original reports

Patient-Reported Outcomes in Patients With *PIK3CA*-Mutated Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer From SOLAR-1

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abstract

PURPOSE In the phase III SOLAR-1 trial (NCT02437318), the PI3Kα-selective inhibitor and degrader alpelisib significantly improved median progression-free survival when added to fulvestrant in patients with phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*)–mutated, hormone receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer. We assessed health-related quality of life using patient-reported outcome measures in these patients.

MATERIALS AND METHODS In the *PIK3CA*-mutant cohort, 341 patients were randomly assigned 1:1 to receive alpelisib 300 mg daily or placebo plus fulvestrant 500 mg on days 1 and 15 of cycle 1 and on day 1 of subsequent 28-day cycles. Patient-reported outcomes were evaluated with the European Organisation for Research and Treatment of Cancer QoL of Cancer Patients and Brief Pain Inventory-Short Form questionnaires. Changes from baseline and time to 10% deterioration were analyzed using repeated measurement models and Cox models, respectively.

RESULTS Global Health Status/QoL and functional status were maintained from baseline (mean changes < 10 points) in the alpelisib (overall change from baseline [95% CI], −3.50 [−8.02 to 1.02]) and placebo arms (overall change from baseline [95% CI], 0.27 [−4.48 to 5.02]). Overall treatment effect in Global Health Status/QoL was not significantly different between arms (−3.77; 95% CI, −8.35 to 0.80; $P = .101$). Time to 10% deterioration for Global Health Status/QoL was similar between arms (hazard ratio, 1.03; 95% CI, 0.72 to 1.48). Compared with placebo, deterioration in social functioning and in diarrhea, appetite loss, nausea or vomiting, and fatigue symptom subscales occurred with alpelisib. Numerical improvement in Worst Pain was observed with alpelisib versus placebo (42% *v* 32%, week 24; $P = .090$).

CONCLUSION In SOLAR-1, there was no statistical difference in deterioration of Global Health Status/QoL between arms, whereas symptom subscales favored placebo for diarrhea, appetite loss, nausea or vomiting, and fatigue, known side effects of alpelisib. Treatment decisions must consider efficacy and tolerability; taken with clinical efficacy, these results support the benefit-risk profile of alpelisib in patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative *PIK3CA*-mutated advanced breast cancer.

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ASSOCIATED CONTENT

Data Supplement
Protocol

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

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INTRODUCTION

Hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2−) breast cancer subtypes comprise > 70% of breast cancer cases in the United States.[1,2] The recommended standard of care for initial treatment in patients with HR+, HER2− advanced breast cancer (ABC) is the sequential use of multiple lines of endocrine-based therapy (ET).[3] This approach is justified by the need to maintain quality of life (QoL) as long as possible in patients with ABC, before switching to chemotherapy. Three classes of targeted therapies—mammalian target of rapamycin inhibitors, CDK4/6 inhibitors, and PI3K inhibitors—improved progression-free survival (PFS) when combined with ET and therefore delayed chemotherapy.[1,4,5] These three classes of targeted therapies are now considered standard of care. The strategy of adding targeted therapies to ET, before initiating chemotherapy, implies that these treatments maintain QoL. Several studies have

CONTEXT

Key Objective

In SOLAR-1, alpelisib plus fulvestrant demonstrated efficacy in patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*)–mutated advanced breast cancer. This analysis examined the effect of the addition of alpelisib to fulvestrant on health-related quality of life (HRQoL) using the European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients and Brief Pain Inventory-Short Form questionnaires in patients with *PIK3CA*-mutated disease.

Knowledge Generated

Patients had high baseline HRQoL; overall HRQoL was maintained despite some adverse events. The European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients Social functioning subscale and several symptom subscale scores (diarrhea, appetite loss, nausea or vomiting, and fatigue) favored placebo over alpelisib but are consistent with adverse events observed with alpelisib plus fulvestrant in clinical trials.

Relevance

Building on previous SOLAR-1 data demonstrating the efficacy and tolerability of alpelisib plus fulvestrant in patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative *PIK3CA*-mutated advanced breast cancer, this analysis supports further consideration of alpelisib as a well-tolerated treatment option for this population.

consistently shown that CDK4/6 inhibitors maintain QoL in patients with ABC.[6-8] However, QoL data have not been reported for patients treated with a PI3K inhibitor. Mutations in the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) gene occur in about 40% of patients with HR+, HER2− breast cancer[1,9-11] and are associated with poor prognosis for patients with ABC.[11,12]

SOLAR-1, a phase III, randomized, placebo-controlled trial, evaluated alpelisib, an α-selective PI3K inhibitor, in combination with fulvestrant in patients with recurrence or progression of HR+, HER2− ABC on or after previous treatment with aromatase inhibitor–based treatment.[1,13] Alpelisib plus fulvestrant increased median PFS (mPFS) (11.0 months; 95% CI, 7.5 to 14.5) versus placebo plus fulvestrant (5.7 months; 95% CI, 3.7 to 7.4; hazard ratio [HR], 0.65; $P < .001$) in patients with *PIK3CA*-mutated ABC.[1] Because PI3Kα is involved in the physiology of normal tissues, targeting PI3Kα led to several expected adverse events (AEs), including hyperglycemia, diarrhea, and rash.[1,14]

Given the palliative nature of many ABC treatments, health-related QoL (HRQoL) is an important factor in assessing the risk-benefit profile of treatments.[15,16] Patients with breast cancer often experience chronic pain, fatigue, and impaired QoL.[17] In advanced stages, pain is more prevalent and causes distress. Pain is associated with disease progression and treatment side effects and is a factor in treatment decisions for patients with advanced cancer.[18,19] Thus, understanding the effect of alpelisib on HRQoL and pain is key to further discerning its therapeutic benefit and use in treatment sequence.[20] Here, we evaluated the combination of alpelisib plus fulvestrant on HRQoL in patients with *PIK3CA*-mutant, HR+, HER2− ABC in the SOLAR-1 trial using standardized patient-reported outcomes (PROs) frequently used in clinical trials of patients with ABC[7,21-23] and report the results from our analysis.

