original reports

Capivasertib Plus Paclitaxel Versus Placebo Plus Paclitaxel As First-Line Therapy for Metastatic Triple-Negative Breast Cancer: The PAKT Trial

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abstract

PURPOSE The phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway is frequently activated in triple-negative breast cancer (TNBC). The AKT inhibitor capivasertib has shown preclinical activity in TNBC models, and drug sensitivity has been associated with activation of PI3K or AKT and/or deletions of PTEN. The PAKT trial was designed to evaluate the safety and efficacy of adding capivasertib to paclitaxel as first-line therapy for TNBC.

PATIENTS AND METHODS This double-blind, placebo-controlled, randomized phase II trial recruited women with untreated metastatic TNBC. A total of 140 patients were randomly assigned (1:1) to paclitaxel 90 mg/m^2 (days 1, 8, 15) with either capivasertib (400 mg twice daily) or placebo (days 2-5, 9-12, 16-19) every 28 days until disease progression or unacceptable toxicity. The primary end point was progression-free survival (PFS). Secondary end points included overall survival (OS), PFS and OS in the subgroup with *PIK3CA*/*AKT1*/*PTEN* alterations, tumor response, and safety.

RESULTS Median PFS was 5.9 months with capivasertib plus paclitaxel and 4.2 months with placebo plus paclitaxel (hazard ratio [HR], 0.74; 95% CI, 0.50 to 1.08; 1-sided $P = .06$ [predefined significance level, 1-sided $P = .10$]). Median OS was 19.1 months with capivasertib plus paclitaxel and 12.6 months with placebo plus paclitaxel (HR, 0.61; 95% CI, 0.37 to 0.99; 2-sided $P = .04$). In patients with *PIK3CA*/*AKT1*/*PTEN*-altered tumors (n = 28), median PFS was 9.3 months with capivasertib plus paclitaxel and 3.7 months with placebo plus paclitaxel (HR, 0.30; 95% CI, 0.11 to 0.79; 2-sided $P = .01$). The most common grade ≥ 3 adverse events in those treated with capivasertib plus paclitaxel versus placebo plus paclitaxel, respectively, were diarrhea (13% *v* 1%), infection (4% *v* 1%), neutropenia (3% *v* 3%), rash (4% *v* 0%), and fatigue (4% *v* 0%).

CONCLUSION Addition of the AKT inhibitor capivasertib to first-line paclitaxel therapy for TNBC resulted in significantly longer PFS and OS. Benefits were more pronounced in patients with *PIK3CA*/*AKT1*/*PTEN*-altered tumors. Capivasertib warrants further investigation for treatment of TNBC.

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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Triple-negative breast cancer (TNBC) accounts for approximately 10% to 15% of all breast cancers and is defined by the absence of expression of the estrogen receptor (ER), progesterone receptor (PgR), and nonamplified human epidermal growth factor receptor 2 (HER2) expression.[1] TNBC is a heterogeneous disease, with subtypes characterized by distinct pathologic, genetic, and clinical features.[2,3] Chemotherapy remains the mainstay of treatment, but benefits are frequently short lived, with rapid development of resistance.[1,4] Treatment results for patients with metastatic TNBC remain poor compared with results for those with other subtypes, with a median survival of approximately 1 year, and novel treatment approaches that target biologically defined subpopulations are urgently needed.[1,4]

The phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway is frequently activated in TNBC through activating mutations in *PIK3CA* or *AKT1* and/or inactivating alterations in *PTEN*.[5-7] In addition, deficient expression of PTEN is a common finding in TNBC and has been associated with a higher degree of AKT pathway activation.[8,9] Additional ways of activating the PI3K/AKT pathway include lack of INPP4B expression and/or amplification of *PIK3CA*, *AKT1*, *AKT2*, or *AKT3*.[5,7]

AKT is the central node of multiple signaling pathways promoting cell survival, growth, invasion, and migration.[9,10] Activation of the PI3K/AKT pathway has been associated with poor prognosis and resistance.[11-14] Induction of AKT activity by chemotherapy can also be an early compensatory mechanism that can be exploited to increase the efficacy of chemotherapy. Multiple lines of preclinical investigation have demonstrated that inhibition of AKT increases the activity of chemotherapy in TNBC and can overcome resistance.[15]

Capivasertib (AZD5363) is a potent highly selective, orally active small-molecule kinase inhibitor with similar activity against the isoforms *AKT1*, *AKT2*, and *AKT3*.[16,17] Capivasertib has shown preclinical activity in TNBC models, with activation of *PI3K* or *AKT* and/or deletions of *PTEN*, but increased activity has been seen with alterations of *PIK3CA/AKT1/PTEN*.[16,18,19] Preclinical TNBC models have also demonstrated synergistic activity between capivasertib and taxane-based chemotherapy.[16,19]

Most preclinical and clinical applications of PI3K/AKT pathway inhibitors use continuous daily dosing. However, intermittent administration has been explored to maximize the therapeutic benefit and reduce toxicities by allowing for recovery of nontarget tissues during dosing breaks.[20-22] Phase I studies established the maximum tolerated doses for continuous daily and intermittent dosing of capivasertib, with substantial activity demonstrated for both schedules.[23,24] On the basis of the accumulated efficacy and safety data, the intermittent schedule (4 days on, 3 days off) of capivasertib was selected for further clinical development.

The PAKT trial was designed to evaluate whether addition of capivasertib can increase progression-free survival (PFS) and other measures of antitumor activity of paclitaxel in women with metastatic TNBC who have not received prior therapy for metastatic disease. The study was also designed to evaluate whether *PIK3CA/AKT1/PTEN* alterations can define a subgroup with increased benefit from the combination.

PATIENTS AND METHODS

PAKT was an investigator-led, placebo-controlled, randomized phase II trial performed in 42 academic medical centers in the United Kindom, South Korea, France, Hungary, Romania, and Georgia. Eligible patients had histologically confirmed, metastatic or locally advanced TNBC (defined as $< 1\%$ of tumor cell expression of ER or PgR on immunohistochemistry [IHC] and negative HER2 status, defined as 0 or 1+ intensity on IHC or no evidence of *HER2* gene amplification on in situ hybridization [HER2/CEP17 ratio < 2.0]) not amenable to curative resection. Previous systemic therapy for locally advanced or metastatic disease was not permitted, but previous adjuvant or neoadjuvant chemotherapy was allowed as long as taxane-based therapy had been completed $\geq$ 12 months before random assignment. Patients were required to have measurable disease according to RECIST (version 1.1) or lytic bone lesions in the absence of measurable disease. Patients had to have adequate hematologic, hepatic, and renal function and an Eastern Cooperative Oncology Group performance status of 0 to 2.

