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ORIGINAL REPORT

Randomized Phase II Trial of Fulvestrant Plus Everolimus or Placebo in Postmenopausal Women With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer Resistant to Aromatase Inhibitor Therapy: Results of PrE0102

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ABSTRACT

Purpose

The mammalian target of rapamycin inhibitor everolimus targets aberrant signaling through the PI3K/AKT/mammalian target of rapamycin pathway, a mechanism of resistance to anti-estrogen therapy in estrogen receptor (ER)–positive breast cancer. We hypothesized that everolimus plus the selective ER downregulator fulvestrant would be more efficacious than fulvestrant alone in ER-positive metastatic breast cancer resistant to aromatase inhibitor (AI) therapy.

Patients and Methods

This randomized, double-blind, placebo-controlled, phase II study included 131 postmenopausal women with ER-positive, human epidermal growth factor receptor 2–negative, AI-resistant metastatic breast cancer randomly assigned to fulvestrant (500 mg days 1 and 15 of cycle 1, then day 1 of cycles 2 and beyond) plus everolimus or placebo. The study was designed to have 90% power to detect a 70% improvement in median progression-free survival from 5.4 months to 9.2 months. Secondary end points included objective response and clinical benefit rate (response or stable disease for at least 24 weeks). Prophylactic corticosteroid mouth rinses were not used.

Results

The addition of everolimus to fulvestrant improved the median progression-free survival from 5.1 to 10.3 months (hazard ratio, 0.61 [95% CI, 0.40 to 0.92]; stratified log-rank $P = .02$), indicating that the primary trial end point was met. Objective response rates were similar (18.2% *v* 12.3%; $P = .47$), but the clinical benefit rate was significantly higher in the everolimus arm (63.6% *v* 41.5%; $P = .01$). Adverse events of all grades occurred more often in the everolimus arm, including oral mucositis (53% *v* 12%), fatigue (42% *v* 22%), rash (38% *v* 5%), anemia (31% *v.* 6%), diarrhea (23% *v* 8%), hyperglycemia (19% *v* 5%), hypertriglyceridemia (17% *v* 3%), and pneumonitis (17% *v* 0%), although grade 3 to 4 events were uncommon.

Conclusion

Everolimus enhances the efficacy of fulvestrant in AI-resistant, ER-positive metastatic breast cancer.

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INTRODUCTION

Breast cancer is the most common cancer in women globally and in the United States.[1] Although metastatic breast cancer is incurable, endocrine therapy prolongs survival and is an effective therapy for the 70% of women who have hormone receptor–positive disease. Current endocrine therapy treatment options include selective estrogen receptor (ER) modulators (eg, tamoxifen), aromatase inhibitors (AIs; eg, anastrozole, letrozole, exemestane), and selective ER downregulators (SERD; eg, fulvestrant).[2] Several agents enhance the efficacy of AIs, including the mammalian target of rapamycin (mTOR) inhibitor everolimus and the CDK4/6 inhibitors (eg, palbociclib, ribociclib, abemaciclib).[3] Although the mechanisms of AI

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resistance are incompletely understood, altered ER signaling and upregulation of the PI3K-Akt-mTOR pathway are contributing factors.[4,5]

Fulvestrant is a SERD that binds, inhibits, and degrades the ER. It binds with 100-fold greater affinity than does tamoxifen, and inhibits estrogen signaling more effectively than either tamoxifen or AIs,[6-8] suggesting that it may be a better platform for combining with agents targeting other pathways. Everolimus is an orally bioavailable first-generation mTOR inhibitor that binds with high affinity to its intracellular receptor FKBP12. The everolimus-FKBP12 complex interacts with mTOR to inhibit downstream signaling events.[9] The addition of everolimus to the corticosteroidal AI exemestane improved median progression-free survival (PFS; 3.2 *v* 7.8 months; $P < .0001$) in patients with disease that was resistant to non-corticosteroidal AIs (ie, anastrozole, letrozole) in the phase III BOLERO-2 trial[10-12] and also improved clinical outcomes when added to tamoxifen in AI-resistant breast cancer in the randomized phase II Tamoxifen and RAD001 Study (TAMRAD) trial.[13] On the basis of these considerations, we hypothesized that the addition of everolimus to fulvestrant would be more efficacious than the use of fulvestrant alone, and that fulvestrant might represent a potentially more efficacious endocrine therapy platform for combination with everolimus than either exemestane or tamoxifen. We therefore performed a randomized, double-blind phase II trial comparing fulvestrant with everolimus or placebo in patients with hormone receptor–positive metastatic breast cancer who had disease that was resistant to AIs, a common indication for fulvestrant therapy.[14]

