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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Introduction

Approximately 40% of patients with hormone receptor-positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) advanced breast cancer (ABC) have tumors with a *PIK3CA* mutation, resulting in phosphatidylinositol 3-kinase (PI3K) pathway hyperactivation^{1–6}

Alpelisib is a small-molecule inhibitor targeting the α -isoform of PI3K⁷ that has been evaluated in SOLAR-1 (NCT02437318), a phase 3 randomized, placebo-controlled trial in patients HR+, HER2– ABC who had received endocrine therapy previously^{8–10} (**Figure 1**)

Figure 1. Study Design^{8–10}

^aMore than 90% of patients had mutational status identified from archival tissue.
^bFulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.
ABC, advanced breast cancer; AI, aromatase inhibitor; ALP, alpelisib; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; FUL, fulvestrant; HER2–, human epidermal growth factor receptor-2–negative; HR+, hormone receptor-positive; IM, intramuscular; ORR, overall response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; PO, oral; PRO, patient-reported outcome; QD, once daily; R, randomization.

In SOLAR-1, use of alpelisib plus fulvestrant versus placebo plus fulvestrant significantly improved both progression-free survival (PFS) (median 11.0 vs 5.7 months, respectively; hazard ratio [HR] 0.65; 95% confidence interval [CI], 0.50–0.85; $P < 0.001$) and objective response rate (ORR) (36% vs 16%, respectively [in those with measurable disease]; $P < 0.001$) in patients with tumors harboring a *PIK3CA* mutation⁸

In addition to primary efficacy and safety measures, patient-reported outcomes (PROs) offer valuable insight into the therapeutic benefit of a drug by measuring whether quality of life (QoL) is maintained during treatment

Recently updated European School of Oncology/European Society for Medical Oncology guidelines recommended that health-related quality of life (HRQoL) be evaluated in trials of novel agents using validated, standardized PRO measures, in addition to clinical efficacy and safety¹¹

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients (EORTC QLQ-C30), the EuroQoL 5- Dimension 5- Level (EQ-5D-5L) questionnaire, and the Brief Pain Inventory-Short Form (BPI-SF) questionnaire are recognized as reliable and valid PRO measures^{12–14} that are frequently used in clinical trials of patients with advanced or metastatic breast cancer

Objective

To evaluate the impact of alpelisib plus fulvestrant on HRQoL in patients with HR+, HER2– ABC whose tumors harbored a *PIK3CA* mutation in the SOLAR-1 trial

Methods

Overview

Postmenopausal women or men with HR+, HER2– ABC whose disease had progressed on or after an aromatase inhibitor (AI) were randomized to receive once-daily alpelisib 300 mg or matching placebo (continuous dosing), both plus fulvestrant 500 mg (administered on Day 1 and Day 15 of the first 28-day cycle, then on Day 1 of all subsequent 28-day cycles) (**Figure 1**)

PRO measures, including HRQoL and cancer-related pain, were secondary objectives and were collected using the EORTC QLQ-C-30, EQ-5D-5L, and BPI-SF questionnaires

Patient-reported outcomes data were collected at screening, every 8 weeks for 18 months then every 12 weeks thereafter until progression, at the end of treatment, and during follow-up for efficacy

Data Analysis

Patient-reported outcomes data were analyzed in patients in the *PIK3CA* mutant cohort of SOLAR-1

At each assessment point, descriptive statistics were used to summarize the scored scales for

- EORTC QLQ-C30: Global health/QoL, functional subscales and symptoms
- EQ-5D-5L: index values
- BPI-SF: worst pain item, pain severity index, and pain interference indices

Changes from baseline in domain scores, health states, overall health status, and index values at the time of each assessment were summarized

- Patients with an evaluable baseline score and at least one evaluable postbaseline score during the treatment period were included in the change from baseline analyses
- Linear mixed effects models were used to assess score changes from baseline

Time to 10% deterioration (TTD), an established measure of clinically meaningful change in QoL, was compared between the treatment arms' survival distribution using Kaplan-Meier methodology

- Time to 10% deterioration was defined as a worsening in score by $\geq 10\%$ compared with baseline with no later improvement above this threshold during the treatment period, or death owing to any cause

Results

Baseline Characteristics

Baseline characteristics were generally similar between the two treatment arms (**Table 1**)

