ORIGINAL ARTICLE

Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D., Martine Piccart, M.D., Ph.D., Howard A. Burris III, M.D., Hope S. Rugo, M.D., Tarek Sahmoud, M.D., Ph.D., Shinzaburo Noguchi, M.D., Michael Gnant, M.D., Kathleen I. Pritchard, M.D., Fabienne Lebrun, M.D., J. Thaddeus Beck, M.D., Yoshinori Ito, M.D., Denise Yardley, M.D., Ines Deleu, M.D., Alejandra Perez, M.D., Thomas Bachelot, M.D., Ph.D., Luc Vittori, M.Sc., Zhiying Xu, Ph.D., Pabak Mukhopadhyay, Ph.D., David Lebwohl, M.D., and Gabriel N. Hortobagyi, M.D.

From Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston (J.B.); Institut de Cancérologie de l'Ouest/René Gauducheau, Nantes Saint Herblain, France (M.C.); Institute Jules Bordet, Brussels (M.P., F.L.); Sarah Cannon Research Institute, Nashville (H.A.B., D.Y.); University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco (H.S.R.); Novartis, East Hanover, NJ (T.S., Z.X., P.M., D.L.); Osaka University, Department of Breast and Endocrine Surgery, Osaka, Japan (S.N.); the Department of Surgery, Comprehensive Cancer Center, Medical University of Vienna, Vienna (M.G.); Sunnybrook Odette Cancer Centre and the University of Toronto, Toronto (K.I.P.); Highlands Oncology Group, Fayetteville, AR (J.T.B.); Cancer Institute Hospital of Japanese Foundation for Cancer Research, Ariake, Tokyo (Y.I.); Oncology Center, AZ Nikolass, Sint-Niklaas, Belgium (I.D.); Memorial Cancer Institute, Hollywood, FL (A.P.); Centre Léon-Bérard, Lyon, France (T.B.); Novartis Pharma, Basel, Switzerland (L.V.); and the University of Texas M.D. Anderson Cancer Center, Houston (G.N.H.). Address reprint requests to Dr. Baselga at the Division of Hematology/Oncology, Massachusetts General Hospital Cancer Center, 55 Fruit St., Lawrence House 108, Boston, MA 02114, or at jbaselga@partners.org.

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ABSTRACT

BACKGROUND

Resistance to endocrine therapy in breast cancer is associated with activation of the mammalian target of rapamycin (mTOR) intracellular signaling pathway. In early studies, the mTOR inhibitor everolimus added to endocrine therapy showed antitumor activity.

METHODS

In this phase 3, randomized trial, we compared everolimus and exemestane versus exemestane and placebo (randomly assigned in a 2:1 ratio) in 724 patients with hormone-receptor–positive advanced breast cancer who had recurrence or progression while receiving previous therapy with a nonsteroidal aromatase inhibitor in the adjuvant setting or to treat advanced disease (or both). The primary end point was progression-free survival. Secondary end points included survival, response rate, and safety. A preplanned interim analysis was performed by an independent data and safety monitoring committee after 359 progression-free survival events were observed.

RESULTS

Baseline characteristics were well balanced between the two study groups. The median age was 62 years, 56% had visceral involvement, and 84% had hormone-sensitive disease. Previous therapy included letrozole or anastrozole (100%), tamoxifen (48%), fulvestrant (16%), and chemotherapy (68%). The most common grade 3 or 4 adverse events were stomatitis (8% in the everolimus-plus-exemestane group vs. 1% in the placebo-plus-exemestane group), anemia (6% vs. <1%), dyspnea (4% vs. 1%), hyperglycemia (4% vs. <1%), fatigue (4% vs. 1%), and pneumonitis (3% vs. 0%). At the interim analysis, median progression-free survival was 6.9 months with everolimus plus exemestane and 2.8 months with placebo plus exemestane, according to assessments by local investigators (hazard ratio for progression or death, 0.43; 95% confidence interval [CI], 0.35 to 0.54; P<0.001). Median progression-free survival was 10.6 months and 4.1 months, respectively, according to central assessment (hazard ratio, 0.36; 95% CI, 0.27 to 0.47; P<0.001).

