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ORIGINAL ARTICLE

Alpelisib plus fulvestrant for *PIK3CA*-mutated, hormone receptor-positive, human epidermal growth factor receptor-2—negative advanced breast cancer: final overall survival results from SOLAR-1

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Background: Activation of the phosphatidylinositol-3-kinase (PI3K) pathway via *PIK3CA* mutations occurs in 28%-46% of hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2−) advanced breast cancers (ABCs) and is associated with poor prognosis. The SOLAR-1 trial showed that the addition of alpelisib to fulvestrant treatment provided statistically significant and clinically meaningful progression-free survival (PFS) benefit in *PIK3CA*-mutated, HR+, HER2− ABC.

Patients and methods: Men and postmenopausal women with HR+, HER2− ABC whose disease progressed on or after aromatase inhibitor (AI) were randomized 1 : 1 to receive alpelisib (300 mg/day) plus fulvestrant (500 mg every 28 days and once on day 15) or placebo plus fulvestrant. Overall survival (OS) in the *PIK3CA*-mutant cohort was evaluated by Kaplan—Meier methodology and a one-sided stratified log-rank test was carried out with an O'Brien—Fleming efficacy boundary of $P \leq 0.0161$.

Results: In the *PIK3CA*-mutated cohort ($n = 341$), median OS [95% confidence interval (CI)] was 39.3 months (34.1-44.9) for alpelisib-fulvestrant and 31.4 months (26.8-41.3) for placebo-fulvestrant [hazard ratio (HR) = 0.86 (95% CI, 0.64-1.15; $P = 0.15$)]. OS results did not cross the prespecified efficacy boundary. Median OS (95% CI) in patients with lung and/or liver metastases was 37.2 months (28.7-43.6) and 22.8 months (19.0-26.8) in the alpelisib-fulvestrant and placebo-fulvestrant arms, respectively [HR = 0.68 (0.46-1.00)]. Median times to chemotherapy (95% CI) for the alpelisib-fulvestrant and placebo-fulvestrant arms were 23.3 months (15.2-28.4) and 14.8 months (10.5-22.6), respectively [HR = 0.72 (0.54-0.95)]. No new safety signals were observed with longer follow-up.

Conclusions: Although the analysis did not cross the prespecified boundary for statistical significance, there was a 7.9-month numeric improvement in median OS when alpelisib was added to fulvestrant treatment of patients with *PIK3CA*-mutated, HR+, HER2− ABC. Overall, these results further support the statistically significant prolongation of PFS observed with alpelisib plus fulvestrant in this population, which has a poor prognosis due to a *PIK3CA* mutation.

ClinicalTrials.gov Id: NCT02437318.

Key words: alpelisib, overall survival, *PIK3CA*, PI3Kα, breast cancer

INTRODUCTION

Mutations in the *PIK3CA* gene, which encodes the p110α subunit of phosphatidylinositol-3-kinase (PI3K), are present in 28%-46% of people with hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2−) advanced breast cancer (ABC),[1-8] and

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are associated with chemoresistance and poor prognosis.[8,9] This includes reduced overall survival (OS), reported as 19.6 months, versus 23.5 months for those without a *PIK3CA* mutation, in the SAFIR-02 study.[8]

Alpelisib is an orally bioavailable, α-selective, PI3K inhibitor that is 50 times more potent against PI3Kα than other isoforms.[10] In preclinical models, alpelisib demonstrated a dual mechanism of action (MOA) by inhibiting PI3K and inducing p110α degradation in a dose-dependent manner.[11] Alpelisib demonstrated statistically significant efficacy in combination with fulvestrant following prior aromatase inhibitor (AI)-based treatment in the SOLAR-1 trial (NCT02437318).[10,12-14] SOLAR-1 is a global, phase 3, prospective study that assessed a PI3Kα inhibitor—and demonstrated clinically relevant progression-free survival (PFS) benefit—in patients with HR+, HER2−, *PIK3CA*-mutated ABC: median PFS was 11.0 months in the alpelisib plus fulvestrant arm versus 5.7 months in the placebo plus fulvestrant arm [hazard ratio (HR) = 0.65; 95% confidence interval (CI), 0.50-0.85; $P = 0.00065$], with respective overall response rates of 26.6% (95% CI, 20.1-34.0) versus 12.8% (95% CI, 8.2-18.7)[12,15] and a safety profile consistent with previous reports.[16,17] Patients with ≥1 of 11 specific *PIK3CA* mutations as determined in tumor tissue could enroll.[12,18] Consistent PFS benefit was observed regardless of location of *PIK3CA* mutation (E542X, E545X, and H1047X), suggesting that a predictive value of specific *PIK3CA* mutations was not observed.[12,16,17] At the time of the primary analysis, OS data were not yet mature.[13] Here, we report results from the prespecified final inferential analysis of OS for the *PIK3CA*-mutated cohort of SOLAR-1.

