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ORIGINAL REPORT

Randomized Phase II Trial of Everolimus in Combination With Tamoxifen in Patients With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer With Prior Exposure to Aromatase Inhibitors: A GINECO Study

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See accompanying editorial on page 2707

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ABSTRACT

Purpose
Cross-talk between signal transduction pathways likely contributes to hormone resistance in metastatic breast cancer (mBC). Everolimus, an oral inhibitor of the mammalian target of rapamycin, has restored sensitivity in endocrine-resistance models and shown anticancer activity in early-phase mBC clinical trials. This analysis evaluated efficacy and safety of everolimus in combination with tamoxifen in patients with mBC resistant to aromatase inhibitors (AIs).

Patients and Methods
This open-label, phase II study randomly assigned postmenopausal women with hormone receptor–positive, human epidermal growth factor receptor 2–negative, AI-resistant mBC to tamoxifen 20 mg/d plus everolimus 10 mg/d (n = 54) or tamoxifen 20 mg/d alone (n = 57). Randomization was stratified by primary and secondary hormone resistance. Primary end point was clinical benefit rate (CBR), defined as the percentage of all patients with a complete or partial response or stable disease at 6 months. No formal statistical comparison between groups was planned.

Results
The 6-month CBR was 61% (95% CI, 47 to 74) with tamoxifen plus everolimus and 42% (95% CI, 29 to 56) with tamoxifen alone. Time to progression (TTP) increased from 4.5 months with tamoxifen alone to 8.6 months with tamoxifen plus everolimus, corresponding to a 46% reduction in risk of progression with the combination (hazard ratio [HR], 0.54; 95% CI, 0.36 to 0.81). Risk of death was reduced by 55% with tamoxifen plus everolimus versus tamoxifen alone (HR, 0.45; 95% CI, 0.24 to 0.81). The main toxicities associated with tamoxifen plus everolimus were fatigue (72% *v* 53% with tamoxifen alone), stomatitis (56% *v* 7%), rash (44% *v* 7%), anorexia (43% *v* 18%), and diarrhea (39% *v* 11%).

Conclusion
This study suggests that tamoxifen plus everolimus increased CBR, TTP, and overall survival compared with tamoxifen alone in postmenopausal women with AI-resistant mBC.

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INTRODUCTION

Most patients with estrogen receptor (ER) –positive breast cancer benefit from aromatase inhibitors (AIs) as first-line endocrine therapy for metastatic disease. Unfortunately, approximately 30% do not respond to treatment, with the remainder ultimately progressing after disease control.[1-3] Patients with ER-positive metastatic breast cancer (mBC) with progression or recurrence after first-line endocrine therapy have limited objective responses and disease-free survival rates with additional lines of hormone therapy.[2,4]

Hormone resistance is linked to cross-talk between signal transduction pathways, particularly ER signaling and the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway.[5-7] Estrogen-dependent

cells cultured long term in estrogen-depleted medium (mimicking AI resistance) rely on mTOR signaling for growth and are excessively sensitive to its inhibition.[5,6] In addition, mTOR inhibition restores sensitivity of endocrine-resistant breast cancer cells to endocrine therapy.[8-10]

Everolimus, a potent oral mTOR inhibitor, has shown anticancer activity in early-phase clinical trials.[11-15] Hormone resistance was reversed in a phase IB clinical trial of a letrozole and everolimus combination in women with disease resistant to letrozole alone.[14] In a phase II study in the neoadjuvant setting, letrozole plus everolimus improved the disease response rate over letrozole alone.[15]

The TAMRAD (Tamoxifen Plus Everolimus) study tested the hypothesis that mTOR inhibition combined with endocrine therapy may be effective in restoring sensitivity in endocrine therapy–resistant patients. Furthermore, we hypothesized that selecting AI-pretreated patients would enrich for tumors driven by the PI3K/AKT/mTOR pathway, which would be more likely to be sensitive to mTOR inhibition.

