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ORIGINAL REPORT

Randomized Phase III Placebo-Controlled Trial of Letrozole Plus Oral Temsirolimus As First-Line Endocrine Therapy in Postmenopausal Women With Locally Advanced or Metastatic Breast Cancer

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A B S T R A C T

Purpose

Recent data showed improvement in progression-free survival (PFS) when adding everolimus to exemestane in patients with advanced breast cancer experiencing recurrence/progression after nonsteroidal aromatase inhibitor (AI) therapy. Here, we report clinical outcomes of combining the mammalian target of rapamycin (mTOR) inhibitor temsirolimus with letrozole in AI-naive patients.

Patients and Methods

This phase III randomized placebo-controlled study tested efficacy/safety of first-line oral letrozole 2.5 mg daily/temsirolimus 30 mg daily (5 days every 2 weeks) versus letrozole/placebo in 1,112 patients with AI-naive, hormone receptor–positive advanced disease. An independent data monitoring committee recommended study termination for futility at the second preplanned interim analysis (382 PFS events).

Results

Patients were balanced (median age, 63 years; 10% stage III, 40% had received adjuvant endocrine therapy). Those on letrozole/temsirolimus experienced more grade 3 to 4 events (37% *v* 24%). There was no overall improvement in primary end point PFS (median, 9 months; hazard ratio [HR], 0.90; 95% CI, 0.76 to 1.07; $P = .25$) nor in the 40% patient subset with prior adjuvant endocrine therapy. An exploratory analysis showed improved PFS favoring letrozole/temsirolimus in patients ≤ age 65 years (9.0 *v* 5.6 months; HR, 0.75; 95% CI, 0.60 to 0.93; $P = .009$), which was separately examined by an exploratory analysis of 5-month PFS using subpopulation treatment effect pattern plot methodology ($P = .003$).

Conclusion

Adding temsirolimus to letrozole did not improve PFS as first-line therapy in patients with AI-naive advanced breast cancer. Exploratory analyses of benefit in younger postmenopausal patients require external confirmation.

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INTRODUCTION

The selective estrogen receptor (ER) modulator tamoxifen has been the primary choice for treating ER-positive metastatic breast cancer (MBC), but ultimately most patients have disease progression.[1,2] Aromatase inhibitors (AIs), like the nonsteroidal inhibitor letrozole, significantly inhibit estrogen biosynthesis[3] and improve clinical outcomes at least temporarily.[4,5] Endocrine responsiveness may be lost by upregulating proliferation/survival signal transduction pathways, like upstream signaling transmembrane growth factor receptors such as the human epidermal growth factor receptor 2 (HER2)[6] and downstream intracellular signaling such as the PI3K/Akt/mammalian target of rapamycin (mTOR) pathways.[7,8] Modulation of these pathways may circumvent resistance mechanisms when combined with antiestrogens.[6,9-13]

Temsirolimus, an inhibitor of mTOR, has clinical activity as intravenous (IV) monotherapy in heavily pretreated locally advanced breast

cancer or MBC.[14] In a randomized phase II study in postmenopausal women,[9] an intermittent 30-mg oral temsirolimus schedule (daily for 5 days every 2 weeks) added to daily oral letrozole 2.5 mg was safe and reached desired blood levels with a slightly higher mean relative dose-intensity than with a 10-mg daily temsirolimus schedule. Here, we report a prospective phase III study (HORIZON) testing the efficacy/safety of adding temsirolimus to letrozole in postmenopausal women with ER-positive and/or progesterone receptor (PR) –positive (hereon described just as ER-positive) locally advanced breast cancer or MBC with no prior exposure to AIs.

PATIENTS AND METHODS

Study Design

In this multinational, randomized, double-blind phase III study of letrozole/temsirolimus or letrozole/placebo, patients were stratified by geography (United States; Western Europe, Australia, New Zealand, India, and Canada; or Asia-Pacific, Eastern Europe, Africa, and South America) and according to presence or absence of bone metastasis. Patients were randomly assigned (1:1) to letrozole 2.5 mg once daily continuously plus oral temsirolimus 30 mg or placebo once daily for 5 days every 2 weeks (one cycle). Treatment was stopped in the event of excessive toxicity or disease progression.

The study was designed by the sponsor (Wyeth) and representatives of the academic investigators. Data were collected by the sponsor's data management team and initially analyzed by the sponsor's statistical team. A medical writer contributed to the first manuscript draft. A separate independent statistical review was recommended by the academic first and last authors of this article, who then prepared all subsequent drafts aided by the statistician coauthors. All coauthors made additional contributions to the interpretation of the data and subsequent editing. No one else contributed to the manuscript.