PATIENTS AND METHODS

Trial design and patients

Details of the SOLAR-1 trial were described previously.[12] Briefly, postmenopausal women or men with confirmed estrogen receptor-positive (ER+) and/or progesterone receptor-positive (PgR+), HER2− ABC that progressed on or after prior AI were eligible for SOLAR-1. No prior chemotherapy in the advanced setting was allowed. Patients were enrolled in one of two cohorts based on the presence of a *PIK3CA* mutation as tested in tumor tissue at the time of study screening. Patients were stratified by the presence of lung or liver metastases and by prior treatment with cyclin-dependent kinase 4/6 inhibitors (CDK4/6i). Patients in both the *PIK3CA*-mutant and non-mutant cohorts were randomized 1 : 1 to receive either 300 mg alpelisib orally (p.o.) once daily (od) or placebo in combination with 500 mg fulvestrant intramuscularly (i.m.), starting on days 1 and 15 of cycle 1, then on day 1 of every subsequent 28-day cycle (±3 days). Treatment crossover from placebo plus fulvestrant to alpelisib plus fulvestrant was not permitted. Dose modifications were permitted in the event of severe to intolerable adverse reaction; up to two dose reductions were allowed (only one was allowed for pancreatitis), after which the patient was discontinued from treatment with alpelisib or placebo. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all participants for trial participation and biomarker sample collection.[12]

Endpoints

As previously reported, the primary endpoint in SOLAR-1 was investigator-assessed PFS per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in the cohort of patients with *PIK3CA*-mutated cancer.[12] The key secondary endpoint, OS in the cohort of patients with *PIK3CA*-mutated cancer, was to be evaluated if the primary study endpoint was met. Exploratory endpoints analyzed included progression-free survival 2 (PFS2) and time to chemotherapy (TTC), with the latter evaluated post hoc. Per protocol, PFS2 was defined as the time from randomization to the first documented disease progression (PD) on the first new systemic antineoplastic therapy initiated after discontinuation of study treatment, or death from any cause, censored at last contact date. TTC was defined as the time from randomization to date of first administration of chemotherapy. Exploratory OS analysis was conducted in patients with *PIK3CA* mutation in plasma circulating tumor DNA (ctDNA), regardless of their assignment to the *PIK3CA*-mutant or non-mutant cohort per tissue at the time of study screening. Plasma ctDNA was collected at baseline and tested for a *PIK3CA* mutation using the Qiagen therascreen PIK3CA RGQ polymerase chain reaction (PCR) kit. Safety was assessed continuously, per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, in the safety population (mutant and non-mutant cohorts) until 30 days after the last dose of study treatment, as previously reported.[12,19]

Statistical analysis

The key secondary endpoint had 72% power at a one-sided overall 2.0% level of significance to reject the null hypothesis of no treatment effect, using a stratified log-rank test and a three-look sequential design, if the true HR was 0.67, corresponding to an improvement of 15 months in the median OS (assuming 30 months for the control arm and 45 months for the alpelisib arm). The final inferential analysis of OS was prespecified in the protocol to be conducted in the cohort of patients with *PIK3CA*-mutated cancer after documentation of approximately 178 deaths. The type I error probability was controlled using an O'Brien—Fleming spending function independent of the Haybittle—Peto spending function used for PFS; final OS would be statistically significant if $P \leq 0.0161$. OS was analyzed using Kaplan—Meier methodology, and Cox regression, adjusted for stratification parameters, to estimate HR and 95% CIs.

RESULTS

Patients and treatment

Of the 572 patients enrolled in SOLAR-1, 341 were confirmed to have *PIK3CA* mutations detected in tissue and enrolled in the *PIK3CA*-mutant cohort (169 patients in the

Table 1. Patient disposition at data cut-off

Cohort of patients with *PIK3CA*-mutated cancer Patients, *n* (%)[a]	Alpelisib + fulvestrant (*n* = 169)	Placebo + fulvestrant (*n* = 172)
On treatment	21 (12.4)	7 (4.1)
Discontinued treatment	148 (87.6)	164 (95.3)
PD	111 (65.7)	138 (80.2)
Patient/guardian decision	17 (10.1)	7 (4.1)
Physician decision	8 (4.7)	9 (5.2)
AE	5 (3.0)	3 (1.7)
Protocol deviation	4 (2.4)	3 (1.7)
Death	3 (1.8)	4 (2.3)

AE, adverse event; PD, disease progression.
[a] Patients ongoing at the time of the 23 April 2020, data cut-off.

alpelisib plus fulvestrant arm and 172 patients in the placebo plus fulvestrant arm); 231 patients were enrolled in the non-mutant cohort (115 and 116 patients, respectively, in the two treatment arms).

In the *PIK3CA*-mutant cohort, the median follow-up from randomization to data cut-off (23 April 2020) was 42.4 months (range, 33.1-55.7 months). By the time of data cut-off, 21 (12.4%) patients in the alpelisib plus fulvestrant arm versus 7 patients (4.1%) in the placebo plus fulvestrant arm were still receiving study treatment (Table 1). The most common reason for discontinuation in both arms was progressive disease: 65.7% and 80.2% of patients in the alpelisib plus fulvestrant versus placebo plus fulvestrant arms, respectively; 3.0% (n = 5) and 1.7% (n = 3) patients discontinued the treatment phase due to an adverse event (AE). The median duration of exposure to study drug in the cohort of patients with *PIK3CA*-mutated cancer was 5.5 months for alpelisib (range 0-51.4 months) and 8.3 months for fulvestrant (range 0.4-51.4 months) in the alpelisib plus fulvestrant arm, and 4.6 months for placebo (range 0-52.5 months) and 5.5 months for fulvestrant (range 0.5-52.5 months) in the placebo plus fulvestrant arm.