PATIENTS AND METHODS

Patients

Key inclusion criteria were as follows: postmenopausal women age ≥ 18 years with hormone receptor–positive, human epidermal growth factor receptor type 2 (HER2) –negative mBC not amenable to curative surgery or radiotherapy who had undergone previous treatment with AIs in the adjuvant or metastatic setting. Patients had to be experiencing progressive disease as assessed by the local investigator. Other inclusion criteria included presence of at least one evaluable lesion (target or nontarget), Eastern Cooperative Oncology Group performance status ≤ 2, aspartate and ALT levels $\leq 1.5 \times$ the upper limit of normal (ULN; or $\leq 3 \times$ ULN in the presence of hepatic metastases), absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, creatinine clearance ≥ 30 mL/min, and alkaline phosphatase level $\leq 2.5 \times$ ULN. Cytologically or histologically confirmed bone lesions were permitted as evaluable lesions if they appeared as hot spots visible on a bone scan or associated with increased CA15-3. Patients could have previously received any chemotherapy and/or radiotherapy before inclusion, either in the adjuvant or metastatic setting. Exclusion criteria included symptomatic brain metastases; lymphangitic carcinomatosis involving $> 50\%$ of the lungs; evidence of metastases involving more than one third of the liver on sonogram or computed tomography; previous tamoxifen treatment, unless the patient received it in the adjuvant setting and did not experience relapse within 1 year of stopping; previous treatment with or known sensitivity to mTOR inhibitors; other malignancy ≤ 5 years before random assignment, except adequately treated in situ uterine carcinoma or nonmelanomatous skin cancer; and any severe or uncontrolled medical condition.

Study Design

In this multicenter, open-label, phase II study, patients were randomly assigned in a 1:1 ratio to receive tamoxifen 20 mg/d or tamoxifen 20 mg/d plus everolimus 10 mg/d. Because the biologic mechanisms underlying primary and secondary hormone resistance may differ, patients were stratified by primary and secondary resistance. Patients with primary resistance were those relapsing during or within 6 months of stopping adjuvant AI treatment or progressing within 6 months of starting AI treatment in the metastatic setting. Patients with secondary resistance were those relapsing > 6 months after stopping adjuvant AIs or responding for ≥ 6 months to AIs in the metastatic setting.

Study treatment continued until disease progression, intolerable toxicity, or patient decision. No cross-over was planned. Tamoxifen doses could be delayed by ≤ 14 days if patients experienced adverse events (AEs) of grade 3 or 4 severity considered tamoxifen related. Everolimus doses could be reduced to 5 mg/d or interrupted for ≤ 14 days if patients experienced AEs of grade 3 or 4 severity considered related to everolimus. For tamoxifen plus everolimus, if the AE did not resolve within 14 days or recurred after treatment resumption, treatment was terminated. Except for everolimus dose reduction, no specific supportive care measures were planned for AE management within the protocol.

Consistent with European and French law, the protocol was approved by a central ethics committee (December 22, 2006). The study was conducted in accordance with Good Clinical Practice principles, the Declaration of Helsinki, and all local regulations. All patients provided written informed consent.

Academic investigators from the French cooperative GINECO (Groupe d'Investigateurs Nationaux pour l'Etude des Cancers de l'Ovaire et du Sein) and the Biostatistics Unit of Léon Bérard Centre (Lyon, France) designed and conducted the study and collected and analyzed the data. All authors contributed to data interpretation and subsequently to manuscript writing, reviewing, and editing. The first manuscript draft was prepared by the first author and a medical writer funded by Novartis. All authors vouch for the accuracy and completeness of the reported data and attest the study was conducted in accordance with the protocol and statistical analysis plan.

Assessments

The primary efficacy end point was the 6-month clinical benefit rate (CBR), defined as the percentage of all patients with a complete or partial response or stable disease at 6 months. Tumor response in measurable lesions was assessed according to RECIST version 1.0.[16] For nonmeasurable bone lesions, complete response was defined as complete lesion disappearance (ie, complete disappearance of uptake on bone scan and by computed tomography) and normalization of CA15-3 levels; progressive disease was defined as the appearance of at least one new lesion or unequivocal progression of an existing lesion. Secondary end points included time to progression (TTP), overall survival (OS), objective response rate, and toxicity determined by AEs and laboratory measures.

All randomly assigned patients who received at least one dose of study medication (intention-to-treat [ITT] population) were assessed for efficacy and safety. Efficacy analyses were also performed for patients in the ITT population who had no predefined major protocol violations (per-protocol population). Tumor assessments were performed with computed tomography scans at baseline and every 2 months until the 6-month visit, then every 3 months until 18 months. Scans were assessed locally, and a medical expert performed a central review of all radiologic reports. Safety assessments, performed monthly until the 6-month visit, then every 3 months until 18 months, included AE monitoring and recording, hematologic and clinical biochemical levels (laboratory evaluations), vital sign measurements, and physical examinations. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.[17]

Statistical Analysis

This study employed a Simon two-stage minimax design.[18] Considering a 20% gain in the CBR as the minimum required to warrant further study of the combination, and assuming a CBR of 50% in the tamoxifen group,[19] it was determined that 53 evaluable patients were needed in the tamoxifen plus everolimus group with 90% power and $\alpha = 5\%$. This design required that ≥ 15 of 27 patients in the tamoxifen plus everolimus group not progress by 6 months at the end of stage I in order to proceed to stage 2 and that ≥ 33 of 53 patients in this group not progress at study end to recommend further investigation of the combination.