Eligibility Criteria

Patients had histologically and/or cytologically confirmed ER-positive breast cancer with evidence of locally advanced or metastatic disease (stage IIIB/C or IV) and one or more measurable lesions by Response Evaluation Criteria in Solid Tumors (RECIST).[15] Baseline ER/PR status (and HER2 expression status, when available) was based on local testing of the most recently analyzed tissue. Patients were ineligible if they had prior adjuvant AI within 12 months before study day 1, if disease recurrence occurred during the first 6 months of adjuvant endocrine therapy, or if prior endocrine therapy (including AIs) was administered for locally advanced/MBC. Patients must have been $\geq$ 18 years old, had a Karnofsky performance status $\geq$ 60, life expectancy $\geq$ 6 months, and have been postmenopausal (ie, age $\geq$ 60 years, age $<$ 60 and amenorrheic for $\geq$ 12 months, age $<$ 60 and amenorrheic for $<$ 12 months before day 1 if luteinizing hormone/follicle-stimulating hormone values within menopausal range assuming no use of drugs that affect luteinizing hormone/follicle-stimulating hormone values, and/or prior bilateral oophorectomy or radiation castration with subsequent amenorrhea for $\geq$ 6 months). Baseline labs required absolute neutrophil count (ANC) $\geq$ 1,500/μL, platelet count $\geq$ 100,000/μL ($\geq$ 80,000/μL in patients in China), hemoglobin $\geq$ 8.0 g/dL, serum creatinine $\leq$ 1.5$\times$ upper limit of normal (ULN), total bilirubin $\leq$ 1.5$\times$ ULN, AST/ALT $\leq$ 3$\times$ ULN ($\leq$ 5$\times$ ULN if liver metastases present), fasting cholesterol $\leq$ 350 mg/dL, serum triglycerides $\leq$ 400 mg/dL, and calcium $\leq$ 12.5 mg/dL. Patients were excluded if bone was the only site of disease, in the event of inflammatory breast cancer, or in the event of one or more prior chemotherapy regimens or more than 14 consecutive days of endocrine therapy for locally advanced/MBC.

Safety

Adverse events (AEs) were coded using the Coding Thesaurus for Adverse Reactions Terminology (COSTART) and graded according to National Cancer Institute Common Terminology Criteria, version 3.0. All patients who received one or more dose of drug were included in the safety analysis. Temsirolimus or placebo administration was withheld if ANC was less than 1,000/μL or platelet counts were less than 50,000/μL and for any grade 3 to 4 nonhematologic toxicity with the exception of hyperglycemia and hypercholesterolemia (for which patients should be receiving concomitant therapy) and nausea/vomiting (unless already receiving optimal antiemetic therapy). Treatment could be reinitiated within 3 weeks if ANC was $\geq$ 1,000/μL, platelets were $\geq$ 50,000/μL, and nonhematologic toxicities recovered to grade $\leq$ 2. First dose reduction was to temsirolimus/placebo 30 mg daily for 4 days every 2 weeks and second was to 3 days every 2 weeks. Protocol therapy stopped if recovery was not achieved within 3 weeks. Letrozole dose reduction was not permitted but could be held for $\leq$ 3 consecutive weeks if associated toxicities

