ORIGINAL ARTICLE

Alpelisib for *PIK3CA*-Mutated, Hormone Receptor–Positive Advanced Breast Cancer

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ABSTRACT

BACKGROUND

PIK3CA mutations occur in approximately 40% of patients with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer. The PI3Kα-specific inhibitor alpelisib has shown antitumor activity in early studies.

METHODS

In a randomized, phase 3 trial, we compared alpelisib (at a dose of 300 mg per day) plus fulvestrant (at a dose of 500 mg every 28 days and once on day 15) with placebo plus fulvestrant in patients with HR-positive, HER2-negative advanced breast cancer who had received endocrine therapy previously. Patients were enrolled into two cohorts on the basis of tumor-tissue *PIK3CA* mutation status. The primary end point was progression-free survival, as assessed by the investigator, in the cohort with *PIK3CA*-mutated cancer; progression-free survival was also analyzed in the cohort without *PIK3CA*-mutated cancer. Secondary end points included overall response and safety.

RESULTS

A total of 572 patients underwent randomization, including 341 patients with confirmed tumor-tissue *PIK3CA* mutations. In the cohort of patients with *PIK3CA*-mutated cancer, progression-free survival at a median follow-up of 20 months was 11.0 months (95% confidence interval [CI], 7.5 to 14.5) in the alpelisib–fulvestrant group, as compared with 5.7 months (95% CI, 3.7 to 7.4) in the placebo–fulvestrant group (hazard ratio for progression or death, 0.65; 95% CI, 0.50 to 0.85; P<0.001); in the cohort without *PIK3CA*-mutated cancer, the hazard ratio was 0.85 (95% CI, 0.58 to 1.25; posterior probability of hazard ratio <1.00, 79.4%). Overall response among all the patients in the cohort with *PIK3CA*-mutated cancer was greater with alpelisib–fulvestrant than with placebo–fulvestrant (26.6% vs. 12.8%); among patients with measurable disease in this cohort, the percentages were 35.7% and 16.2%, respectively. In the overall population, the most frequent adverse events of grade 3 or 4 were hyperglycemia (36.6% in the alpelisib–fulvestrant group vs. 0.7% in the placebo–fulvestrant group) and rash (9.9% vs. 0.3%). Diarrhea of grade 3 occurred in 6.7% of patients in the alpelisib–fulvestrant group, as compared with 0.3% of those in the placebo–fulvestrant group; no diarrhea of grade 4 was reported. The percentages of patients who discontinued alpelisib and placebo owing to adverse events were 25.0% and 4.2%, respectively.

CONCLUSIONS

Treatment with alpelisib–fulvestrant prolonged progression-free survival among patients with *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer who had received endocrine therapy previously. (Funded by Novartis Pharmaceuticals; SOLAR-1 ClinicalTrials.gov number, NCT02437318.)

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More than 70% of breast cancers are hormone receptor (HR)–positive and human epidermal growth factor receptor 2 (HER2)–negative.[1,2] Approximately 40% of patients with HR-positive, HER2-negative breast cancer have activating mutations in the gene *PIK3CA*, inducing hyperactivation of the alpha isoform (p110α) of phosphatidylinositol 3-kinase (PI3K).[3-5] Endocrine therapy, with or without the use of a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor, is the standard treatment for patients with HR-positive, HER2-negative advanced breast cancer.[6-8] However, acquired resistance to endocrine-based therapy remains a challenge.[9,10]

Alpelisib (BYL719) is an orally bioavailable, small-molecule, α-specific PI3K inhibitor that selectively inhibits p110α approximately 50 times as strongly as other isoforms.[11] *PIK3CA*-mutated cancers have been shown to be sensitive to alpelisib in preclinical tumor models[11] and in a phase 1 trial of alpelisib in patients with advanced solid tumors.[12] The combination of alpelisib with fulvestrant had synergistic antitumor activity as compared with either agent alone in *PIK3CA*-mutated, estrogen-receptor–positive xenograft models.[13,14] In a phase 1b trial, alpelisib plus fulvestrant led to a complete or partial response in 29% of patients with heavily pretreated *PIK3CA*-altered, HR-positive advanced breast cancer, as compared with no complete or partial response in patients without *PIK3CA*-mutated tumors.[15] The most frequent adverse events of grade 3 or 4 that were reported with alpelisib were hyperglycemia and maculopapular rash.[15] Here, we present the results of the primary analysis of SOLAR-1 (Clinical Studies of Alpelisib in Breast Cancer 1), a phase 3 trial to evaluate the efficacy and safety of an α-specific PI3K inhibitor plus fulvestrant in patients with *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer who had received endocrine therapy previously.

Methods

Trial Design

We conducted this randomized, double-blind, placebo-controlled, phase 3 trial in 34 countries and enrolled patients at 198 trial centers into two cohorts on the basis of tumor-mutation status (*PIK3CA*-mutated vs. not *PIK3CA*-mutated). Within each cohort, patients were randomly assigned in a 1:1 ratio to receive oral alpelisib (at a dose of 300 mg to be taken with food [one 200-mg tablet and two 50-mg tablets], regardless of body weight, with continuous daily dosing) plus fulvestrant (administered as a 500-mg intramuscular injection on days 1 and 15 of cycle 1 and on day 1 of subsequent 28-day cycles) or placebo plus fulvestrant. Within each cohort, randomization was stratified according to the presence or absence of lung or liver metastases and according to previous receipt of CDK4/6 inhibitor treatment. Patients received treatment until disease progression, an unacceptable level of toxic effects, withdrawal of consent, loss to follow-up, or death. Dose reductions of alpelisib (or matching placebo) were permitted (according to the schedule of changes in the daily dose from 300 mg to 250 mg to 200 mg) to help manage adverse events (see the Supplementary Appendix, available with the full text of this article at NEJM.org). No dose reductions of fulvestrant were allowed. Patients who discontinued alpelisib or placebo could continue receiving fulvestrant.

