Original Reports | Breast Cancer

PACE: A Randomized Phase II Study of Fulvestrant, Palbociclib, and Avelumab After Progression on Cyclin-Dependent Kinase 4/6 Inhibitor and Aromatase Inhibitor for Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor–Negative Metastatic Breast Cancer

Erica L. Mayer, MD, MPH[1,2] ; Yue Ren, MS[3] ; Nikhil Wagle, MD[1,2] ; Reshma Mahtani, DO[4] ; Cynthia Ma, MD, PhD[5] ;
Angela DeMichele, MD, MSCE[6] ; Massimo Cristofanilli, MD[7] ; Jane Meisel, MD[8] ; Kathy D. Miller, MD[9] ; Yara Abdou, MD[10] ;
Elizabeth C. Riley, MD[11] ; Rubina Qamar, MD[12] ; Priyanka Sharma, MD[13] ; Sonya Reid, MD, MPH[14] ; Natalie Sinclair, MD[1] ; Meredith Faggen, MD[1] ;
Caroline C. Block, MD[1,2] ; Naomi Ko, MD[15] ; Ann H. Partridge, MD, MPH[1,2] ; Wendy Y. Chen, MD, MPH[1,2] ; Michelle DeMeo, BS[1] ;
Victoria Attaya, BA[1] ; Amanda Okpoebo, MS[1] ; Jillian Alberti, MS[1] ; Yuan Liu, PhD[16] ; Eric Gauthier, PhD, PharmD[16] ;
Harold J. Burstein, MD, PhD[1,2] ; Meredith M. Regan, ScD[2,3] ; and Sara M. Tolaney, MD, MPH[1,2]

ABSTRACT

PURPOSE Cyclin-dependent kinase (CDK) 4/6 inhibitors (CDK4/6is) are an important component of treatment for hormone receptor–positive/human epidermal growth factor receptor 2–negative (HER2−) metastatic breast cancer (MBC), but it is not known if patients might derive benefit from continuation of CDK4/6i with endocrine therapy beyond initial tumor progression or if the addition of checkpoint inhibitor therapy has value in this setting.

METHODS The randomized multicenter phase II PACE trial enrolled patients with hormone receptor–positive/HER2− MBC whose disease had progressed on previous CDK4/6i and aromatase inhibitor (AI) therapy. Patients were randomly assigned 1:2:1 to receive fulvestrant (F), fulvestrant plus palbociclib (F + P), or fulvestrant plus palbociclib and avelumab (F + P + A). The primary end point was investigator-assessed progression-free survival (PFS) in patients treated with F versus F + P.

RESULTS Overall, 220 patients were randomly assigned between September 2017 and February 2022. The median age was 57 years (range, 25-83 years). Most patients were postmenopausal (80.9%), and 40% were originally diagnosed with de novo MBC. Palbociclib was the most common previous CDK4/6i (90.9%). The median PFS was 4.8 months on F and 4.6 months on F + P (hazard ratio [HR], 1.11 [90% CI, 0.79 to 1.55]; $P = .62$). The median PFS on F + P + A was 8.1 months (HR v F, 0.75 [90% CI, 0.50 to 1.12]; $P = .23$). The difference in PFS with F + P and F + P + A versus F was greater among patients with baseline *ESR1* and *PIK3CA* alterations.

CONCLUSION The addition of palbociclib to fulvestrant did not improve PFS versus fulvestrant alone among patients with hormone receptor–positive/HER2− MBC whose disease had progressed on a previous CDK4/6i plus AI. The increased PFS seen with the addition of avelumab warrants further investigation in this patient population.

ACCOMPANYING CONTENT

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INTRODUCTION

Endocrine therapy (ET) is the mainstay of treatment for patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HER2−) metastatic breast cancer (MBC). Several randomized phase III trials have demonstrated that addition of a cyclin-dependent kinase (CDK) 4/6 inhibitor (CDK4/6i: abemaciclib, palbociclib, or ribociclib) to first-line aromatase inhibitor (AI) therapy significantly improves progression-free survival (PFS) compared with AI alone.[1-5] Moreover, patients with pretreated disease also benefit from the addition of a CDK4/6i to ET.[6-9] The optimal course of therapy for patients with hormone receptor–positive/HER2− MBC who progress on

CONTEXT

Key Objective
The PACE trial was designed for patients with metastatic hormone receptor–positive/HER2– breast cancer progressing on cyclin-dependent kinase (CDK) 4/6 inhibitor and aromatase inhibitor to evaluate whether continuation of CDK4/6 inhibition using palbociclib with a change to fulvestrant improves outcomes over fulvestrant alone.

Knowledge Generated
Continuation of CDK4/6 inhibition with palbociclib after progression on primarily palbociclib-based regimens, with a change in endocrine therapy (ET), did not improve progression-free survival (PFS) over a change in ET alone (median PFS 4.6 v 4.8 months).

Relevance (G. Fleming)
Palbociclib should not be continued beyond progression. The trend toward benefit with the addition of avelumab is intriguing and should spur further research on the use of immune checkpoint inhibition in hormone receptor–positive breast cancer.*

*Relevance section written by *JCO* Associate Editor Gini Fleming, MD.

first-line ET and CDK4/6i has not yet been established[10] as it is not confirmed if patients can derive additional benefit from continuation of CDK4/6 inhibition in combination with a different endocrine agent.

Several putative mechanisms of acquired resistance to CDK4/6is have been identified in preclinical studies and in tumor samples from patients with hormone receptor–positive/HER2– MBC, including loss of retinoblastoma protein,[11-13] *CCNE1* upregulation,[11,14] and phosphatidylinositol 3-kinase (PI3K) pathway alterations.[15] However, the full scope of molecular mediators of resistance to CDK4/6i and the effect of these alterations on outcome with subsequent lines of therapy remain poorly understood. Additional resistance mechanisms undoubtedly remain to be identified, including the ones that might be overcome by continuous ET with CDK4/6 inhibition.

Moreover, in addition to cell cycle regulation, preclinical data suggest that CDK4/6is can enhance antitumor immunity and might have synergistic activity with immune checkpoint inhibitors (ICIs) that target PD-1 or PD-L1.[16,17] Thus far, ICIs have shown relatively low efficacy in hormone receptor–positive MBC; objective response rates (ORRs) with ICI monotherapy have ranged from 2.8% to 12%.[18,19] Furthermore, in a randomized phase II trial of eribulin with or without pembrolizumab in hormone receptor–positive/HER2– MBC, the combination did not provide benefit over chemotherapy alone.[20] Different therapeutic partners might improve the activity of ICIs in this specific tumor type.

