original reports

Everolimus Added to Adjuvant Endocrine Therapy in Patients With High-Risk Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Primary Breast Cancer

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abstract

PURPOSE Everolimus, an oral inhibitor of the mammalian target of rapamycin, improves progression-free survival in combination with endocrine therapy (ET) in postmenopausal women with aromatase inhibitor–resistant metastatic breast cancer. However, the benefit of adding everolimus to ET in the adjuvant setting in early breast cancer is unknown.

PATIENTS AND METHODS In this randomized double-blind phase III study, women with high-risk, hormone receptor–positive, human epidermal growth factor receptor 2–negative primary breast cancer were randomly assigned to everolimus or placebo for 2 years combined with standard ET. Stratification factors included ET agent, receipt of neoadjuvant versus adjuvant chemotherapy, progesterone receptor status, duration of ET before random assignment, and lymph node involvement. The primary end point was disease-free survival (DFS). The trial is registered with ClinicalTrials.gov (identifier: NCT01805271).

RESULTS Between June 2013 and March 2020, 1,278 patients were randomly allocated to receive everolimus or placebo. At the first interim analysis, the trial was stopped for futility and a full analysis undertaken once data snapshot complete. One hundred forty-seven patients have had a DFS event reported and at 3 years, DFS did not differ between patients who received ET plus everolimus (88% [95% CI, 85 to 91]) or ET plus placebo (89% [95% CI, 86 to 91; hazard ratio, 0.95; 95% CI, 0.69 to 1.32; $P = .77$]). Grade ≥ 3 adverse events were reported in 22.9% of patients (29.9% with everolimus *v* 15.9% with placebo, $P < .001$). 53.4% everolimus-treated patients permanently discontinued experimental treatment early compared with placebo-treated 22.3%.

CONCLUSION Among high-risk patients, everolimus added to adjuvant ET did not improve DFS. Tolerability was a concern, with more than half of patients stopping everolimus before study completion. Everolimus cannot be recommended in the adjuvant setting.

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

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INTRODUCTION

Endocrine therapy (ET) is the standard adjuvant treatment for patients with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer. However, approximately 20% of patients experience disease recurrence in the first 10 years.[1] Metastatic breast cancer is treatable but remains incurable, with a median overall survival (OS) for patients with hormone receptor–positive, HER2-negative breast cancer of about 3 years and a 5-year survival rate of 35%.[2] In the metastatic setting, combination therapies associating ET and targeted therapies have therefore emerged as new therapeutic strategies that enhance the efficacy of ET.

Dysregulation of the phosphatidylinositol-3-kinase/Akt/mammalian target of rapamycin (mTOR) pathway has been shown to be largely involved in acquired resistance to ET.[3] In combination with ET, everolimus, an oral mTOR inhibitor, improves progression-free survival for advanced and metastatic hormone receptor–positive HER2-negative breast cancer previously treated by using aromatase inhibitors (AIs).[4,5] In the phase III

CONTEXT

Key Objective

Despite current treatment, at least 20% of patients with high-risk, hormone receptor–positive and human epidermal growth factor receptor 2–negative early breast cancer will relapse within 5 years of diagnosis. The UNIRAD phase III study is the first randomized trial conducted to assess the efficacy of 2-year everolimus combined to adjuvant endocrine therapy in such patients.

Knowledge Generated

There was no difference in 3-year disease-free survival between the control arm and the everolimus arm. Toxicity was important as more than half of the patients receiving everolimus discontinued treatment because of adverse events or per personal choice, and one toxic death was reported in the everolimus arm.

Relevance

Our results do not support the addition of everolimus to conventional adjuvant endocrine therapy for patients with high-risk, hormone receptor–positive early breast cancer. Alternative treatment strategies remain a major need in this population.

BOLERO-2 trial that compared everolimus and exemestane to placebo and exemestane in 724 patients with hormone receptor–positive HER2-negative advanced breast cancer, a 4.6-month prolongation in median progression-free survival was observed (hazard ratio [HR]: 0.45; 95% CI, 0.38 to 0.54; $P < .0001$). There was, however, no improvement in OS.[4,6] In the phase II TAMRAD study that compared everolimus and tamoxifen to tamoxifen alone in 111 patients with hormone receptor–positive HER2-negative AI-resistant metastatic breast cancer, the 6-month clinical benefit rate was 61% (95% CI, 47 to 74) with tamoxifen plus everolimus versus 42% (95% CI, 29 to 56) with tamoxifen alone, and time to progression increased from 4.5 months with tamoxifen alone to 8.6 months with tamoxifen plus everolimus.[5] However, the benefit of adding everolimus to ET in the adjuvant setting in early breast cancer is unknown.

In this double-blind, multicenter, international randomized trial, we aimed to compare the combination of adjuvant everolimus plus standard adjuvant ET to placebo plus ET in women with high-risk hormone receptor–positive HER2-negative early breast cancer (ClinicalTrials.gov identifier: NCT01805271).

PATIENTS AND METHODS

Patients

Eligible patients were women age 18 years or older with estrogen receptor–positive HER2-negative early breast cancer at high risk of relapse, defined as ≥ 4 positive lymph nodes, and ≥ 1 positive lymph node if surgery was performed after neoadjuvant chemotherapy or ET administered for ≥ 3 months; or 1-3 positive lymph nodes at primary surgery and an EndoPredict (EPclin) score ≥ 3.3.[7] Patients had to have their primary tumor completely resected, with no clinically or radiologically detectable metastases at the time of inclusion. Inclusion criteria were initially limited to patients who had already received between 2.5 and 3.5 years of adjuvant ET, but were extended a year later to all patients who had received ET for at least 1 year and up to 4 years of ET, because of low inclusion rate. In 2017, the Protocol (online only) was amended to authorize initiation of the study treatment at the same time as ET and up to 4 years from its beginning. Patients also had to have an Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate hematologic, hepatic, and renal functions. Exclusion criteria included previous cancer ≤ 5 years before study entry, except basal cell carcinoma of the skin or in situ carcinoma of the cervix, significantly impaired lung function, known hypersensitivity to mTOR inhibitors, and any uncontrolled medical conditions.