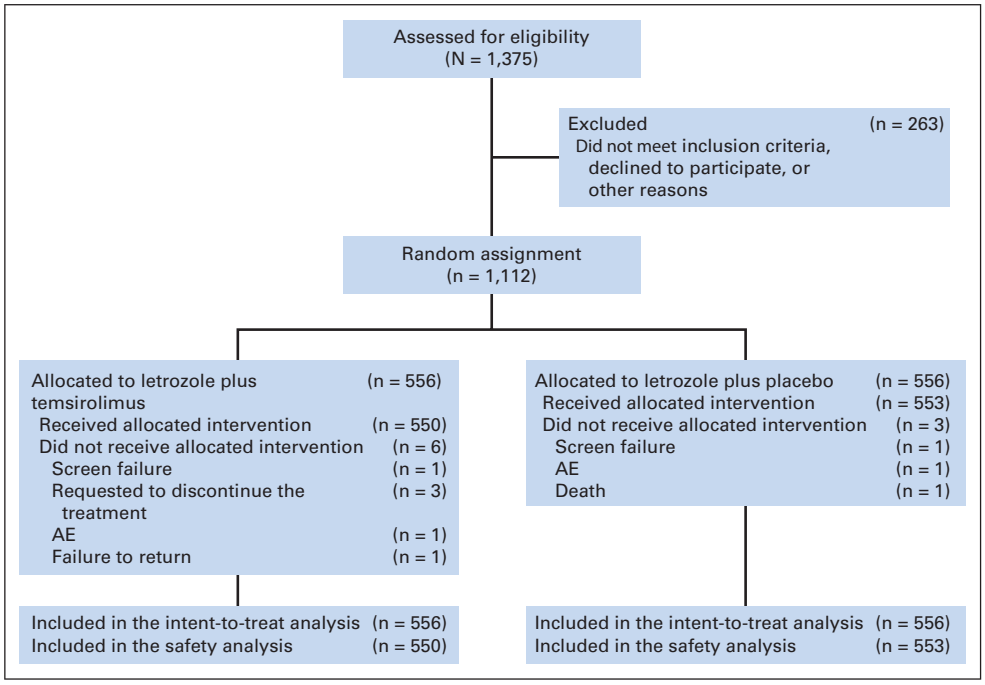

Fig 1. CONSORT flow diagram. AE, adverse event.

Table 1. Demographic and Baseline Characteristics

Characteristic	Letrozole Plus Temsirolimus (n = 555) No.	%	Letrozole Plus Placebo (n = 555) No.	%
Age, years				
Median	63		63	
Range	36-98		28-91	
n	553		553	
≤ 65	322	58	326	59
> 65	231	42	227	41
Histologic grade*				
Well differentiated	47	9	45	8
Moderately differentiated	197	36	184	33
Poorly differentiated	101	18	114	21
Undifferentiated	8	1	9	2
Unknown	197	36	201	36
Estrogen receptor status				
Positive	534	96	530	95
Negative	19	3	25	5
Unknown	2	1	0	
Progesterone receptor status				
Positive	411	74	399	72
Negative	125	23	143	26
Unknown	19	3	13	2
HER2 status				
Positive	130	23	101	18
Negative	224	40	259	47
Unknown	201	36	195	35
Karnofsky performance status*				
≥ 60	547	99	552	99
< 60	1	1	0	
Unknown	2	1	3	1
Prior chemo-, immuno-, hormonal therapy*				
Yes	358	65	327	59
No	0		0	
Unknown	192	35	226	41
Prior endocrine therapy†				
Yes	238	43	223	40
No	318	57	333	60
Duration, months				
Median	34		33	
Range	0.03-126		0.03-186	
Time from last endocrine therapy to study day 1, months				
Median	5		6	
Range	0-284		0.03-159	

Abbreviation: HER2, human epidermal growth factor receptor 2.
*For patients who received at least one dose of drug, 550 in the letrozole/temsirolimus group and 553 in the letrozole/placebo group.
†For the intent-to-treat population of 556 patients per group.

were present. The protocol was approved by the ethics committees/institutional review boards of each site. The study was conducted according to international standards of good clinical practice. All patients gave written informed consent.

Assessment of Outcomes

RECIST criteria were used for efficacy assessment (measurable lesions had to be two times the size of the scan reconstruction interval). Staging was done at screening and every 8 weeks.

End Points and Statistical Analysis

The primary efficacy end point was progression-free survival (PFS) of the intent-to-treat population as assessed by independent review. PFS was the time