Patients with brain metastases were excluded unless they had completed treatment, were asymptomatic, and had been stable for 3 months. Patients were excluded if they had significant pulmonary dysfunction, significant cardiac disease, QT prolongation, ongoing grade $\geq$ 2 peripheral neuropathy, any condition that would interfere with enteral absorption, or clinically significant abnormalities of glucose metabolism, defined as diagnosis of diabetes mellitus type I or II, glycosylated hemoglobin (hemoglobin A1C) $\geq 8.0\%$ at screening, or fasting plasma glucose $\geq$ 7.0 mmol/L. Additionally, patients with previous treatment with PI3K, AKT, or mammalian target of rapamycin inhibitors were excluded.

All patients provided written informed consent. The relevant institutional review board or ethics committee for each participating center approved the study, which was conducted in accordance with the principles of Good Clinical Practice, the provisions of the Declaration of Helsinki, and other applicable local regulations.

Patients were randomly assigned (1:1) to receive paclitaxel plus capivasertib or paclitaxel plus placebo. Stratification was by number of metastatic sites (< 3 *v* ≥ 3) and interval from the end of prior adjuvant or neoadjuvant chemotherapy (≤ 12 *v* > 12 months *v* no prior chemotherapy).

Paclitaxel was administered as a once-per-week intravenous infusion of 90 mg/m^2 over approximately 1 hour on days 1, 8, and 15 of each 28-day treatment cycle. Capivasertib 400 mg or placebo was administered orally twice per day on an intermittent weekly dosing schedule, with treatment on days 2 to 5 of weeks 1, 2, and 3 within each 28-day cycle. All treatments were continued until disease progression, development of unacceptable toxicity, or withdrawal of consent. If paclitaxel treatment was discontinued before disease progression, patients could continue to receive capivasertib or placebo alone. In case of adverse events (AEs), capivasertib or placebo could be reduced to 320 mg twice per day and subsequently to 240 mg twice per day. Capivasertib or placebo could be interrupted for up to 4 weeks for toxicity.

Tumor assessments included computed tomography scanning or magnetic resonance imaging of the chest, abdomen, and pelvis at baseline, every 8 weeks during treatment, and at progression. Patients who discontinued treatment for any reason other than progression were required to follow the same schedule of assessments until progression, initiation of another treatment, death, or withdrawal of consent. All scans were sent for central radiologic review.

All patients were required to provide a representative formalin-fixed, paraffin-embedded tumor specimen from the most recent biopsy. Tumor tissue was centrally assessed for genetic alterations of *PIK3CA*, *PTEN*, and

AKT1 using a next-generation sequencing (NGS) assay (Appendix Fig A1, online only). Tumors were considered *PIK3CA*/*AKT1*/*PTEN* altered if they had ≥ 1 of the following mutations: activating mutation in *AKT1* (E17K) or *PIK3CA* (R88Q, N345K, C420R, E542X, E545X, Q546X, M1043I, H1047X, G1049R mutations [X represents any change in amino acid residue]) and/or a deleterious mutation in *PTEN* or loss of the *PTEN* gene. Cases in which none of these mutations were identified were classified as *PIK3CA*/*AKT1*/*PTEN* nonaltered.

The primary end point was PFS by local assessment. PFS was defined as time from random assignment to disease progression or death resulting from any cause, whichever occurred first. Secondary end points included overall survival (OS), overall response rate, clinical benefit rate, durations of response and clinical benefit, PFS and other efficacy end points in patients with *PIK3CA*/*AKT1*/*PTEN*-altered and -nonaltered tumors, and safety. For all time-to-event analyses performed, patients who did not experience an event were right censored; PFS and duration of response were censored on the last date the patient was known to be progression free; OS was censored at the date of last contact.

The sample size was calculated to provide 80% power at a 10% significance level (1 sided) to detect an improvement in PFS in patients allocated to capivasertib plus paclitaxel with a hazard ratio (HR) of 0.67. With an estimated recruitment time of 24 months and a minimum follow-up of 12 months, a total of 111 PFS events were needed. To allow for loss to follow-up and imprecision in the estimated event rate, 140 patients were recruited.

Comparisons between arms were performed using Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. All efficacy analyses were performed on an intent-to-treat (ITT) basis, including all randomly assigned patients, regardless of whether they were later found to be ineligible, be in violation of the protocol violator, or have received the wrong treatment. Survival end points were shown graphically with Kaplan-Meier plots, and treatment comparisons were made with the log-rank test. HRs were obtained from Cox proportional hazards regression models, with HRs of < 1 favoring capivasertib plus paclitaxel. HRs and treatment comparisons were stratified by the 2 randomization stratification factors for analyses of the ITT population. Analyses of

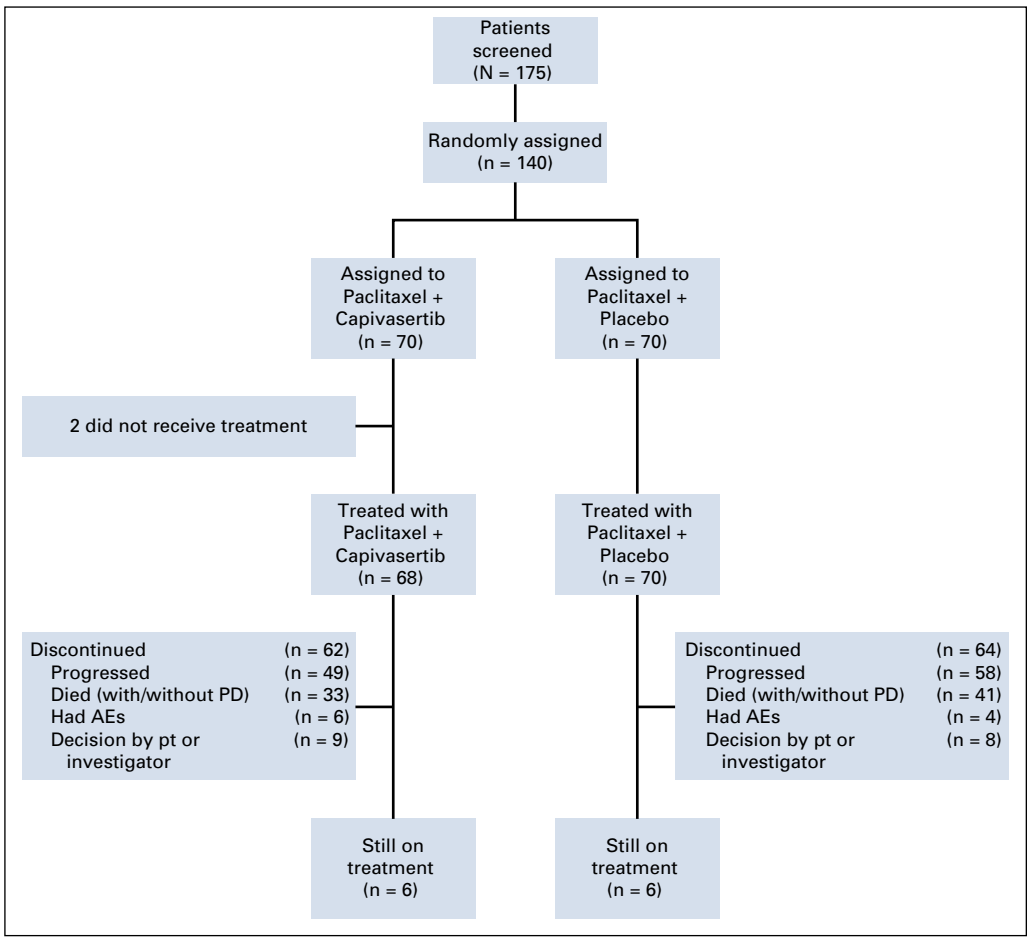

FIG 1. Trial CONSORT diagram. AE, adverse event; PD, progressive disease; pt, patient.