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. The study was approved by the French medicines agency (ANSM—Agence National de Sécurité du médicament des produits de santé), by an ethics committee (Comité de Protection des Personnes Sud-Est IV—Lyon) in September 2012, and by institutional review boards of each participating center. A steering committee supervised the study, and an independent data monitoring committee met every year and was responsible for monitoring safety and efficacy in the trial participants.

Study Design and Treatment

Patients were randomly assigned in a 1:1 ratio to receive 2 years of placebo or 2 years of everolimus, added to ongoing ET. Patients were assigned to one of two treatment arms on the basis of a dynamic randomization method by minimization according to Pocock and Simon algorithm. Random assignment was stratified by ET agent (tamoxifen ± luteinizing hormone-releasing hormone agonists *v* AI), previous adjuvant versus neoadjuvant chemotherapy or ET, progesterone receptor status (positive *v*

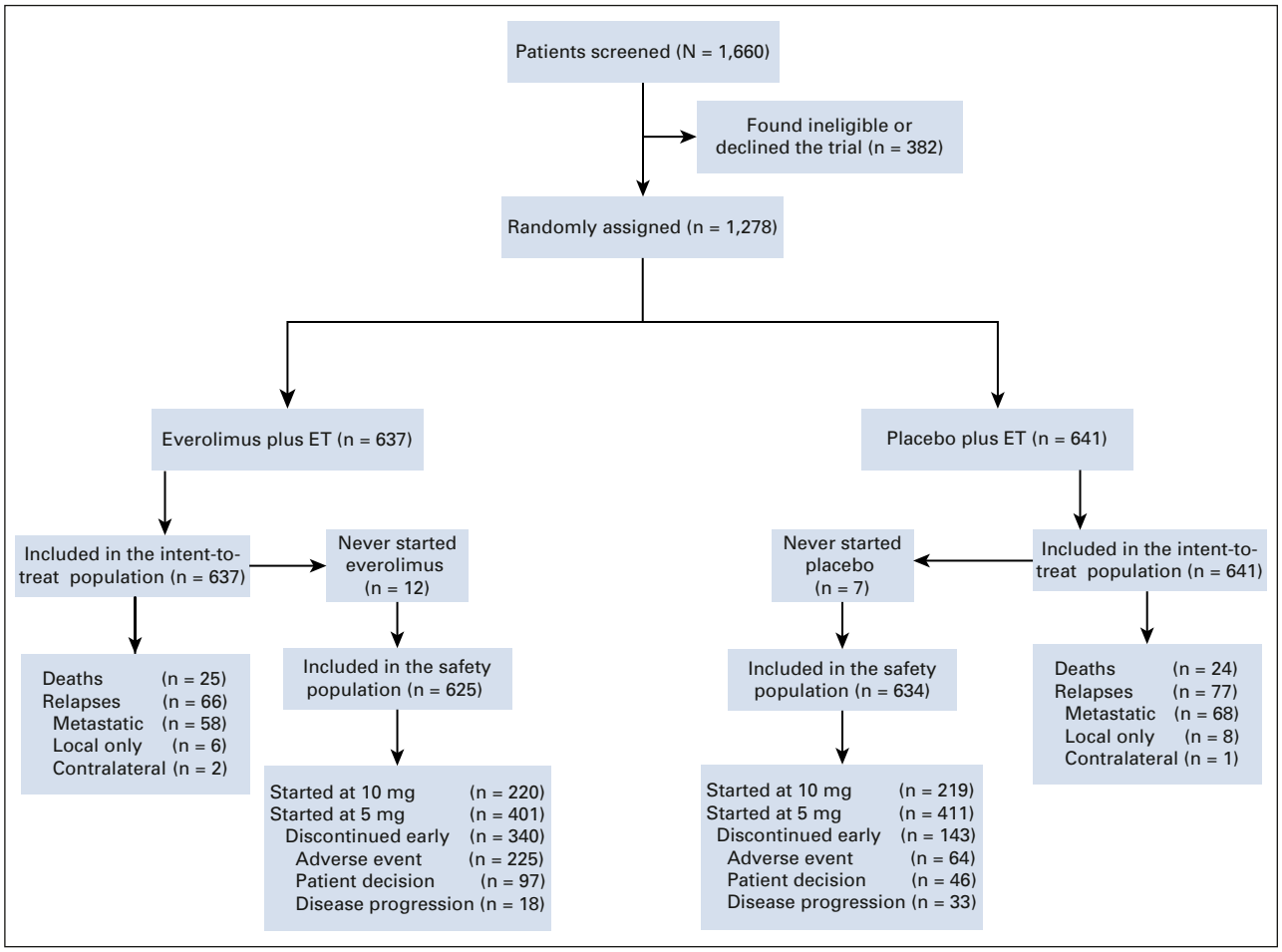

FIG 1. CONSORT diagram. ET, endocrine therapy.

negative), duration of ET (≤ 3 years *v* > 3 years), and lymph node involvement (≥ 4 positive lymph nodes and ≥ 1 positive lymph node after neoadjuvant setting *v* 1-3 positive lymph nodes and high EPclin score).

Everolimus was initially administered at 10 mg once a day. Two years into the trial, toxicity appeared to be a significant problem, and the protocol was amended to allow the starting dose at 5 mg once a day with the possibility to increase to 10 mg once a day between the first month and the third month depending on toxicity so far observed. Patients were to be treated by everolimus/placebo for a maximum of two years. In case of grade 2 or 3 toxicity, treatment was stopped until toxicity was resolved and resumed at 5 mg once a day (if started at 10 mg once a day) or 5 mg once every 2 days (if started at 5 mg once a day). In case of reoccurrence of grade 2 or 3 toxicity, treatment was interrupted and resumed at 5 mg once every 2 days for patients who were receiving 5 mg once a day and permanently discontinued for those who were receiving 5 mg once every 2 days. At third occurrence, treatment was permanently discontinued. Patients were closely monitored for drug-related toxicity with the addition, from April 2013, of follow-up visits and phone calls, to allow for earlier detection of adverse events. Detailed toxicities management was based on the Summary of Product Characteristics for Everolimus and systematically updated with each new version available.