OS

The OS analysis was based on 181 deaths: 87 events in the alpelisib plus fulvestrant arm and 94 in the placebo plus fulvestrant arm. The median follow-up for OS, defined as the time from randomization to OS event or censoring, was 30.8 months (range 0.4-53.4 months). Median OS was 39.3 months (95% CI, 34.1-44.9) in the alpelisib plus fulvestrant arm versus 31.4 months (95% CI, 26.8-41.3) in the placebo plus fulvestrant arm (HR = 0.86; 95% CI, 0.64-1.15; one-sided $P = 0.15$; Figure 1). The prespecified O'Brien—Fleming efficacy boundary ($P \leq 0.0161$) was not crossed.

Subgroup analyses were also carried out and included the study stratification factors of lung/liver metastases and prior CDK4/6is (Figure 2). Although several subgroups had a small number of patients, the OS HR was 0.68 (95% CI, 0.46-1.00) in patients with lung and/or liver metastases. Median OS in patients with lung and/or liver metastases was 37.2 months (95% CI, 28.7-43.6) versus 22.8 months (95% CI, 19.0-26.8) in the alpelisib plus fulvestrant versus placebo plus fulvestrant arms, respectively (Figure 3A).

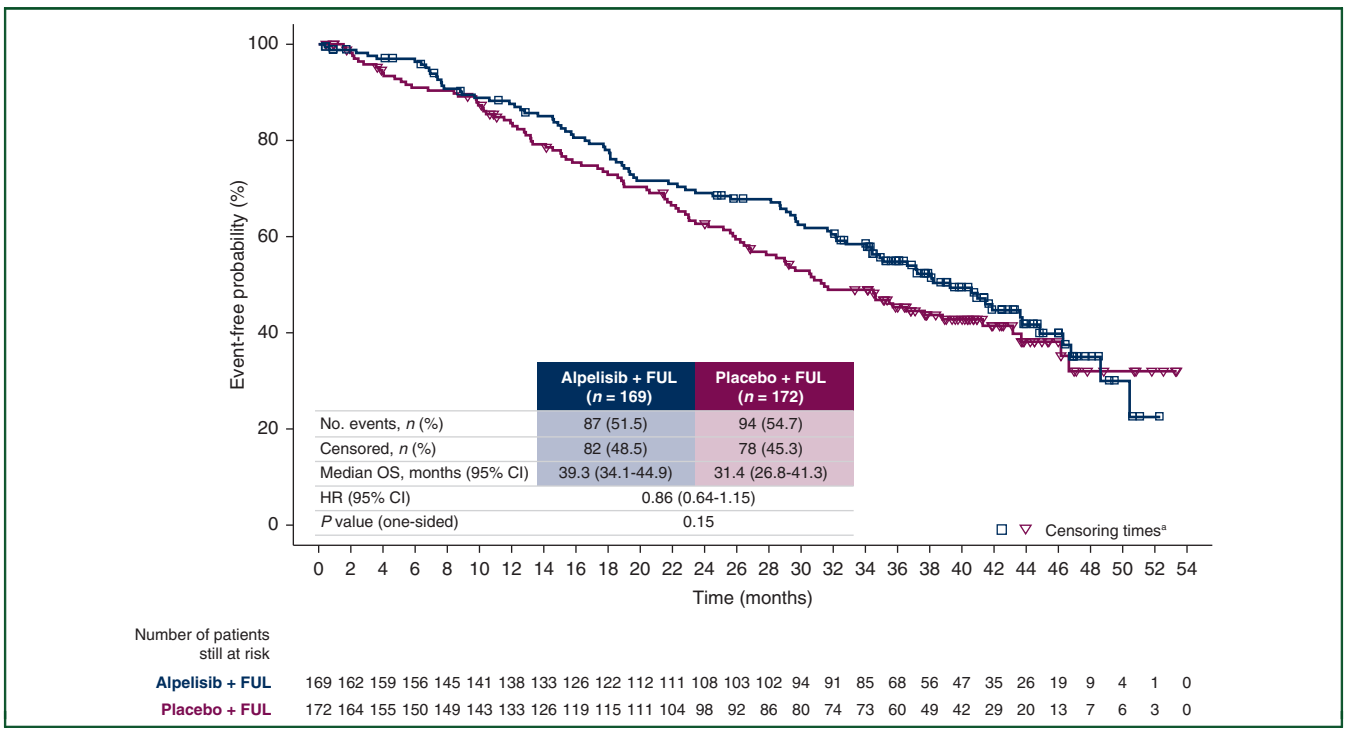

Figure 1. Overall survival in *PIK3CA*-mutant cohort of patients comparing alpelisib plus fulvestrant and placebo plus fulvestrant treatment arms using one-sided stratified log-rank test.
CI, confidence interval; FUL, fulvestrant; HR, hazard ratio; OS, overall survival.
[a] Date of censoring is defined as the last contact date.