MATERIALS AND METHODS

Patients and Study Design

SOLAR-1 was a phase III, randomized, double-blind, placebo-controlled trial and was recently published.[1] Briefly, the study was designed to include two cohorts of patients with HR+, HER2− ABC: (1) *PIK3CA*-mutant and (2) *PIK3CA*-nonmutant. Patients were randomly assigned 1:1 within each cohort to receive alpelisib or placebo, plus fulvestrant. Per-protocol analyses of PROs were secondary or exploratory end points for each cohort separately. Because the trial met the primary efficacy objective only in the *PIK3CA*-mutant cohort, further analyses of PROS were conducted only in this cohort. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by an independent ethics committee and institutional review board at each center. Further details are given in the Data Supplement (online only).

PRO Assessments

The European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients (EORTC QLQ-C30) (Version 3.0)[24] and Brief Pain Inventory-Short Form (BPI-SF)[25] questionnaire were used to evaluate patients' HRQoL, functional status, and pain. Patients considered the past week in responding to items on the EORTC QLQ-C30 and the past 24 hours for the BPI-SF. Further details are given in the Data Supplement.

Statistical Analyses

Analysis of PRO data was conducted from the prespecified *PIK3CA*-mutant cohort of patients who were randomly assigned to study treatment in SOLAR-1. The EORTC QLQ-C30 Global Health Status/QoL (change from baseline score and time to 10% deterioration [TTD]) was prespecified as a secondary end point and a primary PRO variable of interest. Physical, Emotional, and Social functioning of EORTC QLQ-C30 and Worst Pain, Pain Severity Index, and Pain Interference Index of BPI-SF were prespecified as secondary PRO variables of interest, because these are considered important aspects of QoL for patients with ABC. Other scale scores were also assessed for completeness.

Time to deterioration in Global Health Status/QoL and Physical, Emotional, and Social functioning was defined as a worsening in score by ≥ 10% compared with baseline with no later improvement above this threshold during the treatment period or death because of any cause, as supported by EORTC QLQ-C30 interpretation guidelines[26] and previous PRO analyses in patients with HR+, HER2− ABC.[6,7]

Post hoc analyses were conducted for Global Health Status/QoL on subgroups by baseline glucose level as hyperglycemia was one of the most prevalent AEs reported.[27] Post hoc analyses of pattern-mixture models were conducted for the Global Health Status/QoL change from baseline score to assess the impact of missing data that were not missing at random.[28] Further details are given in the Data Supplement.

RESULTS

Patient Baseline Characteristics and Compliance Rates

Between July 26, 2015, and July 21, 2017, 341 patients in the *PIK3CA*-mutant cohort were randomly assigned to the alpelisib plus fulvestrant arm (n = 169) or the placebo plus fulvestrant arm (n = 172).[1] Baseline patient characteristics and mean baseline scores of the *PIK3CA*-mutant cohort were balanced between the two treatment arms (Data Supplement and Table 1).[1] Overall, questionnaire compliance rates were high at baseline (≥ 93% for both treatment arms) and at postbaseline visits (generally approximately 90%, ranging from 79% to 95% in the alpelisib treatment arm and 84% to 95% in the placebo treatment arm of the *PIK3CA*-mutant cohort for visits with ≥ 10 patients in each treatment arm; Data Supplement). The number of missing questionnaires was comparable between the two treatment arms, and no pattern was observed.

EORTC-QLQ-C30

Global Health Status/QoL. The Global Health Status/QoL scale score was the main PRO variable of interest, and baseline scores were similar in both treatment arms, including for functioning and symptom scales. Mean (standard deviation) baseline Global Health Status/QoL scores were 69.7 (21.0) compared with 68.0 (21.6) in the alpelisib and placebo treatment arms, respectively (Table 1). Baseline functioning scales and symptom scale scores in both treatment arms were comparable with other populations in this disease.[23]

Over time, there was a numeric decrease in Global Health Status/QoL scores relative to baseline in both treatment arms. There was no overall change from baseline over time in the alpelisib treatment arm (−3.50; 95% CI, −8.02 to 1.02) or the placebo treatment arm (0.27; 95% CI, −4.48 to 5.02). No statistically significant between-group differences were observed in patterns of change over time (Fig 1A). Similarly, overall treatment effect in Global Health Status/QoL was not statistically significant between both treatment arms (−3.77; 95% CI, −8.35 to 0.80; $P = .101$; Fig 1A). Through week 96, adjusted mean changes from baseline were within five points for all visits in both treatment arms with a mean between-treatment difference of < 3 points for all visits. The results from the TTD analyses were also consistent with the observed mean changes and did not demonstrate differences between the two treatment arms over 28 months (HR, 1.03; 95% CI, 0.72 to 1.48; Fig 2).