Patients

Enrollment was open to men and postmenopausal women who had locally confirmed HR-positive, HER2-negative advanced breast cancer, were eligible to receive further endocrine therapy after relapse or progression, and were receiving or had received aromatase inhibitor treatment in the context of neoadjuvant or adjuvant therapy or for advanced disease. Patients had to have adequate tumor tissue for central analysis of *PIK3CA* mutational status. For postmenopausal women, previous radiation therapy to the ovaries or previous treatment with a luteinizing hormone–releasing hormone agonist for induction of ovarian suppression was prohibited. Patients were excluded if they had received chemotherapy previously for advanced disease, had received fulvestrant therapy previously, or had received any PI3K, AKT, or mTOR (mechanistic target of rapamycin) inhibitor.

Patients had either measurable disease (at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1) or one or more predominantly lytic bone lesions, an Eastern Cooperative

Oncology Group performance-status score of 0 or 1 (on a scale from 0 to 5, with higher numbers indicating greater disability), and adequate organ and bone marrow function. Patients were excluded if they had inflammatory breast cancer, uncontrolled central nervous system metastases, concurrent cancer or cancer within 3 years before randomization (except for adequately treated basal-cell or squamous-cell carcinoma, nonmelanomatous skin cancer, or curatively resected cervical cancer), type 1 diabetes or uncontrolled type 2 diabetes (fasting plasma glucose level, >140 mg per deciliter [7.7 mmol per liter], or a glycosylated hemoglobin level of >6.4%), or currently documented pneumonitis.

Primary resistance was defined as relapse within 24 months while the patient was receiving adjuvant endocrine therapy or progression within 6 months while the patient was receiving endocrine therapy for advanced disease. Secondary resistance was defined as relapse after at least 24 months of adjuvant endocrine therapy, relapse within 12 months after ending adjuvant endocrine therapy, or progression after at least 6 months of endocrine therapy for advanced disease. Patients whose disease relapsed at least 12 months after the completion of adjuvant endocrine therapy and who were not treated for advanced disease were considered to have endocrine-sensitive disease. A subsequent protocol amendment (on August 30, 2016) specified that these patients were ineligible for enrollment, in order to focus the trial on the endocrine-resistant population.

END POINTS

The primary end point was progression-free survival, as assessed by the investigator, according to RECIST, version 1.1, in the cohort of patients with *PIK3CA*-mutated cancer. The key secondary end point was overall survival in the cohort with *PIK3CA*-mutated cancer. Additional secondary end points included progression-free survival and overall survival in the cohort without *PIK3CA*-mutated cancer, progression-free survival according to the level of circulating tumor DNA (ctDNA), overall response, clinical benefit (defined as a complete or partial response or as stable disease for >6 months), and safety. (The ctDNA-related and overall survival analyses are not reported here.)

ASSESSMENTS

Before enrollment, cohort status was centrally determined according to the presence or absence of any *PIK3CA* mutation by means of polymerase-chain-reaction analysis of mutation hot spots in the C2, helical, and kinase domains of PI3K (corresponding to exons 7, 9, and 20, respectively) with the use of a tumor-tissue sample, preferably a sample obtained during the most recent progression. Imaging (computed tomography, magnetic resonance imaging, or both) was performed at screening within 4 weeks before randomization, every 8 weeks for the first 18 months, and then every 12 weeks until disease progression or withdrawal for any other reason. Vital signs and hematologic and biochemical laboratory tests were performed at screening, every 2 weeks for the first 8 weeks, and then every 4 weeks. The fasting glucose level was also assessed on day 8. Adverse events (assessed according to the National Cancer Institute Common Terminology Criteria, version 4.03) were recorded continuously until 30 days after the last dose of trial treatment.

TRIAL OVERSIGHT

The trial protocol, which includes the statistical analysis plan, is available at NEJM.org. The original trial protocol and subsequent amendments were approved by an independent ethics committee and institutional review board at each site. The SOLAR-1 trial was designed and overseen by a steering group of medical oncology experts, including representatives from the trial sponsor (Novartis). The protocol was designed by the steering committee, which included the primary investigator. Written informed consent for trial participation and biomarker-sample collection was obtained from all the participants. An independent data and safety monitoring committee reviewed unblinded efficacy and safety data. The trial was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All the authors had access to all trial data and were involved in the development of the manuscript and approved its submission for publication. The authors confirm that the trial conformed to the protocol and statistical analysis plan, and they vouch for the accuracy and completeness of the reported data, which were analyzed by a statisti-

cian employed by Novartis. A professional medical writer, funded by the sponsor, assisted with the development of the manuscript.