patients with *PIK3CA*/*AKT1*/*PTEN*-altered and -nonaltered tumors and other subgroup analyses were not stratified.

Safety analyses included all patients who received ≥ 1 dose of trial treatment (as treated population), with patients analyzed according to the treatment they actually received. The worst grade of AE during trial treatment was reported. Relative dose-intensity for each study drug was calculated using the actual amount of study drug received in milligrams divided by the expected amount of study drug in milligrams.

RESULTS

Between May 2014 and June 2017, 140 patients were randomly assigned (Fig 1) at 42 sites in 6 countries: 70 patients to capivasertib plus paclitaxel and 70 to placebo plus paclitaxel. With the exception of visceral disease (P = .04), no significant differences were observed in baseline patient or tumor characteristics between treatment arms (Table 1). Median age was 54 years; 69% of patients had visceral involvement; 46% had metastases in ≥ 3 organs; a majority of patients had received adjuvant or neoadjuvant chemotherapy (77%), with 57% of patients having received prior taxane-based treatment; 18 patients presented with de novo metastatic disease (Appendix Fig A2, online only).

At the data cutoff date (January 2018), 6 patients in each group were still receiving study treatment. A higher percentage of patients in the capivasertib group had ≥ 1 dose interruption or delay (34% *v* 15%; P = .02) or required a dose reduction (17% *v* 2%; $P < .01$), although there was

TABLE 1. Patient Demographic and Disease Characteristics at Baseline

	ITT Population			*PIK3CA/AKT1/PTEN*-Altered Subgroup		
	No. (%)*			No. (%)*		
Characteristic	Paclitaxel + Capivasertib (n = 70)	Paclitaxel + Placebo (n = 70)	*P*†	Paclitaxel + Capivasertib (n = 17)	Paclitaxel + Placebo (n = 11)	*P*†
Age, years			.09			.56
Median	55.5	51.9		60.5	60.6	
IQR	48.4-62.3	40.8-60.7		57.1-67.1	36.0-65.2	
ECOG performance status			.48			.51
0	43 (61.4)	48 (68.6)		10 (58.8)	9 (81.8)	
1	26 (37.1)	22 (31.4)		6 (35.3)	2 (18.2)	
2	1 (1.4)	0		1 (5.9)	0	
Visceral disease			.04			1.00
Yes	42 (60.0)	54 (77.1)		12 (70.6)	8 (72.7)	
No	28 (40.0)	16 (22.9)		5 (29.4)	3 (27.3)	
Sites of metastatic disease						
Liver	17 (24.3)	21 (30.0)	.57	6 (35.3)	5 (45.5)	.70
Lung	35 (50.0)	45 (64.3)	.12	9 (52.9)	6 (54.5)	1.00
Bone	29 (41.4)	28 (40.0)	1.00	11 (64.7)	5 (45.5)	.44
Lymph node/soft tissue	49 (70.0)	51 (72.9)	.85	7 (41.2)	10 (90.9)	.02
No. of metastatic sites			1.00			.70
< 3	37 (52.9)	38 (54.3)		11 (64.7)	6 (54.5)	
≥ 3	33 (47.1)	32 (45.7)		6 (35.3)	5 (45.5)	
Prior taxanes			1.00			.46
Yes	40 (57.1)	40 (57.1)		9 (52.9)	4 (36.4)	
No	30 (42.9)	30 (42.9)		8 (47.1)	7 (63.6)	
Adjuvant or neoadjuvant chemotherapy			1.00			.12
End ≤ 12 months	4 (5.7)	4 (5.7)		1 (5.9)	0	
End > 12 months	50 (71.4)	50 (71.4)		11 (64.7)	4 (36.4)	
No prior chemotherapy	16 (22.9)	16 (22.9)		5 (29.4)	7 (63.6)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; ITT, intent to treat.

*All percentages are based on the total No. of patients in that arm.

†*P* values are 2-sided.

no difference in median relative dose-intensity for paclitaxel (P = .07) or capivasertib or placebo (P = .46) between groups (Table 2). Median duration of treatment was longer in the capivasertib group compared with the placebo group.

Frequency of AEs was comparable between treatment groups (P = .27), but the incidence of severe AEs (grade 3-4) was significantly higher with capivasertib ($P < .01$). The most common AEs with capivasertib were GI effects (diarrhea, stomatitis, decreased appetite, nausea, vomiting), alopecia, neuropathy, fatigue, infection, and rash (Table 3). These were typically grade 1 or 2. Grade ≥ 3 AEs occurred in 54% of patients (37 of 68) in the capivasertib group and 26% (18 of 70) in the placebo group (Table 3). The most common grade 3 to 4 AEs in those treated with capivasertib plus paclitaxel versus placebo plus paclitaxel, respectively, were diarrhea (13% *v* 1%), fatigue (4% *v* 0%), rash (4% *v* 0%), infection (4% *v* 1%), and neutropenia (3% in both arms).

After a median follow-up of 18.2 months (95% CI, 13.5 to 24.0), 112 progression events were reported: 51 patients assigned to capivasertib plus paclitaxel and 61 patients assigned to placebo plus paclitaxel. Median PFS was 5.9 months (95% CI, 3.8 to 7.5) with capivasertib plus paclitaxel and 4.2 months (95% CI, 3.5 to 5.2) with placebo plus paclitaxel (HR, 0.74; 95% CI, 0.50 to 1.08; 1-sided P = .06; 2-sided P = 0.11; predefined significance level, 1-sided P = .10; Fig 2A).

Tumor tissue samples were assessed centrally for *PIK3CA/AKT1/PTEN* alterations in 112 patients (80% of the ITT population). In the remaining 28 patients (20%), *PIK3CA/AKT1/PTEN* status could not be determined because of insufficient sample or assay failure. A total of 28 samples (25% of analyzed samples) had activating *PIK3CA/AKT1* mutations or inactivating *PTEN* alterations. Biomarker-assessable populations for *PIK3CA/AKT1/PTEN* alterations showed baseline characteristics similar to those of the ITT population.