To address these issues, we conducted a randomized phase II trial (Palbociclib After CDK and ET [PACE]) in patients with hormone receptor–positive/HER2– MBC whose disease progressed on previous AI or selective estrogen receptor modulator plus any CDK4/6i. Patients were randomly assigned to receive fulvestrant (F), fulvestrant with palbociclib (F + P), or fulvestrant with palbociclib and the PD-L1 inhibitor avelumab (F + P + A). Here, we report efficacy, safety, and the results of initial correlative analyses.

METHODS

Study Design

PACE (ClinicalTrials.gov identifier: NCT03147287) is an investigator-initiated, multicenter, open-label, randomized phase II trial, open at 13 sites in the United States. Eligible patients had hormone receptor–positive/HER2– MBC (by institutional guidelines), with previous progression on ET (AI or tamoxifen) and any CDK4/6i after at least 6 months of therapy in the metastatic setting or within 12 months of CDK4/6i exposure in the adjuvant setting. Participants were allowed to receive up to one previous line of chemotherapy and up to two lines of ET for MBC.

Participants were randomly assigned 1:2:1 to receive F, F + P, or F + P + A. Random assignment was stratified according to receipt or nonreceipt of chemotherapy between previous CDK4/6i and random assignment. Participants who had been randomly assigned to receive F were allowed to cross over to palbociclib monotherapy on disease progression.

Treatment Procedures

All treatments were given in 28-day cycles. Fulvestrant was administered 500 mg intramuscularly (IM) once on days 1 and 15 in cycle 1 and 500 mg IM once on day 1 of each subsequent monthly cycle. Palbociclib 125 mg was taken orally once daily, for days 1-21 of each cycle. Patients who required a dose reduction of palbociclib before trial entry

were allowed to start at that reduced dose. Avelumab 10 mg/kg was administered as an intravenous infusion once every 14 days. All participants were treated with unblinded protocol therapy until disease progression or relapse, unacceptable toxicity, intercurrent illness that prevented further administration of therapy, withdrawal of consent, or death, whichever occurred first. Tumor assessments according to RECIST 1.1 criteria[21] were performed every 8 weeks for the first six cycles and every 12 weeks thereafter. Toxicity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Correlative End Points

Baseline and serial ctDNA samples were obtained and evaluated using the Guardant360 assay, which applies next-generation sequencing to evaluate genomic alterations in complete or critical exons of 73 genes (Guardant Health, Redwood, CA).[22] Analyses were limited to single-nucleotide variants, indels, and high amplifications of the prespecified genes *ESR1*, *PIK3CA*, and *RB1*.

Statistical Considerations

The primary end point was PFS, defined as the interval from random assignment until progression according to RECIST1.1 criteria[21] or death; in the absence of an event, PFS was censored at the date of last disease assessment. The sample sizes, using a 1:2:1 ratio to randomly assign 220 patients to F, F + P, and F + P + A, were determined primarily to compare F + P versus F and secondarily to compare F + P + A versus F. For the primary objective, a sample size of 55 + 110 patients was planned to observe 119 PFS events, assuming that the median PFS was 4 months among patients treated with F and 6.5 months in those treated with F + A (hazard ratio [HR], 0.6154), with a two-sided α = .10 log-rank test with an 80% power. F + P + A was assumed to improve PFS to a median of 7.5 months, requiring 63 PFS events among the 55 patients per group assigned to F + P + A and F, to have an 80% power using a two-sided α = .10 log-rank test. The Dana-Farber/Harvard Cancer Center Data and Safety Monitoring Board (DF/HCC DSMB) reviewed one interim analysis for futility[23] of F + P versus F after approximately 60% of PFS events were documented and recommended the trial to proceed as planned.

The analyses used an intention-to-treat approach. The distributions of PFS were estimated using the Kaplan-Meier method, summarized by median value with two-sided 90% CI, and compared using log-rank tests (F + P *v* F; F + P + A *v* F), with two-sided *P* values reported and *P* ≤ .10 considered as statistically significant. HRs with two-sided 90% CIs were estimated using a Cox model. Subgroup analyses estimated treatment-by-covariate interaction within Cox models. The median follow-up was calculated using the Kaplan-Meier estimate of the overall survival (OS) censoring distribution.

For secondary end points, rates of objective response, defined as best overall response of complete or partial response, and

of clinical benefit (defined as objective response or stable disease at least 24 weeks duration) were reported with two-sided 90% CIs; confirmation of response was not required. OS was an added end point, defined from random assignment until death from any cause or censored at date last known alive, and similarly estimated using the Kaplan-Meier method and HRs, but without testing.

Exploratory objectives included assessment of PFS and ORR among patients who had received chemotherapy between initial exposure to CDK4/6i and initiation of protocol therapy. Efficacy outcomes were also assessed in predefined molecular subgroups, including patients with baseline genomic alterations in *ESR1*, *PIK3CA*, and *RB1*.

Compliance With Ethical Standards

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Standards and the Declaration of Helsinki. Institutional review board approval was obtained at all participating sites. All patients provided written informed consent before any study-related procedures. The DF/HCC DSMB reviewed trial progress and the interim analysis at its 6 monthly meetings.

RESULTS

Patient Characteristics

Between September 5, 2017, and February 23, 2022, 220 patients were randomly assigned to F (n = 55), F + P (n = 111), and F + P + A (n = 54; Fig 1). Baseline patient characteristics are included in Table 1. The median age was 57 years (range, 25-83). Most patients were postmenopausal (80.9%), and 40% were diagnosed with de novo MBC; 60% had visceral disease, and 13.6% had bone-only disease.

Palbociclib was the most common previous CDK4/6i (90.9%). Most (75.9%) patients had received >12 months of CDK4/6i therapy with ET before initiating protocol therapy. Protocol therapy represented second-line treatment for MBC in 76.8%. A minority (16.4%) had received one previous chemotherapy for MBC, and 11.8% had received another systemic therapy between previous CDK4/6i and initiation of trial therapy (11 [5%] chemotherapy, 14 [6.4%] ET, 1 [0.4%] targeted therapy).