PATIENTS AND METHODS

Patient Population

Eligibility included postmenopausal women with histologically or cytologically confirmed unresectable locally advanced or metastatic, ER-positive, human epidermal growth factor receptor 2/neu negative breast cancer (as defined by local institutional laboratories using ASCO—College of American Pathologists guidlelines[15,16]), measurable and/or nonmeasurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria,[17] AI-resistant disease (defined either as relapse while receiving adjuvant AI therapy or disease progression while receiving an AI for metastatic disease), and no more than one prior chemotherapy regimen for metastatic disease. Other eligibility criteria included age ≥ 18 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and adequate organ and marrow function (leukocytes ≥ 3,000/μL, absolute neutrophil count ≥ 1,500/μL, platelet count ≥ 100,000/μL, total bilirubin ≤ 2.0 mg/dL, AST and/or ALT ≤ 2.5× institutional upper limit of normal, serum creatinine ≤ 1.5 mg/dL). Patients were allowed to receive up to two doses of fulvestrant administered within a 4-week period before trial consent and registration.

Study Design and Treatment

This was a randomized, double-blind, placebo-controlled phase II trial. Patients were randomly assigned in a 1:1 fashion to fulvestrant plus everolimus or a matching placebo. Random assignment was conducted centrally using permuted blocks within strata. Stratification factors for random assignment included ECOG performance status (0 *v* 1), measurable disease (yes *v* no), and prior chemotherapy for metastatic disease (yes *v* no). The trial was coordinated by PrECOG (Philadelphia, PA). The local institutional review board at each participating institution approved the protocol. All patients provided written informed consent.

All patients received fulvestrant (AstraZeneca, Wilmington, DE) at a standard dose and schedule (500 mg intramuscularly days 1, 15 in cycle 1, and day 1 of each subsequent 28-day cycle). For those randomly assigned to everolimus (Novartis, New York, NY), the dose was 10 mg orally once per day. Treatment continued until evidence of disease progression, unacceptable toxicity, or withdrawal of consent, for a maximum of 12 cycles (48 weeks). Patients who did not experience progression by week 48 underwent unblinding of the treatment arm because it was believed that sufficient follow-up would have elapsed to detect the difference being sought in median PFS, the primary trial end point. Patients randomly assigned initially to placebo continued fulvestrant alone, whereas those randomly assigned initially to everolimus continued fulvestrant plus open label everolimus. Patients without evidence of disease progression before week 48 could continue fulvestrant and discontinue everolimus or placebo for excessive toxicity attributed to everolimus or placebo. Concurrent treatment with bone antiresorptive agents (eg, bisphosphonates, denosumab) was permitted for patients with bone metastases. Dose reduction for fulvestrant was not allowed. Dose reductions for everolimus and placebo were permitted according to guidelines in the product information brochure, and as described in the Data Supplement. Prophylactic corticosteroid mouth rinses were not specified in the protocol.

Tumor Assessments and Clinical Evaluations

All patients underwent computed tomography of the chest and abdomen and a bone scan within 4 weeks of registration. Tumor response was assessed every 12 weeks (± 1 week) after cycle 1, day 1 by computed tomography using RECIST criteria version 1.1, and bone scans were repeated every 24 weeks (± 2 weeks).[17] If the baseline bone scan showed metastases, and if the bones were the only site of nonmeasurable disease, then the bone scan was repeated every 12 weeks (± 1 week). Response assessment for the primary and secondary trial end points was performed by the treating physician. Physician visits occurred on day 1 of each fulvestrant cycle. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology for Adverse Events (version 4.0).

