER+/HER2– ABC without previous systemic therapy for ABC were randomly assigned 2:1 to palbociclib plus letrozole or placebo plus letrozole. After a median follow-up of 90.1 months, 405 deaths were observed and 155 patients were known to be alive. The median OS was 53.9 months (95% CI, 49.8 to 60.8) with palbociclib plus letrozole versus 51.2 months (95% CI, 43.7 to 58.9) with placebo plus letrozole (hazard ratio [HR], 0.96 [95% CI, 0.78 to 1.18]; stratified one-sided $P = .34$). An imbalance in the number of patients with unknown survival outcome between the treatment arms (13.3% *v* 21.2%, respectively) limited interpretation of OS results. With recovered survival data, the median OS was 53.8 (95% CI, 49.8 to 59.2) versus 49.8 months (95% CI, 42.3 to 56.4), respectively (HR, 0.92 [95% CI, 0.76 to 1.12]; one-sided $P = .21$). OS was not significantly improved with palbociclib plus letrozole compared with placebo plus letrozole.

ACCOMPANYING CONTENT

Data Supplement

Protocol

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BACKGROUND

Since the initial development and approval of palbociclib, first-in-class cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, for estrogen receptor–positive/human epidermal growth factor receptor 2–negative (ER+/HER2–) advanced breast cancer (ABC) on the basis of PALOMA-1 in 2015,[1-4] the CDK4/6 inhibitor class has transformed the treatment landscape and, in combination with endocrine therapy (ET), has become the standard of care for the disease.[5] PALOMA-2 confirmed the results of PALOMA-1 with statistically and clinically significant improvement in progression-free survival (PFS) for palbociclib plus letrozole versus placebo plus letrozole in ER+/HER2– ABC.

At the time of the final analysis of the primary end point of PFS, overall survival (OS) data were immature. Here, we report results of the final OS analysis and updated safety data.

METHODS

Details of PALOMA-2 study design have been previously published[6] and are provided in the Data Supplement (online only). OS was a secondary end point, defined as the time from the date of random assignment to the date of death because of any cause. In the absence of confirmation of death, survival time was censored to the last date the patient was known to be alive.

The median OS was assumed to be 34 months in first-line treatment with letrozole for ABC at the time of study design.[7] The final OS analysis was planned to be performed after at least 390 events, providing an 80% power to detect a hazard ratio [HR] ≤0.74, using a stratified log-rank test with a one-sided significance level of 0.025.

OS analysis was conducted in the intent-to-treat (ITT) population. Median OS was estimated using the Kaplan-Meier method with the one-sided stratified log-rank test adjusting for the disease site at the $\alpha = .025$ overall significance level. The HRs and two-sided 95% confidence intervals were estimated using Cox proportional hazards regression stratified by disease site (visceral *v* nonvisceral). The proportional hazard assumption was evaluated using Schoenfeld's residual test.

RESULTS AND DISCUSSION

Patients

Between February 2013 and July 2014, 666 patients were randomly assigned: 444 patients to palbociclib plus letrozole and 222 patients to placebo plus letrozole (ITT population; Data Supplement, Fig S1). Demographics and baseline disease characteristics were balanced between treatment arms and similar to those previously reported (Table 1).[6,8]

OS

OS data were analyzed with a data cutoff date of November 15, 2021. The median follow-up time was 90.1 months. Among the 666 patients, 405 deaths were observed: 273 of 444 in the palbociclib plus letrozole arm and 132 of 222 in the placebo plus letrozole arm. The median OS was 53.9 months (95% CI, 49.8 to 60.8) for palbociclib plus letrozole versus 51.2 months (95% CI, 43.7 to 58.9) for placebo plus letrozole (HR, 0.96 [95% CI, 0.78 to 1.18]; stratified one-sided P = .34; Fig 1A). Proportional hazards assumption was evaluated using Schoenfeld residual, and the test for nonproportionality was not significant (P value = .77).

A series of prespecified exploratory subgroup analyses were performed on the basis of stratification factors and baseline characteristics with no formal statistical testing (Data Supplement, Supplementary Results; Fig 1B).