Functional subscales. In both treatment arms, baseline EORTC QLQ-C30 functioning scale scores were similar (Table 1). In the alpelisib treatment arm (*v* the placebo treatment arm), the mean changes from baseline were −2.89 for Physical (95% CI, −6.86 to 1.08; *v* −3.57; 95% CI, −7.66 to 0.51), −1.84 for Emotional (95% CI, −6.58 to 2.90; *v* −1.97; 95% CI, −6.85 to 2.91), −5.29 for Social (95% CI, −10.27 to −0.31; *v* −0.31; 95% CI, −5.48 to 4.86), −6.59 for Role (95% CI, −12.55 to −0.63; *v* −7.07; 95% CI, −13.18 to −0.96), and −2.05 for Cognitive (95% CI, −6.00 to 1.90; *v* −3.47; 95% CI, −7.54 to 0.59). There was no difference in overall adjusted mean changes from baseline in functioning subscale scores between treatment arms except for a larger deterioration in Social functioning in the alpelisib treatment arm (treatment difference, −4.98; 95% CI, −8.86 to −1.09; $P = .012$; Fig 1B). TTD analyses of functional scales showed no statistical differences in the TTD of Physical (HR, 0.86; 95% CI, 0.58 to 1.27), Emotional (HR, 0.92; 95% CI, 0.62 to 1.37), or Social (HR, 1.06; 95% CI, 0.70 to 1.61) functioning subscale scores (Fig 3).

Symptom subscales. Baseline EORTC QLQ-C30 symptom subscale scores were similar between treatment arms (Table 1). Overall mean changes from baseline in appetite loss (10.96 *v* 1.83; $P < .001$), diarrhea (13.39 *v* 1.63; $P < .001$), nausea or vomiting (6.97 *v* 4.14; $P = .019$), and fatigue (9.85 *v* 3.34; $P = .014$) displayed worsening scores, whereas the constipation score (−8.54 *v* −3.61; $P = .004$) improved in the alpelisib treatment arm. Other symptom scores indicated no statistical differences between treatment arms; however, there was numeric worsening of pain

TABLE 1. Mean Baseline Scores of the *PIK3CA*-Mutant Cohort

Baseline Characteristic	Alpelisib Plus Fulvestrant (n = 169[a])	Placebo Plus Fulvestrant (n = 172[b])
EORTC QLQ-C30 mean baseline (SD) scores		
Global Health Status/QoL	69.7 (21.0)	68.0 (21.6)
EORTC QLQ-C30 functioning scales		
Physical functioning	80.9 (19.1)	79.7 (20.2)
Emotional functioning	78.9 (19.7)	74.5 (21.0)
Social functioning	87.2 (20.9)	84.0 (23.3)
Role functioning	82.3 (27.0)	80.9 (26.5)
Cognitive functioning	89.6 (16.9)	88.4 (15.5)
EORTC QLQ-C30 symptom scales		
Pain	26.0 (24.9)	25.1 (23.5)
Fatigue	24.4 (20.3)	28.9 (22.4)
Nausea and vomiting	3.7 (9.6)	4.6 (12.5)
Dyspnea	12.0 (23.1)	11.5 (23.2)
Insomnia	21.5 (26.8)	28.4 (25.6)
Appetite loss	9.9 (18.3)	12.1 (20.4)
Constipation	13.3 (21.7)	13.2 (21.3)
Diarrhea	3.7 (11.1)	3.0 (10.3)
Financial Impact	10.1 (20.9)	15.3 (23.7)
BPI-SF mean baseline (SD) scores		
Worst Pain	2.7 (2.8)	2.9 (2.8)
Pain Severity Index (worst, least, average, and current pain)	2.2 (2.2)	2.2 (2.1)
Pain Interference Index	1.7 (2.35)	1.9 (2.42)

Abbreviations: BPI-SF, Brief Pain Inventory Short Form; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients questionnaire; *PIK3CA,* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SD, standard deviation.

[a]One man was enrolled in the alpelisib group in the cohort of patients with *PIK3CA*-mutated tumors. All other study participants were postmenopausal women.

[b]One patient in the cohort of patients with *PIK3CA*-mutated tumors who was randomly assigned to placebo was not treated.