Prespecified analyses in the subgroup of patients with *PIK3CA/AKT1/PTEN*-altered tumors showed a median PFS of 9.3 months (95% CI, 3.7 to 17.7) with capivasertib plus paclitaxel and 3.7 months (95% CI, 1.9 to 5.9) with placebo plus paclitaxel (HR, 0.30; 95% CI, 0.11 to 0.79; 2-sided P = .01; Fig 2B). Exploratory analysis of the interaction between *PIK3CA/AKT1/PTEN* alteration and treatment showed a significantly reduced risk of 66% (HR, 0.34; 95% CI, 0.13 to 0.93; 2-sided P = .04) for those patients who had *PIK3CA/AKT1/PTEN* alteration and received capivasertib. In patients with *PIK3CA/AKT1/PTEN*-nonaltered tumors, median PFS was 5.3 months (95% CI, 3.5 to 7.3) with capivasertib plus paclitaxel and 4.4 months (95% CI, 3.5 to 5.7) with placebo plus paclitaxel (HR, 1.13; 95% CI, 0.70 to 1.82; 2-sided P = .61; Fig 2C).

On the basis of central review assessments, median PFS was 5.5 months (95% CI, 3.8 to 7.5) with capivasertib plus paclitaxel and 3.6 months (95% CI, 3.2 to 4.8) with placebo plus paclitaxel (HR, 0.64; 95% CI, 0.43 to 0.95; 1-sided P = .01; 2-sided P = .02; predefined significance level, 1-sided P = .10). In patients with *PIK3CA/AKT1/PTEN*-altered tumors, median PFS was 9.3 months (95% CI, 3.8 to not reached [NR]) with capivasertib plus paclitaxel compared with 3.6 months (95% CI, 1.4 to 5.3) with placebo plus paclitaxel (HR, 0.14; 95% CI, 0.05 to 0.44; 2-sided $P < .001$; Appendix Fig A3, online only).

Secondary end points of objective response and clinical benefit rate are summarized in Table 4. Median duration of response was 7.6 months (95% CI, 5.6 to 12.5) with capivasertib plus paclitaxel and 7.3 months (95% CI, 3.5 to 9.1) with placebo plus paclitaxel. In patients with *PIK3CA/AKT1/PTEN*-altered tumors, median duration of response was 13.3 months (95% CI, 8.9 to NR) with capivasertib plus paclitaxel and 3.5 months (95% CI, 3.5 to NR) with placebo plus paclitaxel.

At the time of data cutoff, 74 patients had died (53%): 33 (47%) in the capivasertib plus paclitaxel group and

TABLE 2. Treatment Summary

Treatment Compliance	Paclitaxel + Capivasertib (n = 65)	Paclitaxel + Placebo (n = 65)	*P**
Patients with ≥ 1 dose interruption/delay because of AE, No. (%)†	22 (33.8)	10 (15.4)	.02
Patients with ≥ 1 dose reduction of capivasertib or placebo, No. (%)†	11 (16.9)	1 (1.5)	< .01
Median (IQR) duration of treatment, months			
Capivasertib or placebo	4.8 (1.7-7.5)	4.1 (2.2-7.6)	.86
Paclitaxel	4.8 (1.9-6.1)	3.7 (1.7-5.4)	.50
Median (IQR) relative dose-intensity, %			
Capivasertib or placebo	91.1 (80.6-100.0)	93.8 (86.4-100.0)	.46
Paclitaxel	96.6 (81.8-100.0)	100.0 (91.7-100.0)	.07

NOTE. Patients are presented based on the treatment they received.
Abbreviations: AE, adverse event; IQR, interquartile range.
*P values are 2-sided.
†All percentages are based on the total No. of patients in that arm with complete compliance data.

TABLE 3. AEs Occurring in ≥ 8% of Patients in ≥ 1 Treatment Group

	No. (%)*					
	Paclitaxel + Capivasertib (n = 68)		Paclitaxel + Placebo (n = 70)		*P*†	
AE	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Patients with ≥ 1 AE	66 (97.1)	37 (54.4)	64 (91.4)	18 (25.7)	0.27	< 0.01
Diarrhea	49 (72.1)	9 (13.2)	19 (27.1)	1 (1.4)	< 0.01	< 0.01
Fatigue	30 (44.1)	3 (4.4%)	18 (25.7)	0	0.03	0.12
Nausea	24 (35.3)	1 (1.5)	23 (32.9)	0	0.86	0.49
Rash	28 (41.2)	3 (4.4)	11 (15.7)	0	< 0.01	0.12
Neuropathy	17 (25.0)	1 (1.5)	13 (18.6)	0	0.41	0.49
Stomatitis	18 (26.5)	1 (1.5)	10 (14.3)	0	0.09	0.49
Infection	15 (22.1)	3 (4.4)	10 (14.3)	1 (1.4)	0.27	0.36
Decreased appetite	14 (20.6)	0	8 (11.4)	0	0.17	1.00
Alopecia	11 (16.2)	0	9 (12.9)	0	0.63	1.00
Vomiting	13 (19.1)	1 (1.5)	6 (8.6)	1 (1.4)	0.09	1.00
Constipation	5 (7.4)	0	10 (14.3)	0	0.27	1.00
Abdominal pain	7 (10.3)	0	7 (10.0)	0	1.00	1.00
Dry skin	10 (14.7)	0	2 (2.9)	0	0.02	1.00
Dyspnoea	6 (8.8)	0	5 (7.1)	0	0.76	1.00
Headache	8 (11.8)	0	3 (4.3)	0	0.13	1.00
Edema	6 (8.8)	0	4 (5.7)	0	0.53	1.00
Dysgeusia	7 (10.3)	0	3 (4.3)	0	0.20	1.00
Joint pain	2 (2.9)	0	6 (8.6)	0	0.27	1.00
Neutropenia	6 (8.8)	2 (2.9)	2 (2.9)	2 (2.9)	0.16	1.00
Cough	1 (1.5)	0	6 (8.6)	0	0.12	1.00
Hyperglycemia	6 (8.8)	1 (1.5)	1 (1.4)	0	0.06	0.49

NOTE. Worst toxicity for each patient during the entire treatment is reported. AE instances with missing grade are not included in table.
Abbreviation: AE, adverse event.
*All percentages are based on the total No. of patients in that arm who received ≥ 1 dose of the study drug, with patients analyzed according to the treatment they actually received (safety population).
†*P* values are 2-sided.