The CBR was calculated with its 95% CI. TTP was calculated as the time from random assignment to date of event defined as the first documented progression or death resulting from underlying cancer. Patients alive and progression free at the date of last contact and patients who died as a result of causes not related to the disease were censored at the date of last contact and the date of death, respectively.[20] OS was defined as the time from random assignment to death. Patients alive at the date of last contact were censored at this date. TTP and OS were estimated by the Kaplan-Meier method. Although no formal statistical between-group comparison was planned, Fisher's exact test was used to compare between-group CBRs, and the log-rank test was used to compare the survival curves for exploratory purposes. Cox proportional hazards regression models were used to estimate hazard ratios (HRs). All expressed P values and CIs were two sided. Subgroup analyses were exploratory.

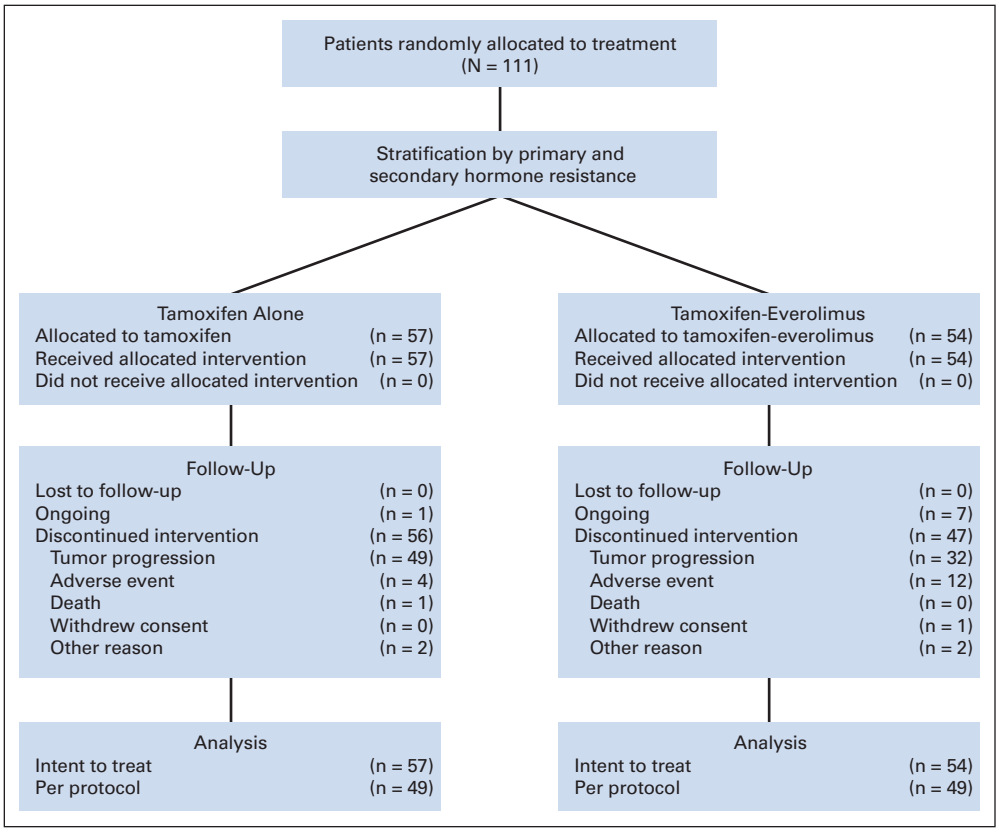

Fig 1. CONSORT flow diagram.