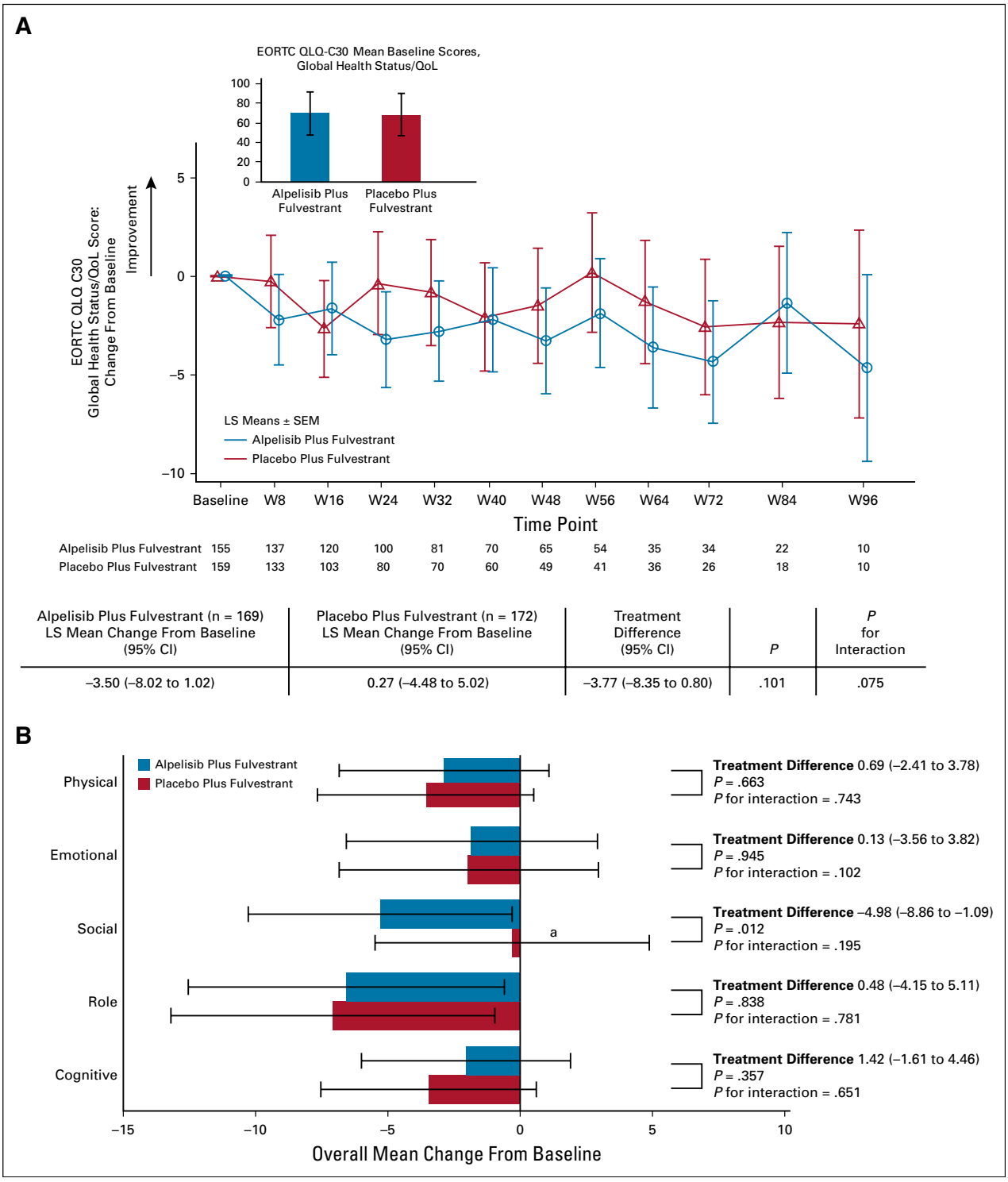
in the placebo arm (0.95 [95% CI, −4.60 to 6.50] *v* 4.34 [95% CI, −1.38 to 10.05]; Fig 4).

Pattern-Mixture Model Sensitivity Analysis for EORTC-QLQ-C30 Global Health Status/QoL

As of the data cutoff, the sample size reduced to < 50% of the randomly assigned sample by week 32 in both treatment arms because of disease progression or treatment discontinuation. To assess the impact of missing data, we conducted the pattern-mixture model as a sensitivity analysis for Global Health Status/QoL. Patients were grouped into three dropout pattern groups based on treatment status and reason for discontinuation: (1) treatment ongoing as of the data cutoff date (19% in the alpelisib treatment arm and 17% in the placebo treatment arm; these are missing data because of administrative reasons), (2) experiencing an AE that led to treatment termination (25% and 5%, respectively), and (3) others. Among patients remaining treated as of data cutoff, the treatment differences in least squares mean change from baseline scores were between −0.1 and −6.3 for all timepoints up to week 84 (after when, < 10 patients remained in each treatment group). Among patients with AEs and treatment discontinuation, the least squares mean change scores differed from −6.8 to 15.5 between treatment arms, with large variation in the placebo arm (n ≤ 8). Among patients with treatment discontinuation because of other reasons, the results resemble the group of ongoing treatment (Data Supplement). In all three groups, there was no significant difference in Global Health Status/QoL between the alpelisib and the placebo treatment arms.

EORTC-QLQ-C30 Global Health Status/QoL Based on Baseline Glucose Level

The change from baseline in Global Health Status/QoL was analyzed using mixed-effects models for repeated measures by baseline glucose level to ascertain the impact of hyperglycemia, the most frequent grade 3 or 4 AE for patients receiving alpelisib, on patients' HRQoL. There were no significant changes from baseline in global QoL in



Alpelisib Plus Fulvestrant (n = 169) LS Mean Change From Baseline (95% CI)	Placebo Plus Fulvestrant (n = 172) LS Mean Change From Baseline (95% CI)	Treatment Difference (95% CI)	*P*	*P* for Interaction
−3.50 (−8.02 to 1.02)	0.27 (−4.48 to 5.02)	−3.77 (−8.35 to 0.80)	.101	.075