STATISTICAL ANALYSIS

The primary end point (progression-free survival in the cohort with *PIK3CA*-mutated cancer) was compared between groups by means of a stratified log-rank test at a one-sided 2.0% significance level. We calculated that 243 events of disease progression or death would be required for the trial to detect a hazard ratio of 0.6 with 83.8% power. Two interim analyses were conducted after 42% (in a futility analysis) and 78% (in an efficacy analysis) of the expected numbers of events of progression or death were documented. The overall type I error rate for this group-sequential design was controlled with the use of a Haybittle–Peto boundary. Of the overall alpha level of 0.02 for the *PIK3CA*-mutation cohort, 0.0001 was spent at the interim efficacy analysis; this left an alpha level of 0.0199 remaining to declare statistical significance at the final analysis.

Proof-of-concept criteria, designed to assess whether a treatment benefit was obtained in the biomarker-negative control cohort, required a hazard ratio of 0.60 or less and a posterior probability of at least 90% that the true hazard ratio was less than 1.00; data from the cohort without *PIK3CA* mutations were analyzed with the use of a one-sided 0.5% significance level. A separate O'Brien–Fleming alpha-spending function, which was independent of the Haybittle–Peto boundary that was used for the primary efficacy analysis, guaranteed protection of the overall type I error (at an alpha level of 2.5%, equivalent to a two-sided level of 5%, on the basis of a Bonferroni adjustment) across all hypotheses and repeated testing of the overall survival hypotheses at the interim and the final analyses.

A stratified Cox regression model was used to estimate the hazard ratio and 95% confidence interval in the analysis of progression-free survival. To provide supportive evidence regarding the primary end point, progression-free survival was also assessed in an audit-based random subgroup of 50% of the cohort of patients with *PIK3CA*-mutated cancer by an independent review committee whose members were unaware of the trial-group assignments. Within each cohort, overall survival was tested only if there was a significant difference between the trial groups with regard to progression-free survival. Efficacy analyses were performed with the use of data from all the patients in the two cohorts (with and without *PIK3CA*-mutated cancer) who underwent randomization, and safety analyses included all the patients who received at least one dose of any trial agent. Additional details regarding the trial design are included in the Supplementary Appendix.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between July 26, 2015, and July 21, 2017, a total of 572 patients underwent randomization. A total of 1244 patients were tested for *PIK3CA* mutation status, and interpretable results were available for 1173 (94.3%). A total of 341 patients had *PIK3CA*-mutated disease, including 169 who were assigned to receive alpelisib plus fulvestrant and 172 who were assigned to receive placebo plus fulvestrant (Fig. S1 in the Supplementary Appendix). The characteristics of the patients in the cohort with *PIK3CA*-mutated cancer were balanced between the two trial groups at baseline (Table 1). The median age of these patients was 63 years. Lung or liver metastases were present in 170 patients (49.9%), and 77 (22.6%) had bone-only disease. A total of 20 patients (5.9%) had received CDK4/6 inhibitor therapy previously. At randomization, 292 patients (85.6%) had endocrine-resistant disease. An additional cohort of 231 patients without *PIK3CA*-mutated cancer underwent randomization for the proof-of-concept analysis (Table 1).

TREATMENT IN THE COHORT WITH *PIK3CA*-MUTATED CANCER

At the data cutoff (June 12, 2018), in the cohort with *PIK3CA*-mutated cancer, the trial intervention was ongoing in 42 patients (24.9%) receiving alpelisib–fulvestrant and in 32 (18.6%) receiving placebo–fulvestrant. The median duration of exposure to alpelisib was 5.5 months (interquartile range, 1.6 to 13.0), and the median duration of exposure to placebo was 4.6 months (interquartile range, 1.9 to 13.1). The most common reasons for discontinuation of a trial agent were progressive disease (in 93 patients [55.0%] in the alpelisib–fulvestrant group and 117 [68.0%] in the placebo–fulvestrant group) and decision by the patient or the patient's guardian (in 16 patients [9.5%] and 6 patients [3.5%], respectively). The median relative dose intensity was 82.7% for

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Cohort with *PIK3CA*-Mutated Cancer		Cohort without *PIK3CA*-Mutated Cancer	
	Alpelisib–Fulvestrant Group (N=169)	Placebo–Fulvestrant Group (N=172)	Alpelisib–Fulvestrant Group (N=115)	Placebo–Fulvestrant Group (N=116)
Age — yr				
Median	63	64	62	63
Range	25–87	38–92	39–82	32–88
Female sex — no. (%)	168 (99.4)	172 (100)	115 (100)	116 (100)
ECOG performance-status score — no. (%)†				
0	112 (66.3)	113 (65.7)	84 (73.0)	79 (68.1)
1	56 (33.1)	58 (33.7)	30 (26.1)	37 (31.9)
Missing data	1 (0.6)	1 (0.6)	1 (0.9)	0
Sites of metastases — no. (%)‡				
Breast	1 (0.6)	3 (1.7)	5 (4.3)	4 (3.4)
Bone only	42 (24.9)	35 (20.3)	26 (22.6)	23 (19.8)
Visceral site				
Any	93 (55.0)	100 (58.1)	66 (57.4)	74 (63.8)
Liver	49 (29.0)	54 (31.4)	41 (35.7)	36 (31.0)
Lung	57 (33.7)	68 (39.5)	37 (32.2)	55 (47.4)
Lung or liver	84 (49.7)	86 (50.0)	56 (48.7)	56 (48.3)
No. of metastatic sites — no. (%)				
0	0	1 (0.6)	0	0
1	63 (37.3)	52 (30.2)	44 (38.3)	33 (28.4)
2	58 (34.3)	60 (34.9)	35 (30.4)	38 (32.8)
≥3	48 (28.4)	59 (34.3)	36 (31.3)	45 (38.8)
Previous treatment — no. (%)§				
Any CDK4/6 inhibitor	9 (5.3)	11 (6.4)	7 (6.1)	8 (6.9)
Chemotherapy¶	101 (59.8)	107 (62.2)	78 (67.8)	72 (62.1)
Line of treatment in advanced disease — no. (%)‖				
First line	88 (52.1)	89 (51.7)	71 (61.7)	62 (53.4)
Second line	79 (46.7)	82 (47.7)	42 (36.5)	53 (45.7)
Endocrine status — no. (%)**				
Primary resistance	23 (13.6)	22 (12.8)	31 (27.0)	26 (22.4)
Secondary resistance	120 (71.0)	127 (73.8)	66 (57.4)	65 (56.0)
Sensitivity	20 (11.8)	19 (11.0)	16 (13.9)	20 (17.2)