A preplanned pooled analysis combining PALOMA-1 and PALOMA-2 studies was performed (Fig 2A); the median OS was 51.8 months (95% CI, 47.8 to 56.9) in the palbociclib plus letrozole arm (n = 528) and 46.8 months (95% CI, 38.8 to 52.3) in the comparator arm (n = 303; PALOMA-1, letrozole alone; PALOMA-2, placebo plus letrozole). The HR stratified by study was 0.93 (95% CI, 0.78 to 1.12).

At data cutoff, 45 (10.1%) and five (2.3%) patients were still receiving active treatment in the palbociclib plus letrozole and placebo plus letrozole arms, respectively. The median duration of treatment was 22.0 and 13.8 months, respectively (Data Supplement, Fig S2).

Revised Results Including Recovered Data

At the data cutoff, 15.9% of the ITT population was no longer being followed for survival (lost to follow-up or withdrew consent) with an imbalance between treatment arms (59 patients [13.3%] for palbociclib plus letrozole *v* 47 patients [21.2%] for placebo plus letrozole; Data Supplement, Fig S3). Given the potential impact on the OS results, efforts were undertaken to retrieve survival data for these patients

TABLE 1. Patient Demographics and Clinical Characteristics

Characteristic	Palbociclib + Letrozole (n = 444)	Placebo + Letrozole (n = 222)
Age, years		
Median (range)	62 (30-89)	61 (28-88)
<65	263 (59.2)	141 (63.5)
≥65	181 (40.8)	81 (36.5)
Race, No. (%)		
White	344 (77.5)	172 (77.5)
Black	8 (1.8)	3 (1.4)
Asian	65 (14.6)	30 (13.5)
Other, not reported, or missing	27 (6.1)	17 (7.7)
ECOG performance status, No. (%)		
0	257 (57.9)	102 (45.9)
1	178 (40.1)	117 (52.7)
2	9 (2.0)	3 (1.4)
Disease stage at initial diagnosis, No. (%)		
I	52 (11.7)	30 (13.5)
II	137 (30.9)	68 (30.6)
III	72 (16.2)	39 (17.6)
IV	138 (31.1)	72 (32.4)
Unknown, other, or missing	45 (10.2)	13 (5.9)
Disease site, No. (%)		
Visceral	214 (48.2)	110 (49.5)
Nonvisceral	230 (51.8)	112 (50.5)
Disease-free interval since completion of previous (neo)adjuvant therapy, No. (%)		
De novo metastatic	167 (37.6)	81 (36.5)
≤12 months	98 (22.1)	48 (21.6)
>12 months	179 (40.3)	93 (41.9)
No. of disease sites, No. (%)		
1	138 (31.1)	66 (29.7)
2	117 (26.4)	52 (23.4)
≥3	189 (42.6)	104 (46.8)
Recurrence type, No. (%)		
Locoregional	2 (0.5)	2 (0.9)
Local	6 (1.4)	3 (1.4)
Regional	3 (0.7)	1 (0.5)
Distant	294 (66.2)	145 (65.3)
Newly diagnosed	139 (31.3)	71 (32.0)
Involved disease sites, No. (%)		
Breast	137 (30.9)	74 (33.3)
Bone	326 (73.4)	162 (73.0)
Liver	75 (16.9)	46 (20.7)
Lung	150 (33.8)	71 (32.0)
Lymph node	212 (47.7)	111 (50.0)
Other	115 (25.9)	64 (28.8)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

(Data Supplement, Supplementary Methods). With the recovered data, the imbalance between the treatment arms was reduced to 41 (9.2%) versus 26 (11.7%), respectively, resulting in a median OS of 53.8 months (95% CI, 49.8 to 59.2) for palbociclib plus letrozole versus 49.8 months (95% CI, 42.3 to 56.4) for placebo plus letrozole (HR, 0.92 [95% CI, 0.76 to 1.12];

