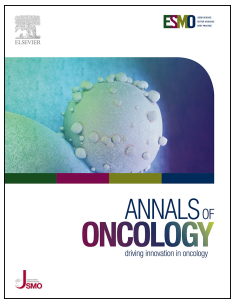

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# Time Course and Management of Key Adverse Events During the Randomized Phase 3 SOLAR-1 Study of PI3K Inhibitor Alpelisib Plus Fulvestrant in Patients With HR-Positive Advanced Breast Cancer

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**Abstract**

***Background*** Alpelisib (α-selective PI3K inhibitor) plus fulvestrant is approved in multiple countries for men and post-menopausal women with *PIK3CA*-mutated, hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer following progression on or after endocrine therapy. A detailed understanding of alpelisib's safety profile should inform adverse event (AE) management and enhance patient care.

***Patients and methods*** AEs in the phase 3 SOLAR-1 trial were assessed in patients with and without *PIK3CA* mutations. The impact of protocol-specified AE-management recommendations was evaluated, including an amendment to optimize hyperglycemia and rash management.

***Results*** Patients were randomized to fulvestrant plus alpelisib (*n*=284) or placebo (*n*=287). The most common grade 3/4 AEs with alpelisib were hyperglycemia (grade 3, 32.7%; grade 4, 3.9%), rash (grade 3, 9.9%), and diarrhea (grade 3, 6.7%). Median time to onset of grade ≥3 toxicity was 15 days (hyperglycemia, based on fasting plasma glucose), 13 days (rash), and 139 days (diarrhea). Metformin alone or in combination with other anti-diabetic agents was used by most patients (87.1%) with hyperglycemia. Preventive anti-rash medication resulted in lower incidence (any grade, 26.7% vs 64.1%) and severity of rash (grade 3, 11.6% vs 22.7%) vs no preventative medication. Discontinuations due to grade ≥3 AEs were lower following more-detailed AE management guidelines (7.9% vs 18.1% previously). Patients with *PIK3CA* mutations had a median alpelisib dose intensity of 248 mg/day. Median progression-free survival (PFS) with alpelisib was 12.5 and 9.6 months for alpelisib dose intensities ≥248 mg/day and <248 mg/day, respectively, compared with 5.8 months with placebo.

***Conclusions*** Hyperglycemia and rash occurred early during alpelisib treatment, while diarrhea occurred at a later timepoint. Early identification, prevention, and intervention, including concomitant medications and alpelisib dose modifications, resulted in less severe toxicities. Reductions in treatment discontinuations and improved PFS at higher alpelisib dose intensities support the need for optimal AE management.

ClinicalTrials.gov Id: NCT02437318

**Key words:** alpelisib, hyperglycemia, rash, diarrhea, breast cancer

**Highlights**

- Hyperglycemia, rash, and diarrhea were the most common grade 3/4 adverse events in patients receiving alpelisib
- These adverse events were predictable, manageable with concomitant medications, and generally reversable
- Implementation of more detailed AE management guidelines improved various markers of safety during the study

## Introduction

Hormone receptor–positive (HR+) and human epidermal growth factor receptor 2–negative (HER2–) breast cancer is the most common form of the disease [1]. Mutations in the *PIK3CA* gene, which encodes the α isoform of phosphatidylinositol 3-kinase (PI3K), are observed in approximately 40% of patients with HR+/HER2– breast cancer and are a negative prognostic factor [2-4]. *PIK3CA* mutations induce hyperactivation of PI3K, which is associated with tumor growth, and contributes to resistance to endocrine therapy, the backbone of treatment for HR+/HER2– advanced breast cancer (ABC) [4-6]. Consequently, there is a need for a targeted therapy for HR+/HER2– ABC patients whose tumors harbor a *PIK3CA* mutation.

While targeting *PIK3CA*-mutated breast cancer with PI3K inhibitors is a promising strategy, treatment-related toxicities complicated the development of pan-PI3K inhibitors, prompting the need for more selective PI3K inhibitors with a more tolerable side-effect profile and higher efficacy [7]. Alpelisib is an orally available PI3K inhibitor that selectively targets the α isoform of PI3K with 50-fold more potency than other PI3K isoforms (β, δ, γ) [8]. Recent results from SOLAR-1, a randomized, double-blind, placebo-controlled, phase 3 trial, demonstrated significantly prolonged progression-free survival (PFS) with alpelisib plus fulvestrant vs placebo plus fulvestrant in postmenopausal women and men with *PIK3CA*-mutated, HR+/HER2– ABC who received prior aromatase inhibitor treatment (median, 11.0 vs 5.7 months; HR, 0.65 [95% CI, 0.50-0.85]; one-sided $P < .001$) [9]. Overall response rates (26.6% vs 12.8%) and clinical benefit rates (61.5% vs 45.3%) were also greater for the alpelisib arm vs placebo [9]. These data led to ongoing regulatory approval of alpelisib plus fulvestrant as treatment for *PIK3CA*-mutated ABC in global markets, including the United States, and to its inclusion in treatment guidelines, such as the National Comprehensive Cancer Center guidelines (category 1) [6,10].

A detailed understanding of the safety profile of new agents, such as alpelisib, inform appropriate detection and management of adverse events (AE). The safety profile of alpelisib plus fulvestrant in SOLAR-1 has been published, with hyperglycemia, diarrhea, and rash among the most common grade 3/4 AEs (no grade 4 rash or diarrhea was reported) [9,11]. Hyperglycemia, rash, diarrhea, and low-grade stomatitis

are expected AEs of PI3K inhibitors [7,12]. Rates of discontinuation of alpelisib and placebo due to adverse events were 25.0% and 4.2%, respectively [9]. Here, we report a comprehensive analysis of the time course and impact of intervention for these AEs of special interest (AESI), as well as protocol guidelines for their management in patients who received alpelisib in the SOLAR-1 study.