* Any differences between the two trial groups were less than 10% in the cohort of patients with *PIK3CA*-mutated cancer. The gene *PIK3CA* encodes for the alpha isoform of phosphatidylinositol 3-kinase (PI3Kα). Percentages may not total 100 because of rounding. Further data regarding the baseline characteristics of the patients are provided in Table S10 in the Supplementary Appendix. CDK denotes cyclin-dependent kinase.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a scale from 0 to 5, with higher numbers indicating greater disability.

‡ One patient in the placebo group in the cohort with *PIK3CA*-mutated cancer had locally advanced disease with no metastases.

§ All patients had previously received treatment with an aromatase inhibitor.

¶ Chemotherapy was for patients receiving neoadjuvant or adjuvant therapy only. One patient in the placebo group of the cohort with *PIK3CA*-mutated cancer received chemotherapy for advanced disease (which was a protocol deviation).

‖ Three patients in each trial cohort (two patients in the alpelisib–fulvestrant group and one in the placebo–fulvestrant group in each cohort) were excluded because of protocol deviations.

** Primary endocrine resistance was defined as relapse within 24 months while the patient was receiving adjuvant endocrine therapy or progression within 6 months while the patient was receiving endocrine therapy in the context of metastatic disease. Secondary endocrine resistance was defined as relapse that occurred after at least 24 months while the patient was receiving adjuvant endocrine therapy, relapse that occurred within 12 months after the end of adjuvant endocrine therapy, or progression that occurred after at least 6 months while the patient was receiving endocrine therapy in the context of metastatic disease. After enrollment began, the trial protocol was updated to exclude patients who had a relapse at least 12 months after the completion of neoadjuvant or adjuvant endocrine therapy and had not been treated for metastatic disease (endocrine sensitive).

alpelisib and 100% for placebo. Dose interruptions for alpelisib or matching placebo occurred in 125 patients (74.0%) receiving alpelisib–fulvestrant and in 55 (32.2%) receiving placebo–fulvestrant, and dose reductions occurred in 108 (63.9%) and 15 (8.8%), respectively.

Efficacy of Alpelisib–Fulvestrant in the Cohort with *PIK3CA*-Mutated Cancer

In the cohort with *PIK3CA*-mutated cancer, the median duration of follow-up from randomization to data cutoff was 20.0 months (range, 10.7 to 33.3). The median progression-free survival was 11.0 months (95% confidence interval [CI], 7.5 to 14.5) in the alpelisib–fulvestrant group, as compared with 5.7 months (95% CI, 3.7 to 7.4) in the placebo–fulvestrant group (hazard ratio for progression or death, 0.65; 95% CI, 0.50 to 0.85; P<0.001) (Fig. 1A). At 12 months, the percentage of patients with progression-free survival was 46.3% in the alpelisib–fulvestrant group and 32.9% in the placebo–fulvestrant group. These results were supported by the blinded independent review, which showed a median progression-free survival of 11.1 months (95% CI, 7.3 to 16.8) among 85 patients who had been assigned to receive alpelisib–fulvestrant, as compared with 3.7 months (95% CI, 2.1 to 5.6) among 88 patients assigned to receive placebo–fulvestrant (hazard ratio, 0.48; 95% CI, 0.32 to 0.71). Analyses of progression-free survival according to stratification criteria and important demographic and prognostic factors showed consistent benefit of treatment with alpelisib–fulvestrant across prespecified subgroups (Fig. 2).

Overall response among all the patients in this cohort was greater with alpelisib–fulvestrant than with placebo–fulvestrant (26.6% vs. 12.8%), and clinical benefit was also greater with alpelisib–fulvestrant (61.5% vs. 45.3%) (Table 2). Among patients with measurable disease, overall response was 35.7% in the alpelisib–fulvestrant group and 16.2% in the placebo–fulvestrant group; the percentages of patients with clinical benefit were 57.1% and 44.1%, respectively (Table 2). The trial-group assignments remained concealed from the investigators and patients during follow-up for the assessment of overall survival at the time of the primary end-point analysis.