RESULTS

Patients and Treatment

Between March 2008 and May 2009, 111 women with mBC previously treated with AIs were randomly allocated to receive tamoxifen plus everolimus (n = 54) or tamoxifen alone (n = 57; Fig 1). Between-group baseline demographic and clinical characteristics were generally well balanced, although Eastern Cooperative Oncology Group performance status of 0 was more common with tamoxifen plus everolimus (60% *v* 43%; Table 1). The median age was 64 years (range, 41 to 86 years), the median duration of metastatic disease before inclusion was 1.2 years, and approximately 78% and 53% of patients had bone and visceral metastases, respectively (Table 1). Previous AI treatment occurred in 41% of patients in the adjuvant setting and 67% in the first-line metastatic setting. Adjuvant chemotherapy was used in 51% of patients; 25% received chemotherapy in the metastatic setting. Primary resistance occurred in 49% of patients; 51% had secondary resistance. Major protocol violations were nonmetastatic disease (n = 1, tamoxifen plus everolimus), HER2 status positive or unknown (n = 4, tamoxifen alone), inadequate hepatic function (n = 1, tamoxifen alone), previous treatment with tamoxifen in the metastatic setting or relapse within 1 year of stopping in the adjuvant setting (n = 1, tamoxifen alone; n = 2, tamoxifen plus everolimus), participation in another clinical trial (n = 1, tamoxifen plus everolimus), radiotherapy during the course of the study (n = 1 each, tamoxifen alone and tamoxifen plus everolimus), and intercurrent cancer (n = 1, tamoxifen alone).

Median duration of follow-up was similar for tamoxifen plus everolimus and tamoxifen alone: 23.7 months (range, 2.6 to 32.7 months) and 24.2 months (range, 0.9 to 36.2 months), respectively. At stage I of the study, 16 of the first 27 patients included in the tamoxifen plus everolimus group had not progressed at 6 months, allowing for trial continuation.

At study end, the combination was ongoing for seven patients (13%) receiving tamoxifen plus everolimus, whereas one patient (2%) receiving tamoxifen alone was still receiving study treatment (Fig 1). Median treatment duration was 6.2 months (range, 0.7 to 31 months) and 4.8 months (range, 0.7 to 27 months) in the tamoxifen plus everolimus and tamoxifen alone groups, respectively. The primary reasons for study treatment discontinuation (including discontinuation of at least one of the two drugs for the tamoxifen plus everolimus group) were disease progression (59%, tamoxifen plus everolimus *v* 86%, tamoxifen alone), AEs (22% *v* 7%), death (0% *v* 2%), and withdrawal of consent (2% *v* 0%). Among the 12 patients (22%) receiving tamoxifen plus everolimus who discontinued the combination because of an AE, six discontinued everolimus only and continued tamoxifen until disease progression or study end, one discontinued tamoxifen alone and was still treated with everolimus at study end, and five discontinued both treatments simultaneously.

Efficacy

The CBR at 6 months in the ITT population (primary study end point) was 61% (95% CI, 47 to 74) among patients treated with tamoxifen plus everolimus versus 42% (95% CI, 29 to 56) among those treated with tamoxifen alone (exploratory $P = .045$). Results in

Table 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	Tamoxifen Alone (n = 57) No.	%	Tamoxifen Plus Everolimus (n = 54) No.	%
Age, years				
Median	66		63	
Range	42-86		41-81	
Duration of metastatic disease, years				
Median	1.2		1.1	
Range	0.02-8.5		0.06-7.9	
Hormone receptor status*				
ER positive/PR positive	41	72	35	65
ER positive/PR negative	15	26	19	35
ER negative/PR positive	1	2	0	0
HER2 negative†	53	93	53	98
Previous aromatase inhibitor treatment‡				
Adjuvant	24	42	21	39
Metastatic	37	65	37	69
Hormone resistance				
Primary	28	49	26	48
Secondary	29	51	27	50
Missing	0	0	1	2
ECOG performance status				
0	23	40	32	59
1	28	49	18	33
2	3	5	3	6
Missing	3	5	1	2
Histologic status of tumor				
Well differentiated	5	9	6	11
Moderately differentiated	17	30	16	30
Poorly differentiated or undifferentiated	23	40	26	48
Unknown	12	21	6	11
Disease stage				
Bone	45	79	41	76
Bone only	14	25	16	30
Visceral	28	49	31	57
Three or more metastatic sites	16	28	13	24
RECIST measurable disease	31	55	21	39
Previous adjuvant tamoxifen	24	42	18	33
Previous chemotherapy§				
Adjuvant	32	56	25	46
Metastatic (first line)	15	26	13	24

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

*Data based on receptor status of the metastases when available and of the initial tumor otherwise.

†One patient in the tamoxifen plus everolimus arm with HER2-positive status had a tumor that only slightly overexpressed HER2 and therefore was not considered a major protocol violation.

‡Patients could receive aromatase inhibitor therapy in both the adjuvant and metastatic settings.