FIG 1. (A) Changes from baseline in EORTC QLQ-C30 Global Health Status/QoL scale score and (B) overall mean change from baseline in EORTC QLQ-C30 functioning subscale scores, *PIK3CA*-mutant cohort. In (A), error bars for mean baseline scores indicate ± SD; error bars for LS means for change from baseline indicate ± SEM. Changes from baseline over time were estimated from a repeated measurement model that included terms for treatment, stratification factors, time, treatment-by-time interaction, and baseline score; to ensure the model provided stable estimates, data were cut when patient numbers were < 10 in each treatment arm. Overall mean changes from baseline scores were estimated using repeated measurement models that included terms for treatment, stratification factors, time, and baseline score. The treatment-by-time interaction term was tested, and none was significant. This analysis only included assessments up to the time point at which there were at least 10 patients in each of the treatment groups. Changes > 0 indicate improvement from baseline. In (B), error bars indicate 95% CIs; [a]indicates $P < .05$ for treatment difference. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients questionnaire; LS, least squares; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QoL, quality of life; W, week.

either treatment arm in patients with normal baseline glucose levels or patients with elevated glucose levels at baseline (Data Supplement). No differences between treatment arms were observed in patients with normal or elevated baseline glucose levels; however, formal interaction tests were not conducted. The results in the diabetic subgroup are not reported because of small sample size.

BPI-SF Worst Pain, Pain Severity Index, and Pain Interference Index Analyses

Baseline scores were similar in both treatment arms for the BPI-SF Worst Pain, Pain Severity Index, and Pain Interference Index (Table 1). Worst Pain item and Pain Severity Index suggested a delay in worsening of pain and pain severity in the alpelisib treatment arm compared with the placebo treatment arm (Fig 5A and 5B). At week 24, higher numeric improvement (42% *v* 32%) and lower numeric worsening (24% *v* 35%) in Worst Pain were observed in the alpelisib treatment arm ($P = .090$), with similar numeric changes observed at week 8 and week 16 (Data Supplement). Similar observations were made for patients with and without pain at baseline (Data Supplement). Responder analysis in the subset of patients with pain at baseline showed consistently greater numeric response with alpelisib treatment versus placebo at week 16 and week 24 (Data Supplement).

DISCUSSION

The combination of alpelisib plus fulvestrant significantly improved mPFS compared with placebo plus fulvestrant in the *PIK3CA*-mutant cohort in SOLAR-1. Data in this analysis demonstrated no clinically meaningful differences in HRQoL in the alpelisib plus fulvestrant arm versus the placebo plus fulvestrant arm based on previously established criteria of EORTC-QLQ-C30 meaningful change (5%).[26,29] Baseline Global Health Status/QoL and Functioning subscale scores were maintained, except with reduction in Social functioning. No statistical or clinically meaningful difference was observed in TTD for EORTC QLQ-C30 Global Health Status/QoL scores and Physical, Emotional, or Social functioning subscale scores between treatment arms. The EORTC QLQ-C30 and BPI-SF results signaled a delay in worsening of pain and numeric improvement in worst pain in patients receiving alpelisib treatment.

Patients treated with alpelisib plus fulvestrant experienced some deterioration in the EORTC QLQ-C30 Social functioning subscale and some worsening in EORTC QLQ-C30 symptom subscale scores such as diarrhea and appetite loss. The declines in these symptom scores were consistent with the AE profiles observed with alpelisib plus fulvestrant treatment.[1,27] Diarrhea and appetite loss could have contributed to the reduction in social functioning observed in our analysis, as diarrhea is known to have an adverse impact on HRQoL.[30-32]

Recognizing that GI AEs are associated with poor HRQoL,[33] our observation that overall HRQoL is maintained in patients taking alpelisib plus fulvestrant suggests that the negative impact of AE-related symptoms on HRQoL is mitigated in part by the delay in disease progression. In SOLAR-1, some patients permanently discontinued alpelisib treatment or placebo because of AEs, but were allowed to continue fulvestrant,[1] which might have also contributed to the delay in worsening of HRQoL. Interestingly, mPFS is shorter than TTD in each functioning subscale, suggesting that negative impacts on functioning scores are primarily due to progressive disease, not study treatment. These results support the role of PROs in assessing drug efficacy and assisting in identifying preferred therapies by weighing the impact of maintaining QoL with increasing life expectancy.[34,35] Another potential explanation is that a delay in worsening of pain might have reduced the negative impact on QoL because of AE-related symptoms.

Considering the goal of maintaining or improving HRQoL in patients with HR+, HER2− ABC, data from the phase III BOLERO-2 trial indicated that treatment with everolimus plus exemestane versus placebo plus exemestane did not diminish patient HRQoL.[21] More recently, HRQoL was maintained in patients with HR+, HER2− ABC treated with CDK4/6 inhibitors compared with their respective control arms in the phase III MONALEESA-3 (ribociclib), PALOMA-3 (palbociclib), and MONARCH-2 (abemaciclib) trials,[6-8] whereas a longer TTD was observed in patients treated with ribociclib plus ET compared with the placebo arm in the phase III MONALESSA-7 trial.[36] Similarly, an improvement in HRQoL was observed in patients with a germline *BRCA1* or *BRCA2* mutation and HER2− metastatic breast cancer treated with olaparib monotherapy compared with chemotherapy.[37] However, an important consideration in trials that evaluate targeted therapies, including in SOLAR-1, is that patients with HR+, HER2− ABC already begin with a relatively high HRQoL.[7,21]