The primary end point was disease-free survival (DFS), measured from the date of random assignment. DFS events were defined as invasive local, regional, or metastatic relapse, contralateral breast cancer, or death from any cause. New second cancers of nonbreast origin were not taken into account. Preplanned subgroup analysis was performed on the stratification factors. Secondary end points included OS, event-free survival, distant metastasis-free survival, second malignancies, and toxicity.

Statistical Analysis

To detect a difference of 3% in the 2-year DFS (90% *v* 93%; HR, 0.7), 1,984 patients were to be randomly assigned (992 in each treatment group) with 286 events required for the final analysis (85% power, two-sided test [log-rank test], and a significance level of 5%). Two interim analyses were planned after 95 (efficacy and futility) and 191 events (efficacy). All efficacy data were summarized and analyzed in the intention-to-treat population, which included all the patients who had

TABLE 1. Baseline Patient Characteristics

Characteristic	Treatment Arm		
	Placebo and ET (n = 641)	Everolimus and ET (n = 637)	All Patients (N = 1,278)
Age, years			
Median (min; max)	53.5	53.8	53.7
IQR (Q1-Q3)	48.3-62.7	47.8-62.6	48.1-62.7
Missing	2	0	2
ECOG performance status			
0	560 (89.2)	564 (89.8)	1,124 (89.5)
1	68 (10.8)	64 (10.2)	132 (10.5)
Missing	13	9	22
Menopausal status			
Premenopausal	200 (31.2)	204 (32)	117 (9.2)
Postmenopausal	419 (65.6)	419 (66.0)	838 (65.8)
Unknown	20 (3.1)	12 (1.9)	32 (2.5)
Missing	2	2	4
Pathologic tumor size			
pT1	171 (26.9)	191 (30.1)	362 (28.6)
pT2	308 (48.6)	324 (51.2)	632 (49.9)
pT3	137 (21.6)	102 (16.1)	239 (18.9)
pT4	15 (2.4)	13 (2.1)	28 (2.2)
Missing	10	7	17
Lymph node involvement			
≥ 4 N+	328 (52)	335 (53.3)	663 (52.7)
1-3 N+ after neoadjuvant treatment	85 (13.2)	85 (13.3)	170 (13.3)
1-3 N+ and EPclin score ≥ 3.3	208 (32.4)	204 (32)	412 (32.2)
Histologic grade			
1	43 (6.8)	50 (7.9)	93 (7.3)
2	375 (59.1)	370 (58.3)	745 (58.7)
3	191 (30.1)	189 (29.8)	380 (29.9)
Unknown	26 (4.1)	26 (4.1)	52 (4.1)
Missing	6	2	8
IHC subtypes			
ER+/PR+	537 (85.6)	529 (84.4)	1,066 (85)
ER+/PR–	90 (14.4)	98 (15.6)	188 (15)
Missing	14	10	24
Adjuvant or neoadjuvant treatment			
Neoadjuvant chemotherapy	156 (25.0)	135 (22.1)	291 (23.6)
Adjuvant chemotherapy	476 (76.3)	479 (78.4)	955 (77.3)
ET	14 (2.2)	18 (2.9)	32 (2.6)
Radiotherapy	616 (97.2)	620 (97.8)	1,236 (97.5)
ET agent			
Tamoxifen	279 (44.2)	266 (42.9)	545 (43.6)
Letrozole	197 (31.2)	200 (32.3)	397 (31.7)
Anastrozole	115 (18.2)	121 (19.5)	236 (18.9)

(continued on following page)

TABLE 1. Baseline Patient Characteristics (continued)

Characteristic	Treatment Arm		
	Placebo and ET (n = 641)	Everolimus and ET (n = 637)	All Patients (N = 1,278)
Exemestane	39 (6.2)	28 (4.5)	67 (5.4)
Other	1 (0.2)	5 (0.8)	6 (0.5)
Missing	10	17	27
ET duration at random assignment, months			
No.	631	621	1,252
Median (min; max)	14.6 (–1.6; 52.6)	15.2 (–9.9; 57.3)	14.8 (–9.9; 57.3)
IQR (Q1-Q3)	4.9-28.9	4.9-30.3	4.9-29.9
0-1 year of ET	278 (44.0)	262 (42.2)	540 (43.1)
2-3 years of ET	261 (41.3)	265 (42.7)	526 (42.0)
More than 3 years	92 (14.6)	94 (15.1)	186 (14.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EPclin score, EndoPredict score; ER, estrogen receptor; ET, endocrine therapy; IHC, immunohistochemistry; IQR, interquartile range; N, node; PR, progesterone receptor.

undergone random assignment, regardless of the intervention received. Safety data were summarized in the safety analysis set (all patients who received at least one dose of everolimus or placebo).

The Kaplan-Meier method was used to estimate DFS and 3-year event rates. The HR and associated 95% CI were calculated with the use of a Cox proportional-hazards model. A preplanned DFS analysis was performed in stratification subgroups for which HR and 95% CI were calculated by using the Cox model. Analyses of secondary efficacy end points used a method similar to that used in the DFS analysis.