Efficacy

After a median follow-up of 23.6 months, with 148 patients experiencing a PFS event, the median PFS was 4.8 months with F (90% CI, 2.1 to 8.2) and 4.6 months with F + P (90% CI, 3.6 to 5.9; HR, 1.11 [90% CI, 0.79 to 1.55]; *P* = .62). The median PFS with F + P + A was 8.1 months (90% CI, 3.2 to 10.7; HR *v* F, 0.75 [90% CI, 0.50 to 1.12]; *P* = .23; Fig 2). An additional 39 patients had PFS censored at last tumor assessment after discontinuing treatment for non–RECIST-confirmed
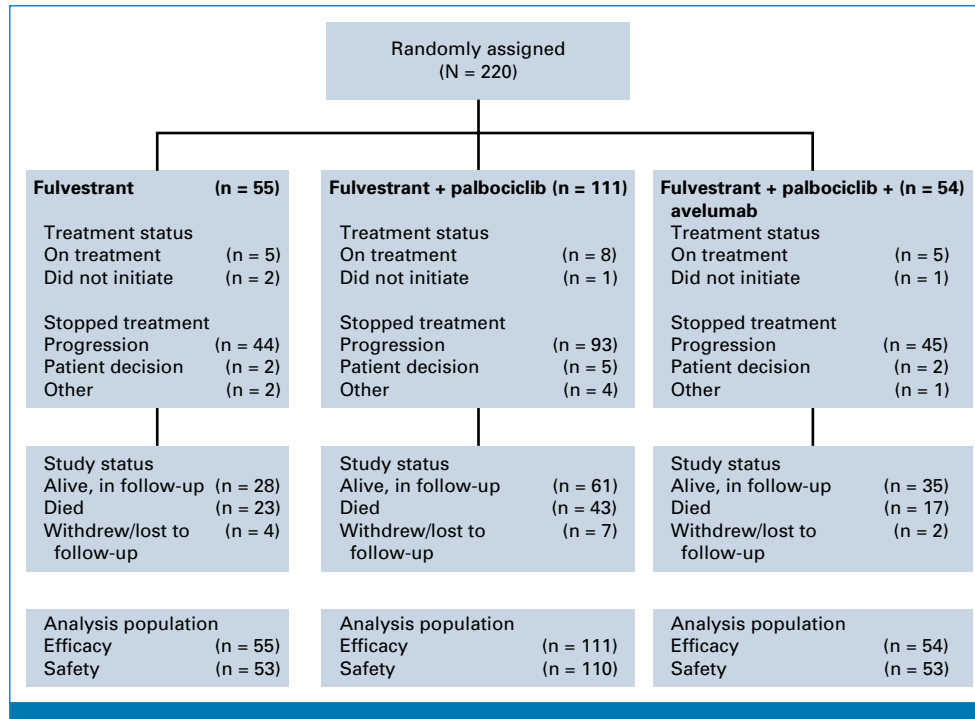
FIG 1. CONSORT diagram.

progression. When considering these as PFS events in a sensitivity analysis, the results were consistent, although with shorter median PFS estimates (Data Supplement, Fig S1 [online only]).

Among patients with endocrine-resistant disease (defined as recurrence on or within 1 year of completing adjuvant ET), the median PFS was 1.9 months with F (90% CI, 1.7 to 8.5), 5.4 months with F + P (90% CI, 2.3 to 8.3), and 3.0 months with F + P + A (90% CI, 1.8 to 3.7). Among patients with endocrine-sensitive disease (defined as de novo MBC with no receipt of adjuvant ET or recurrence >1 year after completing adjuvant ET), the median PFS was 5.7 months with F (90% CI, 2.3 to 9.9), 4.6 months with F + P (90% CI, 3.5 to 5.9), and 8.5 months with F + P + A (90% CI, 5.7 to 19.0; Data Supplement, Fig S2). The PFS distributions and treatment effects were similar among patients who had ≥12 months previous duration of CDK4/6i and those who had only 6-12 months previous duration (data not shown). Subsets with exposure to previous CDK4/6i other than palbociclib, as well as those with any systemic therapy between previous CDK4/6i and initiation of protocol therapy, were too small for meaningful evaluation.

The ORR was 7.3% with F, 9.0% with F + P, and 13.0% with F + P + A. The clinical benefit rate was 29.1% with F, 32.4% with F + P, and 35.2% with F + P + A (Table 2). The median OS was 27.5 months for F and 24.6 months for F + P (HR, 1.02 [90% CI, 0.67 to 1.56]). The median OS was 42.5 months for F + P + A (HR v F, 0.68 [90% CI, 0.40 to 1.15]; Fig 3).

Safety

The safety population included 216 patients who initiated treatment. A total of 84 (38.9%) experienced a grade 3/4 treatment-related adverse event (TRAE), one (1.9%) with F alone, 46 (41.8%) with F + P, and 37 (69.8%) with F + P + A. There were no grade 5 toxicity events. Among patients treated with F, the most common all-grade TRAE was fatigue (34.0%). With F + P, the most common all-grade TRAEs included neutropenia (65.5%; 32.7% grade 3 to 4), fatigue (34.5%), and anemia (21.8%). The most common TRAEs with F + P + A included neutropenia (73.6%; 49.1% grade 3 to 4), fatigue (64.2%), anemia (34.0%), and thrombocytopenia (32.1%; Table 3).

Potential immune-related adverse events (irAEs) were experienced by 28 (52.8%) receiving F + P + A. The most common all-grade irAEs were increased AST (11.3%) and ALT (9.4%). Grade 3 to 4 irAEs were rare and included increased liver function tests, increased cardiac troponin T, hypoxia, bullous dermatitis, and infusion-related reaction, one patient each (1.9%; Data Supplement, Table S1). No cases of pneumonitis or interstitial lung disease were observed with avelumab.

For patients receiving F + P, 68 (61.3%) started P at 125 mg once daily. For those receiving F + P + A, 28 (51.9%) started P at 125 mg once daily. The remaining patients started P at either 100 mg or 75 mg once daily. P dose hold for toxicity was required for 40 on F + P (36.0%) and 31 on F + P + A (57.4%). P dose reduction was required in 25 on F + P (22.5%) and 11 on F