§Patients could receive chemotherapy in both the adjuvant and metastatic settings.

the per-protocol population were similar (59%; 95% CI, 44 to 73 *v* 41%; 95% CI, 27 to 56). Five patients in each treatment group experienced a complete or partial response. For patients with RECIST-measurable disease, the response rate was 14% in the tamoxifen plus everolimus and 13% in the tamoxifen alone groups. In an exploratory subgroup analysis, patients with secondary hormone resistance had a higher CBR with tamoxifen plus everolimus (20 of 27 patients; 74%) than tamoxifen alone (14 of 29 patients; 48%). Patients with primary hormone resistance had only a slightly higher CBR with tamoxifen plus everolimus (12 of 26 patients; 46%) than tamoxifen alone (10 of 28 patients; 36%).

The median TTP in the ITT population increased to 8.6 months (95% CI, 5.9 to 13.9) with tamoxifen plus everolimus from 4.5 months (95% CI, 3.6 to 8.7) with tamoxifen alone (exploratory $P = .002$). This difference in TTP corresponded to a 46% reduction in the risk of progression associated with tamoxifen plus everolimus (HR, 0.54; 95% CI, 0.36 to 0.81; Fig 2A). In an exploratory subgroup analysis, the everolimus benefit was mostly for patients with secondary hormone resistance, with a reduction in the risk of progression associated with everolimus of 54% in this subgroup (HR, 0.46; 95% CI, 0.26 to 0.83). In contrast, patients with primary resistance benefited to a lesser degree (HR, 0.70; 95% CI, 0.40 to 1.21; Figs 2B and 2C).

At the last update of OS in September 2011, 16 patients in the tamoxifen plus everolimus and 31 patients in the tamoxifen alone groups had died. Median OS was not reached with tamoxifen plus everolimus; it was 32.9 months with tamoxifen alone, which translated

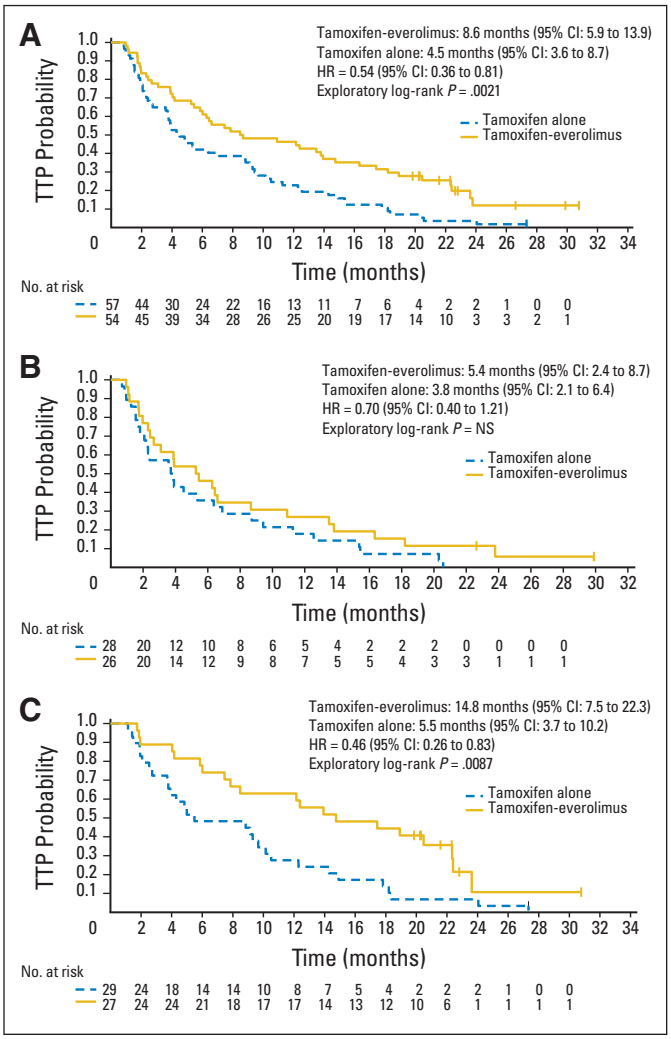

Fig 2. Time to progression (TTP) in the intention-to-treat population for (A) the overall patient population and patients with (B) primary and (C) secondary hormone resistance. HR, hazard ratio; NS, nonsignificant.