Futility rules at the interim analysis were calculated on the basis of the information fraction observed at this time (ratio between the number of events observed at the time of the

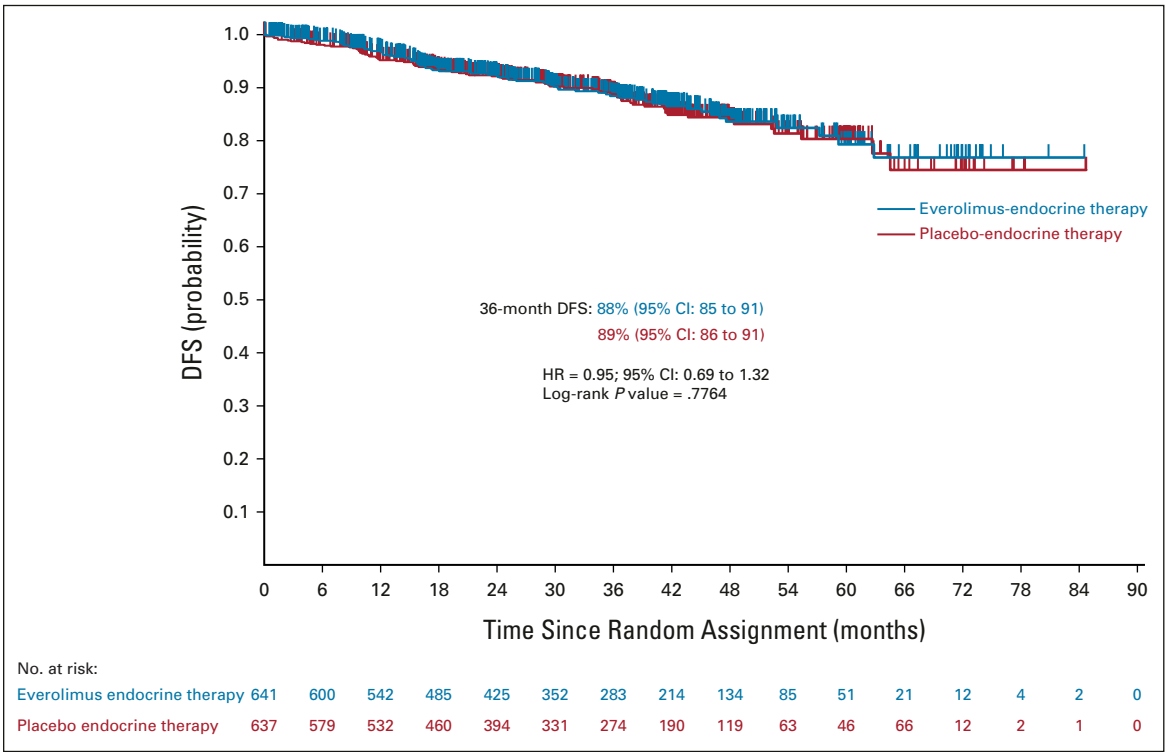

FIG 2. DFS. DFS, disease-free survival; HR, hazard ratio.

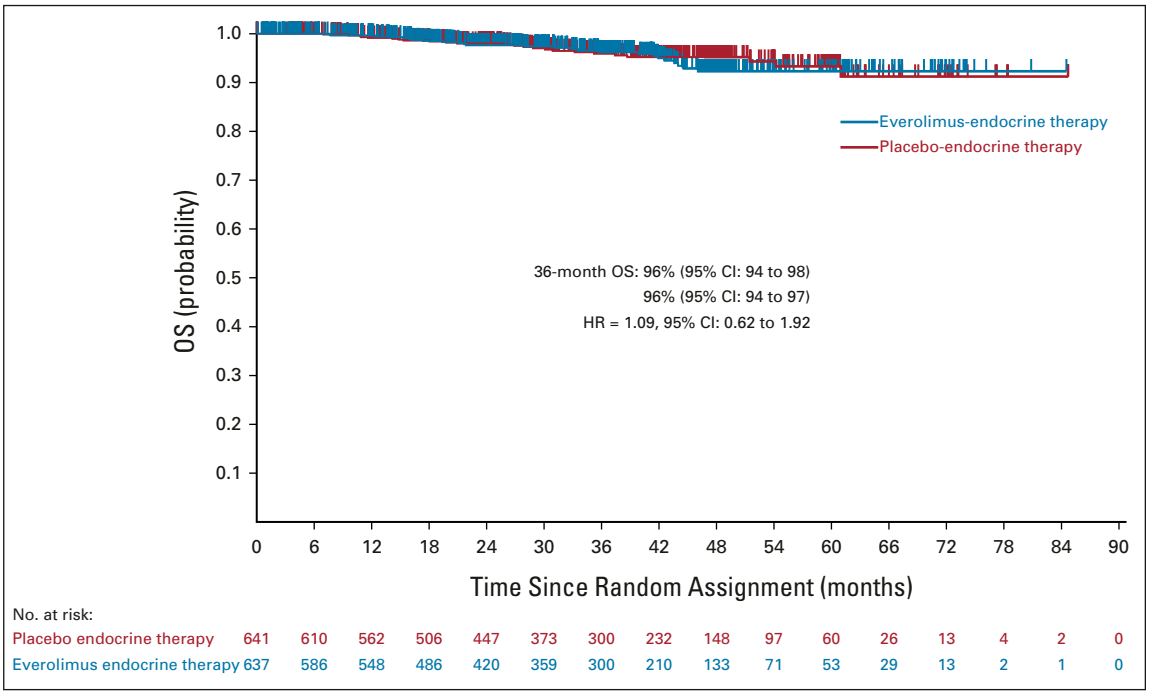

FIG 3. OS. HR, hazard ratio; OS, overall survival.

interim analysis and the total number of events required for the final analysis). For the first interim analysis, futility was to be declared if the HR estimate was above 0.962.