TABLE 1. Baseline Patient, Disease, and Prior Treatment Characteristics

Characteristic	F (n = 55)	F + P (n = 111)	F + P + A (n = 54)	Overall (N = 220)
Sex, No. (%)				
Female	55 (100)	109 (98.2)	54 (100)	218 (99.0)
Median age, years (range)	58 (36-77)	55 (28-77)	58 (25-83)	57 (25-83)
Race, No. (%)				
White	47 (85.5)	88 (79.3)	44 (81.5)	179 (81.4)
Black	3 (5.5)	13 (11.7)	4 (7.4)	20 (9.1)
Asian	0 (0)	4 (3.6)	3 (5.6)	7 (3.2)
Other	5 (9.1)	6 (5.4)	3 (5.6)	14 (6.4)
Menopausal status, No. (%)				
Postmenopausal	47 (85.5)	87 (78.4)	44 (81.5)	178 (80.9)
Premenopausal	8 (14.5)	22 (19.8)	10 (18.5)	40 (18.2)
De novo versus recurrent MBC, No. (%)				
De novo MBC	28 (50.9)	40 (36.0)	20 (37.0)	88 (40.0)
Recurrent MBC	27 (49.1)	71 (64.0)	34 (63.0)	132 (60.0)
Visceral disease, No. (%)				
No	25 (45.5)	41 (36.9)	21 (38.9)	87 (39.5)
Yes	29 (52.7)	70 (63.1)	33 (61.1)	132 (60.0)
Unknown	1 (1.8)	0 (0)	0 (0)	1 (0.5)
Bone-only disease, No. (%)				
No	50 (90.9)	93 (83.8)	46 (85.2)	189 (85.9)
Yes	4 (7.3)	18 (16.2)	8 (14.8)	30 (13.6)
Unknown	1 (1.8)	0 (0)	0 (0)	1 (0.5)
Measurable disease, No. (%)				
No	18 (32.7)	38 (34.2)	15 (27.8)	71 (32.3)
Yes	37 (67.3)	73 (65.8)	39 (72.2)	149 (67.7)
Previous adjuvant endocrine exposure,[a] No. (%)				
Endocrine-resistant	10 (18.2)	32 (28.8)	16 (29.6)	58 (26.4)
Endocrine-sensitive	45 (81.8)	78 (70.3)	37 (68.5)	160 (72.7)
Unknown	0 (0)	1 (0.9)	1 (1.9)	2 (0.9)
Previous CDK4/6 inhibitor, No. (%)				
Palbociclib	52 (94.5)	102 (91.9)	46 (85.2)	200 (90.9)
Ribociclib	1 (1.8)	5 (4.5)	4 (7.4)	10 (4.5)
Abemaciclib	2 (3.6)	3 (2.7)	4 (7.4)	9 (4.1)
Unknown	0 (0)	1 (0.9)	0 (0)	1 (0.5)
Duration of previous CDK4/6 inhibitor, months, No. (%)				
6-12	10 (18.2)	26 (23.4)	16 (29.6)	52 (23.6)
>12	45 (81.8)	84 (75.7)	38 (70.4)	167 (75.9)
Previous chemotherapy for MBC, No. (%)				
Yes	11 (20.0)	16 (14.4)	9 (16.7)	36 (16.4)
No	44 (80.0)	95 (85.6)	45 (83.3)	184 (83.6)
Line of MBC therapy initiated in PACE, No. (%)				
First line	3 (5.5)	5 (4.5)	2 (3.7)	10 (4.5)
Second line	42 (76.4)	83 (74.8)	44 (81.5)	169 (76.8)
>Second line	10 (18.2)	21 (18.9)	7 (13.0)	38 (17.3)
Unknown	0 (0)	2 (1.8)	1 (1.9)	3 (1.4)
Any systemic therapy between previous CDK4/6 inhibitor and random assignment, No. (%)				
Yes	5 (9.1)	16 (14.4)	5 (9.3)	26 (11.8)
No	50 (90.9)	95 (85.6)	49 (90.7)	194 (88.2)

Abbreviations: ET, endocrine therapy; MBC, metastatic breast cancer.
[a]Endocrine-resistant: disease recurrence on or within 1 year of completing adjuvant ET. Endocrine-sensitive: de novo metastatic breast cancer, no adjuvant ET, or disease recurrence ≥1 year after completion of adjuvant ET.
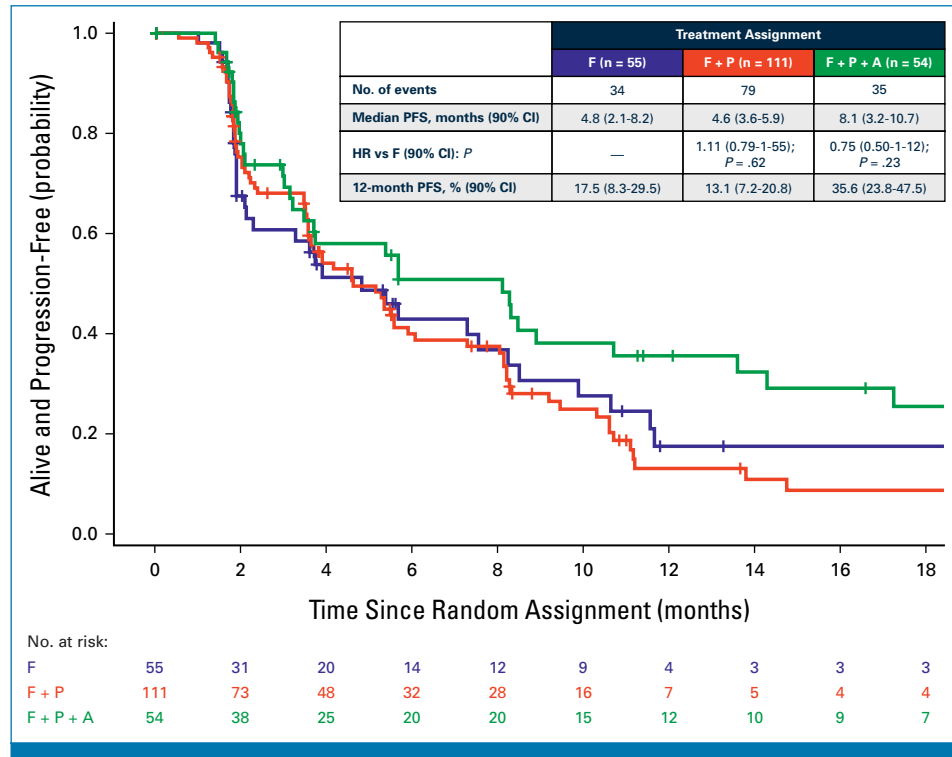
FIG 2. Kaplan-Meier estimate of progression-free survival for all patients. F, fulvestrant; F + P, fulvestrant plus palbociclib; F + P + A, fulvestrant plus palbociclib and avelumab.

+ P + A (20.4%). Avelumab dose hold for toxicity was required for 21 (38.9%) on the A-containing treatment arm (Data Supplement, Table S2).

Efficacy in Predefined Molecular Subgroups

Baseline ctDNA samples were available from 200 patients. This analysis revealed *ESR1* mutations in 54%, *PIK3CA* mutations in 35%, and *RB1* alterations in 11.5% (Table 4). For wild-type *ESR1*, the median PFS was 7.6 months on F versus 4.6 on F + P (HR, 1.70 [90% CI, 0.99 to 2.95]). For *ESR1* mutation, the median PFS was 3.3 months on F versus 5.2 months on F + P (HR, 0.68 [90% CI, 0.42 to 1.09]; Data Supplement, Fig S3). For wild-type *PIK3CA*, the median PFS was 7.6 months on F versus 5.2 months on F + P (HR, 1.44 [90% CI, 0.91 to 2.29]). For *PIK3CA* mutation, the median PFS was 2.0 months on F versus 4.6 months on F + P (HR, 0.56 [90% CI, 0.32 to 0.99]; Data Supplement, Fig S4). For wild-type *RB1*, the median PFS was 5.7 months on F versus 5.2 months on F + P (HR, 1.23 [90% CI, 0.83 to 1.81]). For *RB1* alteration, the median PFS was 1.9 months for on both F and F + P (HR, 0.95 [90% CI, 0.36 to 2.49]; Data Supplement, Fig S5).