Table 2. Summary of Efficacy End Points

Parameter	Letrozole Plus Temsirolimus (n = 556)	Letrozole Plus Placebo (n = 556)
Total population		
Progression-free survival		
No. censored	290	270
%	52	49
Median, months	8.9	9.0
95% CI	7.4 to 9.6	7.2 to 9.4
Hazard ratio*	0.90	
95% CI	0.76 to 1.07	
P†	.25	
Overall survival		
No. censored	483	475
%	87	85
Median, months	NE	NE
Hazard ratio*	0.89	
95% CI	0.65 to 1.23	
P†	.50	
Tumor response		
Complete response		
No.	14	10
%	3	2
Partial response		
No.	137	139
%	25	25
Objective response rate, %	27	27
Subgroups		
Prior endocrine therapy, progression-free survival		
No.	237	221
%	43	40
Median, months	6.5	5.2
95% CI	5.5 to 8.5	3.7 to 6.5
Hazard ratio*	0.84	
95% CI	0.66 to 1.08	
P†	.17	
No prior endocrine therapy, progression-free survival		
No.	316	332
%	57	60
Median, months	11.0	9.4
95% CI	9.2 to 12.9	9.1 to 11.1
Hazard ratio*	0.87	
95% CI	0.69 to 1.11	
P†	.27	
Age ≤ 65 years, progression-free survival		
No.	322	326
No. censored	168	146
%	52	45
Median, months	9.0	5.6
95% CI	7.3 to 10.9	4.8 to 9.0
Hazard ratio*	0.75	
95% CI	0.60 to 0.93	
P†	.009	
Age > 65 years, progression-free survival		
No.	231	227
No. censored	122	124
%	53	55
Median, months	8.5	10.1
95% CI	5.6 to 10.6	9.0 to 11.4
Hazard ratio*	1.21	
95% CI	0.92 to 1.59	
P†	.17	

Abbreviation: NE, not estimable.
*Letrozole plus temsirolimus compared with letrozole plus placebo based on Cox proportional hazards model stratified by prior bone disease status and geographic region.
†Letrozole plus temsirolimus compared with letrozole plus placebo based on log-rank test stratified by prior bone disease status and geographic region.

from first treatment to earliest time of disease progression, symptomatic deterioration, or death. As independent assessments of progression were not completed at the time the study was stopped, investigator-assessed PFS is reported. Secondary end points included overall survival (OS), tumor response and clinical benefit, time to tumor progression, duration of response, time to treatment failure, safety, and quality of life using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30 and Q-TwiST (Quality-Adjusted Time Without Symptoms of Disease or Toxicity of Treatment) methodologies. This article reports only OS, tumor response, and safety. Key predefined covariate analyses included prior adjuvant tamoxifen. Analyses of molecular markers phosphatase and tensin homolog and p27 on tissues (~20% of patients) did not comply with Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) criteria and are not reported.

A sample size of 1,236 patients (expecting 15% nonevaluable) and 726 events were needed to detect a PFS hazard ratio (HR) of 0.8 (median PFS, 11.75 *v* 9.4 months) favoring the investigational arm (85% power, two-sided log-rank test, 5% significance). Expected accrual time was ~16.4 months.

The patients and whole study team were blinded, as were Wyeth senior management personnel. An independent statistician (not part of the study team) generated the randomization sequence list with different seed numbers using SAS with proc plan procedure (SAS v9; SAS Institute, Cary, NC; Rv2.10). The generated list (with random number, stratification, and treatment information) was sent to a central computerized randomization enrollment system. Formal review and approval processes were in place before the random allocation sequence could be released. Each site received temsirolimus/placebo without treatment information directly from a group independent of the study team. In cases of emergency, the patient was unblinded via the computerized randomization enrollment system. When this occurred, the investigator notified the sponsor medical monitor immediately and documented the reason for unblinding.

Two preplanned interim analyses evaluating safety and efficacy would occur after 145 (~20%) and after 363 (~50%) events (disease progression or death) with appropriate adjustments and predefined terms for early success or futility. PFS/OS were estimated using the Kaplan-Meier method.[16] HRs and 95% CIs were calculated using a stratified Cox proportional hazards model. The proportional hazards assumption was assessed using a standard approach based on the Cox extended model (ie, time-dependent covariates).

A planned subset analysis based on the subject's age (age ≤ 65 *v* > 65 years) was intended but not prospectively documented before the interim analyses. Age findings reported in a 2006 San Antonio Breast Cancer Symposium poster then led the first and last academic authors to conduct exploratory and independent statistical analyses using the subpopulation treatment effect pattern plot (STEPP) methodology to illustrate graphically the relationship between age and outcome (PFS or OS) across the age continuum. Significance of treatment-effect heterogeneity as a function of age was calculated using a permutation test.[17,18] Planning for the STEPP analyses was locked before analyses, and the 5-month PFS analysis (*y*-axis of Fig 4) was designated as the