CONCLUSIONS

Everolimus combined with an aromatase inhibitor improved progression-free survival in patients with hormone-receptor–positive advanced breast cancer previously treated with nonsteroidal aromatase inhibitors. (Funded by Novartis; BOLERO-2 ClinicalTrials.gov number, NCT00863655.)

Endocrine therapy is the cornerstone of treatment for patients with hormone-receptor (HR)–positive advanced breast cancer. In postmenopausal patients, aromatase inhibitors (e.g., letrozole and anastrozole) have become the treatment of choice in first-line therapy.[1-5] Unfortunately, not all patients have a response to first-line endocrine therapy (primary or de novo resistance), and even patients who have a response will eventually relapse (acquired resistance). On disease progression, second-line treatment options include other classes of aromatase inhibitors (steroidal or nonsteroidal) and the estrogen-receptor (ER) antagonists fulvestrant and tamoxifen.[6,7]

The study of resistance to endocrine therapies in HR-positive breast cancer has aimed at identifying new therapeutic strategies that would enhance the efficacy of endocrine therapies.[8] An emerging mechanism of endocrine resistance is aberrant signaling through the phosphatidylinositol 3-kinase (PI3K)–Akt–mammalian target of rapamycin (mTOR) signaling pathway.[9-11] Growing evidence supports a close interaction between the mTOR pathway and ER signaling. A substrate of mTOR complex 1 (mTORC1), called S6 kinase 1, phosphorylates the activation function domain 1 of the ER, which is responsible for ligand-independent receptor activation.[12,13]

Everolimus (Afinitor, Novartis) is a sirolimus (formerly called rapamycin) derivative that inhibits mTOR through allosteric binding to mTORC1.[14] In preclinical models, the use of everolimus in combination with aromatase inhibitors results in synergistic inhibition of the proliferation and induction of apoptosis.[15] In a randomized, phase 2 study comparing neoadjuvant everolimus plus letrozole with letrozole alone in patients with newly diagnosed ER-positive breast cancer, the response rate for the combination was higher than that for letrozole alone.[16] The Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study reported here evaluated the efficacy and safety of the combination of everolimus and exemestane in patients with HR-positive breast cancer refractory to nonsteroidal aromatase inhibitors.

METHODS

ROLES OF THE SPONSOR AND AUTHORS

The study was designed by the academic investigators and by representatives of the sponsor, Novartis. The data were collected with the use of the sponsor's data-management systems and were analyzed by the sponsor's statistical team. All authors vouch for the accuracy and completeness of the reported data and attest that the study conformed to the protocol and statistical analysis plan, available with the full text of this article at NEJM.org. Contributions to the interpretation of data and the subsequent writing, reviewing, and amending of the manuscript were made by all authors. The first draft of the manuscript was prepared by the first and last authors and by the trial's lead physician at Novartis. No one who is not an author contributed to writing the manuscript.

PATIENTS

Eligible patients were postmenopausal women with ER-positive, human epidermal growth factor receptor type 2 (HER2)–nonamplified advanced breast cancer whose disease was refractory to previous letrozole or anastrozole, defined as recurrence during or within 12 months after the end of adjuvant treatment or progression during or within 1 month after the end of treatment for advanced disease. Letrozole or anastrozole did not have to be the most recent treatment before randomization, but recurrence or progression during receipt of the most recent systemic therapy had to be documented before randomization. Other previous anticancer endocrine treatments and a single prior chemotherapy regimen for advanced disease were also allowed.

Patients had to have at least one measurable lesion or mainly lytic bone lesions in the absence of measurable disease. Patients also had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less (on a scale from 0 to 5, with 0 indicating that the patient is fully active, 1 indicating that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, and 2 indicating that the patient is ambulatory and capable of all self-care but unable to work) and adequate organ and hematologic functions.[17] Exclusion criteria included a history of brain metastases and previous treatment with exemestane or mTOR inhibitors.