DISCUSSION

CDK4/6is are integral agents for hormone receptor–positive/HER2– MBC, typically used in the first-line setting with an ET partner. However, optimal therapy after progression on CDK4/6i has not been well established. Furthermore, recent trial experiences have suggested that fulvestrant monotherapy in this setting provides minimal benefit,[24,25] and improved options are needed for this large subset of patients. In the PACE study, continuing a CDK4/6i with palbociclib in addition to switching ET to fulvestrant did not significantly improve PFS compared with F monotherapy in patients with hormone receptor–positive/HER2– MBC who experienced disease progression on previous CDK4/6i with AI.

As the majority of patients in the PACE trial received palbociclib as initial CDK4/6i, PACE primarily addressed the question of whether switching ET and continuing the *same* CDK4/6i was superior to a new ET alone. This question was similarly addressed in the randomized phase II PALMIRA trial (ClinicalTrials.gov identifier: NCT03809988), in which

TABLE 2. Objective Response Rate and Clinical Benefit Rate in All Patients

Response	F (n = 55)	F + P (n = 111)	F + P + A (n = 54)
		Treatment Assignment, % (90% CI)	
Objective response rate	7.3 (1.5 to 13.0)	9.0 (4.5 to 13.5)	13.0 (5.4 to 20.5)
Clinical benefit rate	29.1 (19.0 to 39.2)	32.4 (25.1 to 39.7)	35.2 (24.5 to 45.9)

	Treatment Assignment		
	F (n = 55)	F + P (n = 111)	F + P + A (n = 54)
No. of events	23	43	17
Median OS, months (90% CI)	27.5 (21.1-38.0)	24.6 (21.5-33.3)	42.5 (26.8-46.0)
12-month OS, % (90% CI)	80.0 (67.9-88.0)	83.6 (76.0-89.0)	82.6 (70.9-89.9)
24-month OS, % (90% CI)	60.0 (45.5-71.7)	53.9 (43.3-63.3)	77.0 (64.1-85.7)

No. at risk:

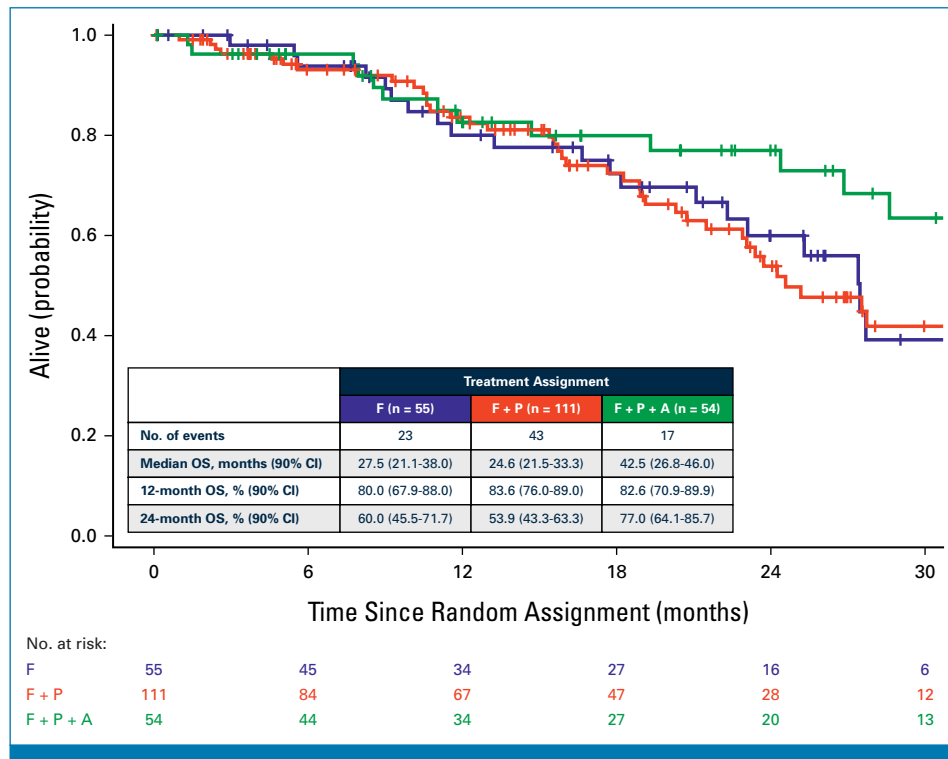|						
F	55	45	34	27	16	6
F + P	111	84	67	47	28	12
F + P + A	54	44	34	27	20	13

FIG 3. Kaplan-Meier estimate of overall survival for all patients. F, fulvestrant; F + P, fulvestrant plus palbociclib; F + P + A, fulvestrant plus palbociclib and avelumab.

patients with hormone receptor–positive/HER2– MBC with previous palbociclib plus ET did not benefit from continuation of palbociclib beyond progression, with median PFS 4.9 months with ET and palbociclib versus 3.6 months with ET alone (HR, 0.84 [95% CI, 0.66 to 1.07]; $P = .149$).[26,27] These results contrast with those from the randomized phase II MAINTAIN trial, in which patients with hormone receptor–positive/HER2– MBC with progression on previous CDK4/6i and ET were randomly assigned to receive ribociclib or placebo in combination with change in ET. Since the initial CDK4/6i therapy was also palbociclib for the majority (84%), MAINTAIN primarily addressed the question of whether switching to a *different* CDK inhibitor with ET was better than ET alone. The median PFS among patients in MAINTAIN was 5.29 months with ET and ribociclib versus 2.76 months for ET and placebo (HR, 0.57 [95% CI, 0.39 to 0.95]; $P = .006$).[10]

Several factors could explain the different results among the reported CDK4/6i after CDK4/6i randomized trials. In all trials, palbociclib was the most common previous CDK4/6i exposure; in both PACE and PALMIRA, patients continued palbociclib, whereas in MAINTAIN, they switched to ribociclib. These agents might have differences in receptor targeting, which could lead to differences in efficacy in sequence, as palbociclib has similar potency against CDK4 and CDK6, whereas ribociclib has greater potency against CDK4 than CDK6.[28,29] The outcome of switching from palbociclib to a different CDK4/6i has also been examined in single-arm observational studies, suggesting activity of

new CDK4/6i combinations after previous progression.[30,31] It is thus possible that switching to a different CDK4/6i rather than continuing the same agent may overcome resistance and provide greater antitumor efficacy.