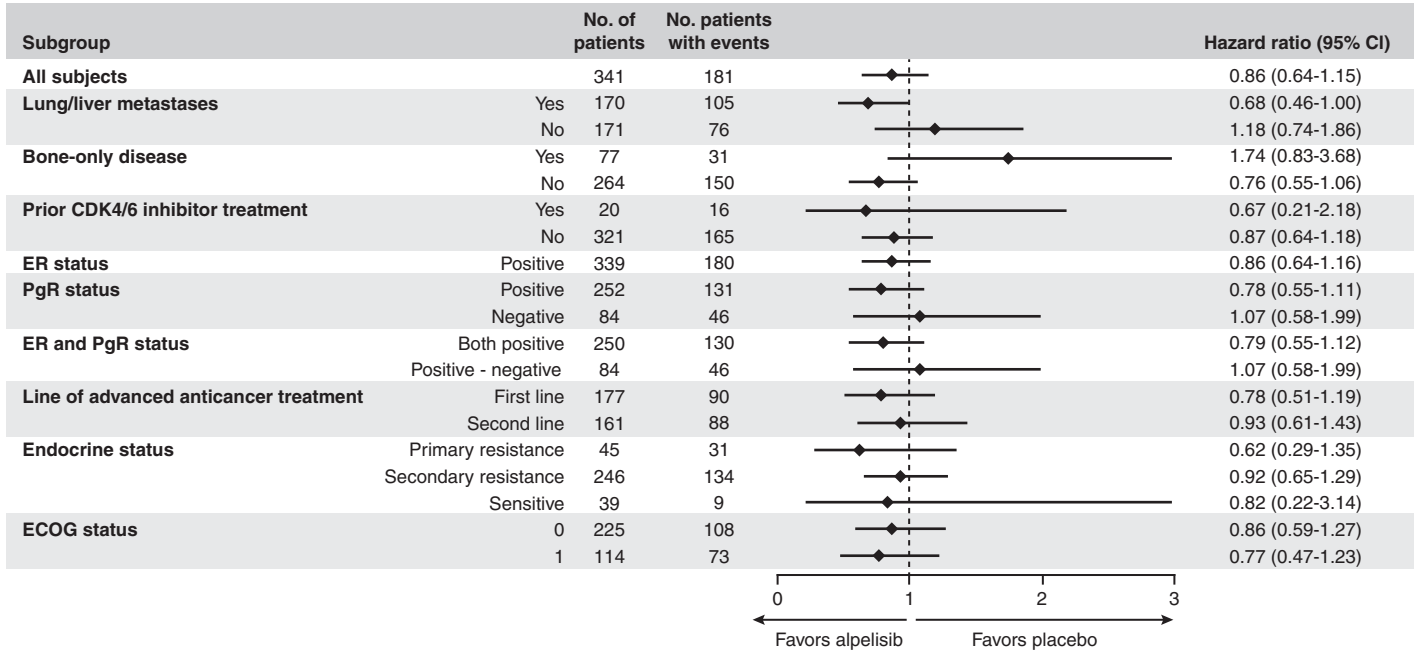

Figure 2. Overall survival by subgroups in the cohort of patients with *PIK3CA*-mutated cancer.

Full analysis set, *PIK3CA*-mutant cohort. Presence of lung and/or liver metastases (yes/no) and prior CDK4/6 inhibitor treatment (yes/no) were stratification factors. Within each randomization stratum, Cox proportional hazards model was stratified by the other randomization stratum.

CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PgR, progesterone receptor.