Efficacy of Alpelisib–Fulvestrant in the Cohort without *PIK3CA*-Mutated Cancer

Proof-of-concept criteria were not met in the cohort of patients without *PIK3CA*-mutated cancer at the final efficacy analysis. The median progression-free survival was 7.4 months (95% CI, 5.4 to 9.3) in the alpelisib–fulvestrant group and 5.6 months (95% CI, 3.9 to 9.1) in the placebo–fulvestrant group (hazard ratio for progression or death, 0.85; 95% CI, 0.58 to 1.25; posterior probability of true hazard ratio <1.00, 79.4%) (Fig. 1B). At 12 months, the percentage of patients with progression-free survival was 28.4% in the alpelisib–fulvestrant group and 22.2% in the placebo–fulvestrant group. The median duration of follow-up was 7.4 months (range, 0.1 to 16.4) at the time of data cutoff (December 23, 2016). A majority of patients in this cohort went on to receive either chemotherapy or hormonal therapy plus a targeted therapy as their next treatment after progression.

Safety

The total safety population included 284 patients who received alpelisib–fulvestrant and 287 who received placebo–fulvestrant. The adverse events of any grade that occurred in at least 35% of the patients in either group were hyperglycemia (in 63.7% of the patients who received alpelisib–fulvestrant and 9.8% of those who received placebo–fulvestrant), diarrhea (in 57.7% and 15.7%, respectively), nausea (in 44.7% and 22.3%), decreased appetite (in 35.6% and 10.5%), and rash (in 35.6% and 5.9%) or maculopapular rash (in 14.1% and 1.7%) (Table 3). The most common adverse events of grade 3 or 4, occurring in at least 5% of patients in either group, were hyperglycemia (in 36.6% of the patients who received alpelisib–fulvestrant and 0.7% of those who received placebo–fulvestrant), rash (in 9.9% and 0.3%, respectively), maculopapular rash (in 8.8% and 0.3%), and diarrhea (in 6.7% and 0.3%).

Permanent discontinuation of alpelisib or placebo due to adverse events occurred in 71 patients (25.0%) receiving alpelisib–fulvestrant and in 12 (4.2%) receiving placebo–fulvestrant. The most frequent adverse events leading to the discontinuation of alpelisib were hyperglycemia (in 18 patients [6.3%]) and rash (in 9 [3.2%]); no patients discontinued placebo owing to hyperglycemia or rash.