Table 1. Baseline Characteristics (Patients With *PIK3CA*-Mutated Tumors)^a

Baseline Characteristic, n (%)	Alpelisib + Fulvestrant (n=169) ^b	Placebo + Fulvestrant (n=172) ^b
Median age, years (range)	63 (25–87)	64 (38–92)
Race		
Caucasian	117 (69.2)	109 (63.4)
Asian	34 (20.1)	40 (23.3)
Other/unknown	18 (10.7)	23 (13.4)
ECOG PS		
0	112 (66.3)	113 (65.7)
1	56 (33.1)	58 (33.7)
Missing data	1 (0.6)	1 (0.6)
Metastatic sites		
Visceral disease	93 (55.0)	100 (58.1)
Lung/liver metastases	84 (49.7)	86 (50.0)
Bone-only disease	42 (24.9)	35 (20.3)
First-line advanced anticancer treatment	88 (52.1)	89 (51.7)
Second-line advanced anticancer treatment	79 (46.7)	82 (47.7)
Endocrine-resistance status ^c		
Primary resistance	23 (13.6)	22 (12.8)
Secondary resistance	120 (71.0)	127 (73.8)
Endocrine sensitive	20 (11.8)	19 (11.0)
Prior chemotherapy		
Neoadjuvant	25 (14.8)	29 (16.9)
Adjuvant	78 (46.2)	86 (50.0)

^aOne man was enrolled in the alpelisib group in the cohort of patients with *PIK3CA*-mutated tumors. All other study participants were postmenopausal women.
^bOne patient in the cohort of patients with *PIK3CA*-mutated tumors who was randomized to placebo was not treated.
^cPrimary and secondary resistance as per ESMO definition¹⁵
ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESMO, European Society for Medical Oncology.

Completion Rates

At baseline, $\geq 93\%$ of patients completed the EORTC QLQ C-30, EQ-5D-5L, and BPI-SF questionnaires

At each postbaseline visit, completion rates ranged from 75% to 100%

EORTC QLQ-C30

Global Health Status/Quality of Life

Global health status/QoL scores were generally similar in patients treated with alpelisib plus fulvestrant and placebo plus fulvestrant (**Figure 2**), and changes from baseline over time were not clinically meaningful (as defined by Ringash et al¹⁶ and Osoba et al¹⁷) in either treatment arm

Figure 2. Change From Baseline in EORTC QLQ-C30 Global Health Status/QoL Scale Score^a

^aData represented in this graph were estimated from a statistical model; to ensure the model provided stable estimates, data were cut when patient numbers were < 10 in each treatment arm. The time profile provides the average estimates for the change from baseline for the interval from baseline up to the respective week as derived from the repeated-measurement model. The mixed-effect model includes terms for treatment, stratification factors, baseline value, time and time $\times$ treatment interaction. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients; LS, least squares; QoL, quality of life; SEM, standard error of the mean; W, week.

- There was no significant between-group difference in the pattern of change over time
- Adjusted mean changes from baseline were $< 10\%$ for all visits through Week 96 in the alpelisib plus fulvestrant and placebo plus fulvestrant arms, with a mean between-treatment difference of $< 3\%$ for all visits

Of patients treated with alpelisib plus fulvestrant, estimated change from baseline to last observation in EORTC QLQ-C30 Global Health Status/QoL was -0.03 (95% CI, -6.12 to 6.07 ; $P = 0.993$) in patients who remained on treatment ($n = 32$), -0.77 (95% CI, -6.53 to 4.98 ; $P = 0.792$) in patients who discontinued due to AEs ($n = 43$), and -4.22 (95% CI, -8.88 to 0.44 ; $P = 0.076$) in patients who discontinued owing to other reasons ($n = 94$)

There was no difference between the two treatment arms in TTD in EORTC QLQ-C30 global health/QoL status (HR 1.03; 95% CI, 0.72–1.48) (**Figure 3, Table 2**)

Figure 3. Kaplan-Meier Plot of TTD in EORTC QLQ-C30 Global Health Status/QoL Scale Score

CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients; QoL, quality of life; TTD, time to 10% deterioration.

Functioning Subscales

Analyses of EORTC QLQ-C30 functional subscale scores generally showed no clinically meaningful changes from baseline in the alpelisib plus fulvestrant or the placebo plus fulvestrant arms (**Figure 4**)

Figure 4. Overall Mean Change From Baseline^a in EORTC QLQ-C30 Functioning Subscale Scores

^aOverall mean changes from baseline scores were estimated using repeated-measurement models; changes > 0 indicate improvement from baseline, with bars indicating 95% confidence intervals. At baseline, functioning subscale scores were available for 155 patients in the alpelisib plus fulvestrant arm and 157 patients in the placebo plus fulvestrant arm. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients.

- There were no significant between-group differences in the alpelisib plus fulvestrant and the placebo plus fulvestrant arms, with the exception of the social functioning subscale
- There was deterioration in the social functioning subscale in patients treated with alpelisib plus fulvestrant, while it was maintained in patients treated with placebo plus fulvestrant

No meaningful between-treatment differences were observed in TTD in EORTC QLQ-C30 physical, emotional, and functioning subscale scores (**Table 3**)

Table 3. Time to 10% Deterioration in EORTC QLQ-C30 Functioning Subscale Scores

Functioning Subscale		Alpelisib + Fulvestrant (N=169)	Placebo + Fulvestrant (N=172)		HR (95% CI)
Physical	Number of events, n	50	53		0.86 (0.58–1.27)
	Median TTD, mo	19.4	19.7		
Emotional	Number of events, n	53	48		0.92 (0.62–1.37)
	Median TTD, mo	17.8	20.4		
Social	Number of events, n	51	41		1.06 (0.70–1.61)
	Median TTD, mo	17.8	22.1

CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients; FAS, full analysis set; HR, hazard ratio; TTD, time to 10% deterioration.