RESULTS

Patients and Treatment

A total of 1,278 patients were randomly assigned between June 2013 and March 2020 in 72 centers in France,United Kingdom, and Belgium, to receive everolimus (n = 637) or placebo (n = 641; Fig 1). Baseline characteristics were well balanced between the two treatment groups (Table 1). Median age was 54 years (interquartile range [IQR], 48-63), 90% of patients had an Eastern Cooperative Oncology Group performance score 0, and 66% were postmenopausal. At random assignment, median ET treatment duration was 15 months (IQR, 4.9-29.9). The most frequent ETs were tamoxifen (44%), letrozole (32%) and anastrozole (19%). Only seven patients (0.5%) received a luteinizing hormone-releasing hormone agonist in combination with tamoxifen or an AI.

Thirty-four percent (n = 439) of patients initiated everolimus/placebo at 10 mg and 64% (n = 812) started at 5 mg. Of the remaining 2%, one patient started at 2.5 mg, 19 did not take the treatment, and seven had missing data. Median everolimus/placebo treatment duration was 16.1 months (IQR, 4.4-23.8), the treatment being shorter in those allocated everolimus (9.2 months; IQR, 2.1-23.4) than placebo (22.5 months; IQR, 9.7-23.9). Dose reduction occurred in 22.9% (n = 293) of patients (34.2% allocated everolimus *v* 11.7% allocated placebo, Fisher's exact test $P < .001$). Among the patients who started at 10 mg/day (n = 439), at least one dose reduction occurred in 46.8% (103/220) of patients allocated everolimus, compared with 11.0% (24/219) in the placebo group. Among those who started at 5 mg/day (n = 812), at least one dose reduction occurred in 28.4% (114/401) of patients allocated everolimus, compared with 12.4% (51/411) in the placebo group. Thirty-eight percent of patients permanently discontinued treatment early: 53.4% (n = 340) of those allocated everolimus, compared with 22.3% (n = 143) in the placebo group. The main reasons for discontinuation were adverse events (35.3% everolimus *v* 10.0% placebo), patient decision (15.2% *v* 7.2%), and disease progression (2.8 *v* 5.1%). Of interest, within the everolimus group, patients receiving tamoxifen as ET agent had a longer median everolimus treatment duration (12.8 months; IQR, 2.7-23.6) than those receiving AI (7.7 months; IQR, 1.9-22.6; log-rank $P = .007$). No similar difference was observed for the patients receiving placebo with either ET backbone (median duration on placebo 23.2 months; IQR, 10.7-23.9 *v* 21.1 months; IQR, 8.5-23.9 for patients receiving tamoxifen or AI).

Efficacy

The number of DFS events to trigger the first interim analysis was reached in 2019, and the database was cleaned and locked on December 3, 2019. At that time point, 122 DFS events were notified on 1,249 randomly assigned patients. This analysis showed a HR of 1.08 (95% CI, 0.76 to 1.54), above the predefined threshold for concluding futility. The independent data monitoring

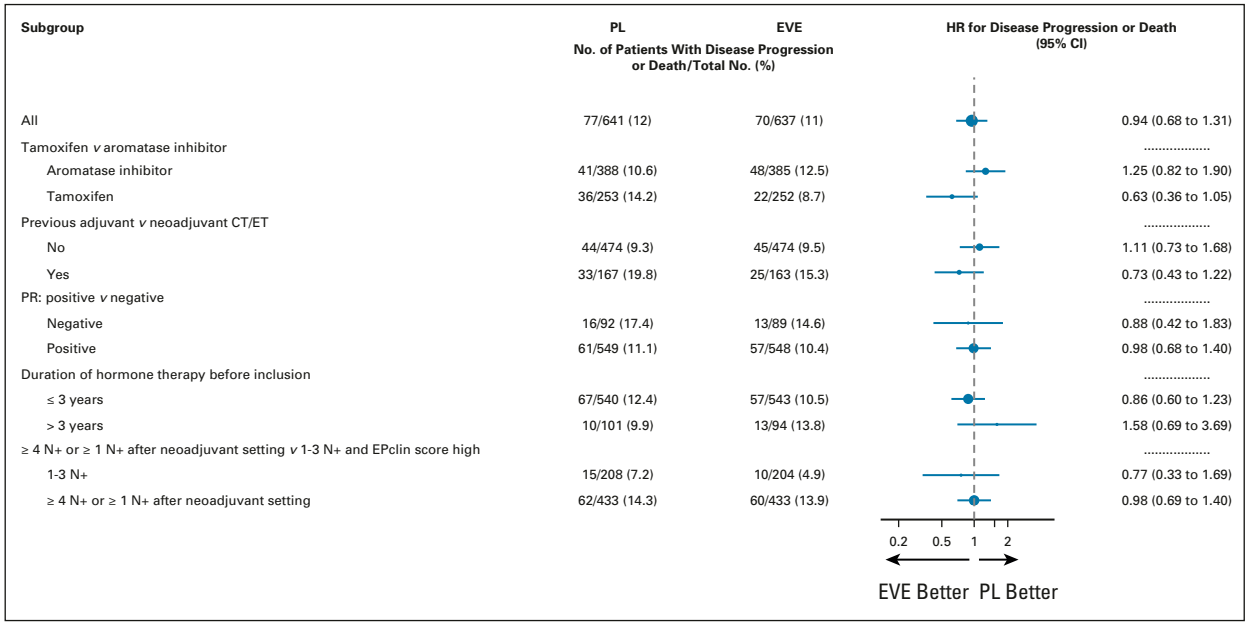

FIG 4. Forest plot of HRs for DFS according to stratification factors. CT, chemotherapy; DFS, disease-free survival; EPclin score, EndoPredict score; ET, endocrine therapy; EVE, Everolimus arm; HR, hazard ratio; N, node; PL, Placebo arm; PR, progesterone receptor.