Study End Points

The primary end point for the trial was investigator-assessed PFS, defined as the time from random assignment to disease progression or death from any cause, whichever occurred first. Patients who were still alive and free of disease progression were censored at last disease assessment date. Patients without any disease assessment after random assignment were censored at time of random assignment. Secondary end points included objective response rate (complete or partial response) as defined by RECIST criteria,[17] clinical benefit rate (objective response or stable disease for at least 24 weeks), and overall survival (OS), which was defined as the time from random assignment to death from any cause. Patients who were still alive were censored at the last date known to be alive. For the 11 patients who received up to two fulvestrant doses within 4 weeks of registration and random assignment, time to event analysis was measured from random assignment.

Statistical Consideration

On the basis of the subgroup of patients with AI-resistant disease treated with 500 mg fulvestrant in the first report of the Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) trial, it was projected that the median PFS among patients with AI-resistant disease who were receiving fulvestrant alone would be approximately 5.4 months.[18] We hypothesized that the addition of everolimus to fulvestrant would result in a 70% improvement in median PFS, to 9.2 months. To have 90% power to detect the hypothesized improvement with a one-sided type I error rate of 10% using a stratified log-rank test, approximately 120 eligible patients (60 per arm) would be required with full information on 98 events (progressions or deaths). Allowing up to 10 patients (approximately 10%) to be ineligible or to not start study treatment, approximately 130 patients were targeted for enrollment. PFS and OS were

estimated using the Kaplan-Meier method and were compared between treatment arms using the stratified log-rank test. Clinical benefit rate, objective response rate, and incidence of treatment-related grade 3 or higher AEs were estimated using binomial proportions and 95% exact CIs and were compared between arms using Fisher's exact test. All tests were two sided, and the significance level was set at 0.1 for the primary end point and 0.05 for all other end points. All analyses were conducted using STATA 13.0 (STATA, College Station, TX). The primary analysis for PFS was based on data as of December 2016, when a sufficient number of events to trigger the primary analysis had occurred; at that time, 101 PFS events (96 disease progression plus five deaths without disease progression) had occurred. Information on treatment, AEs, and OS were based on updated data using a cutoff date of March 28, 2017, at which point six patients were still receiving protocol therapy, including four receiving fulvestrant alone, and two receiving fulvestrant plus everolimus. AEs were coded and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). The intent-to-treat population was used for all efficacy analyses.

RESULTS

Patient Characteristics

Between May 2013 and November 2015, a total of 131 patients from 23 institutions were randomly assigned, 66 to the everolimus arm and 65 to the placebo arm (Fig 1). Two patients randomly assigned to everolimus did not receive any protocol therapy (one patient withdrew consent and one patient was deemed ineligible because of performance status deterioration). The characteristics of the 131 enrolled patients are listed in Table 1. There were no significant differences between arms with regard to age (median, 64 *v* 59 years), ECOG performance status (0/1, 61%/39% *v* 58%/42%), prior chemotherapy for metastasis (17% *v* 18%), fulvestrant therapy before registration (9% *v* 8%), prior CDK4/6 inhibitor therapy (0% *v* 3%), or presence of liver metastases (27% *v* 26%).

PFS

The addition of everolimus significantly improved the median PFS from 5.1 months (95% CI, 3.0 to 8.0 months) to 10.3 months (95% CI, 7.6 to13.8 months; stratified log-rank *P* value = .02; hazard ratio, 0.61 [95% CI, 0.40 to 0.92]), indicating that the end point was met (Fig 2A; Table 2).

Objective Response and Clinical Benefit Rate

Secondary efficacy end points included objective response and clinical benefit rate (Table 2). Objective response occurred in 12 patients in the everolimus arm (18.2% [95% CI, 9.8% to 29.6%]) and eight patients in the placebo arm (12.3% [95% CI, 5.5% to 22.8%]), which was not significantly different (*P* = .47). The