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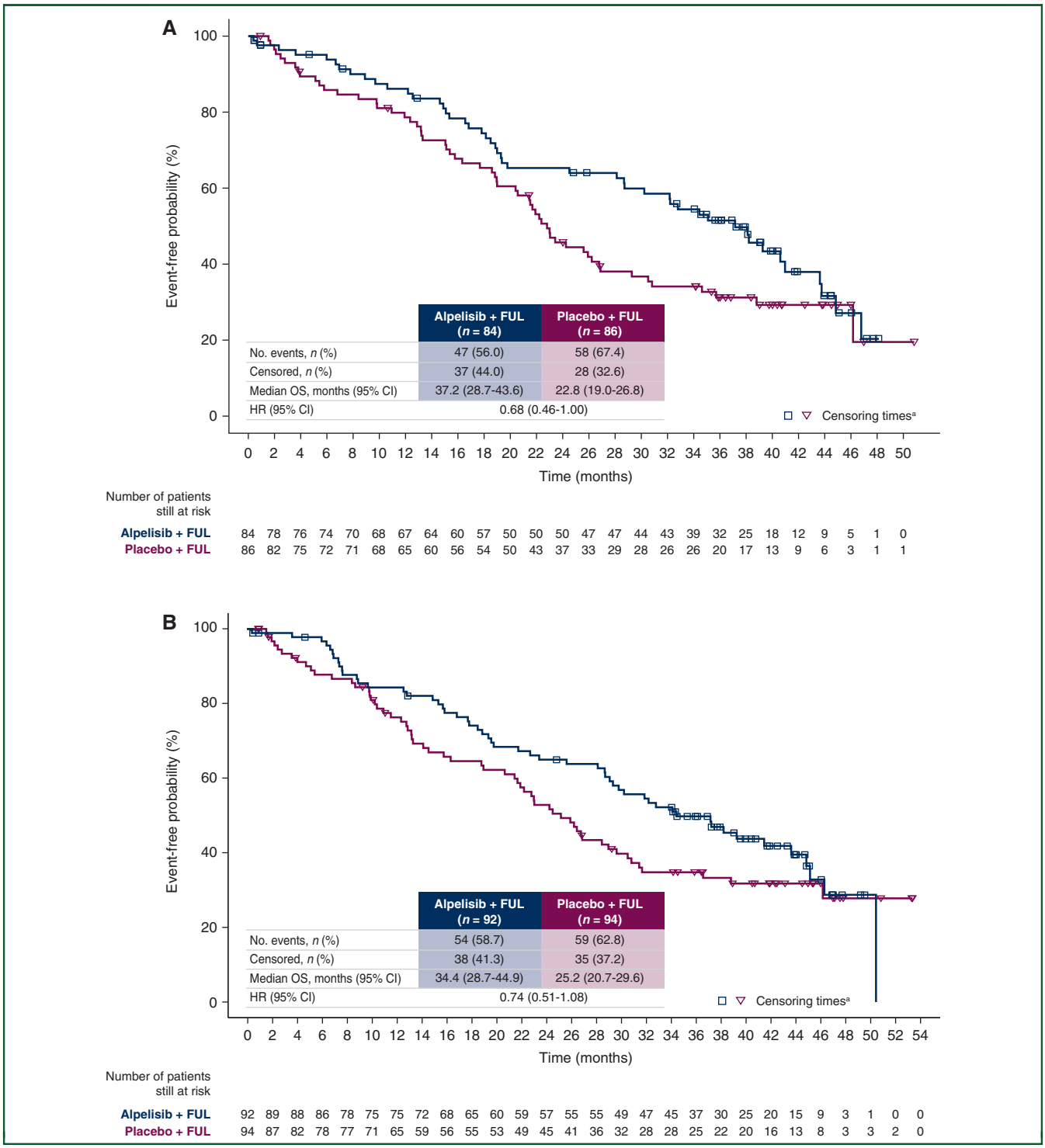

Figure 3. (A) Overall survival in patients with *PIK3CA*-mutated cancer with lung/liver metastases. (B) Overall survival in patients with *PIK3CA* mutation detected in plasma ctDNA.

CI, confidence interval; ctDNA, circulating tumor DNA; FUL, fulvestrant; HR, hazard ratio; OS, overall survival.

[a] Date of censoring is defined as the last contact date. Includes patients with a *PIK3CA* mutation in plasma ctDNA, regardless of assignment to *PIK3CA*-mutant or non-mutant cohort per tissue.

Among patients with *PIK3CA*-mutated disease as detected using plasma ctDNA (Figure 3B), median OS was 34.4 months (95% CI, 28.7-44.9) in the alpelisib plus fulvestrant arm, compared with 25.2 months (95% CI, 20.7-29.6) in the placebo plus fulvestrant arm (HR = 0.74; 95% CI, 0.51-1.08).

First antineoplastic medication after discontinuation of study treatment

Overall, 148 and 164 patients in the alpelisib plus fulvestrant versus placebo plus fulvestrant arms discontinued study treatment. Of these patients, 116 (78.4%) and 134 (81.7%),

Table 2. First new antineoplastic medication after discontinuation of study treatment, cohort of patients with *PIK3CA*-mutated cancer

Patients, *n* (%)	Alpelisib + fulvestrant (*n* = 169)	Placebo + fulvestrant (*n* = 172)
Patients starting subsequent medication/patients discontinuing treatment, *n*/*N* (%)	116[a]/148 (78.4)	134[a]/164 (81.7)
Chemotherapy	38 (32.8)	49 (36.6)
Chemotherapy + other[b]	20 (17.2)	26 (19.4)
Hormonal therapy alone	20 (17.2)	21 (15.7)
Hormonal therapy + other[c]	37 (31.9)	35 (26.1)
Everolimus	20 (17.2)	21 (15.7)
CDK4/6i	17 (11.5)	22 (13.4)
Targeted therapy alone	1 (0.1)	2 (1.5)
Other	0	1 (0.1)

A patient was counted only once in one of the medication types. Medication type was based on medical review.
CDK4/6, cyclin-dependent kinase 4/6.
[a] Used as the denominator for the percentages.
[b] Includes patients who received chemotherapy plus hormonal therapy.
[c] Includes patients who received hormonal therapy plus targeted therapy plus other.

respectively, initiated a new subsequent treatment with an antineoplastic medication (Table 2). Among patients who received a subsequent therapy, chemotherapy-based treatment—including patients who received chemotherapy plus hormonal therapy—was most common across both arms: 50.0% and 56.0%, respectively, as the first therapy to be received. Hormone therapy-based regimens—including patients who received hormonal therapy plus targeted therapy plus other therapies—were initiated by 49.1% and 41.8% of patients in the alpelisib plus fulvestrant and placebo plus fulvestrant arms, respectively. Subsequent treatment included a targeted therapy alone or in combination with hormone therapy in 38 (32.8%) and 37 (27.6%) patients in the alpelisib plus fulvestrant and placebo plus fulvestrant arms, respectively. These regimens included a CDK4/6i in a similar proportion of patients across the two treatment arms: 17 (11.5%) and 22 (13.4%) patients, respectively.