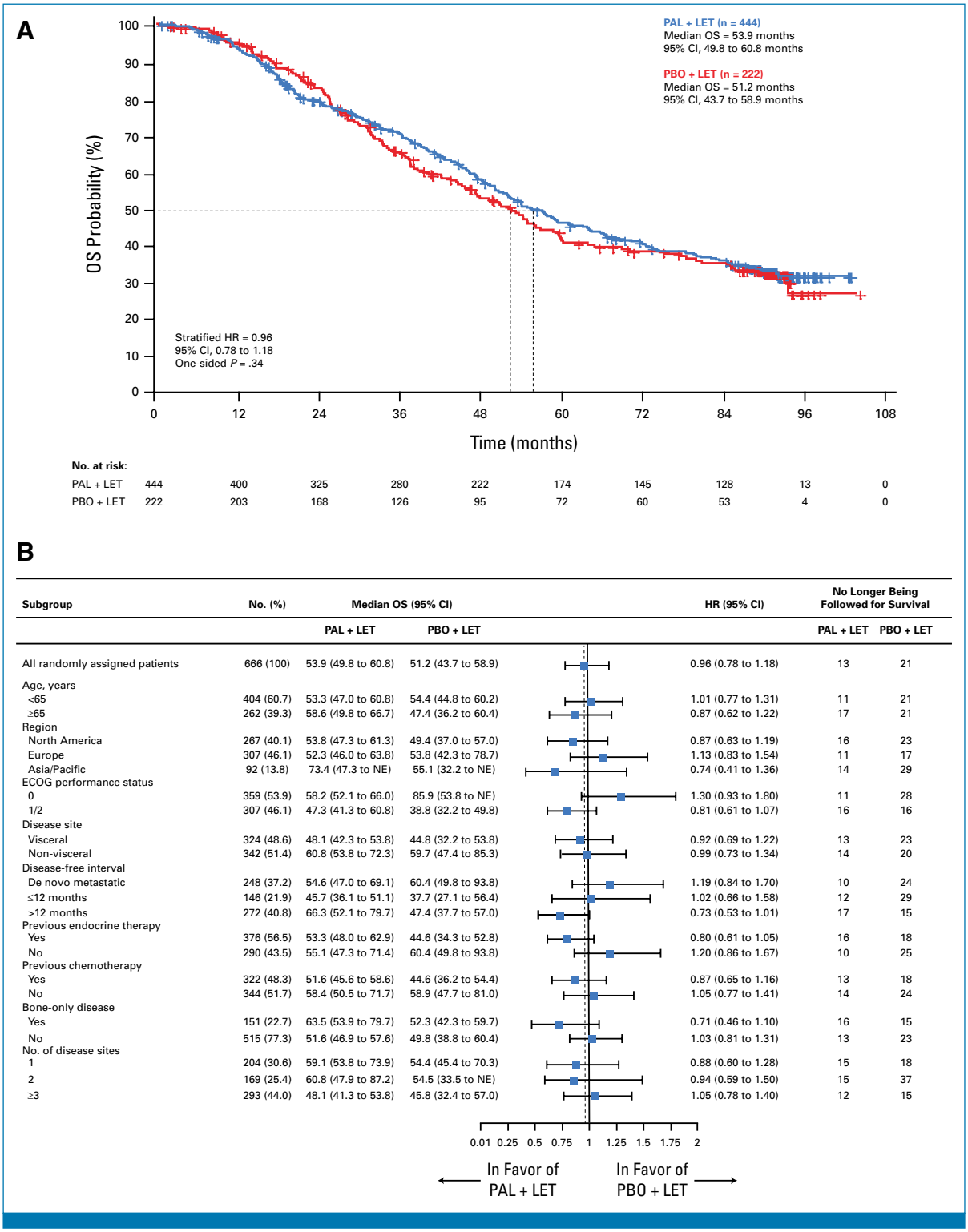

FIG 1. OS in the ITT population and by subgroup. (A) Kaplan-Meier curve of OS in the ITT population. (B) Forest plot of OS by subgroup. (C) Kaplan-Meier curve of OS in the ITT population after recovery of data. (D) Forest plot of OS by subgroup after recovery of data. ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; LET, letrozole; NE, not estimable; OS, overall survival; PAL, palbociclib; PBO, placebo. (continued on following page)