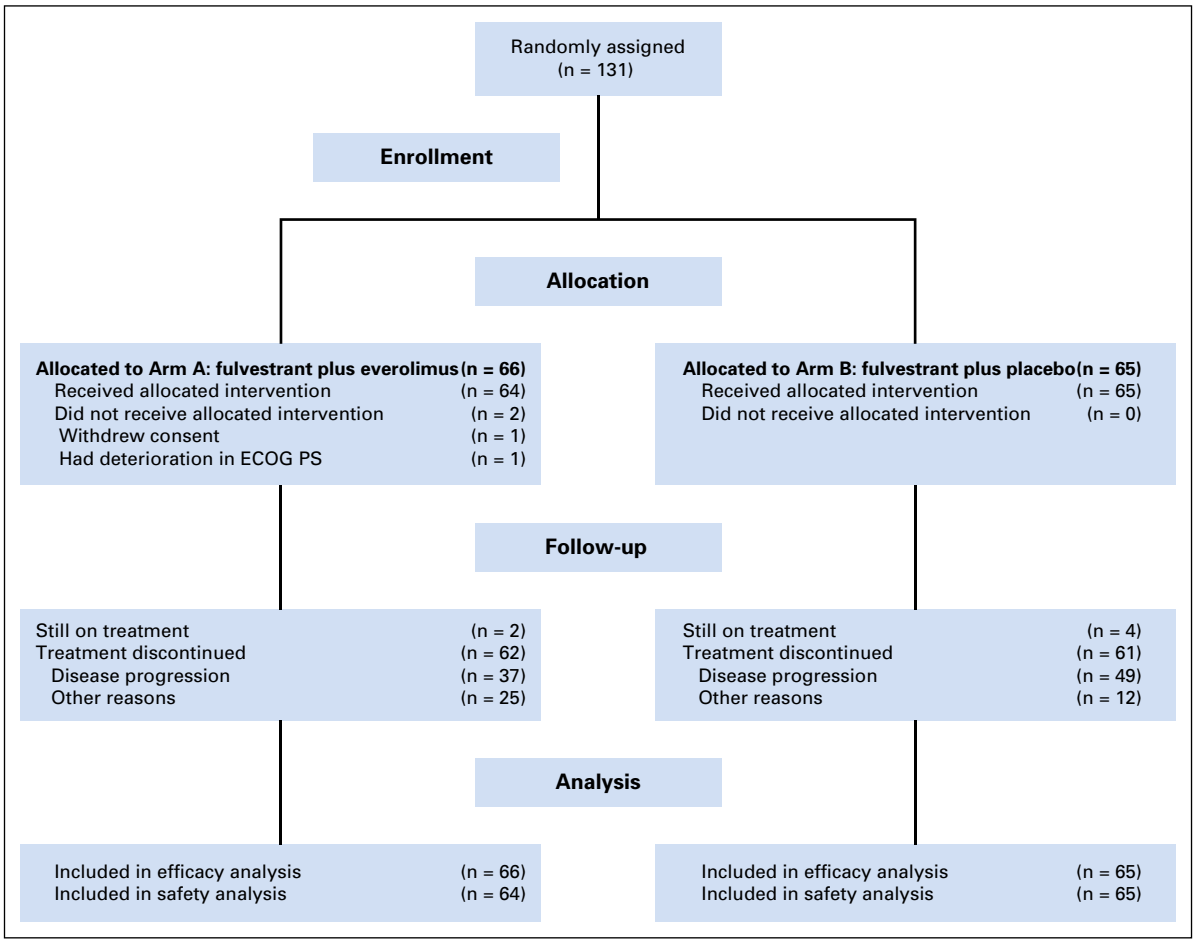

Fig 1. CONSORT diagram. ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 1. Patient Characteristics at Registration

Characteristic	Fulvestrant Plus Everolimus	Fulvestrant Plus Placebo
No. of randomly assigned patients	66	65
Age, years, median (range)	64 (39-92)	59 (35-85)
Ethnicity		
White	56 (85)	49 (75)
Black	8 (12)	11 (17)
Other	2 (3)	5 (8)
ECOG performance status		
0	40 (61)	38 (58)
1	26 (39)	27 (42)
Measurable disease	44 (67)	42 (65)
Metastatic disease site		
Bone	44 (67)	46 (71)
Lung	28 (42)	23 (35)
Liver	18 (27)	17 (26)
Lymph nodes	27 (41)	28 (43)
Prior therapy		
Prior chemotherapy for metastatic disease	11 (17)	12 (18)
Fulvestrant before C1D1	6 (9)	5 (8)
Prior CDK4/6 inhibitor	0 (0)	2 (3)

NOTE. Data are presented as No. (%) unless indicated otherwise.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

clinical benefit rate was 63.6% (95% CI, 50.9% to 75.1%) in the everolimus arm and 41.5% (95% CI, 29.4% to 54.4%) in the placebo arm, which was significantly different (P = .01).