PFS on next subsequent therapy and TTC

By the time of data cut-off, 118 patients in the alpelisib plus fulvestrant arm and 126 patients in the placebo plus fulvestrant arm had progressed on the next subsequent therapy after discontinuation of study treatment or had died from any cause (defined as PFS2). In an exploratory analysis, median PFS2 in the cohort of patients with *PIK3CA*-mutated cancer was 22.8 months (95% CI, 18.5-26.3) with alpelisib plus fulvestrant versus 18.2 months (95% CI, 12.8-22.2) with placebo plus fulvestrant (HR = 0.80; 95% CI, 0.62-1.03; Figure 4A).

In a post hoc exploratory analysis, 95 patients (56.2%) in the alpelisib plus fulvestrant arm and 109 patients (63.4%) in the placebo plus fulvestrant arm went on to receive their first chemotherapy in the metastatic setting (with censoring at the last contact date or death), following discontinuation of study treatment. Median TTC was 23.3 months (95% CI, 15.2-28.4) in the alpelisib plus fulvestrant arm versus 14.8 months (95% CI, 10.5-22.6) in the placebo plus fulvestrant arm (HR = 0.72; 95% CI, 0.54-0.95; Figure 4B).

Safety

With longer follow-up, discontinuations due to AEs at end of treatment in the *PIK3CA*-mutant cohort (Table 1) and AEs leading to discontinuations in both *PIK3CA*-mutant and non-mutant cohorts (Table 3) were consistent with those previously reported for SOLAR-1[12]; no new safety signals or cumulative toxicity for any AE were observed. The incidence of hyperglycemia did not increase with longer time on treatment. Observed AEs continued to be generally manageable with close monitoring, administration of concomitant medication, and dose modifications when necessary, as described previously.[12,19]

Rash AEs of special interest, comprising the preferred terms of rash, rash maculo-papular, rash macular, dermatitis, dermatitis acneiform, rash papular, rash pruritic, drug eruption, genital rash, and rash pustular, were observed in 54% of patients in the alpelisib plus fulvestrant arm, versus 9% of patients in the placebo plus fulvestrant arm. However, most of these events were low grade (grade 1 or grade 2). Considering the current coronavirus disease (COVID-19) pandemic, there were no cases of confirmed or suspected COVID-19 infection, and no COVID-19-related deaths were reported.

DISCUSSION

In this final inferential, protocol-specified OS analysis of SOLAR-1, the addition of alpelisib to fulvestrant resulted in a prolongation of median OS of 7.9 months in patients with HR+, HER2−, *PIK3CA*-mutated ABC, although the prespecified O'Brien—Fleming efficacy boundary was not crossed. After more than 3 years of follow-up, three times as many patients still remained on therapy in the alpelisib plus fulvestrant arm than in the placebo plus fulvestrant arm (21 versus 7 patients). It is notable that more patients were still receiving treatment in the alpelisib plus fulvestrant arm considering the poor prognosis of these patients with *PIK3CA*-mutated disease. Because *PIK3CA* mutations are shown to be associated with reduced survival, there exists a high unmet need in HR+, HER2− ABC.[8]

To assess the value of alpelisib in addressing this unmet need, the SOLAR-1 trial was specifically designed to prospectively evaluate this PI3Kα-selective inhibitor in combination with fulvestrant for patients with HR+, HER2− ABC, including patients with or without *PIK3CA*-mutated disease, and demonstrated clinically relevant PFS benefit in patients with a *PIK3CA* mutation.[12] However, an important part of the trial design was evaluation of alpelisib plus fulvestrant in patients without *PIK3CA*-mutated disease. The efficacy proof-of-concept criteria were not met for the addition of alpelisib to fulvestrant in the cohort of patients with *PIK3CA*-non-mutated cancer, demonstrating that *PIK3CA* is a predictive biomarker for alpelisib activity. Other phase 2/3 trials of nonselective PI3K or CDK4/6is have reported