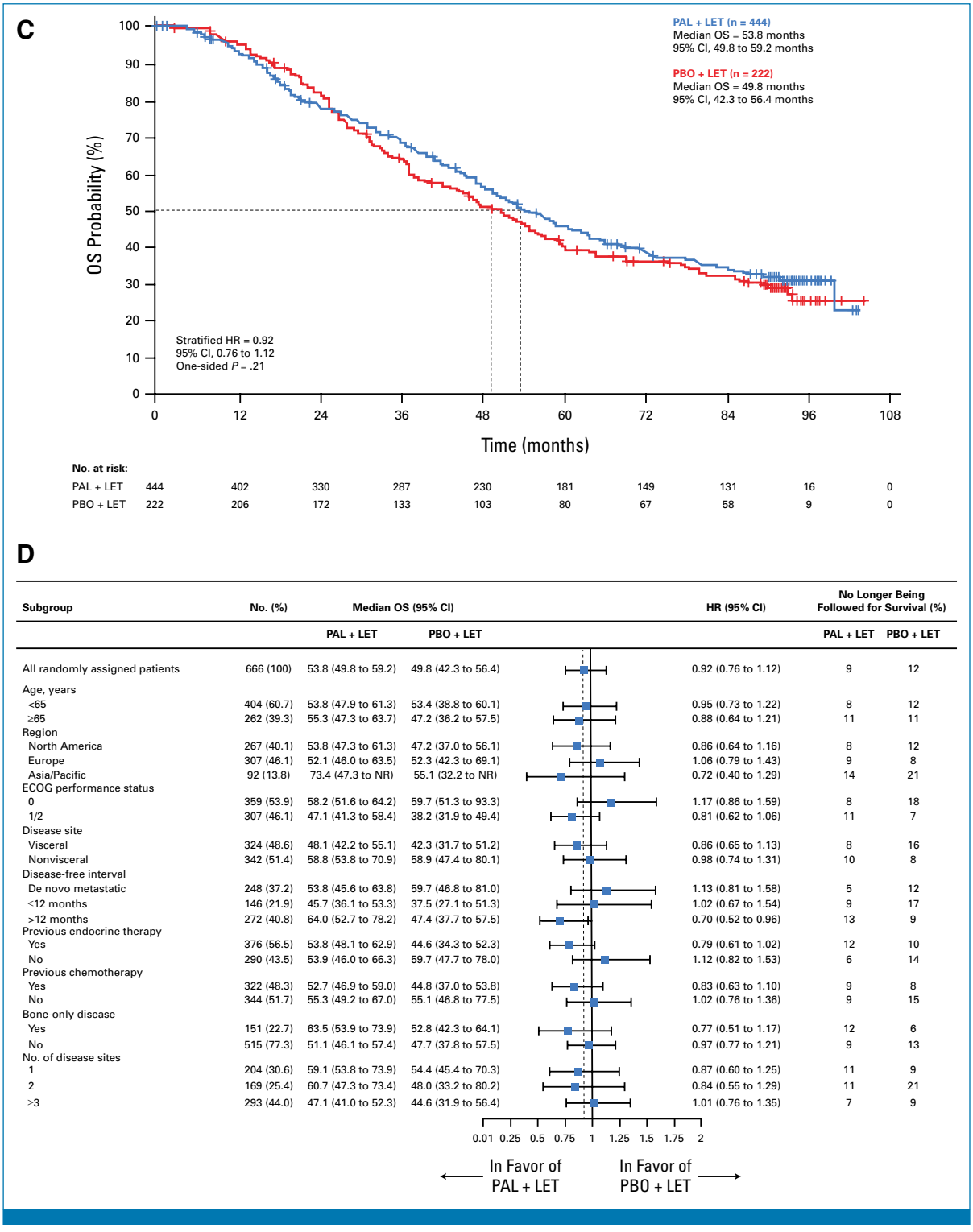

FIG 1. (Continued).

one-sided $P = .21$; Fig 1C). As per the original analysis, a series of prespecified subgroup analyses including the recovered data were performed, and the results were consistent with the original analysis (Fig 1D).