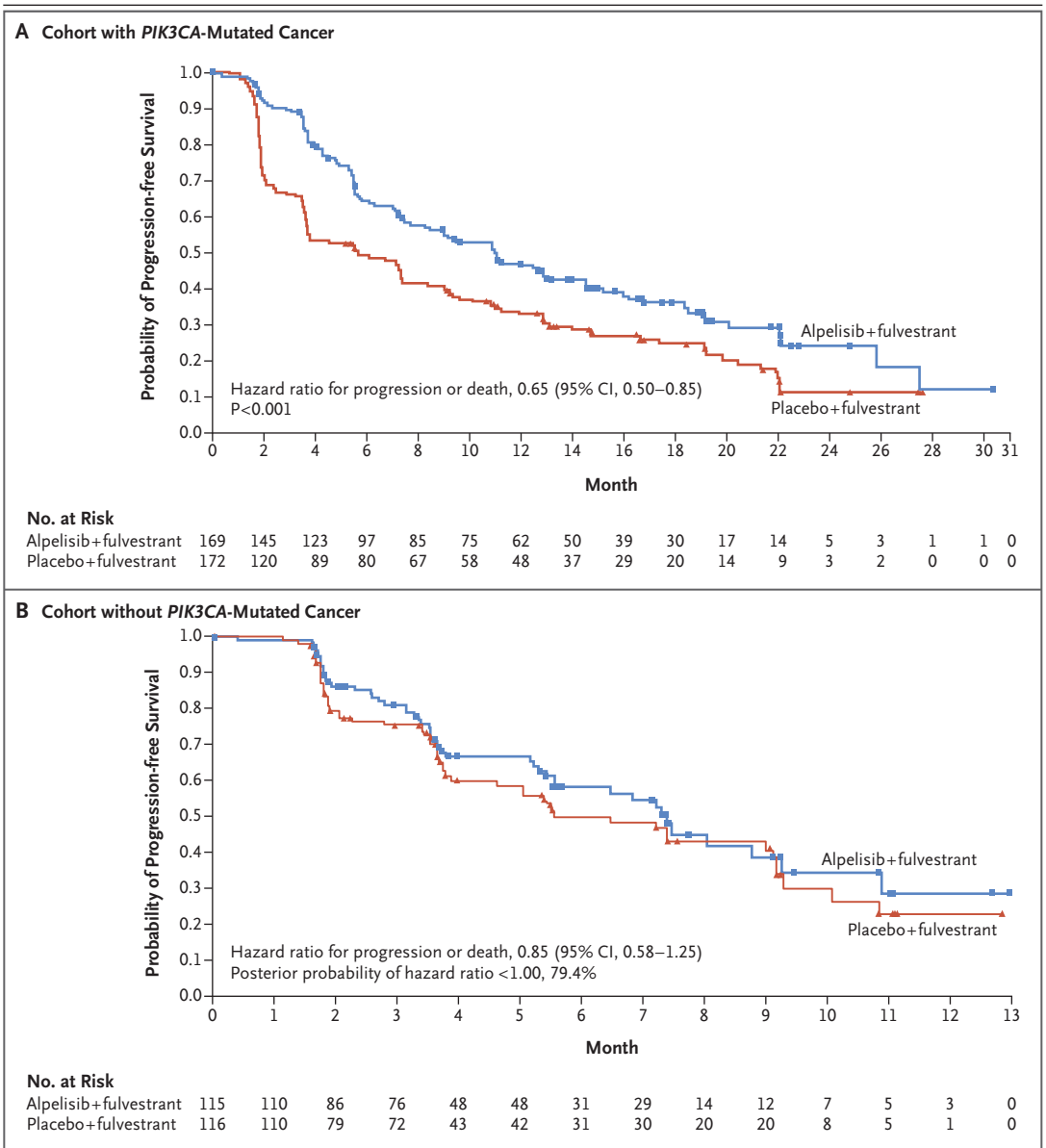

Figure 1. Kaplan–Meier Analysis of Progression-free Survival.

In the cohort of patients with *PIK3CA*-mutated cancer, the median progression-free survival was 11.0 months in the alpelisib–fulvestrant group and 5.7 months in the placebo–fulvestrant group (Panel A). The primary end point crossed the prespecified Haybittle–Peto boundary (one-sided P≤0.0199) (Panel A). Symbols indicate censored data. In the cohort without *PIK3CA*-mutated cancer, the median progression-free survival was 7.4 months in the alpelisib–fulvestrant group and 5.6 months in the placebo–fulvestrant group (Panel B). The gene *PIK3CA* encodes for the alpha isoform of phosphatidylinositol 3-kinase (PI3Kα).

Serious adverse events occurred in 99 patients (34.9%) receiving alpelisib–fulvestrant and 48 (16.7%) receiving placebo–fulvestrant (Table S3 in the Supplementary Appendix). There were 19 deaths during the trial (including during the 30-day postintervention safety period): 7 deaths (2.5%) in patients receiving alpelisib–fulvestrant and 12 (4.2%) in those receiving placebo–fulvestrant. A total of 5 patients receiving alpelisib–fulvestrant and 8 receiving placebo–fulvestrant

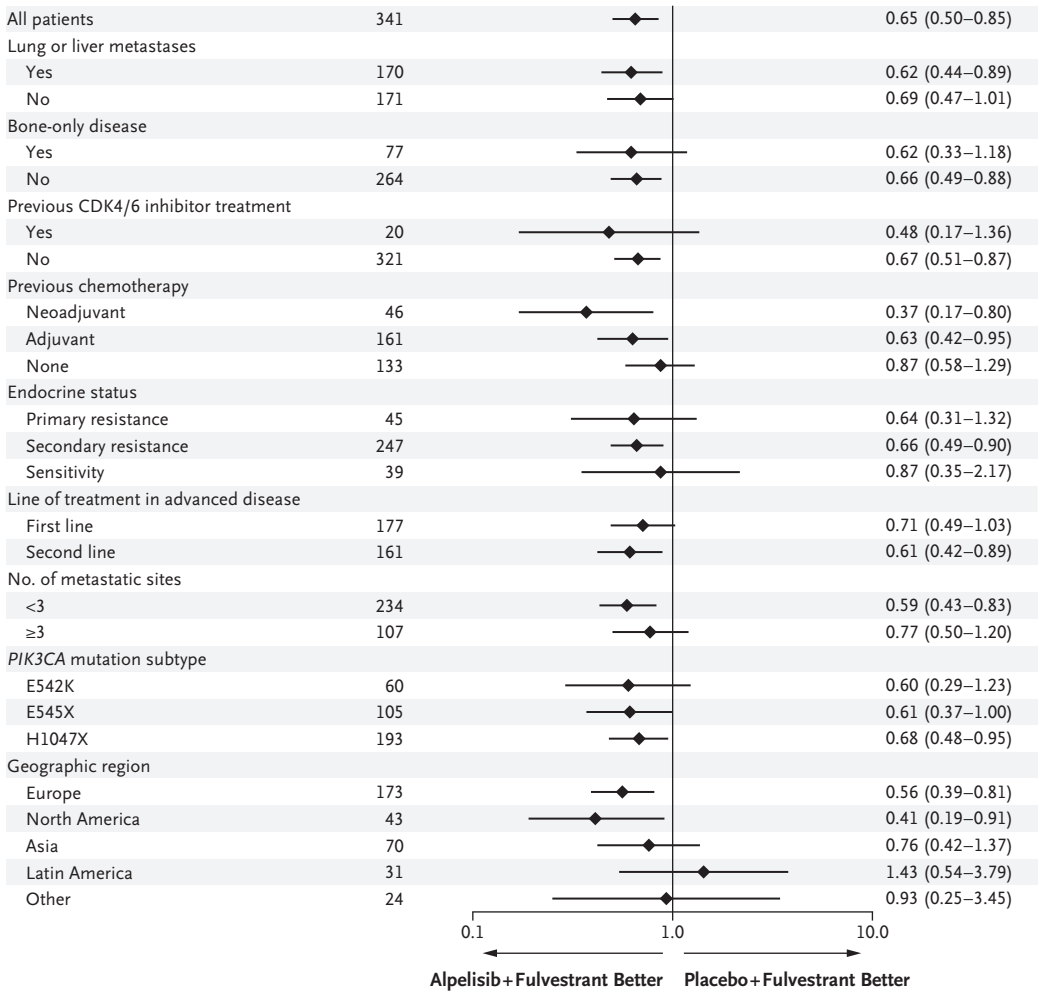

Figure 2. Subgroup Analysis of Progression-free Survival in the Cohort with *PIK3CA*-Mutated Cancer.