## Methods

### *Study design*

Details of the design of SOLAR-1 (NCT02437318) were recently published [9]. Postmenopausal women or men with HR+/HER2– ABC that progressed on or after treatment with an aromatase inhibitor were enrolled into *PIK3CA*-mutant and *PIK3CA*-non-mutant cohorts. Within each cohort, patients were randomized 1:1 to receive alpelisib (300 mg/day with food) plus fulvestrant (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. Randomization was stratified by the presence or absence of lung or liver metastases and prior CDK4/6 inhibitor treatment. Patients with a history of well-controlled type 2 diabetes were eligible to enroll; however, patients with type 1 and uncontrolled type 2 diabetes were excluded. Study treatment was continued until disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, or death. Stepwise dose reductions of alpelisib or placebo were permitted (300 mg/day, 250 mg/day, 200 mg/day) to manage AEs. Patients who discontinued one of the study drugs for any reason other than disease progression could continue the other study drug at the investigator's discretion. The primary objective of the study was to determine whether treatment with alpelisib plus fulvestrant prolongs PFS compared with placebo plus fulvestrant in patients with *PIK3CA*-mutant ABC. The trial was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.

### *Safety assessments*

Vital signs and hematological and biochemical laboratory parameters were assessed at screening, every 2 weeks for the first 8 weeks, and then every 4 weeks. Fasting plasma glucose (FPG) was also assessed on days 8 and 15 in the first 4 weeks. AEs were assessed continuously per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 until 30 days after the last dose of study medication.

AESIs were defined as adverse events of specific interest relating to treatment with alpelisib. They were based on the preferred term and/or grouped term (noted throughout); a summary of the grouped terms for hyperglycemia, rash, and gastrointestinal (GI) toxicity is outlined in **Supplemental Table 1**. Hyperglycemia was assessed over time using laboratory markers (FPG, and glycosylated hemoglobin [HbA1c]). Baseline glycemic status was defined according to the American Diabetes Association as follows: normal (FPG, < 5.6 mmol/L and HbA1c, < 5.7%), prediabetic (FPG, 5.6 to < 7.0 mmol/L and HbA1c, 5.7 to < 6.5%), and diabetic (FPG, ≥ 7.0 mmol/L or HbA1c, ≥ 6.5%). Glycemic status for each patient was determined using values measured before alpelisib dosing (before randomization), regardless of medical history.

*On-study management of AESI*

Protocol-specified AE management recommendations by AESI following a protocol amendment are summarized in **Table 1**. Supportive medications (coded using the World Health Organization Drug Reference List and summarized by Anatomical Therapeutic Chemical class and preferred term) were permitted to manage AEs as well as cancer symptoms and concurrent diseases. Medications not permitted per the study protocol included other investigational or anticancer therapies, medications with a known risk for torsade de pointes, and herbal preparations or dietary supplements.

The study protocol was amended to improve monitoring and management of hyperglycemia and skin toxicity after 317 (56.6%) of approximately 560 planned patients had been randomized to study treatment. The amendments were introduced based on recommendations by an advisory board of experts in managing these AESIs. At the start of the study, the HbA1c criterion for inclusion was < 8%, which was then modified

to < 6.5%, excluding patients with uncontrolled diabetes. Instruction on lifestyle changes at screening and consultation with a healthcare specialist were recommended for patients with baseline FPG ≥ 100 mg/dL (5.6 mmol/L) and/or HbA1c ≥ 5.7%. Consultation with a dermatologist was recommended for better assessment and management of alpelisib-induced skin toxicity. Topical steroids (3 or 4 times daily) were recommended for any-grade skin toxicity, as were oral antihistamines for skin toxicity with burning, stinging, or pruritus or for prophylaxis of hypersensitivity based on the patient's medical history (e.g., prior seasonal allergy, allergic asthma, or drug-induced exanthema).

*Statistical analysis*

The safety population comprised all patients who received at least one dose of study treatment. Data from patients with *PIK3CA*-mutant and non-mutant disease were combined, since no significant difference in safety profile existed between the alpelisib and placebo group across the two *PIK3CA* cohorts [9]. Investigations of time to first occurrence of an AESI of grade ≥ 2 and grade ≥ 3, as well as PFS by alpelisib dose intensity, were assessed using Kaplan-Meier methodology. Qualitative data were summarized by means of contingency tables and quantitative data by appropriate descriptive statistics in each treatment group. Time to onset of CTCAE grade ≥ 2 or 3 events was defined as the time from the start of treatment to the start date of the first incidence of an event of CTCAE grade ≥ 2 or 3. In the absence of an event during the on-treatment period, the censoring date applied was the earliest of the following dates: end date of on-treatment period (end of study treatment plus 30 days), death date, start date of new antineoplastic therapy (with the exception of palliative radiotherapy or fulvestrant monotherapy) before experiencing a CTCAE grade ≥ 2 or 3 event, data cutoff date, or date of withdrawal of informed consent.