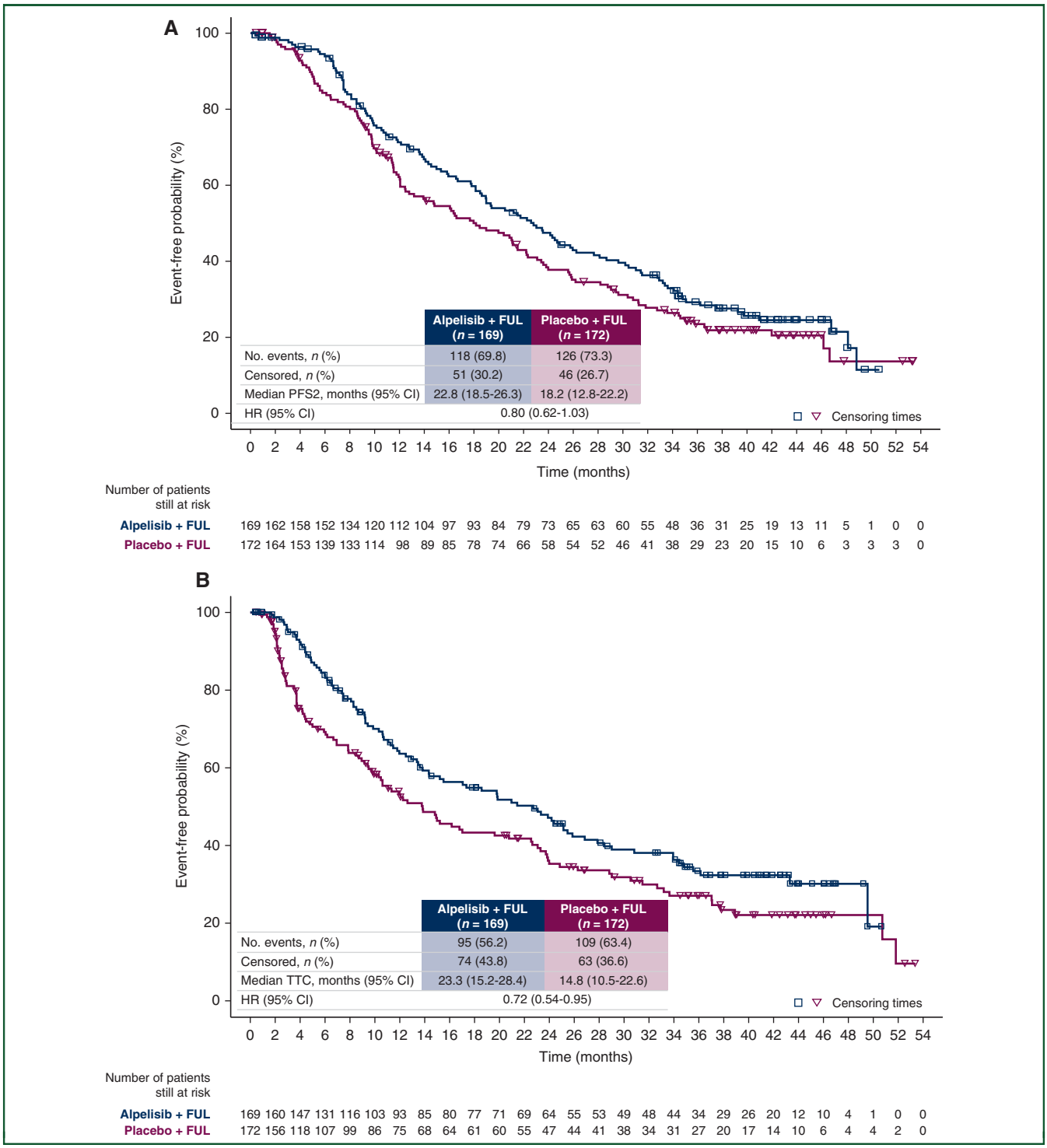

Figure 4. (A) Progression-free survival on next subsequent therapy (PFS2) and (B) time to first chemotherapy (TTC) in the cohort of patients with *PIK3CA*-mutated cancer.

PFS2 is defined as the time from randomization to the first documented PD on the first new (systemic) antineoplastic therapy initiated after discontinuation of study treatment, or death from any cause. TTC is defined as time from randomization to first chemotherapy, censored at last contact date or death.
CI, confidence interval; FUL, fulvestrant; HR, hazard ratio.

retrospective subgroup analyses wherein a PFS benefit was observed regardless of *PIK3CA* mutation status.[1,20,21]

As clinically meaningful improvement in PFS confers the greatest immediate benefit to address unmet need for these patients,[22] assessing OS is an important clinical question. The prospective SOLAR-1 trial demonstrated an approximate 8-month numeric improvement in median OS with the addition of alpelisib to fulvestrant in patients with *PIK3CA*-mutated HR+, HER2− ABC, a population known to have poor prognosis.

Although CDK4/6is are now standard of care, this was not the case during SOLAR-1 enrollment; only a small number of

Table 3. Updated adverse events

Most frequent AEs (≥20% in either arm), *n* (%)	Alpelisib + fulvestrant (*n* = 284)[a]			Placebo + fulvestrant (*n* = 287)[a]		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Any AE	282 (99.3)	187 (65.8)	35 (12.3)	267 (93.0)	90 (31.4)	17 (5.9)
Hyperglycemia	184 (64.8)	94 (33.1)	11 (3.9)	27 (9.4)	2 (0.7)	1 (0.3)
Diarrhea	169 (59.5)	20 (7.0)	0	47 (16.4)	2 (0.7)	0
Nausea	133 (46.8)	8 (2.8)	0	65 (22.6)	1 (0.3)	0
Decreased appetite	103 (36.3)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash	103 (36.3)	28 (9.9)	0	20 (7.0)	1 (0.3)	0
Vomiting	81 (28.5)	2 (0.7)	0	29 (10.1)	1 (0.3)	0
Weight decreased	79 (27.8)	15 (5.3)	0	7 (2.4)	0	0
Fatigue	72 (25.4)	10 (3.5)	0	51 (17.8)	3 (1.0)	0
Stomatitis	71 (25.0)	7 (2.5)	0	20 (7.0)	0	0
Asthenia	64 (22.5)	7 (2.5)	0	39 (13.6)	0	0
Alopecia	58 (20.4)	0	0	7 (2.4)	0	0

Safety set ($N = 571$). Numbers (n) represent counts of patients. A patient with multiple severity grades for an AE is only counted under the maximum grade. Medical Dictionary for Regulatory Activities version 23.0, Common Terminology Criteria for Adverse Events version 4.03.