OS

There were 51 deaths at the time of the analysis, including 30 in the everolimus arm and 21 in the placebo arm. The median follow-up was 19.3 months (range, 0 to 36.3 months) for the 80 surviving patients. The estimated median OS was 28.3 months (95% CI, 19.5 to 29.6 months) in the everolimus arm and 31.4 months (95% CI, 21.8 to month not reached) in the placebo arm (stratified log-rank test P value = .37; HR=1.31 [95% CI, 0.72 to 2.38; Fig 2B), indicating no significant difference between the everolimus arm and the placebo arm.

Treatment Administered and Reasons for Treatment Discontinuation

Information regarding treatment administered and reasons for treatment discontinuation are summarized in Table 3. A total of 1,102 cycles were administered in 129 treated patients (567 cycles in the everolimus arm and 535 cycles in the placebo arm) by the cutoff date. The median number of treatment cycles was 5.5 (range, 0 to 31) for everolimus and 7.5 (range, 1 to 31) for fulvestrant for patients in the everolimus arm, and five (range, one to14) for placebo and five (range, one to 36) for fulvestrant for patients in the placebo arm. The median duration of treatment was 5.1 months (range, zero to 28.6 months) for everolimus and 6.9 months (range, 1.4 to 29.8 months) for fulvestrant for patients in the everolimus arm, and 4.6 months (range, 0.03 to 12.4 months) for placebo and 4.6 months (range, 0.5 to 33.8 months) for fulvestrant for patients in the placebo arm. Dose modification of everolimus or placebo was higher in the everolimus arm than in the placebo arm, including any modification (66% *v* 37%), dose held (45% *v* 22%), dose reduced (23% *v* 3%), and dose missed because of noncompliance (14% *v* 9%). The most common reason for treatment discontinuation was disease progression, occurring in 37 patients (58%) in the everolimus arm and 49 patients (75%) in the placebo arm. Everolimus and placebo were discontinued because of AEs in 13 patients (20%) and five patients, (8%), respectively. Other reasons included patient withdrawal, symptomatic disease progression (before RECIST progression), and noncompliance, which were comparable in the two arms. At the time of unblinding at week 48, all patients assigned originally to everolimus during the blinded portion of the study before week 48 continued open-label everolimus after week 48.