Symptoms

Patients in the alpelisib plus fulvestrant versus placebo plus fulvestrant arm had worsening of certain symptoms, including diarrhea and nausea/vomiting (**Figure 5**)

Figure 5. Estimated Overall Mean Change From Baseline^a in EORTC QLQ-C30 Symptom Scores

^aOverall mean changes from baseline scores were estimated using repeated-measurement models; changes < 0 indicate improvement from baseline, with bars indicating 95% confidence intervals. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients.

- The results of symptom scale analyses are consistent with the side effect profile of alpelisib, including a higher frequency of gastrointestinal toxicities⁸

EuroQoL 5-Dimension 5-Level

For the EQ-5D-5L index score, there was a trend for a decrease in the placebo plus fulvestrant arm, while scores were maintained in the alpelisib plus fulvestrant arm (data not shown)

Brief Pain Inventory-Short Form

For the BPI-SF pain severity index and worst pain item, there was a slight delay in worsening of pain in the alpelisib plus fulvestrant arm compared with the placebo plus fulvestrant arm (**Figure 6**)

Figure 6. BPI-SF Worst Pain Item (A) and Pain Severity Index (B) (Patients With *PIK3CA*-Mutated Tumors)

BPI-SF, Brief Pain Inventory-Short Form; LS, least squares; SEM, standard error of the mean; W, week. The time profile provides the average estimates for the change from baseline for the interval from baseline up to the respective week as derived from the repeated-measurement model. The mixed-effect model includes terms for treatment, stratification factors, baseline value, time and time $\times$ treatment interaction. This analysis only includes assessments up to the time point where there are at least 10 patients in each of the treatment groups.

Regarding BPI-SF worst pain, patients in the alpelisib plus fulvestrant arm had a higher improvement rate (42% vs 32%) and lower worsening rate (25% vs 35%) compared with patients in the placebo plus fulvestrant arm at week 24. A similar trend was observed at week 16 (**Figure 7**)

Figure 7. Change in BPI-SF Worst Pain Over Time

BPI-SF, Brief Pain Inventory-Short Form.

- Similar trends in pain improvements and worsening were observed for patients with and without pain at baseline

There was also a tendency for a greater response in BPI-SF worst pain over time with alpelisib plus fulvestrant versus placebo plus fulvestrant in the subset of patients with pain at baseline (**Figure 8**)

Figure 8. BPI-SF Worst Pain Response Over Time (Patients With Pain at Baseline)^a

^aResponders defined as at least 1-point improvement on worst pain score compared to baseline.
^bMantel-Haenszel chi-square test stratified by stratification factor (presence of lung/liver metastases and prior CDK4/6 inhibitor treatment).
BPI-SF, Brief Pain Inventory-Short Form.

Conclusions

Patient-reported outcomes provide further insight into the benefit-risk profile of alpelisib from a patient perspective and enable an evaluation of whether the observed efficacy benefit of alpelisib plus fulvestrant versus placebo plus fulvestrant in SOLAR-1 was achieved at the expense of a deterioration in QoL

In addition to significantly improving PFS and ORR, these data indicate that while there were some changes in subscale and symptom scores, overall HRQoL and functioning were maintained in patients with HR+, HER2– ABC with *PIK3CA*-mutated tumors who were treated with alpelisib plus fulvestrant in the SOLAR-1 study, with no meaningful differences versus placebo plus fulvestrant

Based on previously established criteria, there was no clinically meaningful overall change from baseline in EORTC QLQ-C30 global health status/QoL score in patients treated with either alpelisib plus fulvestrant or placebo plus fulvestrant

- Similarly, no statistical difference was observed in terms of TTD for EORTC QLQ-C30 physical, emotional, and social functioning subscale scores. However, there was deterioration in the social functioning subscale in patients treated with alpelisib plus fulvestrant
- Some EORTC QLQ-C30 symptom scores, such as diarrhea and nausea/vomiting, were worsened in patients treated with alpelisib plus fulvestrant; this is not surprising given that gastrointestinal toxicities are commonly observed with alpelisib plus fulvestrant treatment

Based on BPI-SF findings, there was a slight delay in worsening of pain and a trend for improvements in worst pain in the alpelisib plus fulvestrant arm versus the placebo plus fulvestrant arm

Collectively, these data indicate that while there were some changes in subscale and symptom scores, overall QoL and functioning were maintained in patients with HR+, HER2– ABC with *PIK3CA*-mutated tumors who were treated with alpelisib plus fulvestrant in the SOLAR-1 study, with no meaningful differences versus placebo plus fulvestrant

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