committee met on February 19, 2020, and, on the basis of the futility analysis results, coupled with other features of the trial, including accrual duration, treatment exposure, and adverse events, recommended stopping inclusions and experimental treatment for futility, which was validated by the steering committee on March 2, 2020. Message was sent to stop the inclusions and experimental treatment for the 238 patients still on study on March 4, 2020. A letter to patients was sent to sites on March 16, 2020. The database for the current analysis was locked on November 16, 2020. For the current analysis, median follow-up was 35.7 months (range, 0.7-85 months; IQR, 19.9-47.4). A total of 147 DFS events were recorded (143 recurrences and 4 deaths before relapse). No difference was observed in 3-year DFS between the two groups: 88% (95% CI, 85 to 91) in those allocated everolimus and 89% (95% CI, 86 to 91) in the placebo group (HR, 0.95; 95% CI, 0.69 to 1.32; log-rank $P = .77$; Fig 2). A total of 49 deaths were reported, no difference was observed in 3-year OS (96%: 95% CI, 94 to 98 in those allocated everolimus *v* 96%: 95% CI, 94 to 97 in the placebo group; HR, 1.09; 95% CI, 0.62 to 1.92; $P = .75$; Fig 3), and similar results were observed with the other secondary efficacy end points (Appendix Fig A1, online only).

In a preplanned subgroup analysis of DFS benefit, effects in each subgroup were consistent with the overall HR estimate. There was some suggestion of heterogeneity of estimates of effect between those treated on tamoxifen versus AI backbone ($P = .044$; Fig 4). For the subgroup of patients receiving tamoxifen, 3-year DFS was 91% (95% CI, 86 to 94) in the everolimus arm and 86% (95% CI, 81 to 90) in the placebo arm (HR, 0.62; 95% CI, 0.37 to 1.06). For the subgroup of patients on AI, 3-year DFS was 87% (95% CI, 82 to 90) in the everolimus arm versus 91% (95% CI, 87 to 93) in the placebo arm (HR, 1.25; 95% CI, 0.83 to 1.90; Appendix Fig A2, online only). However, different biology of premenopausal versus postmenopausal patients could have been a confounding factor in this analysis.

Safety

Safety analysis was performed on patients who took at least one dose of study treatment (n = 1,259; Fig 1). Ninety-seven percent of patients had at least one adverse event (98.1% in those allocated everolimus *v* 96.5% in the placebo group). Grade ≥ 3 adverse events were reported among 22.9% (n = 288) of patients (29.9% in the everolimus-treated group *v* 15.9% in the placebo group, $P < .001$; Table 2). Serious adverse events were reported among 10.6% (n = 133) of patients (11.8% in the everolimus-treated group *v* 9.3% in the placebo group, $P = .144$). Among the patients who started at 10 mg/day, grade ≥ 3 adverse events were reported among 38.2% (n = 84) everolimus-treated patients, compared with15.5% (n = 34) in the placebo group (chi-square test, $P < .001$). Among those who started at 5 mg/day, grade ≥ 3 adverse events occurred in 25.4% (n = 102) of everolimus-treated patients, compared with 16.1% (n = 66) in the placebo group (chi-square test, $P < .001$). In 243 patients (19.3%), grade ≥ 3 adverse events led to treatment withdrawal (29.6% in everolimus group *v* 9.1% in placebo group, $P < .001$). One treatment related death (0.2%) was attributed to everolimus (septic shock because of streptococcus septicemia in a patient who was treated at 10 mg/day).

The most common grade 3 or 4 adverse events were oral mucositis (7.4% in the everolimus-treated group *v* 0.3% in

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

	Placebo and ET (n = 634)		Everolimus and ET (n = 625)	
Adverse Events	**Any Grade, No. (%)**	**Grade ≥ 3, No. (%)**	**Any Grade, No. (%)**	**Grade ≥ 3, No. (%)**
Oral mucositis	206 (32.5)	2 (0.3)	417 (66.7)	46 (7.4)
Fatigue	305 (48.1)	8 (1.3)	339 (54.2)	12 (1.9)
High cholesterol	163 (25.7)	0 (0.0)	219 (35.0)	5 (0.8)
Cough	156 (24.6)	1 (0.2)	202 (32.3)	1 (0.2)
Hypertriglyceridemia	100 (15.8)	1 (0.2)	195 (31.2)	19 (3.0)
Rash	71 (11.2)	0 (0.0)	183 (29.3)	3 (0.5)
Hepatic ALT/AST/GGT increase	122 (19.2)	11 (1.7)	179 (28.6)	14 (2.2)
Diarrhea	127 (20.0)	2 (0.3)	161 (25.8)	6 (1.0)
Headache	89 (14.0)	1 (0.2)	136 (21.8)	1 (0.2)
Lymphocyte count decreased	86 (13.6)	4 (0.6)	130 (20.8)	6 (1.0)
Nausea	129 (20.3)	3 (0.5)	129 (20.6)	2 (0.3)
Dyspnea	78 (12.3)	1 (0.2)	116 (18.6)	2 (0.3)
Neutrophil count decreased	36 (5.7)	3 (0.5)	114 (18.2)	5 (0.8)
Dry skin	57 (9.0)	0 (0.0)	113 (18.1)	0 (0.0)
Hyperglycemia	68 (10.7)	1 (0.2)	112 (17.9)	9 (1.4)
Anemia	34 (5.4)	0 (0.0)	108 (17.3)	0 (0.0)
Arthralgia	182 (28.7)	1 (0.2)	107 (17.1)	2 (0.3)
Dysgeusia	31 (4.9)	0 (0.0)	90 (14.4)	1 (0.2)
Hot flashes	163 (25.7)	2 (0.3)	86 (13.8)	1 (0.2)
Limb edema	20 (3.2)	0 (0.0)	75 (12.0)	2 (0.3)
Pain	87 (13.7)	2 (0.3)	75 (12.0)	2 (0.3)
Anorexia	32 (5.0)	1 (0.2)	67 (10.7)	1 (0.2)
Skin infection	35 (5.5)	1 (0.2)	66 (10.6)	1 (0.2)
Pruritus	37 (5.8)	1 (0.2)	65 (10.4)	0 (0.0)
Lymphedema	35 (5.5)	1 (0.2)	63 (10.1)	1 (0.2)

Abbreviations: ET, endocrine therapy; GGT, gamma-glutamyl transferase.

the placebo group), hypertriglyceridemia (3.0% *v* 0.2%), hepatic alanine aminotransferase/aspartate aminotransferase/gamma-glutamyl transferase increase (2.2% *v* 1.7%), fatigue (1.9% *v* 1.3%), and hyperglycemia (1.4% *v* 0.2%; Table 2).