Written informed consent was obtained from all patients before enrollment. The institutional review board at each participating center approved the study, which was conducted in accordance with the principles of Good Clinical Practice, the provisions of the Declaration of Helsinki, and other applicable local regulations. A steering com-

mittee supervised the conduct of the study, and an independent data and safety monitoring committee performed semiannual safety reviews and reviewed the interim efficacy results.

STUDY DESIGN AND TREATMENT

In this international, double-blind, phase 3 study, patients were randomly assigned to treatment with oral everolimus or matching placebo (at a dose of 10 mg daily), in conjunction with exemestane (25 mg daily). Randomization, at a 2:1 ratio in favor of the everolimus–exemestane group, was stratified according to the presence of visceral metastasis and previous sensitivity to endocrine therapy. The latter was defined as at least 24 months of endocrine therapy before recurrence in the adjuvant setting or a response or stabilization for at least 24 weeks of endocrine therapy for advanced disease.

The primary end point was progression-free survival, on the basis of radiographic studies assessed by the local investigators, with central as-

Table 1. Patient and Tumor Characteristics at Baseline.*

Characteristic	Everolimus and Exemestane (N=485)	Placebo and Exemestane (N=239)
Age (yr)		
Median	62	61
Range	34–93	28–90
Race (%)†		
White	74	78
Black	3	1
Asian	20	19
Other	3	2
Disease-free interval‡		
Median (mo)	58	57
Range (mo)	1–340	5–316
<12 mo (%)	2	4
12–24 mo (%)	5	6
>24 mo (%)	56	54
No adjuvant therapy (%)	31	31
Previous sensitivity to endocrine therapy (%)	84	84
Visceral disease (%)	56	56
Measurable disease (%)§	70	68
Metastatic site (%)		
Lung	29	33
Liver	33	30
Bone	76	77
No. of metastatic sites (%)		
1	32	29
2	31	34
≥3	36	37
ECOG performance status (%)¶		
0	60	59
1	36	35
2	2	3

Table 1. (Continued.)

Characteristic	Everolimus and Exemestane (N=485)	Placebo and Exemestane (N=239)
Purpose of most recent treatment (%)		
Adjuvant therapy	21	16
Treatment of advanced or metastatic disease	79	84
Previous treatment with letrozole or anastrozole (%)	100	100
Letrozole or anastrozole as most recent treatment (%)	74	75
Previous treatment with antiestrogen (%)		
Any antiestrogen	57	59
Tamoxifen	47	49
Fulvestrant	17	16
Previous chemotherapy (%)		
Neoadjuvant or adjuvant therapy only	44	40
Treatment of metastatic disease (with or without neoadjuvant or adjuvant therapy)	26	26
No. of previous therapies (%)‖		
1	16	18
2	30	30
≥3	54	53

* There were no significant differences in baseline characteristics between the two treatment groups.
† Race was determined by self-report.
‡ Disease-free interval is defined as the time from diagnosis of breast cancer to first relapse in patients who received adjuvant therapy (308 patients in the combination-therapy group and 153 patients in the exemestane-alone group).
§ All other patients had at least one mainly lytic bone lesion.
¶ Scores for Eastern Cooperative Oncology Group (ECOG) performance status range from 0 to 5, with 0 indicating that the patient is fully active, 1 indicating that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, and 2 indicating that the patient is ambulatory and capable of all self-care but unable to work.
‖ Previous therapies include those used in the adjuvant setting or to treat advanced disease.

sessment by an independent radiology committee used in a supportive analysis. Secondary end points included overall survival, overall response rate, clinical benefit rate, time to deterioration of ECOG performance status, safety, and quality of life, with the use of the European Organization for Research and Treatment of Cancer quality-of-life core questionnaire (QLQ-C30) and the breast cancer module (QLQ-BR23). Blood levels of everolimus and plasma levels of exemestane were assessed 4 weeks after randomization (both before and 2 hours after the medications were taken) in a subgroup of 80 patients. Plasma levels of estradiol were assessed at screening or day 1 before starting trial therapy and at week 4 for the same patients.

Treatment continued until disease progression, the development of unacceptable toxicity, or withdrawal of consent. The protocol provided detailed guidelines for dose interruptions or reductions for everolimus and matched placebo for adverse events. In such cases, two reductions in the everolimus or placebo dose were permitted: an initial reduction to 5 mg daily and a subsequent reduction to 5 mg every other day.