## Results

*Patient characteristics*

Between July 26, 2015, and July 21, 2017, 341 patients with *PIK3CA*-mutated ABC and 231 patients with nonmutated *PIK3CA* ABC from over 30 countries were enrolled. The enrolled population, regardless of *PIK3CA* mutation, included 284 patients randomized to alpelisib plus fulvestrant and 288 randomized to placebo plus fulvestrant. Baseline characteristics of the safety set were balanced between the two treatment groups in this set: median ages were 62 and 64 years in the alpelisib and placebo groups, respectively; in both treatment groups, approximately 86% of patients had endocrine resistance (per protocol definition), 49% of patients had lung or liver metastases, and approximately 6% of patients had previously received CDK4/6 inhibitors [9]. At the data cutoff (June 12, 2018), treatment was ongoing in 55 patients (19.4%) and 46 patients (16.0%) in the alpelisib and placebo groups, respectively (**Supplemental Table 2**). The most common reasons for study treatment discontinuation were disease progression and patient decision. The safety population comprised 571 patients, with 284 patients in the alpelisib group and 287 in the placebo group (1 patient in the placebo group was enrolled but did not receive study treatment).

*Overall safety profile*

The most frequently reported all-grade AEs in the alpelisib group were hyperglycemia, diarrhea, nausea, decreased appetite, and rash (**Table 2**). The most common grade 3/4 AEs by preferred term were hyperglycemia (grade 3, 32.7%; grade 4, 3.9%), rash (grade 3, 9.9%; grade 4, 0%), maculopapular rash (grade 3, 8.8%; grade 4, 0%), and diarrhea (grade 3, 6.7%; grade 4, 0%).

*Time to onset and improvement of AESIs*

Kaplan-Meier estimates of the time to first occurrence of grade ≥ 2 and grade ≥ 3 hyperglycemia, rash, and diarrhea are displayed in **Figure 1**. The median time to onset of grade ≥ 3 events was 15 days for hyperglycemia (range, 5-395 days), 13 days for rash (range, 7-571 days), and 139 days for diarrhea (range, 10-470 days). These grade ≥ 3 events improved by at least one grade in a median of 6 days for hyperglycemia

(range, 4-7 days), 11 days for rash (95% CI, 8.0 days to not evaluable), and 18 days for diarrhea (95% CI, 9-45 days) (**Supplemental Table 3**).

*Hyperglycemia by baseline diabetic status*

Based on laboratory data outlined in the methods, baseline hyperglycemia status in the alpelisib group was considered normal (FPG, < 5.6 mmol/L and HbA1c, < 5.7%), prediabetic (FPG, 5.6 to < 7.0 mmol/L and HbA1c, 5.7 to < 6.5%), and diabetic (FPG, ≥ 7.0 mmol/L or HbA1c, ≥ 6.5%) in 113 patients (40%), 159 patients (56%), and 12 patients (4%), respectively. Increases in FPG were more pronounced in individuals who were diabetic or prediabetic at baseline compared with those with normal glycemic status (**Figure 2A**). Mean FPG values peaked within the first 2 weeks of study treatment, then decreased towards baseline values following antidiabetic supportive medication (**Figure 2A**). A gradual increase in HbA1c was observed with alpelisib, irrespective of baseline glycemic status, and remained slightly elevated throughout study treatment (**Figure 2B**). All patients who developed hyperglycemia had grade 0 or 1 hyperglycemia following discontinuation of alpelisib. Among the patients with prediabetic baseline status randomized to alpelisib plus fulvestrant, 74% experienced hyperglycemia during study treatment (grade 3, 43.4%; grade 4, 5.0%) compared with 52% of the patients with normal baseline glycemic status (grade 3, 16.8%; grade 4, 1.8%).

The PFS advantage seen in patients with *PIK3CA* mutations in the alpelisib group vs placebo group was consistent in patients with prediabetes or diabetes at baseline (11.0 vs 5.6 months; HR, 0.66 [95% CI, 0.47-0.92]) and in those with normal glycemic status at baseline (10.9 vs 6.5 months; HR, 0.65 [95% CI, 0.42-1.02]) (**Supplemental Figure 1**).

*Supportive medications to manage hyperglycemia*

Of the 187 patients experiencing any-grade hyperglycemia by grouped term in the alpelisib cohort, 163 received medication to manage this event. The most frequently used antidiabetic medication was metformin (87.1%) administered either alone or in

combination with other agents. In 67 patients (41.1%), only one antidiabetic medication was required to manage hyperglycemia, whereas in 47 patients (28.8%), three or more medications were required (**Supplemental Table 4**). During the study, insulin was used by 5 of 12 patients with diabetes, 34 of 159 patients with prediabetes, and 13 of 113 patients with normal glycemic status at baseline. Insulin use may have been in combination with other antidiabetic mediations. Of the 52 patients receiving insulin, 33 received it as long-term treatment (> 2 days), while 19 received it as rescue medication.

*Supportive medications to manage rash*

Anti-rash medication was administered to 134 patients in the alpelisib group. The most frequently used anti-rash medications were steroids (including prednisone [23%], dexamethasone [16%], prednisolone [15%], and hydrocortisone [10%]) and antihistamines (including fexofenadine [15%], desloratadine [11%], hydroxyzine [10%], and loratadine [9%]).

In terms of steroid usage in patients that developed rash in the alpelisib group (n = 153), 33.3% used topical steroids, while 72.5% used other routes (including oral, intravenous, and transdermal). In total, 86 patients in the alpelisib group received anti-rash medication prior to the onset of rash (by grouped term; **Figure 3**), with antihistamines being the most frequent treatment (60 of 86 patients; 69.8%). Of the patients who received prophylactic anti-rash medication, 23 patients (26.7%) experienced any-grade rash and 10 patients (11.6%) experienced grade 3 rash compared with 127 patients (64.1%) and 45 patients (22.7%) who did not receive preventive treatment. Of the 60 patients that received antihistamines specifically as anti-rash medication prior to development of rash, 23 patients (38.3%) experienced any-grade rash vs 130 patients (58.0%) of the 198 patients who did not receive an antihistamine in advance.