41 (59%) in the placebo plus paclitaxel group. Median OS was 19.1 months (95% CI, 10.9 to 20.9) with capivasertib plus paclitaxel and 12.6 months (95% CI, 10.4 to 16.9) with placebo plus paclitaxel (HR, 0.61; 95% CI, 0.37 to 0.99; 2-sided $P = .04$; Fig 3A). In the *PIK3CA*/*AKT1*/*PTEN*-altered subgroup, median OS was NR (95% CI, 10.2 to NR) in patients receiving capivasertib versus 10.4 months (95% CI, 4.0 to NR) in those receiving placebo (HR, 0.37; 95% CI, 0.12 to 1.12; 2-sided $P = .07$; Fig 3B). In patients with *PIK3CA*/*AKT1*/*PTEN*-nonaltered tumors, median OS was 16.6 months (95% CI, 10.8 to 20.4) with capivasertib versus 13.2 months (95% CI, 10.8 to 17.3) with placebo (HR, 0.84; 95% CI, 0.48 to 1.49; 2-sided $P = .56$; Fig 3C).

DISCUSSION

This investigator-led, placebo-controlled, double-blind, randomized trial showed that PFS and OS were longer in patients who received the AKT inhibitor capivasertib compared with those who received placebo. The primary end point of PFS did not obtain the prespecified target HR (0.67), as per sample size calculations, when measured based on investigator assessments (HR, 0.74); however, this was achieved when measured based on central review assessments (HR, 0.64). Although the increase in median PFS was relatively small in the overall population, the benefits in patients with *PIK3CA*/*AKT1*/*PTEN*-altered tumors were more pronounced, with a 5.6-month increase in median PFS and 9.8-month increase in duration of response. The addition of capivasertib resulted in a significant increase in OS, from 12.6 to 19.1 months; the OS benefit was also more pronounced in the *PIK3CA*/*AKT1*/*PTEN*-altered subgroup.

The results of PAKT are remarkably consistent with the results of the LOTUS study, providing additional evidence

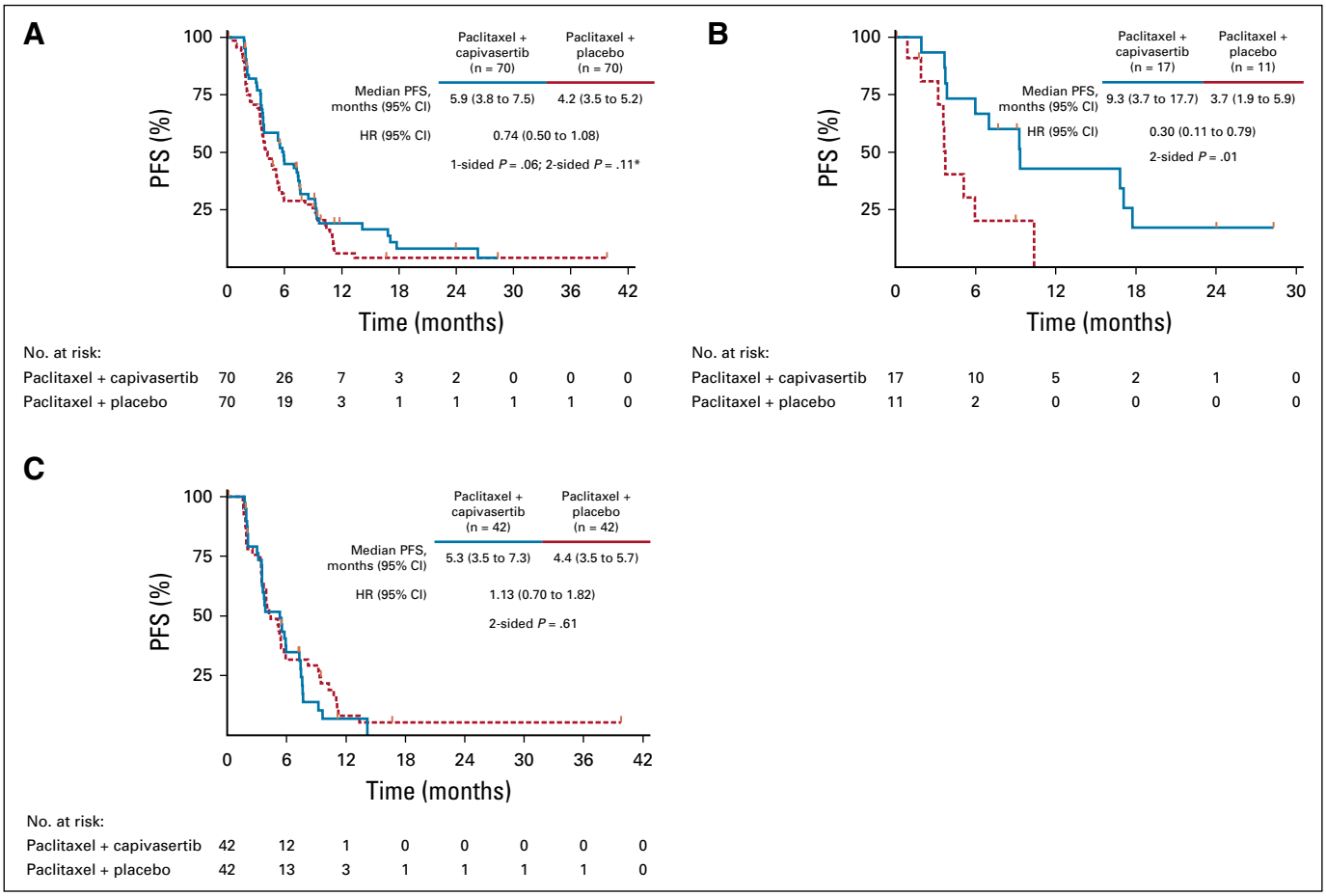

FIG 2. Kaplan-Meier plot of progression-free survival (PFS) in (A) intent-to-treat population, (B) *PIK3CA*/*AKT1*/*PTEN*-altered subgroup, and (C) *PIK3CA*/*AKT1*/*PTEN*-nonaltered subgroup. HR, hazard ratio; PFS, progression-free survival. (*) One-sided predefined significance level, $P = .10$.

for the role of AKT inhibitors in TNBC.[25] LOTUS was a phase II study that evaluated the AKT inhibitor ipatasertib or placebo in combination with paclitaxel as first-line chemotherapy in metastatic TNBC. The trial demonstrated a modest but significant increase in median PFS from 4.9 to 6.2 months with the addition of ipatasertib. Preliminary OS data also suggested a trend toward improved OS, with an approximately 5-month difference.[26]

The PAKT trial was designed to explore whether antitumor activity of capivasertib might be enhanced in the subgroup of patients with *PIK3CA*/*AKT1*/*PTEN*-altered tumors. Preclinical studies demonstrated increased sensitivity in models with activation of *PI3K* or *AKT1* and/or deletions of *PTEN*.[16,18,19] Central assessment of *PIK3CA*/*AKT1*/*PTEN* alterations by NGS was successful in 80% of patients in this trial, which is similar to the NGS success rate in the LOTUS trial (83%).[26] A majority of samples were obtained from primary tumors (82%). The diagnostic prevalence of *PIK3CA*/*AKT1*/*PTEN* alterations in PAKT was 25%. There was no significant difference in the incidence of *PIK3CA*/*AKT1*/*PTEN* alterations between primary tumor samples and tissue from metastases (χ^2 $P = .359$). This is comparable to the results of the METABRIC study, where 23% of patients with TNBC demonstrated *PIK3CA*/*AKT1*/*PTEN* alterations.[6] In contrast, the diagnostic prevalence of *PIK3CA*/*AKT1*/*PTEN* alterations in the LOTUS trial was higher, at 41%.[25] Possible explanations might include differences in NGS assays and variant calling, preselection of patients known to have pathway variants, or differences in patient populations. In this context, it is noteworthy that nearly half of the patients in the LOTUS trial were of Asian ethnicity, compared with 13% in PAKT.