As commonly seen in oncology studies with longitudinal collection of QoL questionnaires, one limitation is missing data. The questionnaire response rates were generally high and similar across treatment arms. Although the sample size was reduced to less than half of that at baseline by week 40, among patients on treatment (patients without disease progression or treatment discontinuation), the response rate for HRQoL assessment remained high. Following United States National Research Council principles for analyzing incomplete data,[28] we assessed reasons for missing data and performed a sensitivity analysis. At the time of data cutoff, 25% of patients in the alpelisib arm and 19% of patients in the placebo remained on treatment.[1] Disease progression (55% in the alpelisib arm and 68% in the placebo arm) was the main reason for treatment discontinuation and missing QoL data.[1] Very few patients discontinued study treatment (alpelisib/placebo plus fulvestrant) because of toxicity (3% and 2% in the alpelisib

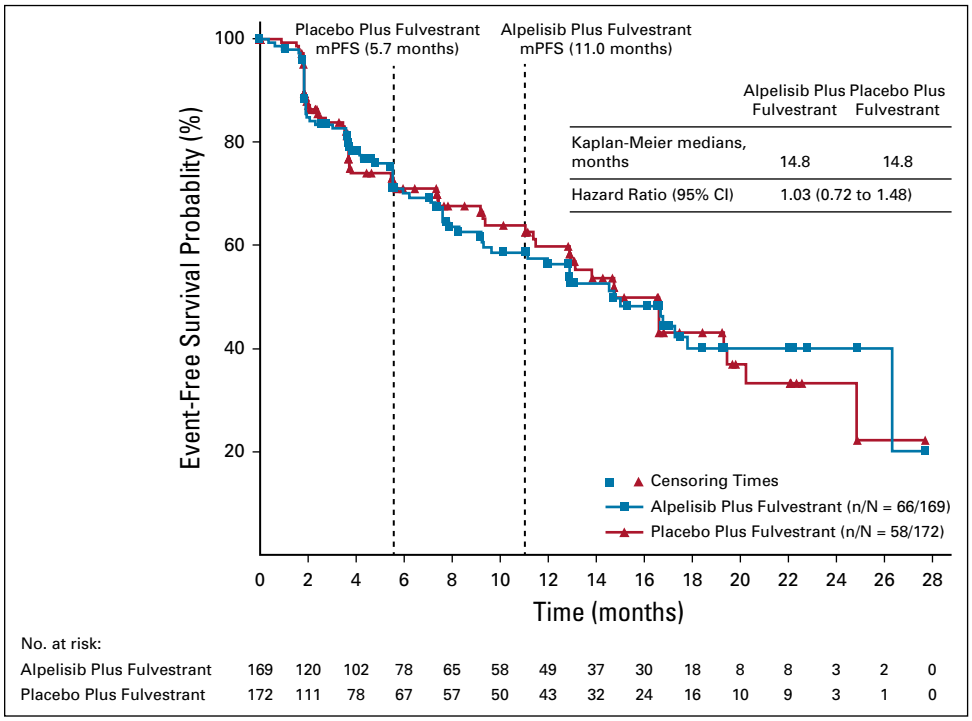


FIG 2. Time to 10% deterioration in European Organisation for Research and Treatment of Cancer Global Health Status/quality of life scale score, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha–mutant cohort. Data include all randomly assigned patients in the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha–mutant cohort. mPFS, median progression-free survival.

and placebo arms, respectively).[1] Whereas missing data because of administrative reasons (eg, the data cutoff occurred when patients had not reached visits for treatment and assessment) can be considered noninformative, missing data because of disease progression or toxicity are often associated with deterioration of QoL. Therefore, censoring patients at the time of disease progression or treatment discontinuation per study design can underestimate the rate of QoL deterioration. Analysis of change from baseline scores using mixed models assumes that data are missing at random, that is, missingness is only related to observed data. The potential for data missing not at random, which could result in a biased estimate of treatment effect, cannot be excluded. Pattern-mixture models, which do not assume that data are missing at random, were used to assess the robustness of the estimated treatment effect. The results of these analyses suggested that in all treatment discontinuation groups, Global Health Status/QoL in the

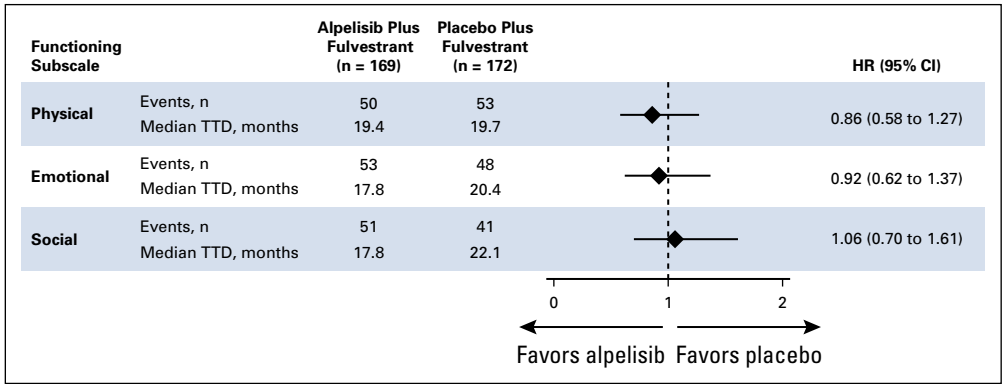


FIG 3. TTD in European Organisation for Research and Treatment of Cancer functioning subscale scores, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha–mutant cohort. HR, hazard ratio; TTD, time to 10% deterioration.