Poststudy Systemic Anticancer Therapy

A total of 399 (89.9%) patients in the palbociclib plus letrozole arm and 217 (97.7%) in the placebo plus letrozole

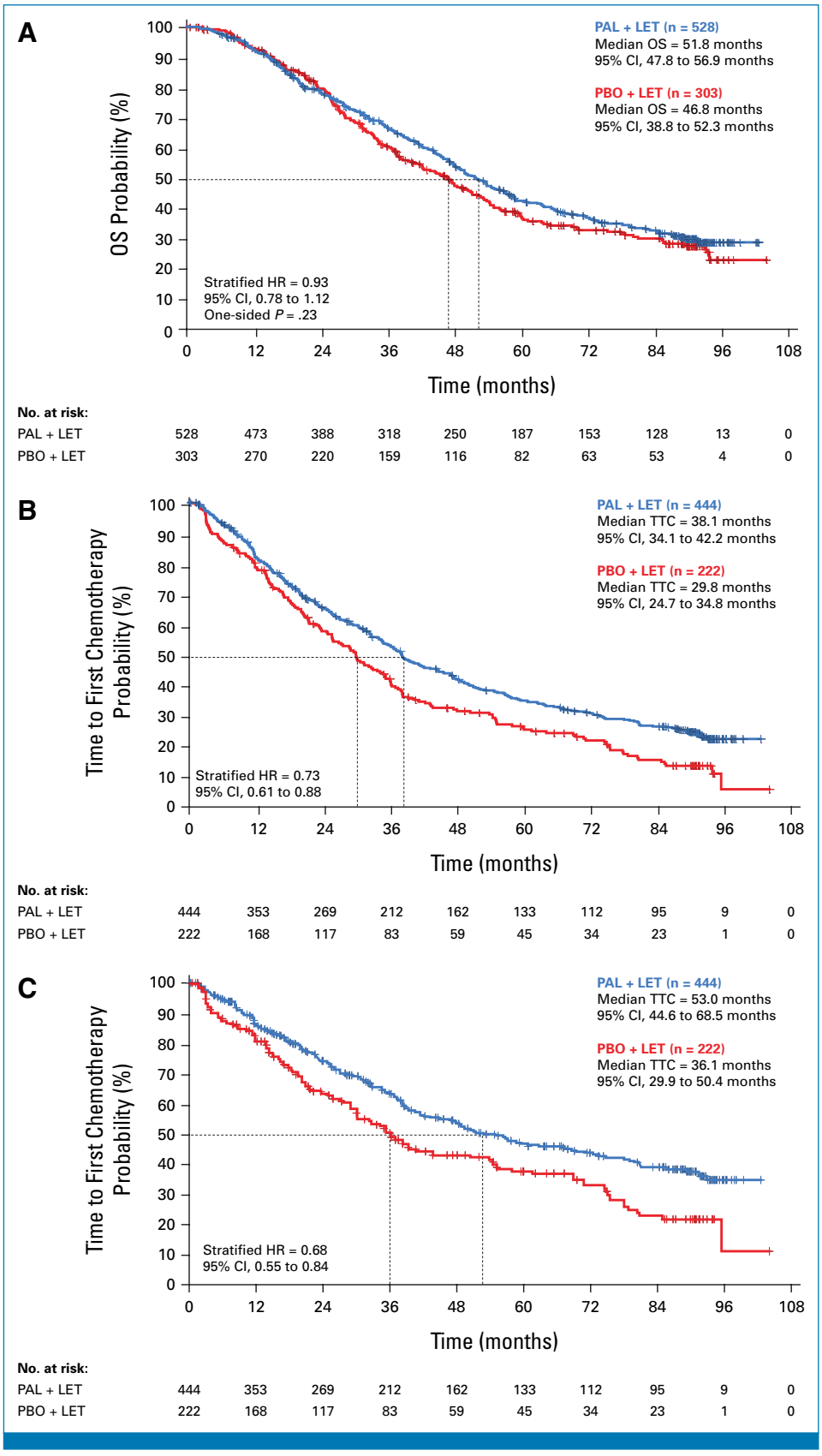

FIG 2. OS and time to chemotherapy. (A) Kaplan-Meier curve of OS in the ITT populations of both PALOMA-1 and PALOMA-2. Control arm was LET alone in PALOMA-1and PBO plus LET in PALOMA-2. Kaplan-Meier curve (B) for time to (continued on following page)