The PAKT trial strongly suggests that the benefits of AKT inhibition might be largely limited to the subgroup of patients with *PIK3CA*/*AKT1*/*PTEN* alterations, although an OS benefit cannot be excluded in patients with nonaltered tumors. Cox proportional hazards models confirmed a significant interaction between *PIK3CA*/*AKT1*/*PTEN* alterations and treatment ($P = .04$).

Although this subgroup is small, and results have to be interpreted with caution, the *PIK3CA*/*AKT1*/*PTEN*-altered and -nonaltered results are further supported by the LOTUS trial, which showed a similar but nonsignificant trend for PFS, with an HR of 0.44 in patients with *PIK3CA*/*AKT1*/*PTEN* alterations compared with an HR of 0.76 in

TABLE 4. Primary and Secondary Efficacy End Points

	ITT Population		*PIK3CA/AKT1/PTEN*-Altered Subgroup	
End Point	**Paclitaxel + Capivasertib**	**Paclitaxel + Placebo**	**Paclitaxel + Capivasertib**	**Paclitaxel + Placebo**
ORR				
No. of patients*	66	66	17	11
No. (%)†	23 (34.8)	19 (28.8)	6 (35.3)	2 (18.2)
2-sided *P*	.58		.42	
Clinical benefit rate				
No. of patients‡	70	70	17	11
No. (%)†	29 (41.4)	26 (37.1)	9 (52.9)	3 (27.3)
2-sided *P*	.73		.25	
Duration of response				
No. of patients§	23	19	6	2
Median (95% CI), months	7.6 (5.6 to 12.5)	7.3 (3.5 to 9.1)	13.3 (8.9 to NR)	3.5 (3.5 to NR)
2-sided *P*	.57		.08	
PFS				
Median (95% CI), months	5.9 (3.8 to 7.5)	4.2 (3.5 to 5.2)	9.3 (3.7 to 17.7)	3.7 (1.9 to 5.9)
HR (95% CI)	0.74 (0.50 to 1.08)		0.30 (0.11 to 0.79)	
P				
1-sided	.06			
2-sided	.11		.01	
OS				
Median (95% CI), months	19.1 (10.9 to 20.9)	12.6 (10.4 to 16.9)	NR (10.2 to NR)	10.4 (4.0 to NR)
HR (95% CI)	0.61 (0.37 to 0.99)		0.37 (0.12 to 1.12)	
P				
1-sided	.02			
2-sided	.04		.07	

Abbreviations: HR, hazard ratio; ITT, intent to treat; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

*No. of patients in the ITT population with measurable disease at baseline.

†All percentages are based on the total No. of patients in that arm based on the specified population.

‡No. of patients in the ITT population.

§No. of patients with measurable disease at baseline and an objective response.

nonaltered tumors.[25] Median OS was 23.1 months with ipatasertib versus 16.2 months with placebo (HR, 0.65; 95% CI, 0.32 to 1.30) in patients with *PIK3CA/AKT1/PTEN*-altered tumors.[26] Although these findings from PAKT and LOTUS have to be interpreted with caution because of their small sample sizes, the fact that 2 independent trials performed with different AKT inhibitors demonstrate comparable results adds substantial weight to these observations.

The combination of capivasertib plus paclitaxel was generally well tolerated. Most common AEs were GI effects, particularly diarrhea, which was generally mild or moderate, clinically manageable, and rapidly reversible; the protocol specified guidelines for symptomatic diarrhea, but prophylactic antidiarrheal medication was not recommended; this might be revisited for future studies. Hyperglycemia was more commonly observed with capivasertib but rarely had sequelae; of note, patients with clinically significant abnormalities of glucose metabolism were excluded. On the basis of our experience, inclusion of patients with well-controlled diabetes might be considered future trials. Overall, the toxicity profile seemed comparable with those of other AKT inhibitors[25] and was largely limited to the known class effects of AKT inhibition. The favorable tolerability profile was also reflected in the comparable dose-intensity in both arms, despite a higher frequency of dose modifications with capivasertib.

Despite the limitations mainly resulting from the sample size and lack of adjustment for multiple testing (for the ITT population and the *PIK3CA/AKT1/PTEN*-altered subgroup), the PAKT study is one of few trials to demonstrate PFS and OS benefits in metastatic TNBC. The numbers and