*Supportive medications to manage diarrhea*

Of the 164 patients in the alpelisib group who experienced diarrhea, approximately two-thirds (104 patients [63.4%]) received supportive medication, of

which antipropulsives were most frequent (69 of 104 patients [66.3%]), particularly loperamide. The incidence and severity of diarrhea was comparable in patients who did and did not receive concomitant treatment with metformin (**Supplemental Table 5**).

*Supportive medication to manage stomatitis*

Of the 70 patients in the alpelisib group who experienced stomatitis, 7 (2.5%) had grade 3 and no patients had grade 4 stomatitis (**Table 2**). Concomitant medications to treat stomatitis were reported in 17 of 70 (24.3%) in the alpelisib group, however this may have been under reported. The most frequent medications reported in these 17 patients included dexamethasone and lidocaine.

*Risk factors related to key AESIs*

In the alpelisib group, the proportion of patients who had hyperglycemia was higher among patients who were overweight (62/84, 73.8%) or obese (50/74, 67.6%) at baseline compared with patients with a normal body mass index (63/110; 57.3%). A similar trend was observed for hyperglycemia of grade 3 (24.5% vs 35.7% vs 39.2% for normal, overweight, and obese, respectively) and grade 4 (2.7% vs 3.6% vs 9.5%, respectively). Older patients receiving alpelisib plus fulvestrant (≥ 75 years old) compared with younger patients showed a trend toward increased incidence of all-grade GI toxicity (29/34 [85.3%] vs 185/250 [74.0%], respectively) and grade 3/4 hyperglycemia (19/34 [55.9%] vs 89/250 [35.6%]).

*Treatment exposure and impact of more detailed AE management guidance on safety outcomes*

Median duration of exposure to study drug was 5.5 months (range, 0-30.8 months) for alpelisib and 8.2 months (0.4-30.8 months) for fulvestrant in the alpelisib treatment group and 5.6 months (range, 0.5-30.1 months) for fulvestrant in the placebo group (**Supplemental Table 6**). Alpelisib dose reductions and interruptions occurred in 59.2% and 72.2% of patients, respectively, and were most commonly due to AEs (57.7% and 66.5%, respectively) (**Supplemental Table 7**).

The study protocol amendment to improve monitoring and management of hyperglycemia and skin toxicity was implemented to reduce treatment discontinuation. The amendment updated the eligibility criteria to include only patients with an HbA1c < 6.5%, recommended the use of oral antihistamines prior to the onset of rash, and added a clinic visit at day 8 to identify hyperglycemia and skin toxicities earlier. To investigate the impact of the amendment, treatment discontinuation rate and median duration of exposure were compared between the first 50% of patients randomized and the last 50%. All-grade hyperglycemia (preferred term) was reported in 63.9% of the first 50% of patients randomized and 63.6% in the last 50%, while grade 3/4 was reported in 40.3% and 32.9%, respectively. All-grade rash (preferred term) was reported in 37.5% and 33.6%, respectively, and grade 3/4 was 11.1% and 8.6%. Discontinuation of alpelisib or placebo due to AEs was less frequent in the last 50% of patients randomized compared with the first 50%: discontinuation rate due to any-grade AEs was 20.7% vs 29.2%, and discontinuation rate due to grade ≥ 3 AEs was 7.9% vs 18.1%, respectively. Discontinuations due to hyperglycemia (3.6% vs 9.0%) were less frequent in the last vs first 50% of randomized patients, respectively (**Figure 4**). Median duration of exposure and the frequency of alpelisib or placebo dose reductions due to AEs or dose interruptions due to AEs were generally consistent in the first and last 50% of patients randomized.

*Efficacy by dose intensity*

In patients with *PIK3CA* mutation, the median dose intensity was 248 mg/day in the alpelisib arm. Relatively longer median PFS was observed in patients who received a higher median dose intensity of alpelisib compared with lower median dose intensity; however, PFS benefit over placebo was still evident even at the lower dose intensity (**Figure 5**).

## Discussion

As previously reported, data from SOLAR-1 demonstrated that alpelisib plus fulvestrant was tolerated by many patients with HR+/HER2– ABC [9]; however, toxicity

limited drug exposure. The most common grade 3/4 AEs in the alpelisib group were hyperglycemia, rash, and diarrhea. These AEs are expected with PI3K inhibition and are also reported with other PI3K inhibitors, along with stomatitis [7,12]. Hyperglycemia in particular is an on-target effect because inhibition of PI3K-α blocks glucose uptake by skeletal muscle and adipose tissue and activates hepatic glyconeogenesis [5]. Importantly, initial occurrences of both higher-grade hyperglycemia and rash were observed within the first two weeks of therapy, whereas diarrhea was seen over the course of the treatment.