[a] AEs (any grade) leading to discontinuations of one or both treatments in the safety set (both *PIK3CA*-mutant and non-mutant cohorts) occurred in 75 patients (26.4%) in the alpelisib plus fulvestrant arm and 16 patients (5.6%) in the placebo plus fulvestrant arm.[12]

patients with *PIK3CA*-mutations and prior CDK4/6i were enrolled in the study ($n = 20$, 5.9%).[12] In cohort A of the ongoing BYLieve trial, alpelisib plus fulvestrant was evaluated in patients who had progressed on immediate prior CDK4/6i plus AI. Alpelisib plus fulvestrant met its primary endpoint in this cohort, with 50.4% of patients ($n = 61$; 95% CI, 41.2-59.6) alive without PD after 6 months of treatment; median PFS was 7.3 months ($n = 72$; 95% CI, 5.6-8.3).[23] Thus, taken together, data from SOLAR-1 and BYLieve cohort A support the use of alpelisib plus fulvestrant in patients with *PIK3CA*-mutant HR+, HER2− ABC regardless of prior exposure to CDK4/6is. In SOLAR-1, many patients in the cohort of patients with *PIK3CA*-mutated cancer presented with aggressive disease that can be harder to treat. Most patients (86%) had disease that was resistant to endocrine therapy (ET), half had lung/liver metastases, and approximately half received study treatment as second-line therapy. Subgroup analyses for OS in the cohort of patients with *PIK3CA*-mutated cancer demonstrated that adding alpelisib to fulvestrant led to a 14-month improvement in median OS in patients with liver/lung metastases, a subgroup of patients that may have more aggressive disease than those without liver/lung metastases. Consistent with these findings, presence of a *PIK3CA* mutation as detected in plasma ctDNA, which may be indicative of greater disease burden, may be associated with better response to alpelisib plus fulvestrant than fulvestrant alone.

The most common subsequent therapies in patients who discontinued study treatment were chemotherapy-based and hormone-therapy-based treatments. The PFS2 data from SOLAR-1, in this study comprising PFS1 + PFS2, suggest that the disease responds to a subsequent therapy. Although chemotherapy may be needed as a next step in treatment, delaying TTC can be meaningful for patients. In SOLAR-1, the addition of alpelisib to fulvestrant delayed median TTC by 8.5 months compared with fulvestrant only. These data demonstrate that patients can respond to other therapies after progression on the addition of alpelisib to fulvestrant, suggesting no evidence of clonal selection by use of a PI3Kα inhibitor in these patients.

The safety profile in SOLAR-1 was consistent with the established safety profile of alpelisib, including that observed in the primary analysis.[12,16] AEs observed with alpelisib were as expected based on its MOA and were reversible and manageable with medications or dose adjustments. The frequency of hyperglycemia did not increase with additional follow-up. With longer follow-up, rash AEs of special interest were consistent with previous reports and most of them were low grade events. Recent analyses of management and patient care in the SOLAR-1 and BYLieve studies demonstrated that prophylactic antihistamines reduced the incidence and severity of rash; similarly, management of hyperglycemia with metformin led to fewer discontinuations.[19,23] SOLAR-1 safety analysis indicated that discontinuation rates due to any-grade AEs (from 29.2% to 20.7%), including any-grade hyperglycemia (from 9.0% to 3.6%), had reduced in the last 50% of randomized patients compared with the first 50% of those randomized.[19] In addition, fewer discontinuations due to any-grade AE (20.5% versus 25%) and due to any-grade hyperglycemia (1.6% versus 6.3%) were observed in BYLieve cohort A compared with SOLAR-1, indicating that experience in monitoring and managing AEs has improved due to better education and implementation of early intervention and detailed management strategies.[12,23] Although AEs can impact health-related quality of life (QoL), patient-reported outcome analyses indicated overall maintained QoL and functioning, despite some changes in subscale and symptom scores—in the alpelisib plus fulvestrant arm (with no meaningful differences versus placebo plus fulvestrant arm) of SOLAR-1, further supporting alpelisib's risk—benefit profile in this patient population.[24]

With additional follow-up currently ongoing, the phase 3 SOLAR-1 trial showed a nearly 8-month numeric improvement in median OS with the addition of alpelisib to fulvestrant and may be associated with numerically longer

survival in patients with greater disease burden. The statistically significant and clinically meaningful PFS benefit observed in this population[12] supports the use of alpelisib plus fulvestrant in patients of HR+, HER2− ABC who have progressed on or after prior AI-based therapy and who have a poor prognosis due to the presence of a *PIK3CA* mutation.

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