Confidence intervals have not been adjusted for multiplicity. Inferences drawn from the confidence intervals may not be reproducible. The previous chemotherapy subgroup was based on the last line of chemotherapy received. Patients may have received chemotherapy in the context of both neoadjuvant and adjuvant therapy. Patients may have had more than one *PIK3CA* mutation. There were multiple subtypes of E545 and H1047 mutations. CDK denotes cyclin-dependent kinase.

died from underlying breast cancer. Other deaths in the alpelisib group were due to cardiorespiratory arrest and a second primary cancer. Safety profiles in the two trial groups were similar in the two cohorts (Tables S4 through S6 in the Supplementary Appendix).

DISCUSSION

These results show improvements in patients' outcomes with the addition of an α-specific PI3K inhibitor to standard treatment for *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer, findings that validate *PIK3CA* as an important treatment target in this population. Patients with *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer that had progressed during or after the receipt of endocrine therapy had significantly longer progression-free survival when they received alpelisib–fulvestrant than when they received placebo–fulvestrant, with an estimated 35% lower risk of progression

Table 2. Best Overall Response, According to Local Assessment, in the Cohort with *PIK3CA*-Mutated Cancer.

Response	Alpelisib–Fulvestrant Group	Placebo–Fulvestrant Group
All patients		
No. of patients	169	172
Confirmed best overall response — no. (%)		
Complete response	1 (0.6)	2 (1.2)
Partial response	44 (26.0)	20 (11.6)
Stable disease	58 (34.3)	63 (36.6)
Neither complete response nor progressive disease*	38 (22.5)	25 (14.5)
Progressive disease	16 (9.5)	53 (30.8)
Unknown status	12 (7.1)	9 (5.2)
Overall response†		
No. of patients	45	22
Percentage of patients (95% CI)	26.6 (20.1–34.0)	12.8 (8.2–18.7)
Clinical benefit‡		
No. of patients	104	78
Percentage of patients (95% CI)	61.5 (53.8–68.9)	45.3 (37.8–53.1)
Patients with measurable disease at baseline		
No. of patients	126	136
Confirmed best overall response — no. (%)		
Complete response	1 (0.8)	2 (1.5)
Partial response	44 (34.9)	20 (14.7)
Stable disease	58 (46.0)	63 (46.3)
Progressive disease	13 (10.3)	45 (33.1)
Unknown status	10 (7.9)	6 (4.4)
Overall response†		
No. of patients	45	22
Percentage of patients (95% CI)	35.7 (27.4–44.7)	16.2 (10.4–23.5)
Clinical benefit§		
No. of patients	72	60
Percentage of patients (95% CI)	57.1 (48.0–65.9)	44.1 (35.6–52.9)

* In this category, the best overall response was evaluated only in patients who had no measurable disease at baseline according to the Response Evaluation Criteria in Solid Tumors, version 1.1.
† Overall response was defined as a complete or partial response.
‡ Clinical benefit in the overall population was defined as a complete or partial response, stable disease lasting at least 24 weeks, or the status of having neither a complete response nor progressive disease for at least 24 weeks.
§ Clinical benefit in patients with measurable disease at baseline was defined as a complete or partial response or as stable disease lasting at least 24 weeks.

or death. A clinically relevant treatment benefit was not observed for alpelisib–fulvestrant in the cohort without *PIK3CA*-mutated cancer. In the cohort with *PIK3CA*-mutated cancer, alpelisib–fulvestrant was also associated with significantly higher percentages of patients with tumor response than was placebo–fulvestrant, a finding that is consistent with observations from the phase 1b study.[15] Progression-free survival was similar in the placebo groups in the two cohorts defined according to *PIK3CA* mutation status.

In previous studies of PI3K inhibitors, patients with *PIK3CA*-mutated breast cancer had prolongation of progression-free survival that was sig-

Table 3. Most Frequent Adverse Events, According to Single Preferred Term and Regardless of Relationship to Intervention, in the Overall Patient Population.*

Adverse Event	Alpelisib–Fulvestrant Group (N=284)			Placebo–Fulvestrant Group (N=287)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia†	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea‡	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea‡	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash§	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting‡	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Weight loss	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0
Alopecia	56 (19.7)	0	0	7 (2.4)	0	0
Mucosal inflammation	52 (18.3)	6 (2.1)	0	3 (1.0)	0	0
Pruritus	51 (18.0)	2 (0.7)	0	16 (5.6)	0	0
Headache	50 (17.6)	2 (0.7)	0	38 (13.2)	0	0
Dysgeusia	47 (16.5)	0	0	10 (3.5)	0	0
Arthralgia	32 (11.3)	1 (0.4)	0	47 (16.4)	3 (1.0)	0

* Safety analyses included all the patients who received at least one dose of any trial agent; one patient who was randomly assigned to the placebo–fulvestrant group did not receive either placebo or fulvestrant. The events that are listed were reported as a single term in at least 15% of the patients for any grade in either group. Three adverse events of special interest (pancreatitis, severe cutaneous reactions, and pneumonitis) fell below the reporting threshold listed here. Hypersensitivity, which occurred in 16.5% of the patients in the alpelisib–fulvestrant group (grade ≥3 in 1.8%) and in 4.2% of those in the placebo–fulvestrant group (grade ≥3 in none), was not reported as any single preferred term that reached the reporting threshold listed here.