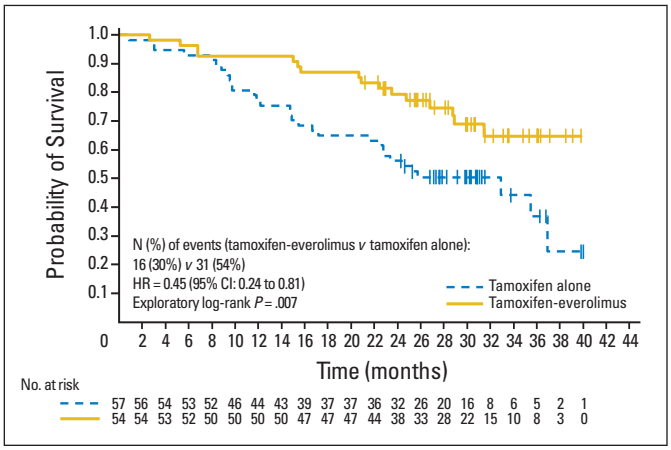

Fig 3. Overall survival in the intention-to-treat population for the overall patient population. HR, hazard ratio.

to a 55% reduction in the risk of death associated with combination therapy (HR, 0.45; 95% CI, 0.24 to 0.81; exploratory $P = .007$; Fig 3).

Safety

Observed AEs were consistent with those previously reported for tamoxifen and everolimus and were mostly of grade 1 or 2 severity. Besides pain, the most common nonhematologic AEs were fatigue (72%, tamoxifen plus everolimus *v* 53%, tamoxifen alone), stomatitis (56% *v* 7%), rash (44% *v* 7%), anorexia (43% *v* 18%), and diarrhea (39% *v* 11%; Table 2). Overall incidence of nonhematologic grade 3 or 4 events was similar in the tamoxifen plus everolimus and tamoxifen alone treatment groups ($P = .2$). Most common hematologic AEs were decreased hemoglobin (69%, tamoxifen plus everolimus *v* 35%, tamoxifen alone) and decreased lymphocyte (48% *v* 21%) and leukocyte (54% *v* 18%) counts.

Drug-related AEs led to everolimus dose reductions in 11 patients (20%). The main reasons for these dose reductions were stomatitis (n = 4), rash (n = 1), thrombocytopenia (n = 1), and pneumonitis (n = 1). Of those 11 patients, only three stopped everolimus later because of additional AEs before disease progression.

The drug-related AEs that led to complete treatment discontinuation were venous thrombosis (n = 2), pulmonary embolism (n = 1), and asthenia (n = 1) in the tamoxifen alone group and venous thrombosis (n = 2), acute renal insufficiency (n = 1), cardiac failure (n = 1), and hemorrhagic risk (n = 1) in the tamoxifen plus everolimus group. Futhermore, in the combination group, patients discontinued everolimus while maintaining tamoxifen after pneumonitis (n = 2), rash (n = 2), hyperglycemia (n = 1), and stomatitis (n = 1). One patient discontinued tamoxifen while maintaining everolimus after venous thrombosis. The overall incidence of serious AEs was 32% in each group.

Table 2. Adverse Events Experienced by ≥ 10% of Patients

	Tamoxifen Alone (n = 57)				Tamoxifen Plus Everolimus (n = 54)			
	Any Grade		Grade 3-4		Any Grade		Grade 3-4	
Adverse Event	No.	%	No.	%	No.	%	No.	%
Nonhematologic events								
Pain	49	86	10	18	44	82	5	9
Fatigue	30	53	6	11	39	72	3	6
Nausea	20	35	0	0	19	35	2	4
Stomatitis	4	7	0	0	30	56	6	11
Anorexia	10	18	2	4	23	43	4	7
Hot flashes	19	33	0	0	12	22	0	0
Infection	11	19	3	5	19	35	4	7
Rash	4	7	0	0	24	44	2	4
Diarrhea	6	11	0	0	21	39	1	2
Constipation	13	23	0	0	9	17	0	0
Vomiting	7	12	2	4	9	17	0	0
Pneumonitis	2	4	2	4	9	17	1	2
Hematologic events								
Decreased hemoglobin	20	35	2	4	37	69	1	2
Decreased leukocyte count	10	18	0	0	29	54	1	2
Decreased lymphocyte count	12	21	2	4	26	48	1	2
PNNs	11	19	3	5	26	48	1	2

NOTE. Adverse events listed regardless of relationship to study drug.
Abbreviation: PNN, polymorphonuclear neutrophil.

DISCUSSION

Several studies targeting pathways thought to contribute to AI resistance have failed to demonstrate any consistent efficacy in ER-positive, HER2-negative mBC.[21] In this trial of postmenopausal women with hormone-resistant mBC, tamoxifen combined with everolimus led to a 6-month CBR of 61% *v* 42% with tamoxifen alone (exploratory $P = .045$). Patients with secondary resistance seemed to exhibit more benefit with tamoxifen plus everolimus than patients with primary resistance (CBR: 74% *v* 48% [secondary resistance]; 46% *v* 36% [primary resistance]). Tamoxifen plus everolimus also increased the median TTP (8.6 *v* 4.5 months with tamoxifen; HR, 0.54; 95% CI, 0.36 to 0.81; exploratory $P = .002$) and OS (HR, 0.45; 95% CI, 0.24 to 0.81; exploratory $P = .007$). Similar to CBR, the TTP benefits seemed to be more prominent in patients with secondary resistance.