AESIs were actively managed during SOLAR-1 to prevent treatment discontinuation and limit dose interruptions and reductions to optimize treatment benefit. This included early identification and intervention to limit grade 3/4 AEs and administering appropriate concomitant medications, such as metformin for hyperglycemia and topical steroid use for stomatitis [13]. A protocol amendment coupled with training for the study investigators provided clear direction on supportive treatments as well as dose management of alpelisib by AESI, which helped prevent discontinuation of alpelisib due to toxicity. Key examples include a more stringent HbA1c inclusion criterion (≤ 6.5%), guidance on prophylaxis for skin toxicities, and diabetologist and dermatologist consultations. Analyses indicate that AESIs of alpelisib are largely manageable with concomitant medications, with or without dose modifications as needed. For example, of the patients who experienced hyperglycemia, most received antidiabetic medication (87.1% received metformin) alone or in combination, and glycemic control was generally rapid (median for improvement by ≥ 1 grade, 6 days; range, 4 to 7 days). Additionally, PFS benefit was maintained regardless of baseline diabetic status. It is noteworthy that insulin sensitizers (e.g., metformin) may be preferable to insulin secretagogues (e.g., sulfonylurea, meglitinides) to manage hyperglycemia in patients treated with alpelisib due to the insulin spikes and relative resistance noted with PI3K inhibitors [5,10]. Beyond metformin, there is no second agent widely accepted as a standard to treat hyperglycemia due to PI3K inhibitors. Some consider sodium-glucose cotransporter 2 (SGLT2) inhibitors to be the best choice, however, more data is needed to support their use [10]. However, short-term insulin is clearly effective for managing acute cases as well as more severe

hyperglycemia associated with alpelisib and not controlled by oral antihyperglycemic medications alone.

Importantly, the more detailed AE management guidelines implemented during the trial and outlined in **Table 1** resulted in fewer patients in the last 50% randomized discontinuing alpelisib due to hyperglycemia (3.6%) compared with the first 50% randomized (9.0%). The decrease in incidence of grade 3/4 hyperglycemia and rash may be attributed to the protocol amendment, as well as other factors, such as earlier identification and appropriate management of AESIs. Prophylactic management also had a positive impact on the incidence and severity of rash. Compared with individuals who did not receive preventive treatment, those who received prophylactic anti-rash medication, such as antihistamines and corticosteroids, experienced both reduced frequency and severity of rash. Guidance on the management of AESIs as well as other AEs is provided in the alpelisib prescribing information to assist HCPs in optimizing the clinical benefit for patients treated with alpelisib plus fulvestrant [10].

This analysis of SOLAR-1 data revealed that, for patients with *PIK3CA*-mutated ABC, the previously reported PFS benefit of alpelisib plus fulvestrant over placebo was evident even at lower median dose intensities of alpelisib [9]. However, higher dose intensities resulted in relatively longer benefits, supporting the need for optimal AE management in the effort to maintain the highest possible dose intensities. These results underscore the importance of education on early, prompt, and effective AE management for patients receiving alpelisib to maximize the intended clinical impact of the treatment on patients' outcomes.

While this analysis of SOLAR-1 provides useful insight into management strategies to limit the impact of AESIs on patients with HR+/HER2– ABC receiving alpelisib plus fulvestrant, data from real-world studies are required. Such observational studies may inform the safety profile of this treatment outside the stringent setting of a phase 3, randomized, placebo-controlled trial, as well as provide insight into the impact of AE management approaches on the clinical benefit of this treatment and how this benefit can be maximized during routine clinical practice.

In summary, this safety analysis of SOLAR-1 demonstrates that AESIs associated with alpelisib, including hyperglycemia, rash, and diarrhea, occurred

relatively early during treatment. These AEs were reversible and manageable with monitoring, early detection, and intervention (including concomitant medications and dose modifications when needed) and was also reversible with alpelisib discontinuation. Implementation of more-detailed AE management guidance during the study improved markers of safety. Exposure-efficacy analyses revealed that the optimal treatment benefit of alpelisib is achieved by maintaining a high median dose intensity while actively managing AEs as needed. Together, these findings illustrate clinical management that may optimize the benefit of alpelisib in HR+/HER2– ABC patients whose tumors harbor *PIK3CA* mutations.

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**Table 1. Management Guidance for AESIs Based on Protocol Amendment**

**Table 2. Most Frequently Reported Adverse Events (≥ 20% incidence of any grade event in either treatment group) in the Safety Population[a]**

**Figure 1. Time to First Occurrence of Grade ≥ 2 (A) and Grade ≥ 3 (B) AESIs in the Safety Population**

**Figure 2. Changes in Hyperglycemia Markers Over Time in the Safety Population**

**Figure 3. Incidence of Rash in Patients Who (A) Received Anti-rash Medication Prior to Onset and (B) Patients Without Anti-rash Medication Prior to Onset.**

Each section represents the highest grade experienced by a given patient.

**Figure 4. AESIs and Discontinuation Rates in the First and Last 50% of Patients Randomized.**

[a] Preferred term.

**Figure 5. Progression-Free Survival by Median Alpelisib Dose Intensity in Patients With *PIK3CA*-Mutated ABC.[a]**

[a]In patients with *PIK3CA* mutations, the median dose intensity for alpelisib was 248 mg/day.

**Table 1. Management Guidance for AESIs Based on Protocol Amendment**

| Grade | Criteria | Recommendation for Alpelisib Dosing | Recommendation for Management |
|---|---|---|---|
| *Hyperglycemia* | | | |
| 1 | FPG > ULN to 160 mg/dL<br>Or<br>FPG >ULN to 8.9 mmol/L | • No alpelisib dose adjustment required | • If FPG is < 140 mg/dL, consider metformin<br>• If FPG is 140-160 mg/dL, start or intensify metformin |
| 2 | FPG > 160 to 250 mg/dL<br>Or<br>FPG > 8.9 to 13.9 mmol/L | • No alpelisib dose adjustment required<br>• If FPG does not resolve to grade ≤ 1 within 21 days after antidiabetic treatment, reduce alpelisib by 1 dose level[a] | • Start oral antidiabetic treatment (eg, metformin)<br>• If FPG keeps rising beyond MTD of metformin, add an insulin sensitizer (eg, pioglitazone) |
| 3 | FPG > 250 to 500 mg/dL<br>Or<br>FPG > 13.9 to 27.8 mmol/L | • Discontinue alpelisib<br>• If FPG resolves to grade ≤ 1 within 3 to 5 days while off alpelisib and on metformin, restart alpelisib and reduce by 1 dose level[a]<br>• If FPG does not resolve to grade ≤ 1 within 21 days after antidiabetic treatment, permanently discontinue alpelisib | • Consider consultation with endocrinologist<br>• Start metformin and add pioglitazone<br>• Insulin may be used as rescue medication for 1 to 2 days |