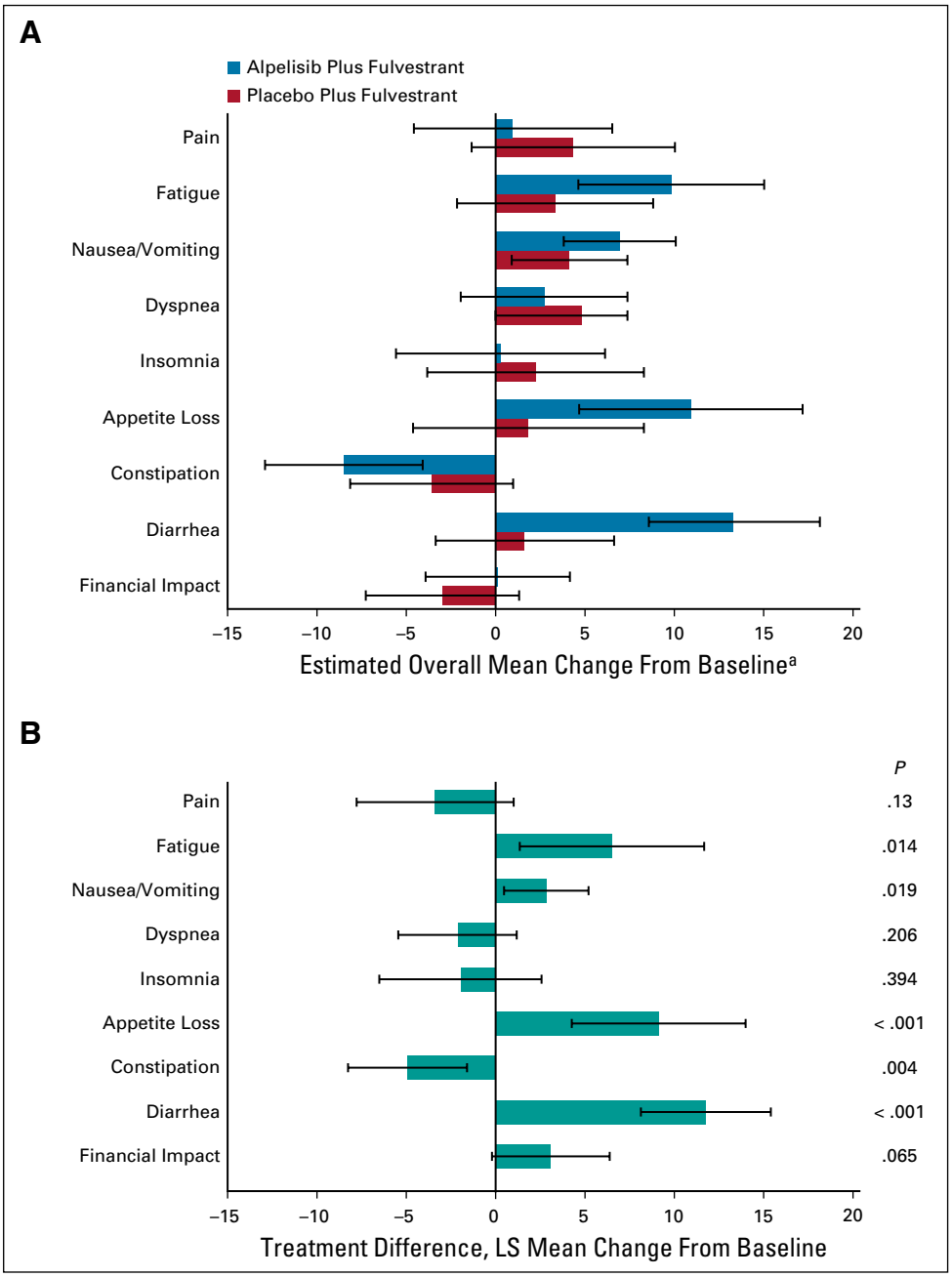


FIG 4. (A) Estimated overall mean changes from baseline[a] and (B) treatment effect in European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients symptom scores, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha–mutant cohort. This analysis only included assessments up to the time point at which there were at least 10 patients in each of the treatment arms. All the time-by-treatment interaction was > 0.05; the overall treatment effects were estimated using the repeated measurements models that included terms for treatment, stratification factors, time, and baseline score, with bars indicating 95% CIs. [a]Overall mean changes from baseline scores were estimated using repeated measurement models that included terms for treatment, stratification factors, time, and baseline score; changes < 0 indicate improvement from baseline, with bars indicating 95% CIs. LS, least squares.

alpelisib arm was not different from the placebo arm, although sample sizes were relatively small. Another potential limitation relates to change over time in Global Health Status/QoL. The 95% CI for the change from baseline in the alpelisib arm ranged from −8.02 to 1.02, and the difference compared with placebo is −3.77 (95% CI, −8.35 to 0.80; $P = .101$). Although a statistical difference between the two treatment arms was not observed, the upper limit of