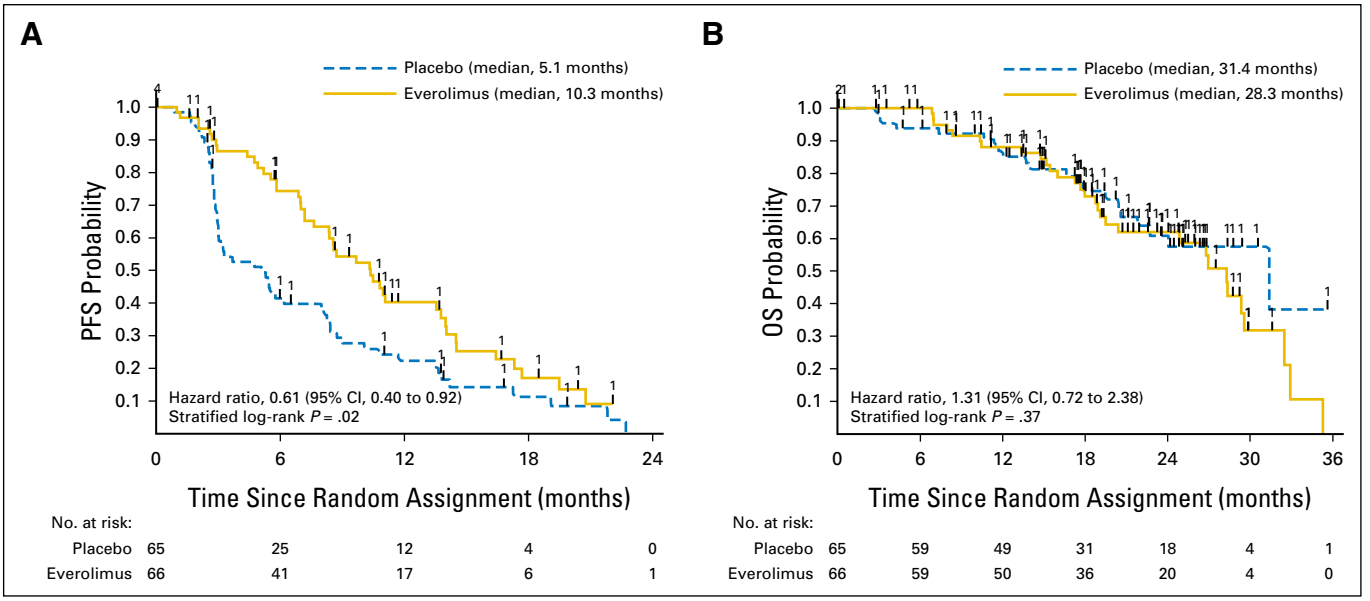

Fig 2. Kaplan-Meier estimates of investigator-assessed (A) progression-free survival (PFS) and (B) overall survival (OS) in the intent-to-treat (ITT) population.

Table 2. Primary and Secondary Efficacy End Points, Intent-to-Treat Population

End Point	Fulvestrant Plus Everolimus (n = 66)	Fulvestrant Plus Placebo (n = 65)	*P*
Median progression-free survival, months (95% CI)	10.3 (7.6 to 13.8)	5.1 (3.0 to 8.0)	0.02* (HR, 0.61 [95% CI, 0.40 to 0.92])
Objective response rate			
No, %	12 (18.2)	8 (12.3)	.47†
95% CI	9.8 to 29.6	5.5 to 22.8	
Clinical benefit rate			
No, %	42 (63.6)	27 (41.5)	.01†
95% CI	50.9 to 75.1	29.4 to 54.4	

Abbreviation: HR, hazard ratio.
*Stratified log-rank test.
†Fisher's exact test

AEs

Worst grade treatment-related AEs (all grades) are summarized in Table 4. The most common AEs of any grade (occurring in at least 5% of patients) in the everolimus arm compared with the placebo arm included oral mucositis (53% *v* 12%), fatigue (42% *v* 22%), rash (38% *v* 5%), anemia (31% *v* 6%), diarrhea (23% *v* 8%), hyperglycemia (19% *v* 5%), hypertriglyceridemia (17% *v* 3%), pneumonitis (17% *v* 0%), dyspnea (16% *v* 3%), hyponatremia (6% *v* 0%), and elevated transaminase (5% *v* 2%). The most common grade 3 or higher treatment-related AEs (occurring in at least 5% of patients) in the everolimus arm compared with the placebo arm included oral mucositis (11% *v* 0%), fatigue (6% *v* 5%), and pneumonitis (6% *v* 0%).There was one grade 4 AE (elevated AST) in the placebo arm, and none in the everolimus arm. Three deaths occurred during, or within 30 days of completing, protocol therapy, including two in the everolimus arm (one sepsis and one cardiac arrest) and one in the placebo arm (one cardiac arrest), none of which were attributed to study treatment by the local treating physician.