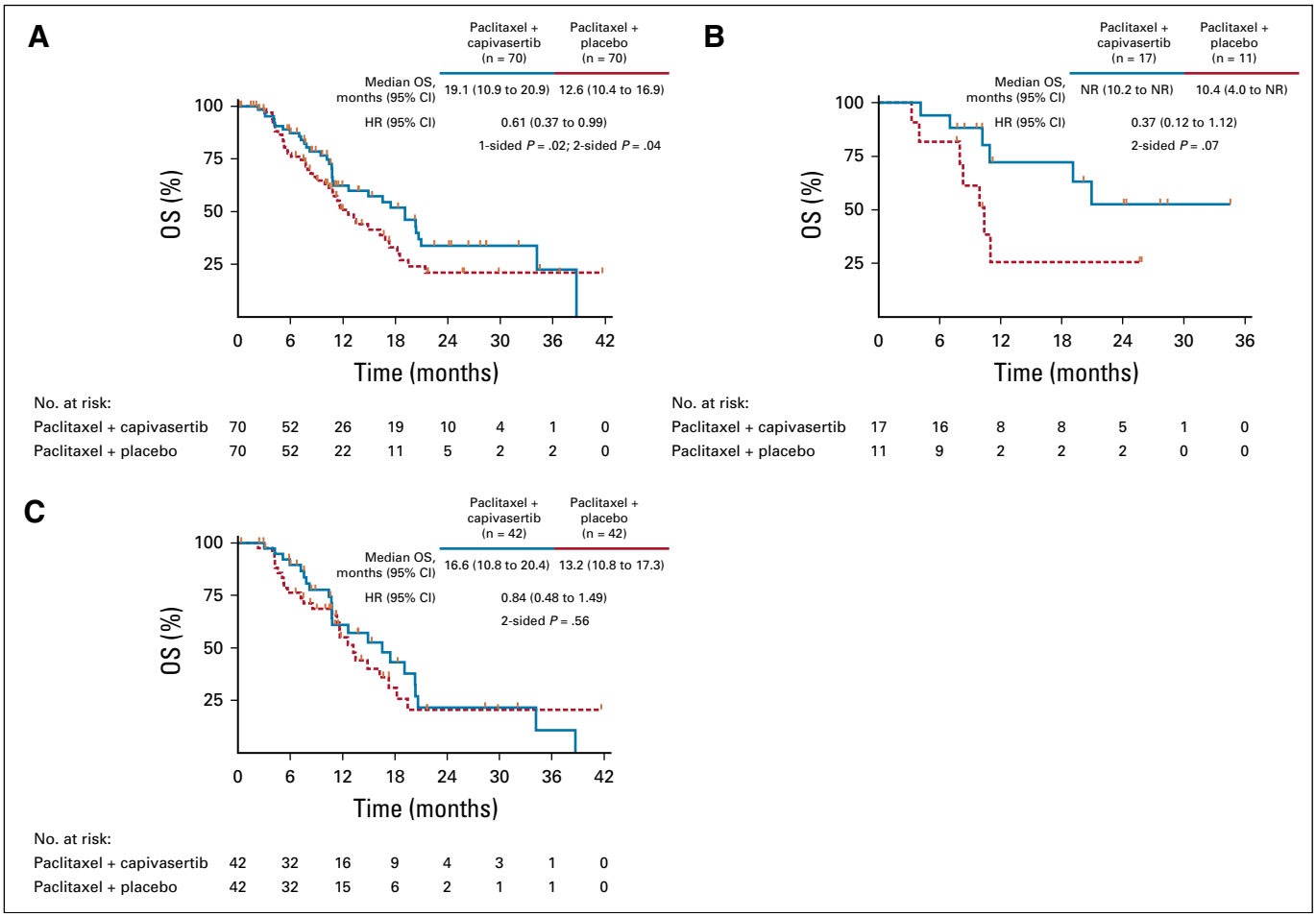

FIG 3. Kaplan-Meier plot of overall survival (OS) in (A) intent-to-treat population, (B) *PIK3CA*/*AKT1*/*PTEN*-altered subgroup, and (C) *PIK3CA*/*AKT1*/*PTEN*-nonaltered subgroup. HR, hazard ratio; NR, not reached; OS, overall survival.

types of subsequent treatments after progression were comparable between treatment groups, suggesting the observed differences resulted from the study treatment. Together with the LOTUS trial, the PAKT study provides important evidence that AKT inhibition might be able to improve patient outcomes in this difficult-to-treat subtype of breast cancer, but confirmatory and adequately powered phase III trials are required. On the basis of the current data, paclitaxel should be considered as the chemotherapy backbone for future studies, but other chemotherapy combinations may also be explored. Capivasertib is being further investigated for the treatment of TNBC in a phase III randomized trial (NCT03997123). Prospectively planned biomarker analyses based on preclinical observations support selection of patients with *PIK3CA*/*AKT1*/*PTEN* alterations for future studies.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Capivasertib Plus Paclitaxel Versus Placebo Plus Paclitaxel As First-Line Therapy for Metastatic Triple-Negative Breast Cancer: The PAKT Trial

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APPENDIX

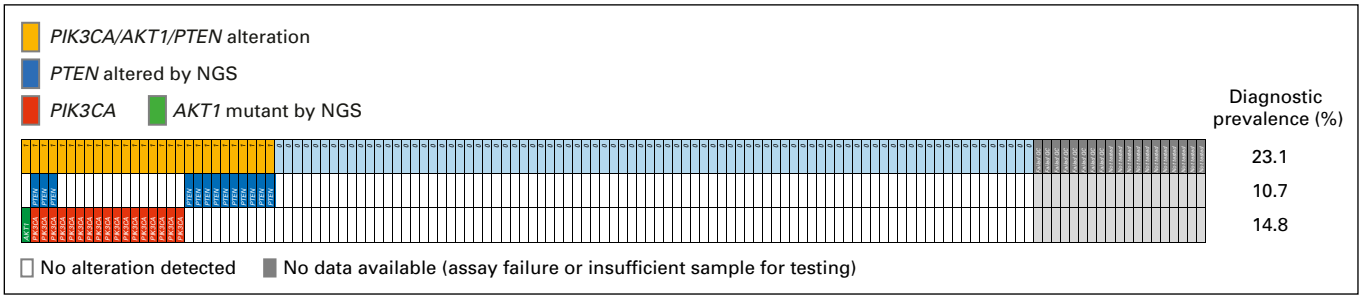

FIG A1. Biomarker prevalence. Prevalence based on all available diagnostic data. Each vertical set of blocks represents an individual patient's tumor. Dark blue blocks represent *PTEN*-altered by NGS; green blocks represent *AKT1*-mutant by NGS; red blocks represent *PIK3CA*-mutant by NGS; gray blocks represent samples with no corresponding data available (assay failure or insufficient sample for testing). The top row shows whether samples are classified as *PIK3CA/AKT1/PTEN*-altered (yellow) or *PIK3CA/AKT1/PTEN*-non-altered (light blue). NGS, next-generation sequencing.