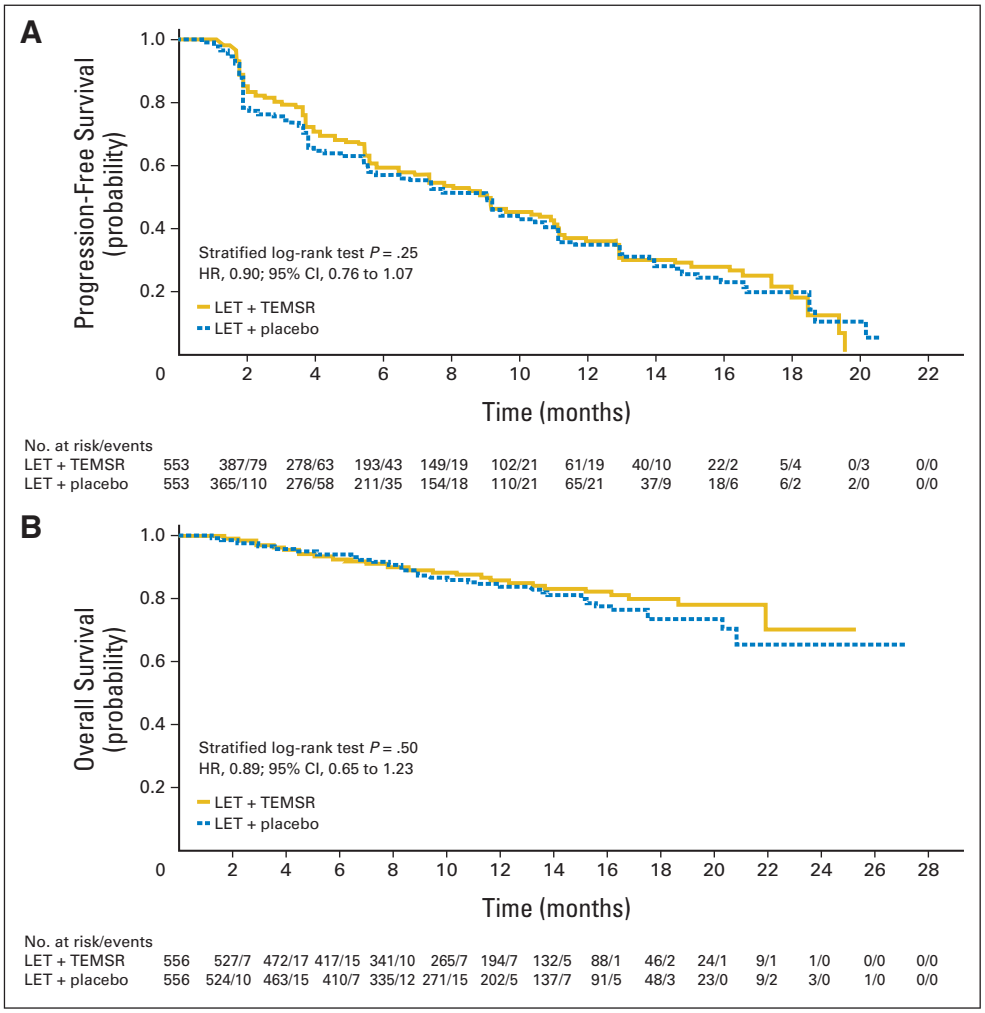

Fig 2. Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival. HR, hazard ratio; LET, letrozole; TEMSR, temsirolimus.

primary STEPP analysis. The additional STEPP analyses looking at 6-, 7-, 8-, and 9-month PFS percentages were conducted to check consistency and followed established recommendations.[17] Two-sided *P* values were reported for all statistical tests, and $P \leq .05$ was considered significant.

RESULTS

Patients

Between May 2004 and March 2006, 1,112 patients (Fig 1) from 263 centers were randomly assigned to receive letrozole plus temsirolimus (550 treated) or letrozole plus placebo (553 treated), and ~10% (51 and 65 patients, respectively) had stage III disease that was considered not amenable to curative surgery and/or radiation. In March 2006, the Independent Data Monitoring Committee concluded at the second predefined interim analysis (382 events) that the study was unlikely to reach its PFS primary end point and recommended its termination. Data reported herein correspond to the final December 2006 data lock (median follow-up, 9.5 months; range, 0 to 27.2 months).

Demographic and disease characteristics were balanced (Table 1). Patients had ER-positive (96%) and/or PR-positive (73%) disease, whereas 23% in the letrozole/temsirolimus group and 18% in the letrozole/placebo group were HER2 positive. No patients had prior endocrine therapy for locally advanced/MBC. Although ~40% received adjuvant endocrine therapy (median duration, ~34 months; median time since last endocrine therapy, ~5 months), none had cancer recurrence during the first 6 months, nor did any patient receive adjuvant AI within 12 months of study entry. Therefore, although data on specific type of adjuvant endocrine therapy were not prospectively collected, it is assumed that they would have received tamoxifen.