DISCUSSION

We performed a randomized phase II trial of the SERD fulvestrant in combination with everolimus or placebo in 131 postmenopausal women with ER-positive metastatic breast cancer who had progressive disease after prior AI therapy. The addition of everolimus to fulvestrant significantly improved median PFS from 5.1 to 10.4 months (hazard ratio, 0.6; $P = .02$), meeting the prespecified

Table 3. Treatment Administered and Reasons for Discontinuation in the Treated Patients

Treatment, Modification, Discontinuation	Fulvestrant Plus Everolimus (n = 64)	Fulvestrant Plus Placebo (n = 65)
Treatment cycles: everolimus or placebo		
Cycles administered in all treated patients	506	407
Cycles administered per protocol	435 (86)	373 (92)
Cycles not administered per protocol	71 (14)	34 (8)
Cycles received by individual patient, median (range)	5.5 (0-31)	5 (1-14)
Patients receiving ≥ 12 cycles of everolimus or placebo	15 (23)	1 (2)
Treatment cycles: fulvestrant		
Cycles administered in all treated patients	630	586
Cycles administered per protocol	630 (100)	584 (99.7)
Cycles not administered per protocol	0 (0)	2 (0.3)
Cycles received by individual patient, median (range)	7.5 (1-31)	5 (1-36)
Patients receiving ≥ 12 cycles of fulvestrant	18 (28)	14 (22)
Patients with everolimus or placebo dose modification	42 (66)	24 (37)
Dose held	29 (45)	14 (22)
Dose level reduced	15 (23)	2 (3)
Dose missed or noncompliance	9 (14)	6 (9)
Reasons for everolimus or placebo discontinuation*		
Disease progression	37 (58)	49 (75)
Adverse events	13 (20)	5 (8)
Patient withdrawal	6 (9)	6 (9)
Symptomatic progression	2 (3)	1 (2)
Noncompliance	1 (2)	0 (0)
Physician decision	3 (5)	0 (0)

NOTE. Data are presented as No. (%) unless indicated otherwise.
*Fulvestrant plus everolimus (n = 62), fulvestrant plus placebo (n = 61). Percentages did not add up to 100% because of rounding. Two patients in the everolimus arm and four patients in the placebo arm were still receiving treatment at the cutoff date for this analysis.

Table 4. Treatment-Related Adverse Events, ITT Population

	Fulvestrant Plus Everolimus (n = 64)					Fulvestrant Plus Placebo (n = 65)				
Toxicity (CTCAE)	Any Grade Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade Event	Grade 1	Grade 2	Grade 3	Grade 4
Oral mucositis	34 (53)	11 (17)	16 (25)	7 (11)	0 (0)	8 (12)	6 (9)	2 (3)	0 (0)	0 (0)
Fatigue	27 (42)	13 (20)	10 (16)	4 (6)	0 (0)	14 (22)	8 (12)	3 (5)	3 (5)	0 (0)
Rash	24 (38)	14 (22)	9 (14)	1 (2)	0 (0)	3 (5)	3 (5)	0 (0)	0 (0)	0 (0)
Anemia	20 (31)	12 (19)	6 (9)	2 (3)	0 (0)	4 (6)	3 (5)	0 (0)	1 (2)	0 (0)
Diarrhea	15 (23)	10 (16)	3 (5)	2 (3)	0 (0)	5 (8)	3 (5)	1 (2)	1 (2)	0 (0)
Hypertriglyceridemia	11 (17)	8 (12)	2 (3)	1 (2)	0 (0)	2 (3)	2 (3)	0 (0)	0 (0)	0 (0)
Hyperglycemia	12 (19)	8 (13)	2 (3)	2 (3)	0 (0)	3 (5)	3 (5)	0 (0)	0 (0)	0 (0)
Dyspnea	10 (16)	6 (9)	2 (3)	2 (3)	0 (0)	2 (3)	0 (0)	2 (3)	0 (0)	0 (0)
Pneumonitis	11 (17)	3 (5)	4 (6)	4 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hyponatremia	4 (6)	1 (2)	1 (2)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Elevated AST	3 (5)	0 (0)	1 (2)	2 (3)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)

NOTE. Data are presented as No. (%).
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events (version 4.0); ITT, intent-to-treat.