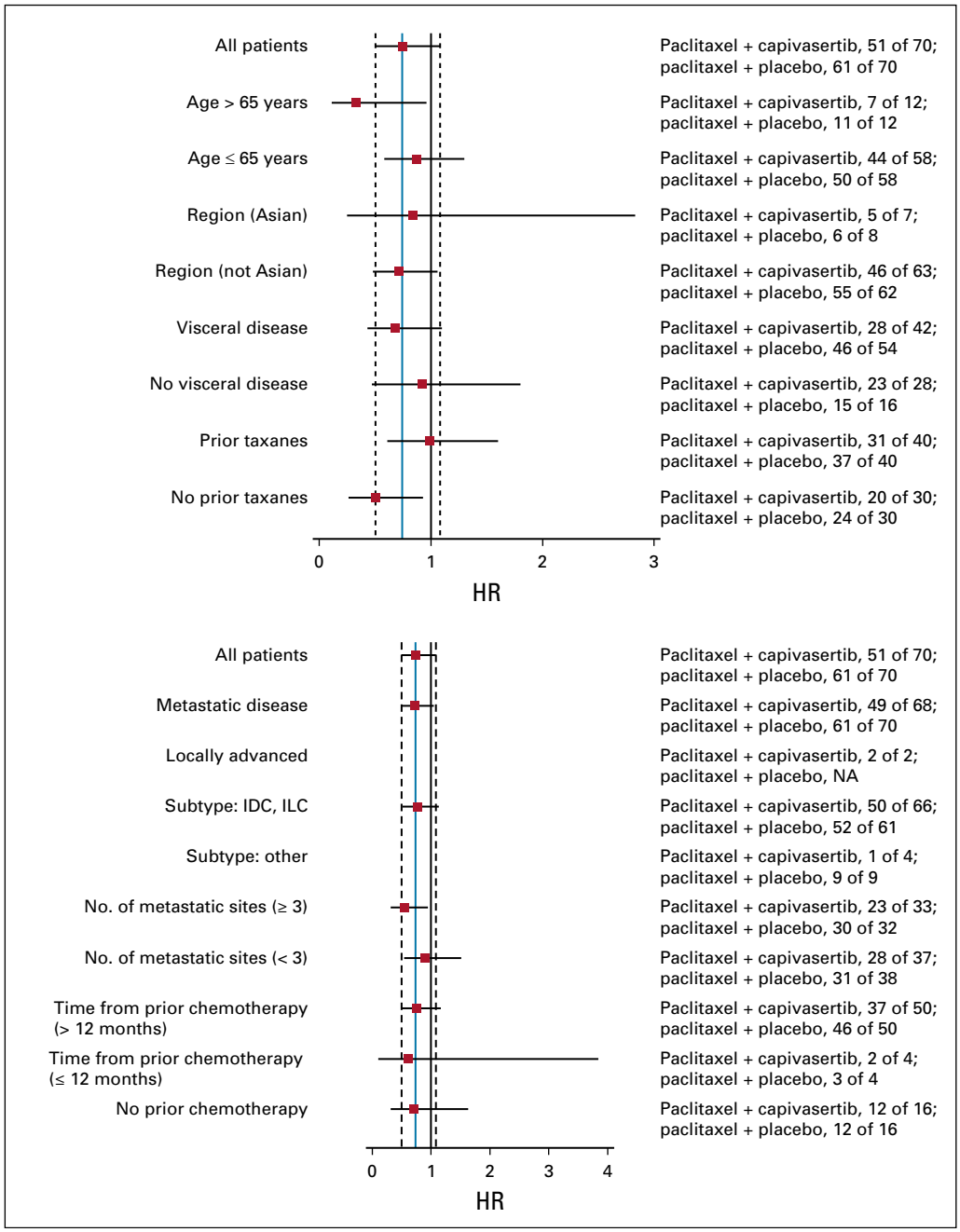

FIG A2. Subgroup analysis of progression-free survival. n is the number of patients who have a progression event (documented progression or death) in each subgroup. N is the number of patients in each subgroup. Dashed lines represent the hazard ratio and its 95% confidence interval for the all patients population. HR, hazard ratio; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

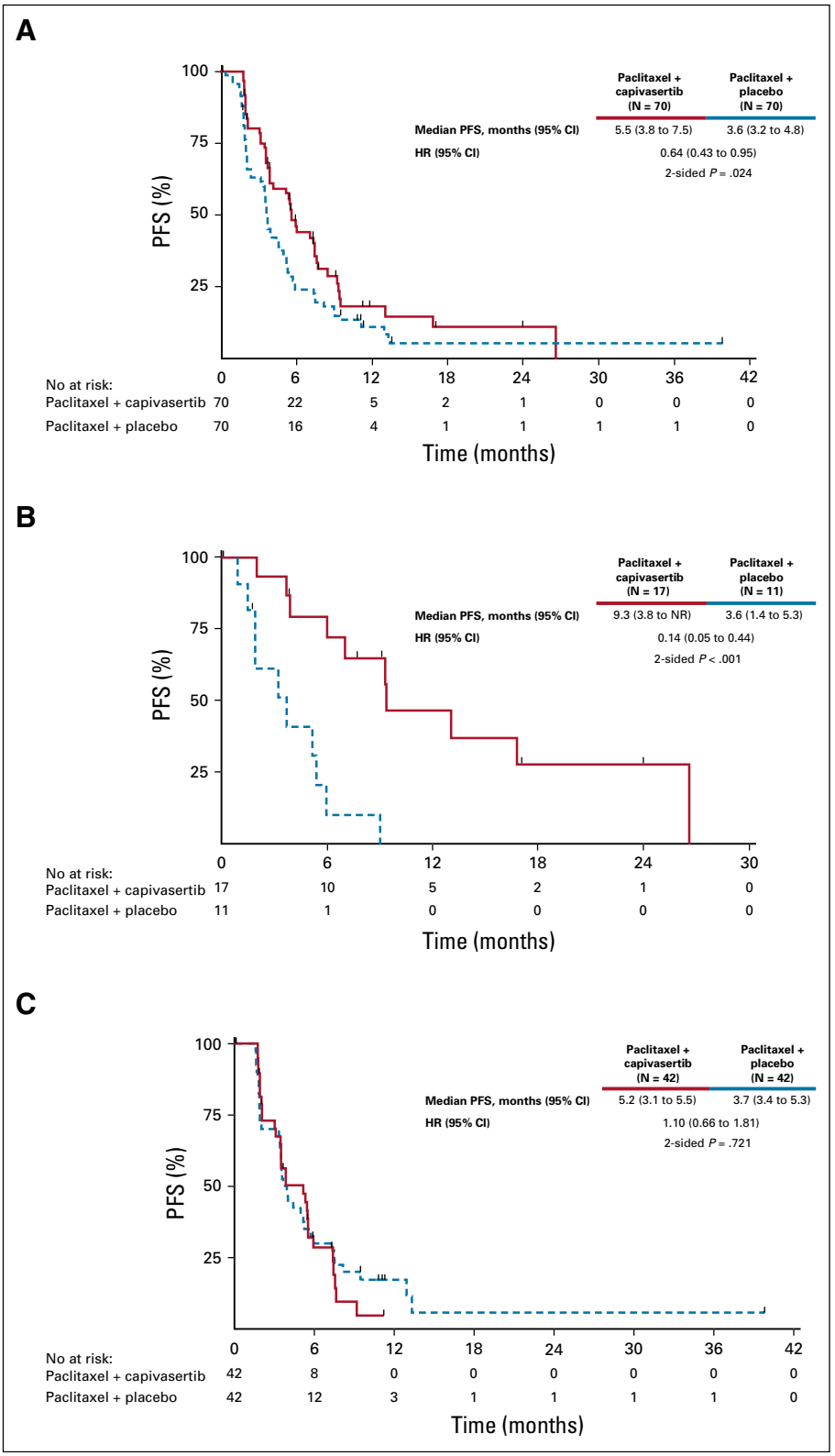

FIG A3. Kaplan-Meier plot of progression-free survival (PFS) based on a blinded independent central review. (A) Intention-to-treat population; (B) PIK3CA/AKT1/PTEN-altered subgroup; (C) PIL2CA/AKT1/PTEN non-altered subgroup. CI, Confidence interval; HR, Hazard Ratio; mths, months; PFS, Progression-free survival; NR, not reached.