Furthermore, in the PACE trial, the median PFS of 4.8 months in the control arm was longer than that observed with fulvestrant monotherapy in other recent post-CDK experiences. Notably, the control arm had a relative enrichment of nonvisceral and de novo MBC, which could be contributory. In addition, the phase II design of the PACE trial and smaller sample size, as well as requirement for disease stability on the previous regimen, likely resulted in a patient population more sensitive to fulvestrant, with a more favorable control arm PFS. Overall, however, all three prospective trials are relatively small phase II studies, with differences in design and study population, and are subject to the variabilities inherent in this trial design structure. Ongoing phase III trials are exploring the question of continuation of CDK4/6 inhibition beyond progression, including postMONARCH (ClinicalTrials.gov identifier: NCT05169567), EMBER-3 (ClinicalTrials.gov identifier: NCT04975308), and ELAINE-3 (ClinicalTrials.gov identifier: NCT05696626), all of which switch to abemaciclib. It is hoped that these studies will provide definitive guidance regarding the value of continuation of a CDK4/6i beyond progression and the selection of which agent is most appropriate.

It is important to note some details about dose and timing. Although the majority of PACE patients started palbociclib at

TABLE 3. Treatment-Related Adverse Events in ≥10% of Patients

	Treatment Assignment, No. (%)					
	F (n = 53)		F + P (n = 110)		F + P + A (n = 53)	
Adverse Event	All Grades	Grade 3 to 4	All Grades	Grade 3 to 4	All Grades	Grade 3 to 4
Neutropenia	2 (3.8)	0 (0)	72 (65.5)	36 (32.7)	39 (73.6)	26 (49.1)
Anemia	2 (3.8)	0 (0)	24 (21.8)	5 (4.5)	18 (34.0)	2 (3.8)
Thrombocytopenia	1 (1.9)	0 (0)	16 (14.5)	1 (0.9)	17 (32.1)	2 (3.8)
Fatigue	18 (34.0)	0 (0)	38 (34.5)	2 (1.8)	34 (64.2)	3 (5.7)
Nausea	5 (9.4)	0 (0)	13 (11.8)	0 (0)	10 (18.9)	0 (0)
Diarrhea	0 (0)	0 (0)	11 (10.0)	0 (0)	9 (17.0)	2 (3.8)
Anorexia	2 (3.8)	0 (0)	4 (3.6)	0 (0)	9 (17.0)	1 (1.9)
Mucositis	0 (0)	0 (0)	10 (9.1)	1 (0.9)	8 (15.1)	1 (1.9)
AST increase	6 (11.3)	0 (0)	6 (5.5)	1 (0.9)	8 (15.1)	1 (1.9)
Pain in extremity	1 (1.9)	0 (0)	0 (0)	0 (0)	8 (15.1)	0 (0)
Pruritus	1 (1.9)	0 (0)	5 (4.5)	0 (0)	7 (13.2)	1 (1.9)
Constipation	2 (3.8)	0 (0)	7 (6.4)	0 (0)	7 (13.2)	0 (0)
Injection site reaction	6 (11.3)	0 (0)	12 (10.9)	0 (0)	3 (5.7)	0 (0)

125 mg once daily, about 40% began at a lower dose. Analyses from the phase III palbociclib studies have suggested no decrement in palbociclib efficacy with dose reduction.[32] Whether this lack of effect extends to the palbociclib starting dose is not confirmed although a small real-world analysis suggested that starting palbociclib at full dose was associated with more favorable survival outcomes than starting at a reduced dose.[33] In addition, the majority of patients in PACE, PALMIRA, and MAINTAIN were enrolled immediately after progression on previous CDK4/6i therapy. As some factors associated with resistance to CDK4/6i, such as changes in expression of CDKs and other signaling proteins, are physiologic and not mutation-based, it is possible that reintroduction of a CDK4/6i after an ensuing interval of time might yield different outcomes.

In addition to the option of continuation of CDK4/6i therapy, multiple other novel treatments are available or being explored after CDK4/6i. Mutations in ESR1, acquired over time during ET, result in resistance to endocrine therapies.[34-37] Multiple oral SERDs are in development to target ESR1 mutations, including the approved agent elacestrant. In PACE, patients with a baseline ESR1 alteration appeared to derive greater benefit from the addition of a targeted agent versus F alone. By contrast, those with baseline ESR1 mutations in MAINTAIN did not appear to benefit from continuation of CDK4/6i. The discordant findings may be related to other imbalances in resistance mechanisms in small subsets of patients and underscore the need for novel approaches in patients whose tumors harbor ESR1 mutations.

TABLE 4. Alterations in *ESR1*, *PIK3CA*, and *RB*

	Treatment Assignment, No. (%)			
Gene Alteration	F (n = 48)	F + P (n = 102)	F + P + A (n = 50)	Overall[a] (n = 200)
ESR1 alteration[b]	23 (47.9)	55 (53.9)	30 (60.0)	108 (54.0)
D538G	15 (31.3)	36 (35.3)	18 (36.0)	69 (34.5)
Y537S	9 (18.8)	26 (25.5)	7 (14.0)	42 (21.0)
Y537N	7 (14.6)	17 (16.7)	6 (12.0)	30 (15.0)
E380Q	1 (2.1)	11 (10.8)	7 (14.0)	19 (9.5)
PIK3CA alteration	12 (25.0)	39 (38.2)	19 (38.0)	70 (35.0)
H1047R	4 (8.3)	11 (10.8)	8 (16.0)	23 (11.5)
E545K	5 (10.4)	12 (11.8)	4 (8.0)	21 (10.5)
RB alteration	6 (12.5)	10 (9.8)	7 (14.0)	23 (11.5)

[a]The most frequent gene alterations are listed, but additional and less common alterations were noted in the patient population beyond what is included in the table.
[b]Some patients had multiple *ESR1* alterations, meaning that the total number of *ESR1* alterations is greater than the total number of patients with *ESR1* alterations.

Alterations in the PI3K/protein kinase B (AKT)/mammalian target of rapamycin pathway have also been implicated in the development of endocrine resistance.[38] Agents approved or in development to target this pathway include the PI3K inhibitor alpelisib and the AKT inhibitor capivasertib. In PACE, continuation of CDK4/6i also appeared to be more favorable in patients whose tumor had a baseline *PIK3CA* mutation. Currently, it is unclear whether alpelisib with ET, capivasertib with fulvestrant, or continuation of CDK4/6i with ET represents the optimal second-line therapy in patients with hormone receptor–positive MBC with *PIK3CA* mutations.