† Adverse events of any grade related to hyperglycemia (including diabetes mellitus, hyperglycemia, insulin resistance, and metabolic syndrome [preferred terms] and others [see the Methods section in the Supplementary Appendix for a complete list]) were reported in 65.8% of the patients in the alpelisib–fulvestrant group (grade ≥3 in 38.0%) and in 10.5% of those in the placebo–fulvestrant group (grade ≥3 in 0.7%).

‡ Gastrointestinal toxic effects of any grade (including nausea, vomiting, and diarrhea [preferred terms] and others [see the Methods section in the Supplementary Appendix for a complete list]) were reported in 75.4% of the patients in the alpelisib–fulvestrant group (grade ≥3 in 8.8%) and in 34.8% of those in the placebo–fulvestrant group (grade ≥3 in 1.0%). Diarrhea was assessed at a maximum grade 2 severity in 18.3% of the patients.

§ Adverse events of any grade related to rash (including rash, rash follicular, rash generalized, and rash maculopapular [preferred terms] and others [see the Methods section in the Supplementary Appendix for a complete list]) were reported in 53.9% of the patients in the alpelisib–fulvestrant group (grade ≥3 in 20.1%) and in 8.4% of those in the placebo–fulvestrant group (grade ≥3 in 0.3%).

nificant but not clinically meaningful. These include the Buparlisib Breast Cancer Clinical Evaluation (BELLE) 2 and 3 clinical trials of pan-PI3K inhibition with buparlisib[16,17] and the SANDPIPER clinical trial of the β-sparing PI3K inhibitor taselisib.[18] However, further development of pan-PI3K and β-sparing PI3K inhibitors has been limited by their narrow therapeutic index, which results in frequent treatment discontinuation and low on-target bioactivity. Specific inhibition of PI3Kα may represent improved biologic targeting, a finding supported by the observed incidence of hyperglycemia of grade 3 or 4 (10.8% with taselisib vs. 36.6% with alpelisib).[18]

The safety profile in the SOLAR-1 trial was similar to that in previous trials of alpelisib plus fulvestrant.[15] The most frequent adverse events were hyperglycemia, gastrointestinal toxic effects, and rash. Adverse events were generally revers-

ible and, with the exclusion of hyperglycemia, mostly of low grade. Hyperglycemia, an on-target effect of alpelisib, led to the permanent discontinuation of alpelisib in 6.3% of the patients. Because this toxic effect may be inextricably linked with α-specific PI3K inhibition,[5] rigorous safety monitoring was performed during the trial to minimize permanent treatment discontinuations and optimize potential benefit. Adverse events were managed by means of dose modifications and early concomitant medical intervention as indicated (Tables S7 through S9 in the Supplementary Appendix).

Alpelisib has activity in patients with *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer that has progressed during or after treatment with an aromatase inhibitor. Therefore, the integration of genomic testing for *PIK3CA* mutation into routine clinical practice may be useful in the selection of therapy; validated diagnostic testing procedures are not yet available. This trial shows that treatment with alpelisib–fulvestrant can provide an extension of progression-free survival among patients with *PIK3CA*-mutated disease. This effect was observed across various subgroups. Preliminary analysis of progression-free survival on the basis of ctDNA results shows a similar effect.[19] With the availability of ribociclib, palbociclib, and abemaciclib for the treatment of HR-positive, HER2-negative advanced breast cancer, there is potential for an increasing number of patients to receive CDK4/6 inhibitors with endocrine therapy in the context of first-line and second-line treatment of advanced breast cancer. However, PI3K-driven treatment resistance remains a problem.[20,21] The BYLieve (Alpelisib [BYL719] in Patients with *PIK3CA*-Mutant, HR+, HER2– Advanced Breast Cancer) trial (ClinicalTrials.gov number, NCT03056755) is recruiting patients who have had disease progression during or after treatment with a CDK4/6 inhibitor in order to further assess the efficacy of alpelisib in this context. In the SOLAR-1 trial, there appeared to be a strong treatment benefit in patients receiving second-line therapy and in patients who had received neoadjuvant or adjuvant chemotherapy previously, which supports the use of alpelisib–fulvestrant for the population of previously treated patients.

Preclinical studies have shown that some tumors with reduced sensitivity to alpelisib have sustained or increased levels of retinoblastoma protein and that the combination of PI3Kα and CDK4/6 inhibitors overcomes intrinsic and adaptive resistance in *PIK3CA*-mutated xenografts.[22] In addition, loss of phosphatase and tensin homologue protein (PTEN) has been shown to confer clinical resistance to alpelisib, which is reverted by PI3Kβ blockade in PTEN-null xenografts and cell lines.[23]

In conclusion, this phase 3 trial showed a significant prolongation of progression-free survival and greater overall response with alpelisib–fulvestrant than with placebo–fulvestrant among patients with *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer who had disease that had relapsed or progressed during or after the receipt of previous endocrine therapy. There was a higher incidence of hyperglycemia, rash, and diarrhea with alpelisib than with placebo.

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APPENDIX

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