DISCUSSION

After a median of three years of follow-up of 1,278 patients with high-risk early breast cancer, no evidence was observed to suggest that everolimus given in combination with adjuvant ET improved DFS compared with ET alone. Insufficient drug exposure and inadequate biological activity in this specific situation could have contributed to this failure to detect benefit in early breast cancer when everolimus is clearly active in metastatic disease.

Despite our requirement for patient monitoring and investigators awareness, 50% of patients stopped everolimus before study completion for toxicities or because of personal decisions, and one patient died of septicemia while receiving everolimus. Consistent with previous reports, the most common grade ≥ 3 adverse event was oral mucositis, observed in 7.4% of patients treated with everolimus-ET.[4,5] BOLERO-II study reported a high discontinuation rate (29% because of adverse events with everolimus *v* 5% with placebo).[6] In the current study, an even higher percentage of patients in the everolimus-treated group stopped treatment early because of adverse events (35.3%). The limited options available to patients in the metastatic setting may explain the difference in patient acceptability faced with similar toxicities. More precise treatment guidelines for common toxicities could have potentially reduced the adverse events rates as well as treatment discontinuation rate. For instance, in 2017, dexamethasone mouthwashes were shown to reduce the risk of stomatitis.[8] Above all, we could not prevent the occurrence of a fatal event that was likely related to the experimental treatment. Everolimus has been linked to fatal events in the metastatic setting, with rates up to 0.7% in a

meta-analysis.[9] At the time of initiation of UNIRAD, few data were available for patients in the adjuvant setting and we expected this risk to be controllable for this selected and disease-free population. Indeed, in 2009, Baselga et al[10] did not report any toxic death for 138 patients treated with neoadjuvant everolimus. In our study, 1 of 625 patients (0.16%) exposed to everolimus experienced a toxic fatal event, which is in line with what is reported for standard adjuvant chemotherapy (68 among 34,882 patients, 0.19%, in the Cochrane analysis of taxanes for adjuvant treatment of early breast cancer).[11] Nevertheless, our data also demonstrate that everolimus may increase the risk of toxic death despite stringent patient's selection and toxicity management awareness.

It is possible that everolimus may not be sufficiently effective to reverse early resistance to AI in the adjuvant setting. In fact, most patients included in randomized studies that showed its efficacy in the metastatic setting had secondary endocrine resistance.[5,6] UNIRAD was stopped early for futility at the first interim analysis, and, as a consequence, we cannot rule out a better efficacy of everolimus for preventing late recurrences. Furthermore, although random assignment was initially limited to patients who had already received between 2.5 and 3.5 years of adjuvant ET, it was subsequently broadened, because of poor recruitment, to 0-4 years of ET, meaning that patients were coming into the trial at varied time points since completion of their primary therapy. This further added a degree of heterogeneity in terms of tumor biology and hormone resistance mechanism. Nevertheless, in the preplanned subgroup analysis, there was no interaction between time on ET before inclusion (more or less than 3 years) and everolimus efficacy.

The DFS analysis showed that 11% of patients of this high-risk population who received standard adjuvant chemotherapy and ET had already relapsed at 3-year follow-up, and the projected 5-year DFS is no more than 80%. This indicates the importance of identifying new agents added to ET in such patients. Following demonstrated efficacy and safety in the metastatic setting,[12-14] studies have been conducted in hormone receptor–positive HER2-negative high-risk early breast cancer combining CDK4/6 inhibitors and ET in the adjuvant setting. The PALLAS trial that compared palbociclib plus ET to ET alone in patients with hormone receptor–positive stage II-III HER2-negative early breast cancer was stopped early for futility.[15] As with UNIRAD, the benefits observed in the metastatic setting were not seen in the adjuvant setting with palbociclib. Of interest, there is high similarity between the populations included in PALLAS and UNIRAD (3-year DFS of 88.5% for the placebo arm of PALLAS, *v* 89% for UNIRAD) and with respect to experimental treatment discontinuation for toxicities/patient decision (42% for PALLAS *v* 48% for UNIRAD).[15] By contrast, in the MonarchE trial that randomly assigned 5,637 patients to receive abemaciclib plus ET, or ET alone, the risk of developing an invasive DFS event was reduced by 29% in the abemaciclib arm.[16] Of note, the MonarchE study population had an even poorer prognosis than the one included in our study. Indeed, the 2-year DFS in the placebo group was 88.7%, equivalent to the 3-year DFS of the UNIRAD population (89%). Furthermore, only 17% of patients in the abemaciclib plus ET group discontinued treatment because of adverse events, as most patients who required dose reduction or interruption because of adverse events remained on treatment.

In summary, to our knowledge, this first phase III clinical trial of adjuvant everolimus in combination to standard hormone therapy for patients with estrogen receptor–positive, HER2-negative early breast cancer failed to show improvement in DFS and was stopped after the initial interim analysis for futility. Added toxicity was significant, and early treatment discontinuation may be in part responsible for the lack of observed benefit. Follow-up will continue to evaluate long-term outcomes. At the present time, everolimus cannot be recommended in the adjuvant setting.