Our results continue to support a synergistic anticancer effect of everolimus when combined with other therapies in mBC.[9-15,22] These positive findings in the hormone-resistant setting contrast with failure of the mTOR inhibitor temsirolimus plus letrozole to provide benefit or prolong TTP over letrozole alone for first-line treatment of mBC in a phase III study.[23]

In the first-line setting, most hormone receptor–positive tumors rely on ER-mediated signaling for growth and are sensitive to hormone therapy. As treatment progresses, adaptive upregulation of growth factor–mediated signaling, including the PI3K/AKT/mTOR pathway, and subsequent cross-talk with ER-mediated signaling result in constitutive activation of cell growth pathways, rendering the patient resistant to hormone treatment.[7] Large proportions of AI-resistant populations may have progressive tumors resulting from PI3K/AKT/mTOR pathway activation. Moreover, this adaptive hypothesis predicts the effectiveness of a PI3K/AKT/mTOR pathway inhibitor and hormone therapy combination in patients with secondary hormone resistance, which this study observed. This result also suggests that this signaling pathway does not play a critical role in mediating primary resistance. To further understand the biologic mechanism behind everolimus activity, we are currently retrieving

primary tumor archival tissue and tumor biopsies (when available) for correlation studies between molecular markers of mTOR activation and efficacy results.

This small open-label, randomized phase II study was prone to bias. In such studies, small imbalances between groups are common and were notable in this trial for performance status. Progression was assessed by local investigators, and this could have been highly subjective for patients without RECIST-measurable disease. As a consequence, our results are intended to be hypothesis generating, showing that the combination of tamoxifen and everolimus warrants further study in hormone receptor–positive, HER2-negative mBC after AI progression. Nevertheless, they are consistent with preclinical data and previous clinical trials.[9-15,22] Moreover, the everolimus benefit in AI-resistant mBC was recently confirmed by the phase III BOLERO-2 (Breast Cancer Trials of Oral Everolimus) study comparing the combination of exemestane and everolimus with exemestane alone in 724 patients (ClinicalTrials.gov identifier NCT00863655).[24] BOLERO-2 had inclusion criteria equivalent to those of the TAMRAD trial, but 84% of patients were previously hormone sensitive (v 50% in TAMRAD). The HR of the benefit in progression-free survival of everolimus plus exemestane over exemestane alone (0.43; 95% CI, 0.35 to 0.54) is consistent with that reported in this trial, suggesting that everolimus activity is not dependent on specific second-line hormone therapy.

The safety profile of our study was consistent with the profiles of previous everolimus studies.[11-15,25-27] As expected, stomatitis, rash, diarrhea, anorexia, and infections were more common among recipients of tamoxifen plus everolimus than tamoxifen only. Most AEs were of grade 1 or 2 severity and could be managed without stopping everolimus. AEs of grade 3 or 4 severity were not more common in recipients of tamoxifen plus everolimus than tamoxifen only. Nevertheless, 19 patients (35%) either discontinued or reduced the dosage of everolimus because of AEs, more than commonly observed with hormone therapy. Stomatitis, the most frequent grade 3 toxicity experienced with everolimus, may be a clinical problem when administering this drug to unselected patients. Furthermore, quality of life was not formerly assessed. This information could have provided more precise information on the consequences of everolimus toxicities in patients' daily life. In future clinical practice, well-written prevention measures and corrective procedures may allow for better tolerance of everolimus.