EFFICACY AND SAFETY ASSESSMENTS

Tumor assessment included computed tomographic (CT) scanning or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis at baseline and every 6 weeks until disease progression. Patients who discontinued one or both study treatments for any reason other than progression were required to follow the same schedule of assessments until progression. All imaging studies were required to be sent for central radiologic review.

A bone scan or skeletal survey was required within 6 weeks before randomization. Abnormalities shown on bone scans were assessed by radiography, CT scanning with bone windows, or MRI before randomization and were assessed using the same method every 6 weeks. Hematologic function, biochemical measures, and vital signs were assessed at baseline and at each visit, and the lipid profile was assessed every 6 weeks. Adverse events were monitored continuously throughout the study and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.[18]

STATISTICAL ANALYSIS

The primary efficacy analysis (progression-free survival), based on local assessment, was a log-rank test stratified according to visceral metastases and previous hormone sensitivity. A total of 528 progression-free survival events were required for the final analysis, in order to detect a hazard ratio of 0.74 with 90% power with the use of a log-rank test and a two-look Lan–DeMets group-sequential design with an O'Brien–Fleming-type boundary[19] at a one-sided cumulative 2.5% level of significance. Further assuming a median progression-free survival of 3.7 months in the control group,[6] 18 months of recruitment, a 10% rate of loss to follow-up, and a 2:1 randomization ratio in favor of the everolimus–exemestane group, 705 patients were to be randomly assigned. The study had a prespecified interim analysis after the observation of approximately 60% of the progression-free survival events (the event count was 359). At the time of the interim analysis, the data and safety monitoring committee was to disclose that the trial met its primary end point only if both analyses of progression-free survival (local and central assessments) crossed the thresholds of significance, as prospectively defined in the charter of the committee.

RESULTS

PATIENTS

A total of 724 women at 189 centers in 24 countries were randomly assigned to the combination either of everolimus and exemestane (485 patients, hereafter called the combination-therapy group) or exemestane and placebo (239 patients, hereafter called the exemestane-alone group), from June 2009 through January 2011 (Fig. 1 in the Supplementary Appendix, available at NEJM.org). Baseline characteristics were well balanced. The median age was 62 years, 56% of the patients had visceral involvement, and 76% had bone metastasis. Sixty-nine percent of the patients had measurable disease, and all other patients had at least one mainly lytic bone lesion. Thirty-six percent had metastases in at least three organs. According to local assessment, all patients had ER-positive tumors, and 72% had progesterone-receptor–positive disease. All patients had HER2-negative tumors (by protein or gene analysis), except 2 for whom the result was missing. Earlier therapies included letrozole or anastrozole (100%), tamoxifen (48%), fulvestrant (16%), and chemotherapy (68%), with a median of three previous therapies. The most recent therapy before randomization was letrozole or anastrozole in 74% of the patients (Table 1). By the protocol definition, 84% of the patients had previous sensitivity to endocrine therapy.

TREATMENT

At the cutoff date (February 11, 2011), 296 patients were still receiving study treatment: 227 (47%) in the combination-therapy group and 69 (29%) in the exemestane-alone group. The median duration of exposure to everolimus was 14.6 weeks, as compared with 12.0 weeks of exposure to placebo; as for exposure to exemestane, the median duration was 17.4 weeks in the combination-therapy group versus 12.0 weeks in the exemestane-alone group. The most frequent primary reason for discontinuation was disease progression (37% in the combination-therapy group and 66% in the exemestane-alone group).

Data from the patients in the clinical pharmacology component of the trial showed that everolimus does not affect plasma concentrations of endogenous estradiol, and estradiol levels were not different between the two treatment groups (data not shown).

SAFETY

Serious adverse events, as defined in the protocol, were reported among 23% of patients in the combination-therapy group (11% attributed to study treatment) and 12% in the exemestane-alone group (1% attributed to study treatment). A higher percentage of patients discontinued everolimus in the combination-therapy group than discontinued placebo in the control group because

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