Alterations in *RB1* have been identified as an uncommon mechanism of resistance to CDK4/6i in patients with hormone receptor–positive MBC.[11-13,39] As has been previously observed, those in PACE with *RB1*-altered tumors had inferior outcomes to those with intact *RB1*, whether they received palbociclib. In addition, the addition of palbociclib to fulvestrant did not improve median PFS regardless of *RB1* status, suggesting additional resistance mechanisms. Overall, the landscape of resistance to CDK4/6i is complex and reflects not only individual mutations but also mutational signatures.[39] Ongoing comprehensive sequencing of serial ctDNA samples from PACE will explore the landscape of resistance not only to CDK4/6i but also to ET.

The combination arm of F + P + A in PACE showed an intriguing signal of prolonged PFS compared with F or F + P, notable among the subset of patients with endocrine-sensitive disease, potentially suggesting a role for ICI in this patient population. In addition to cell cycle regulation, preclinical data suggest that CDK4/6is can enhance antitumor immunity.[16,17] Immune modulatory effects of CDK4/6i have been observed clinically; in a prospective study in hormone receptor–positive/HER2– MBC of CDK4/6i and ET, a significant decrease in the frequency of circulating regulatory T cells and myeloid-derived suppressor cells and increased CD4$^+$ T cells and antitumor CD8$^+$ T cells were observed.[40] The results of PACE suggest that CDK4/6i might have synergistic activity with ICIs in hormone receptor–positive/HER2– MBC, potentially in tumors with fewer resistance pathways, echoing the recently reported activity of pembrolizumab with chemotherapy in the preoperative setting for hormone receptor–positive/HER2– breast cancer.[41] However, clinical attempts to combine ICI with ET and CDK4/6i have been limited by toxicity. A phase I study (ClinicalTrials.gov identifier: NCT02779751) combining abemaciclib, the PD-1 inhibitor pembrolizumab, and anastrozole for advanced disease was complicated by high rates of grade 3 neutropenia, hepatitis, and interstitial lung disease and two deaths from TRAEs.[42] The neoadjuvant CheckMate 7A8 trial (ClinicalTrials.gov identifier: NCT04075604) of the PD-1 inhibitor nivolumab, palbociclib, and anastrozole closed early because of higher than expected rates of grade 3 hepatitis.[43] In PACE, the adverse event profile of the combination of CDK4/6i and PD-L1 inhibitor was more favorable than the previous combinations with PD-1 inhibitor[44,45] and supports selection of this type of ICI agent for any future clinical study.

In summary, the PACE trial demonstrates that continuation of the same CDK4/6i beyond progression in combination with a change from AI to fulvestrant does not yield a PFS benefit compared with fulvestrant alone among patients with hormone receptor–positive/HER2– MBC. The prolonged PFS with the triplet of F + P + A supports preclinical evidence that ICIs may produce synergistic activity with CDK4/6i in this patient population and warrants further research. The results of this trial also support the continuous investigation of predictive biomarkers for hormone receptor–positive/HER2– MBC. Ongoing and future work will help clarify optimal pathways of care for patients beyond progression on CDK4/6is.

AFFILIATIONS

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

[2]Harvard Medical School, Boston, MA

[3]Department of Data Science, Dana-Farber Cancer Institute, Boston, MA

[4]Department of Medical Oncology, Miami Cancer Institute, Miami, FL

[5]Division of Oncology, Department of Medicine, Washington University School of Medicine, St Louis, MO

[6]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA

[7]Department of Medical Oncology, Weill Cornell Medicine, New York, NY

[8]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA

[9]Hematology/Oncology Division, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

[10]Department of Medicine, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC

[11]Department of Medicine, Brown Cancer Center, University of Louisville Health, Louisville, KY

[12]Aurora Cancer Care, Milwaukee, WI

[13]Department of Medical Oncology, University of Kansas Medical Center, Westwood, KS

[14]Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN

[15]Department of Medical Oncology, Boston Medical Center, Boston, MA

[16]Pfizer, La Jolla, CA

CORRESPONDING AUTHOR

Erica L. Mayer, MD, MPH, Department of Medical Oncology, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215; e-mail: Erica_Mayer@dfci.harvard.edu.

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AUTHOR CONTRIBUTIONS

Conception and design: Erica L. Mayer, Nikhil Wagle, Cynthia Ma, Angela DeMichele, Massimo Cristofanilli, Harold J. Burstein, Meredith M. Regan, Sara M. Tolaney
Financial support: Erica L. Mayer, Sara M. Tolaney
Administrative support: Erica L. Mayer, Sara M. Tolaney
Provision of study materials or patients: Erica L. Mayer, Reshma Mahtani, Cynthia Ma, Massimo Cristofanilli, Kathy D. Miller, Yara Abdou, Rubina Qamar, Priyanka Sharma, Natalie Sinclair, Meredith Faggen,

Caroline C. Block, Ann H. Partridge, Wendy Y. Chen, Harold J. Burstein, Sara M. Tolaney
Collection and assembly of data: Erica L. Mayer, Reshma Mahtani, Cynthia Ma, Angela DeMichele, Jane Meisel, Kathy D. Miller, Yara Abdou, Elizabeth C. Riley, Rubina Qamar, Priyanka Sharma, Natalie Sinclair, Meredith Faggen, Naomi Ko, Wendy Y. Chen, Michelle DeMeo, Victoria Attaya, Amanda Okpoebo, Jillian Alberti, Harold J. Burstein, Meredith M. Regan
Data analysis and interpretation: Erica L. Mayer, Yue Ren, Nikhil Wagle, Reshma Mahtani, Cynthia Ma, Angela DeMichele, Jane Meisel, Kathy D. Miller, Sonya Reid, Caroline C. Block, Naomi Ko, Ann H. Partridge, Wendy Y. Chen, Michelle DeMeo, Victoria Attaya, Yuan Liu, Eric Gauthier, Harold J. Burstein, Meredith M. Regan
Manuscript writing: .All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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PACE: A Randomized Phase II Study of Fulvestrant, Palbociclib, and Avelumab After Progression on Cyclin-Dependent Kinase 4/6 Inhibitor and Aromatase Inhibitor for Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor–Negative Metastatic Breast Cancer

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Erica L. Mayer
Consulting or Advisory Role: Lilly, Novartis, AstraZeneca

Nikhil Wagle
Employment: Genentech/Roche
Leadership: Genentech/Roche
Stock and Other Ownership Interests: Relay Therapeutics, Flare Therapeutics
Consulting or Advisory Role: Lilly, Relay Therapeutics, Flare Therapeutics
Research Funding: Puma Biotechnology, AstraZeneca