FIG 2. (Continued). first subsequent chemotherapy and (C) after censoring for deaths without chemotherapy. HR, hazard ratio; ITT, intent-to-treat; LET, letrozole; OS, overall survival; PAL, palbociclib; PBO, placebo; TTC, time to chemotherapy.

arm discontinued treatment (Data Supplement, Table S1). Of these, 322 (80.7%) and 190 (87.6%) received ≥1 poststudy systemic therapy, respectively. Of the 399 and 217 patients who discontinued treatment, 262 (65.7%) and 161 (74.2%) patients in the palbociclib plus letrozole and placebo plus letrozole arms received ET and 221 (55.4%) and 134 (61.8%) patients received chemotherapy, respectively. Forty-seven (11.8%) and 58 (26.7%) patients received a CDK4/6 inhibitor(s) poststudy, respectively; of these, the majority received palbociclib (74.5% in the palbociclib plus letrozole arm and 89.7% in the placebo plus letrozole arm).

Time to chemotherapy

The median time to first subsequent chemotherapy was longer in the palbociclib plus letrozole arm (38.1 months [95% CI, 34.1 to 42.2]) than in the placebo plus letrozole arm (29.8 months [95% CI, 24.7 to 34.8]; HR, 0.73 [95% CI, 0.61 to 0.88]; Fig 2B). A sensitivity analysis of time to chemotherapy censoring for deaths without chemotherapy also showed a substantial delay with palbociclib plus letrozole compared with placebo plus letrozole (53.0 months [95% CI, 44.6 to 68.5] *v* 36.1 months [95% CI, 29.9 to 50.4], respectively; HR, 0.68 [95% CI, 0.55 to 0.84]; Fig 2C).

Safety

The safety profile of palbociclib plus letrozole remained consistent with that reported in the primary analysis (Data Supplement, Table S2).[6] Neutropenia was the most frequent adverse event with palbociclib plus letrozole (82.2% *v* 6.3% with placebo plus letrozole).

Interactive visualization of the data presented in this article is available on the PALOMA-2 dashboard.[9]

In conclusion, all the PALOMA trials demonstrated a statistically significant and clinically meaningful benefit with palbociclib plus ET in the primary end point PFS compared with placebo plus ET or ET alone in patients with HR+/HER2− ABC.[6,8,10-12] OS was a secondary end point in all PALOMA studies and was not significantly longer in the palbociclib arm of PALOMA-1 (37.5 *v* 34.5 months; HR, 0.90), PALOMA-2, and PALOMA-3 (34.9 *v* 28.0 months; HR, 0.81).[13,14] TTC was longer in the palbociclib arm in all three PALOMA trials,[13,14] delaying exposure to therapies associated with increased toxicity. Currently, only ribociclib has shown a statistically significant improvement in OS in this setting.[15,16]

The median OS for the control arm in PALOMA-2 far exceeded the initial assumption of 34 months by almost 16 months. The accelerated US Food and Drug Administration approval and commercial availability of palbociclib in 2015 likely contributed to patients exiting the trial early during study conduct, resulting in loss of survival information. The long follow-up duration of the study, potential cross-over affecting the longer survival for the control arm with multiple subsequent treatments poststudy, and an imbalance in the CDK4/6 inhibitor(s) use poststudy could represent potential confounders to OS results. The overall safety profile of palbociclib plus letrozole remained consistent with previous reports and without evidence of cumulative toxicity with long-term use.

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CLINICAL TRIAL INFORMATION

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DATA SHARING STATEMENT

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/data-and-results for more information.

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