In conclusion, this randomized phase II trial suggests that tamoxifen combined with everolimus may reverse hormone resistance and lead to increased CBR, TTP, and OS compared with tamoxifen alone in postmenopausal women with AI-resistant mBC, particularly those with secondary hormone resistance. The observed toxicities were manageable and consistent with those of previous studies. Taken together with the results of the BOLERO-2 trial (pending survival results), these data may have important implications for the treatment of patients with AI-resistant mBC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Nabholtz JM, Buzdar A, Pollak M, et al: Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: Results of a North American multicenter randomized trial. Arimidex Study Group. J Clin Oncol 18:3758-3767, 2000
2. Dodwell D, Wardley A, Johnston S: Postmenopausal advanced breast cancer: Options for therapy after tamoxifen and aromatase inhibitors. Breast 15:584-594, 2006
3. Mouridsen H, Gershanovich M, Sun Y, et al: Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: Analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol 21:2101-2109, 2003
4. Chia S, Gradishar W, Mauriac L, et al: Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: Results from EFECT. J Clin Oncol 26:1664-1670, 2008
5. Yue W, Fan P, Wang J, et al: Mechanisms of acquired resistance to endocrine therapy in hormone-dependent breast cancer cells. J Steroid Biochem Mol Biol 106:102-110, 2007
6. Miller TW, Hennessy BT, Gonzalez-Angulo AM, et al: Hyperactivation of phosphatidylinositol-3 kinase promotes escape from hormone dependence in estrogen receptor-positive human breast cancer. J Clin Invest 120:2406-2413, 2010
7. Santen RJ, Song RX, Zhang Z, et al: Adaptive hypersensitivity to estrogen: Mechanisms and clinical relevance to aromatase inhibitor therapy in breast cancer treatment. J Steroid Biochem Mol Biol 95:155-165, 2005
8. deGraffenried LA, Friedrichs WE, Russell DH, et al: Inhibition of mTOR activity restores tamoxifen response in breast cancer cells with aberrant Akt Activity. Clin Cancer Res 10:8059-8067, 2004
9. Boulay A, Rudloff J, Ye J, et al: Dual inhibition of mTOR and estrogen receptor signaling in vitro induces cell death in models of breast cancer. Clin Cancer Res 11:5319-5328, 2005
10. Beeram M, Tan QT, Tekmal RR, et al: Akt-induced endocrine therapy resistance is reversed by inhibition of mTOR signaling. Ann Oncol 18:1323-1328, 2007

11. Ellard SL, Clemons M, Gelmon KA, et al: Randomized phase II study comparing two schedules of everolimus in patients with recurrent/metastatic breast cancer: NCIC Clinical Trials Group IND.163. J Clin Oncol 27:4536-4541, 2009

12. O'Donnell A, Faivre S, Burris HA III, et al: Phase I pharmacokinetic and pharmacodynamic study of the oral mammalian target of rapamycin inhibitor everolimus in patients with advanced solid tumors. J Clin Oncol 26:1588-1595, 2008

13. Tabernero J, Rojo F, Calvo E, et al: Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: A phase I tumor pharmacodynamic study in patients with advanced solid tumors. J Clin Oncol 26:1603-1610, 2008

14. Awada A, Cardoso F, Fontaine C, et al: The oral mTOR inhibitor RAD001 (everolimus) in combination with letrozole in patients with advanced breast cancer: Results of a phase I study with pharmacokinetics. Eur J Cancer 44:84-91, 2008

15. Baselga J, Semiglazov V, van Dam P, et al: Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer. J Clin Oncol 27:2630-2637, 2009

16. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205-216, 2000

17. Common Terminology Criteria for Adverse Events version 3.0. http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf

18. Simon R: Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1-10, 1989

19. Thürlimann B, Robertson JF, Nabholtz JM, et al: Efficacy of tamoxifen following anastrozole ('Arimidex') compared with anastrozole following tamoxifen as first-line treatment for advanced breast cancer in postmenopausal women. Eur J Cancer 39:2310-2317, 2003

20. Burzykowski T, Buyse M, Piccart-Gebhart MJ, et al: Evaluation of tumor response, disease control, progression-free survival, and time to progression as potential surrogate end points in metastatic breast cancer. J Clin Oncol 26:1987-1992, 2008

21. Johnston SR: New strategies in estrogen receptor-positive breast cancer. Clin Cancer Res 16:1979-1987, 2010

22. Treeck O, Wackwitz B, Haus U, et al: Effects of a combined treatment with mTOR inhibitor RAD001 and tamoxifen in vitro on growth and apoptosis of human cancer cells. Gynecol Oncol 102:292-299, 2006

23. Chow LWC, Sun Y, Jassem J, et al: Phase 3 study of temsirolimus with letrozole or letrozole alone in postmenopausal women with locally advanced or metastatic breast cancer. Presented at the 29th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 14-17, 2006

24. Baselga J, Campone M, Piccart M, et al: Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 366:520-529, 2012

25. Yao JC, Shah MH, Ito T, et al: Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 364:514-523, 2011

26. Motzer RJ, Escudier B, Oudard S, et al: Efficacy of everolimus in advanced renal cell carcinoma: A double-blind, randomised, placebo-controlled phase III trial. Lancet 372:449-456, 2008

27. Krueger DA, Care MM, Holland K, et al: Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. N Engl J Med 363:1801-1811, 2010