Reshma Mahtani
Consulting or Advisory Role: Agendia, Amgen, Daiichi Sankyo/Astra Zeneca, Eisai, Genentech/Roche, Gilead Sciences, Hologic/Biotheranostics, Lilly, Merck, Novartis, Pfizer, Puma Biotechnology, Sanofi, Sermonix Pharmaceuticals, Stemline Therapeutics
Speakers' Bureau: Seattle Genetics/Astellas
Research Funding: Gilead Sciences (Inst)
Travel, Accommodations, Expenses: Pfizer, Genentech/Roche, Amgen, bioTheranostics, AstraZeneca, Lilly, Novartis, Agendia, Puma Biotechnology, Seagen, Daiichi Sankyo/Lilly, Eisai, Sanofi, Merck

Cynthia Ma
Consulting or Advisory Role: Novartis, AstraZeneca, Bayer HealthCare Pharmaceuticals, Biovica Inc, Olaris, Gilead Sciences, Pfizer, Lilly, Tempus, Genzyme, Tersera, Stemline Therapeutics, Daiichi Sankyo/Astra Zeneca
Research Funding: Pfizer (Inst), Puma Biotechnology (Inst)
Patents, Royalties, Other Intellectual Property: UpToDate: Authorship—served as a co-author on the subject of endocrine therapy for metastatic breast cancer and receives compensation as an author, less than a few hundred dollars a year. It does not affect my patient care or research
Travel, Accommodations, Expenses: SABCS, Total Health Conferencing

Angela DeMichele
Consulting or Advisory Role: Pfizer
Research Funding: Pfizer (Inst), Genentech (Inst), Novartis (Inst), Inivata/NeoGenomics (Inst)

Massimo Cristofanilli
Honoraria: Pfizer
Consulting or Advisory Role: Lilly, Menarini, Olaris, AstraZeneca/Daiichi Sankyo, Syantra, Sermonix Pharmaceuticals, Celcuity
Research Funding: Lilly, Angle, Merck, AstraZeneca, Menarini Silicon Biosystems

Jane Meisel
Honoraria: Total Health Conferencing, Medscape
Consulting or Advisory Role: Novartis, AstraZeneca, Genentech, SeaGen, Curio Science, GlaxoSmithKline, Olema Oncology, GE Healthcare, Pfizer
Research Funding: Seagen, Pfizer, Seagen (Inst), Sermonix Pharmaceuticals (Inst), Olema Oncology (Inst)
Travel, Accommodations, Expenses: Pfizer, Total Health Conferencing, Puma Biotechnology

Kathy D. Miller
This author is Senior Deputy Editor for *Journal Clinical Oncology*. Journal policy recused the author from having any role in the peer review of this manuscript.
Consulting or Advisory Role: Merck, Genentech/Roche, AstraZeneca, Bristol Myers Squibb/Celgene, Celcuity
Research Funding: Pfizer (Inst), Astex Pharmaceuticals (Inst), British Biotech (Inst), CytomX Therapeutics (Inst), alphamab (Inst)

Yara Abdou
Honoraria: WebMD/Medscape, MJH Associates, Clinical Care Options
Consulting or Advisory Role: Exact Sciences, AstraZeneca
Research Funding: Carisma Therapeutics (Inst)
Travel, Accommodations, Expenses: Carisma Therapeutics

Priyanka Sharma
Stock and Other Ownership Interests: Amgen, Johnson & Johnson/Janssen, Roche/Genentech, Gilead Sciences, Sanofi, Pfizer
Consulting or Advisory Role: Novartis, Merck, AstraZeneca, Pfizer, Gilead Sciences, GlaxoSmithKline, Sanofi, Boston Scientific, Cipla, Salient Pharmaceuticals
Research Funding: Novartis (Inst), Bristol Myers Squibb (Inst), Merck (Inst), Novartis (Inst), Gilead Sciences (Inst)
Patents, Royalties, Other Intellectual Property: UpToDate

Sonya Reid
Honoraria: Novartis
Consulting or Advisory Role: AstraZeneca, Daiichi Sankyo/Astra Zeneca
Research Funding: Agendia

Caroline C. Block
Employment: Commonwealth Anesthesia
Other Relationship: American College of Physicians

Naomi Ko
Consulting or Advisory Role: Pfizer
Research Funding: Pfizer
Expert Testimony: Williams and Connolly

Ann H. Partridge
Patents, Royalties, Other Intellectual Property: I receive small royalty payments for co-authoring the breast cancer survivorship section of UpToDate
Open Payments Link: https://openpaymentsdata.cms.gov/physician/835197

Wendy Y. Chen
Research Funding: Bayer (Inst)

Jillian Alberti
Employment: Cardinal Health

Yuan Liu
Employment: Pfizer
Stock and Other Ownership Interests: Pfizer

Eric Gauthier
Employment: Pfizer
Stock and Other Ownership Interests: Pfizer
Travel, Accommodations, Expenses: Pfizer

Harold J. Burstein
This author is a Consultant Editor for *Journal Clinical Oncology*. Journal policy recused the author from having any role in the peer review of this manuscript.

Meredith M. Regan
Consulting or Advisory Role: Ipsen (Inst), Tolmar, Bristol Myers Squibb, Debiopharm Group (Inst), Tersera, AstraZeneca
Research Funding: Pfizer (Inst), Ipsen (Inst), Novartis (Inst), Merck (Inst), AstraZeneca (Inst), Pierre Fabre (Inst), Bayer (Inst), Bristol Myers Squibb (Inst), Roche (Inst), TerSera (Inst), Debiopharm Group (Inst), bioTheranostics (Inst)

Sara M. Tolaney
Consulting or Advisory Role: Novartis, Pfizer, Merck, Lilly, AstraZeneca, Genentech, Eisai, Sanofi, Bristol Myers Squibb, Seagen, CytomX Therapeutics, Daiichi Sankyo, Immunomedics/Gilead, BeyondSpring Pharmaceuticals, OncXerna Therapeutics, Zymeworks, Zentalis, Blueprint Medicines, Reveal Genomics, ARC Therapeutics, Myovant Sciences, Umoja Biopharma, Menarini Group, AADi, Artios Biopharmaceuticals, Incyte, Zetagen, Bayer, Ellipses Pharma, OncoSec, Infinity Pharmaceuticals, Jazz Pharmaceuticals
Research Funding: Genentech/Roche (Inst), Merck (Inst), Exelixis (Inst), Pfizer (Inst), Lilly (Inst), Novartis (Inst), Bristol Myers Squibb (Inst), Eisai (Inst), AstraZeneca (Inst), NanoString Technologies (Inst), Seagen (Inst), OncoPep (Inst), Gilead Sciences (Inst)
Travel, Accommodations, Expenses: Lilly, Sanofi

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