| | | | |
|---|---|---|---|
| 4 | FPG > 500 mg/dL<br>Or<br>FPG ≥ 27.8 mmol/L | • Discontinue alpelisib for 24 hours, then:<br>− If grade ≤ 3, follow specific grade recommendations<br>− If grade 4 persists (with no confounding factors), permanently discontinue alpelisib | • Consult with endocrinologist<br>• See grade 3 recommendations; recheck in 24 hours |
| *Diarrhea* | | | |
| 1 | Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline | • No alpelisib dose adjustment required | • Initiate appropriate medical therapy and monitor as clinically indicated<br>• Medically manage patients according to local practice guidelines for diarrhea[a] |
| 2 | Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared with baseline; limiting instrumental ADL | • Interrupt alpelisib dose until grade ≤ 1 and resume at lower dose level[a]<br>• Only 1 dose reduction is permitted; if toxicity reoccurs, permanently discontinue alpelisib treatment | |
| 3 | Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care ADL | | |
| 4 | Life-threatening consequences; urgent | | |

| | | | |
|---|---|---|---|
| | intervention indicated | | |
| *Rash* | | | |
| 1 | < 10% body surface area with active skin toxicity | • No alpelisib dose adjustment required | • Initiate topical corticosteroid treatment<br>• Consider adding oral antihistamine to manage symptoms |
| 2 | 10-30% body surface area with active skin toxicity | | |
| 3 | > 30% body surface area with active skin toxicity | • Interrupt alpelisib<br>• Once grade ≤ 1, resume alpelisib at the same dose level for first occurrence of rash or at lower dose level[b] in case of second occurrence | • Initiate or intensify topical corticosteroid and oral antihistamine treatment<br>• Consider low-dose systemic corticosteroid treatment |
| 4 | Any % body surface area associated with extensive superinfection, with IV antibiotics indicated | • Permanently discontinue alpelisib | • Treat as medically indicated |

ADL, activity of daily living; AE, adverse event; AESI, adverse event of special interest; FPG, fasting plasma glucose; MTD, maximum tolerated dose; ULN, upper limit of normal.

AEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

[a] Management generally consists of hydration and loperamide. Further interventions may be required for higher-grade diarrhea, persistent low-grade diarrhea, or diarrhea with complications such as fever, sepsis, neutropenia, bleeding, or dehydration.

[b] Starting dose: 300 mg/day continuously. Dose level −1: 250 mg/day continuously. Dose level −2: 200 mg/day continuously.

**Table 2. Most Frequently Reported Adverse Events (≥ 20% incidence of any grade**

| AE, *n* (%) | Alpelisib Plus Fulvestrant (*n* = 284) | | | | | Placebo Plus Fulvestrant (*n* = 287) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Any Grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Any Grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Any AE | 282 (99.3) | 12 (4.2) | 54 (19.0) | 183 (64.4) | 33 (11.6) | 264 (92.0) | 69 (24.0) | 92 (32.1) | 87 (30.3) | 15 (5.2) |
| Hyperglycemia[b] | 181 (63.7) | 32 (11.3) | 45 (15.8) | 93 (32.7) | 11 (3.9) | 28 (9.8) | 19 (6.6) | 7 (2.4) | 1 (0.3) | 1 (0.3) |
| Diarrhea | 164 (57.7) | 93 (32.7) | 52 (18.3) | 19 (6.7) | 0 | 45 (15.7) | 30 (10.5) | 14 (4.9) | 1 (0.3) | 0 |
| Nausea | 127 (44.7) | 90 (31.7) | 30 (10.6) | 7 (2.5) | 0 | 64 (22.3) | 49 (17.1) | 14 (4.9) | 1 (0.3) | 0 |
| Decreased appetite | 101 (35.6) | 75 (26.4) | 24 (8.5) | 2 (0.7) | 0 | 30 (10.5) | 21 (7.3) | 8 (2.8) | 1 (0.3) | 0 |
| Rash[c] | 101 (35.6) | 48 (16.9) | 25 (8.8) | 28 (9.9) | 0 | 17 (5.9) | 14 (4.9) | 2 (0.7) | 1 (0.3) | 0 |
| Vomiting | 77 (27.1) | 64 (22.5) | 11 (3.9) | 2 (0.7) | 0 | 28 (9.8) | 18 (6.3) | 9 (3.1) | 1 (0.3) | 0 |
| Decreased weight | 76 (26.8) | 34 (12.0) | 31 (10.9) | 11 (3.9) | 0 | 6 (2.1) | 1 (0.3) | 5 (1.7) | 0 | 0 |
| Stomatitis | 70 (24.6) | 39 (13.7) | 24 (8.5) | 7 (2.5) | 0 | 18 (6.3) | 15 (5.2) | 3 (1.0) | 0 | 0 |
| Fatigue | 69 (24.3) | 36 (12.7) | 23 (8.1) | 10 (3.5) | 0 | 49 (17.1) | 36 (12.5) | 10 (3.5) | 3 (1.0) | 0 |
| Asthenia | 58 (20.4) | 25 (8.8) | 28 (9.9) | 5 (1.8) | 0 | 37 (12.9) | 29 (10.1) | 8 (2.8) | 0 | 0 |

AE, adverse event.

AEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

[a] AEs reported as a single preferred term regardless of relationship to study medication.

[b] Hyperglycemia is reported in the table as a preferred term. Hyperglycemia AESI (preferred terms listed in **Supplementary Table 1**) were reported in 187 (65.8%) patients in the alpelisib plus fulvestrant group (grade ≥ 3, *n*=108 [38.0%]) and in 30 (10.5%) of those randomized to placebo plus fulvestrant (grade ≥ 3, *n*=2 [0.7%]). [9]

[c] Rash is reported in the table as a preferred term. Rash AESI (preferred terms listed in **Supplementary Table 1**) were reported in 153 (53.9%) of patients in the alpelisib plus fulvestrant group (grade ≥ 3, *n*=57 [20.1%]) and in 24 (8.4%) of those randomized to placebo plus fulvestrant (grade ≥ 3, *n*=1 [0.3%]). [9]

Figure 1-A.

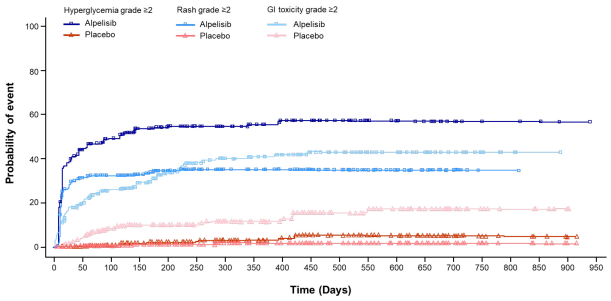



Figure 1-B.

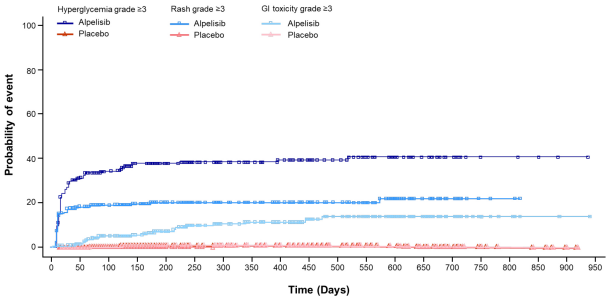


Figure 2-A.

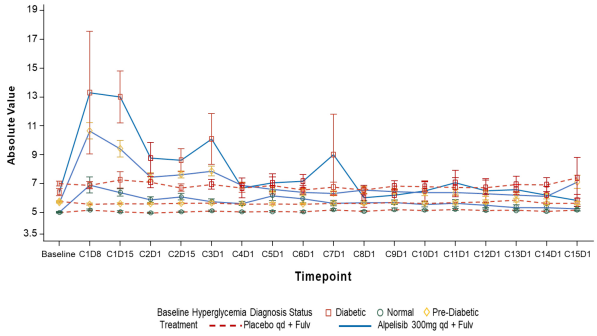



Figure 2-B.

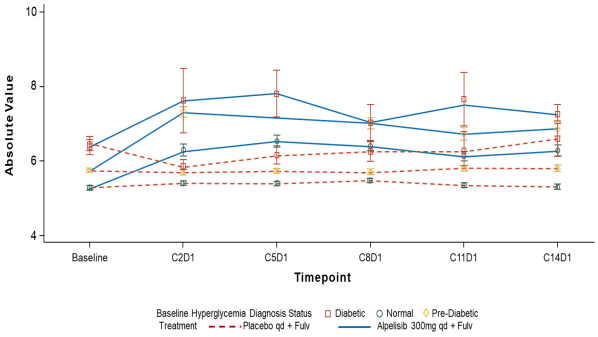


Figure 3-A.

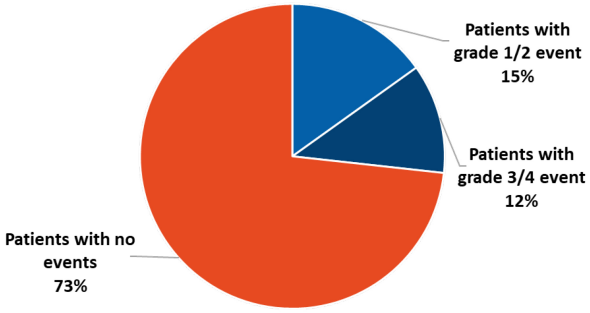



Figure 3-B.

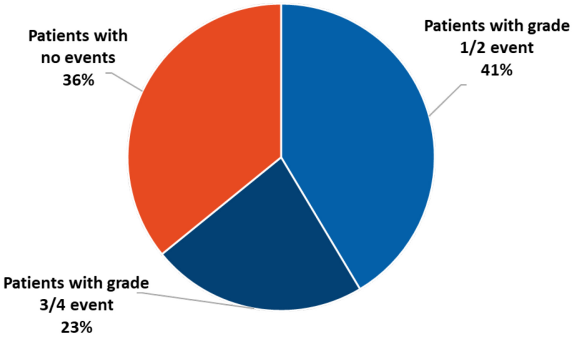


Figure 4.