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Everolimus Added to Adjuvant Endocrine Therapy in Patients With High-Risk Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Primary Breast Cancer

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APPENDIX

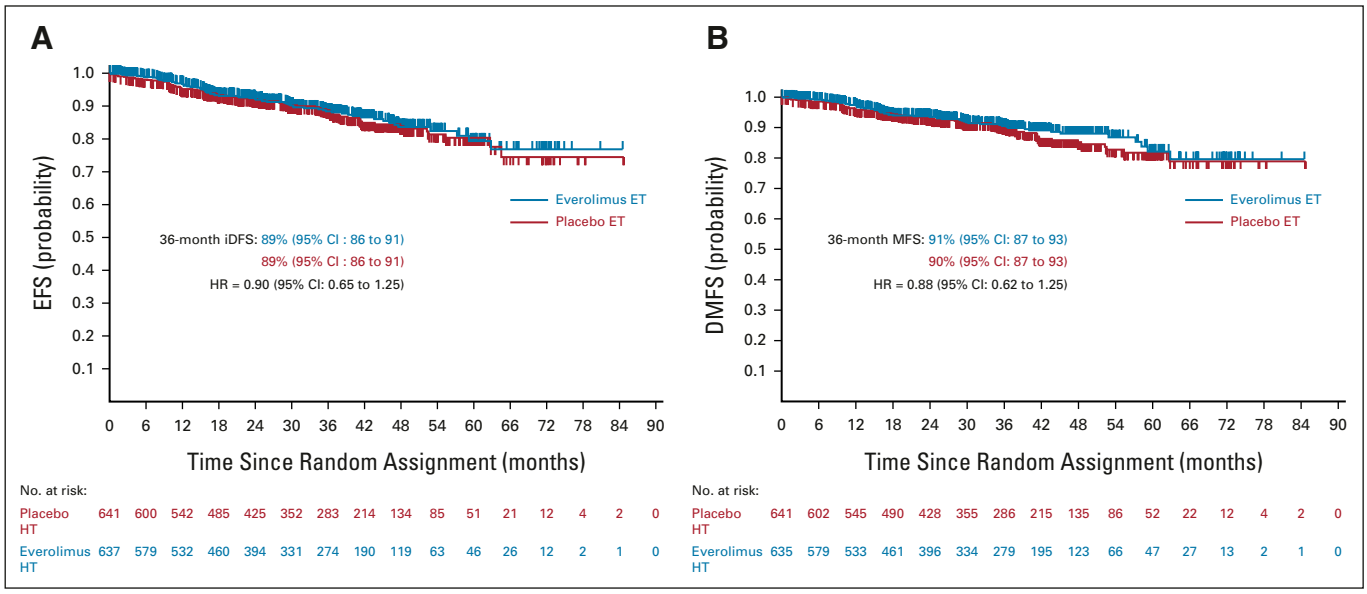

FIG A1. (A) EFS and (B) DMFS. DMFS, distant metastasis-free survival; EFS, event-free survival; ET, endocrine therapy; iDFS, invasive disease-free survival; MFS, metastasis-free survival.

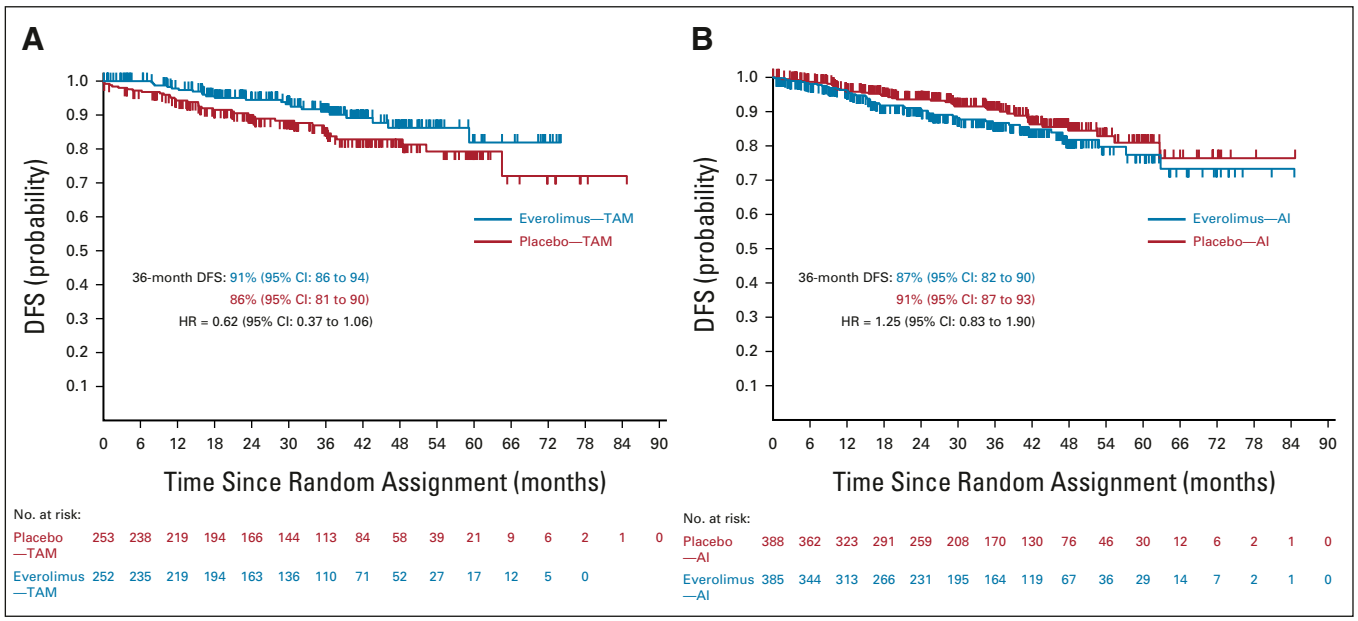

FIG A2. Subgroup analysis on hormone therapy backbone: (A) DFS on everolimus and placebo in the tamoxifen subgroup, and (B) DFS on everolimus and placebo in the AI subgroup. AI, aromatase inhibitor; DFS, disease-free survival; HR, hazard ratio; TAM, tamoxifen.