primary end point. The median PFS for fulvestrant alone was comparable to the 5.4-month median PFS observed for fulvestrant using the same dose and schedule as in an AI-resistant population in the CONFIRM trial.[17] Although there were numerically more deaths in the everolimus arm (30 everolimus *v* 21 placebo) at the time of primary PFS analysis, there was no statistically significant difference in median OS between the everolimus and placebo arms (28.3 *v* 31.4 months, $P = .37$), and the trial was not designed to demonstrate improved survival for the everolimus arm. This study provides additional evidence that adding everolimus to anti-estrogen therapy in AI-resistant disease improves PFS, as noted previously in the BOLERO-2 trial when everolimus was combined with exemestane,[10] and in the TAMRAD trial when everolimus was combined with tamoxifen.[13] In contrast, the mTOR inhibitor temsirolimus did not improve clinical outcomes when added to an AI as -line therapy; one possible explanation among others is that the development of AI resistance may select for tumors that are more dependent on PI3K/AKT/mTOR signaling and hence sensitive to mTOR inhibition.[19]

The addition of everolimus to fulvestrant resulted in more AEs and higher rates of treatment discontinuation as a result of AEs, when compared with placebo (20% *v* 8%). The most common grade 3 AEs occurring in > 5% of patients in the everolimus arm included oral mucositis (11%), pneumonitis (6%), fatigue (5%), and hyperglycemia (6%). The most common AE of all grades was oral mucositis, which occurred in 52% of patients and was grade 1 to 2 in 42%. This safety profile is similar to that of everolimus combined with either exemestane or tamoxifen in the BOLERO-2 trial[10] and TAMRAD trials,[13] respectively. Prophylactic corticosteroid mouthwash was not used in any of these trials, but it has been shown to reduce the risk of grade 1 to 3 oral mucositis (also commonly referred to as stomatitis) to approximately 20%, with the vast majority being grade 1.[20] This may prove to be a helpful strategy to reduce the risk of stomatitis, one of the more common and troublesome adverse effects associated with everolimus that typically manifests within 8 weeks of initiating therapy.[21]

This study was completed before the availability of the CDK 4/6 inhibitors, which are effective when added to both first-line AI therapy and second-line fulvestrant in AI-resistant disease. The PALOMA3 trial demonstrated that the combination of the CDK4/6 inhibitor palbociclib with fulvestrant significantly prolonged median PFS compared with fulvestrant alone (median, 9.5 *v* 4.6 months; $P < .0001$).[22,23] The addition of abemaciclib also improved median PFS when add to fulvestrant in the MONARCH2 trial (median, 16.4 *v* 9.3 months; $P < .001$) in a population of patients resistant to prior endocrine therapy including an AI (approximately 70%) or tamoxifen, with diarrhea being the most common AE.[24] Given the activity of the CDK4/6 inhibitors such as palbociclib, ribociclib, and abemaciclib in combination with AIs as first-line endocrine therapy,[25-28] the use of everolimus may represent an option for combination with fulvestrant as second-line therapy in AI-resistant disease. The findings of our trial were confirmed by the Fulvestrant With AZD2014 or Everolimus for Advanced Breast Cancer (MANTA) trial, in which 333 patients with AI-resistant, ER-positive metastatic breast cancer were randomly assigned to receive fulvestrant alone or in combination with everolimus or the dual target of rapamycin complex 1-2 (TORC 1-2) inhibitor vistusertib; PFS was significantly improved in the fulvestrant plus everolimus arm compared with fulvestrant alone (median PFS, 12.2 *v* 4.6 months; HR, 0.64 [95% CI, 0.43 to 0.94]; $P = .02$), but not in either of the arms that included fulvestrant plus two different vistusertib dosing regimens.[29] Few patients in our trial or the MANTA trial received prior CDK4/6 inhibitor therapy, so the impact of such prior therapy on the efficacy of the fulvestrant-everolimus combination is unknown. However, upregulation of the PI3K-PDK1 pathway has emerged as an important mechanism of resistance to CDK4/6 inhibitor therapy, suggesting that mTOR blockade with everolimus plus fulvestrant may represent a viable strategy for the treatment of patients who have developed resistance to prior treatment including an AI plus a CDK4/6 inhibitor.[30]

In conclusion, our findings provide additional evidence that everolimus plus anti-estrogen therapy is more efficacious than is anti-estrogen therapy alone in patients with metastatic, hormone receptor–positive, human epidermal growth factor receptor 2–negative breast cancer resistant to AI therapy, and that the fulvestrant-everolimus combination represents a new therapeutic option for AI-resistant disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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