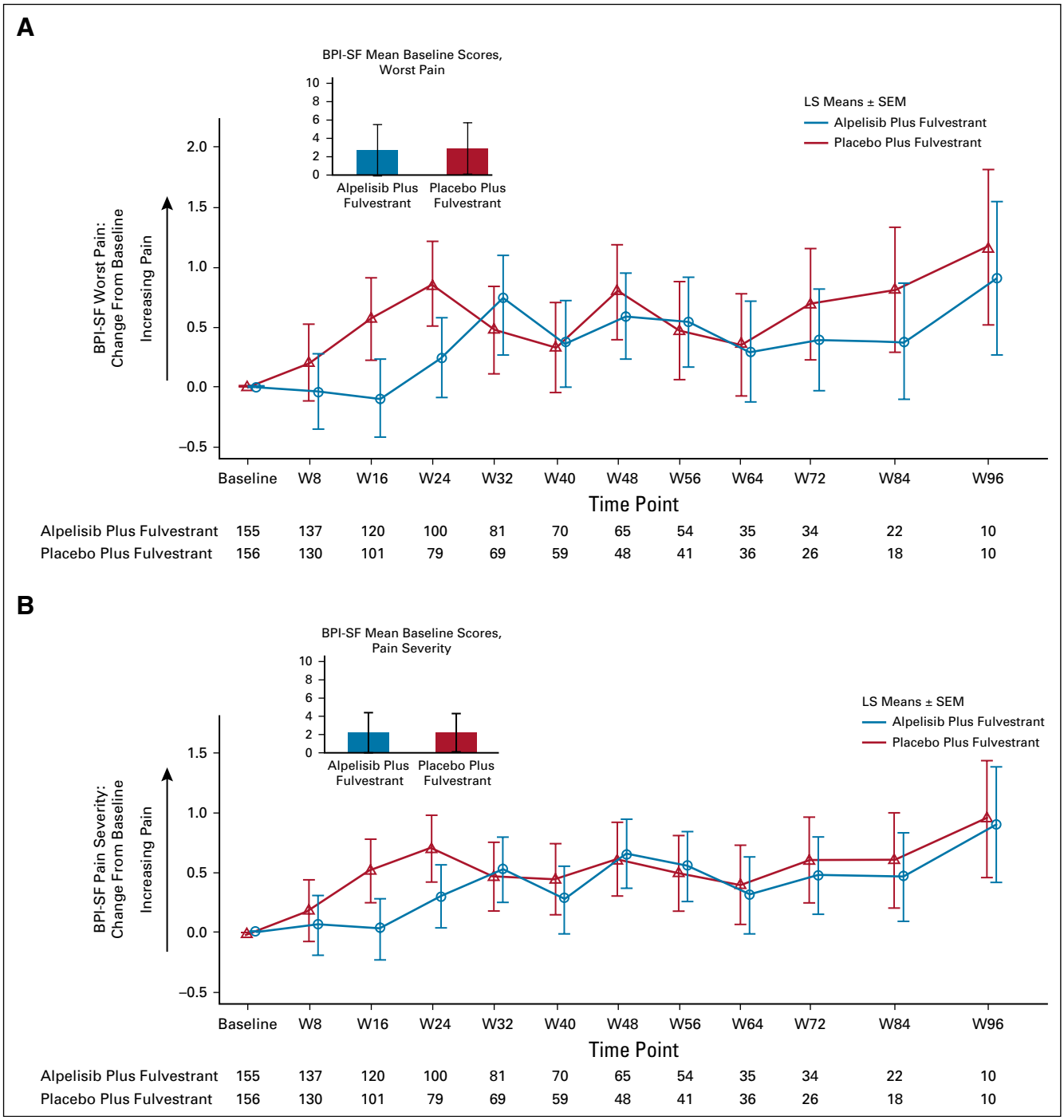


FIG 5. Changes from baseline in (A) BPI-SF Worst Pain and (B) Pain Severity Index, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha–mutant cohort. (A) and (B) The time profile provides the average estimates for the change from baseline for the interval from baseline up to the respective cycle as derived from the repeated measurement model. The mixed-effect model includes terms for treatment, stratification factors, baseline value, time, and time × treatment interaction. This analysis only includes assessments up to the time point at which there were at least 10 patients in each of the treatment arms. Changes from postbaseline could not be calculated for all patients. BPI-SF, Brief Pain Inventory Short Form; LS, least squares; W, week.

the 95% CI was close to 0. However, the magnitude of the difference was small (both the mean difference and the lower limit are within 10 points from 0). When evaluating treatment effects, both the statistical significance and the magnitude should be considered. Together, these results support that Global Health Status/QoL was maintained with alpelisib.

In conclusion, here, we report that patients with HR+, HER2− *PIK3CA*-mutated ABC treated with alpelisib plus fulvestrant did not experience a significant decline in their

overall HRQoL measured as Global Health Status/QoL. Although symptom scores for diarrhea, appetite loss, nausea or vomiting, and fatigue favored the placebo arm, these are known AEs of alpelisib in clinical trials. Physical, Emotional, Cognitive, and Role functioning scores were similar to those observed in the placebo group. Clinical decision making should include consideration of these results along with the statistically significant and clinically meaningful PFS observed with the addition of alpelisib to fulvestrant in patients with HR+, HER2− *PIK3CA*-mutated ABC.

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DATA SHARING STATEMENT

Novartis is committed to sharing with qualified external researchers, access to patient-level data, and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Patient-Reported Outcomes in Patients With *PIK3CA*-Mutated Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer From SOLAR-1

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