Efficacy

The retrospective independent assessment of progression was not complete when the trial was stopped. Therefore, the PFS data are based on investigator assessment with a randomly assigned intent-to-treat population of 1,112 patients. Overall, PFS was comparable in both groups (HR, 0.90; 95% CI, 0.76 to 1.07; $P = .25$; Table 2; Fig 2A). Median PFS (8.9 and 9.0 months, respectively) and OS were also comparable (HR, 0.89; 95% CI, 0.65 to 1.23; $P = .50$; Table 2; Fig 2B). There was no evidence of nonproportional hazards (PFS, $P = .43$; OS, $P = .51$). Few death events occurred by the time of this analysis because of early study termination. Most patients were censored, and median survival could not be calculated. Objective response rate (RR)

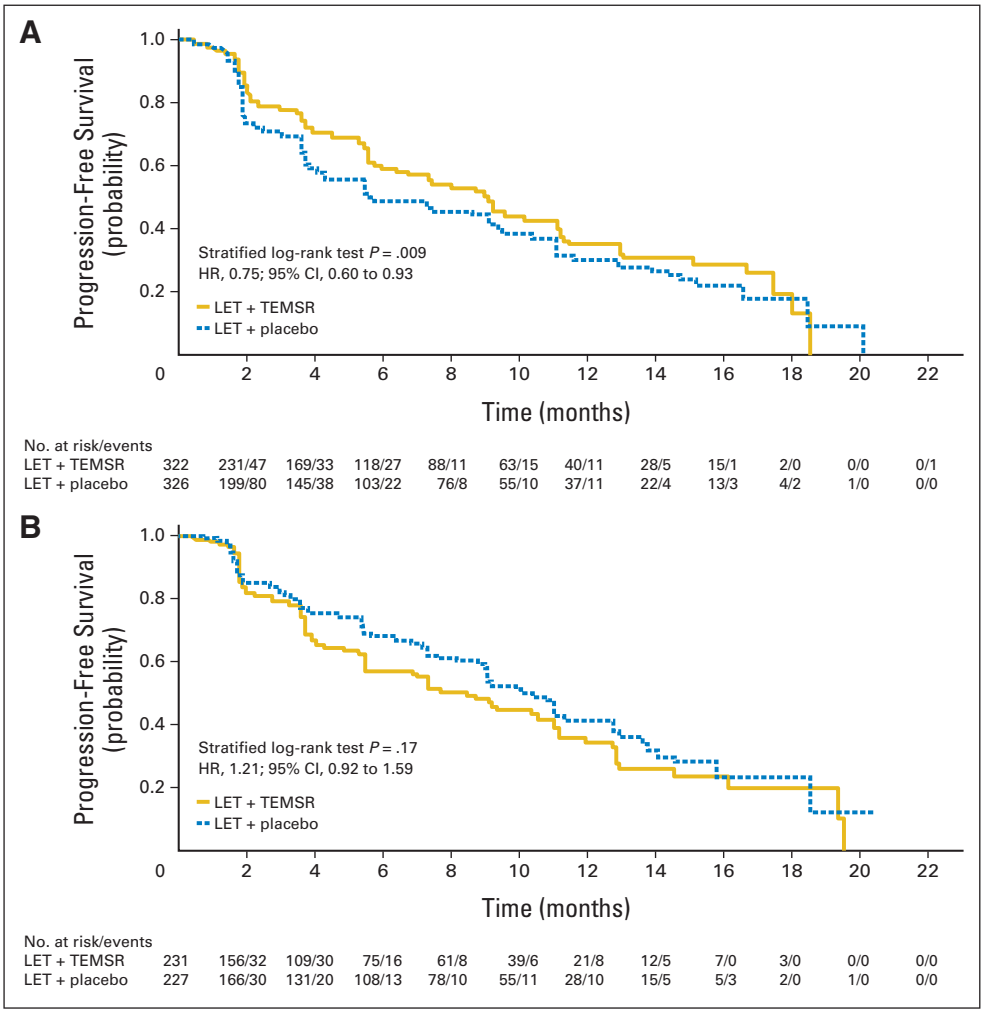

Fig 3. Kaplan-Meier estimates of progression-free survival by patient's age: (A) ≤ 65 years and (B) older than 65 years. HR, hazard ratio; LET, letrozole; TEMSR, temsirolimus.

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