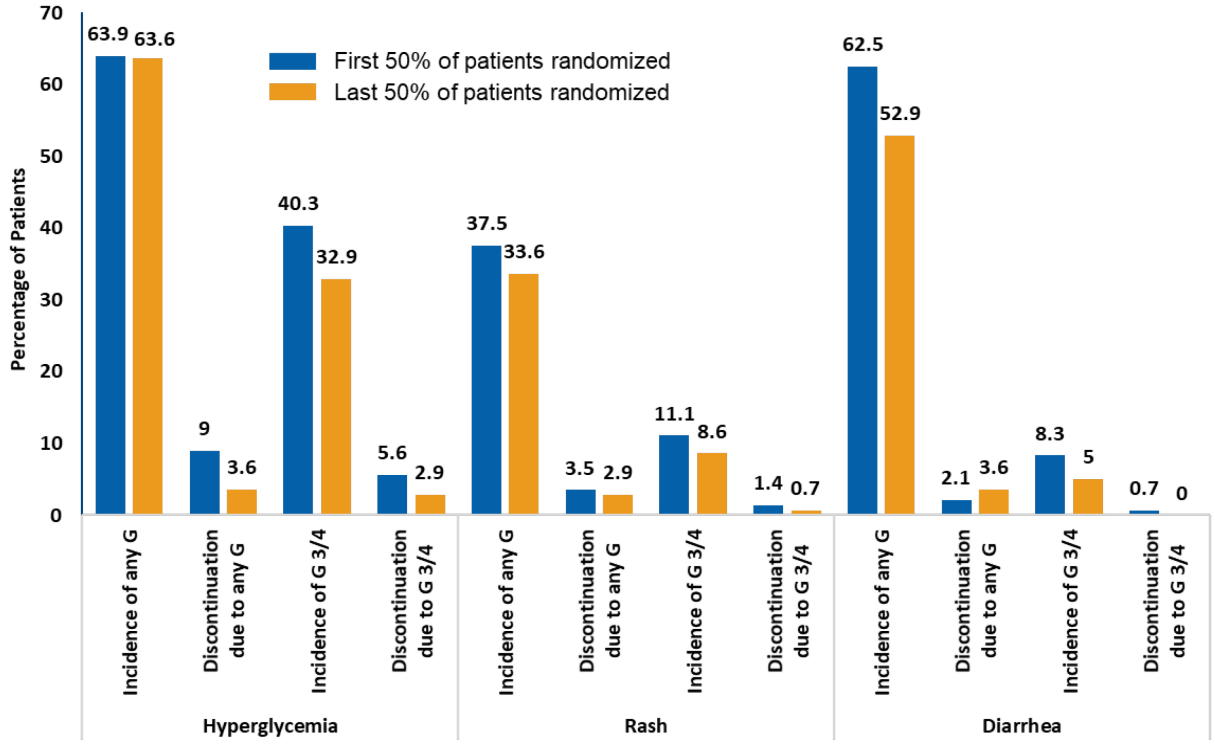
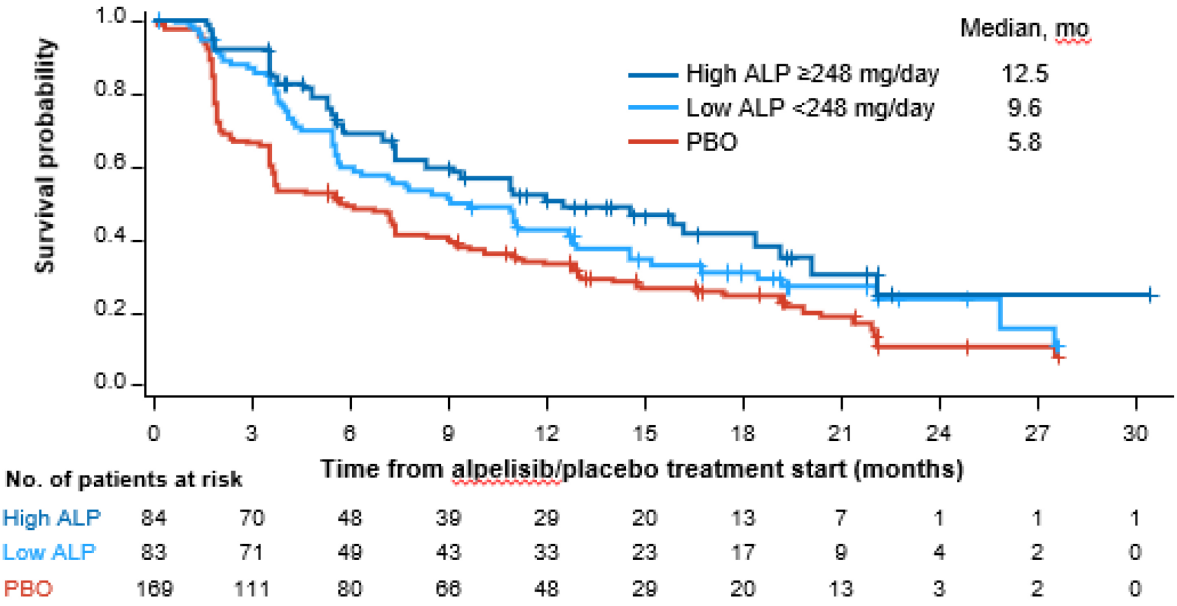


Figure 5.




| No. of patients at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| High ALP | 84 | 70 | 48 | 39 | 29 | 20 | 13 | 7 | 1 | 1 | 1 |
| Low ALP | 83 | 71 | 49 | 43 | 33 | 23 | 17 | 9 | 4 | 2 | 0 |
| PBO | 169 | 111 | 80 | 66 | 48 | 29 | 20 | 13 | 3 | 2 | 0 |