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# **Early intervention for and management of alpelisib (ALP)-induced hyperglycemia: case studies from the Phase III SOLAR-1 trial**

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# Introduction

- In the Phase III SOLAR-1 trial (NCT02437318), ALP (PI3K $\alpha$  inhibitor) plus fulvestrant (FUL) significantly improved progression-free survival (PFS) vs FUL alone in patients with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC) and *PIK3CA* mutations (11.0 vs 5.7 months; hazard ratio, 0.65; 95% CI, 0.50-0.85;  $P < .001$ )<sup>1</sup>
- Hyperglycemia was identified as an on-target adverse event (AE) with ALP and was the most frequent grade (G) 3/4 AE in SOLAR-1 (G3: 32.7%; G4: 3.9%)<sup>1,2</sup>
- A protocol amendment was implemented during the study to provide additional detailed guidance on hyperglycemia and rash management<sup>2</sup>
- Baseline characteristics such as prediabetic or diabetic glycemic status, body mass index (BMI)  $\geq 30$ , and age  $\geq 75$  years have been identified as risk factors for ALP-induced hyperglycemia

ALP, alpelisib; CI, confidence interval; PI3K $\alpha$ , phosphoinositide 3-kinase alpha; P, P value; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; vs, versus.

# Objective

- To understand incidence and management of hyperglycemia and highlight four case studies of early intervention and different management approaches for ALP-induced hyperglycemia in the SOLAR-1 trial

ALP, alpelisib.

# Methods (1 of 5)

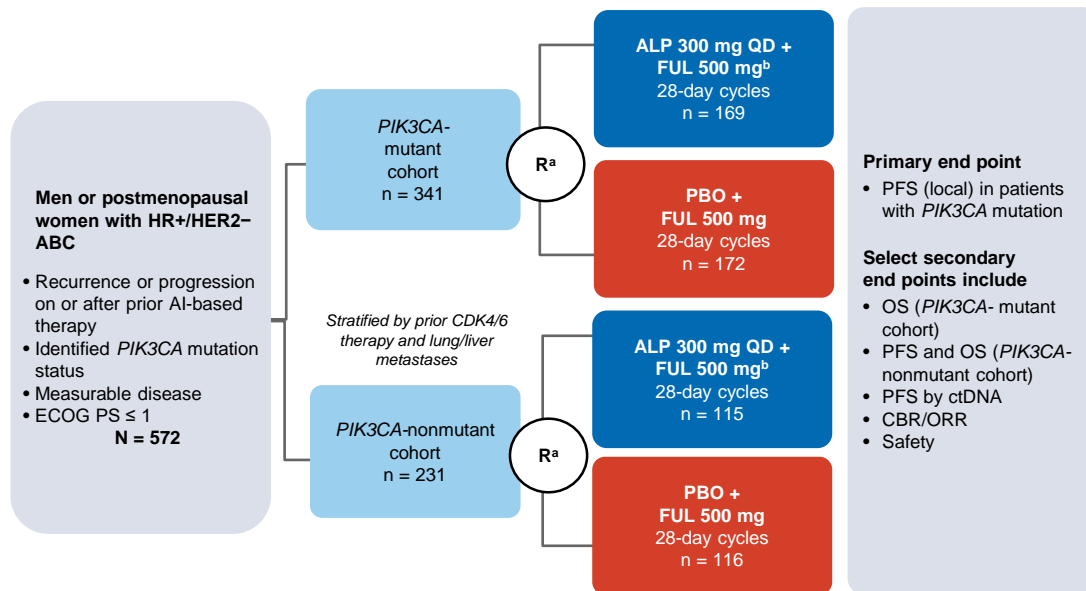
## Patients and Study Details

- Men or postmenopausal women with HR+/HER2- ABC with disease recurrence or progression on or after receiving an aromatase inhibitor-based therapy were randomized to receive ALP plus FUL or placebo (PBO) plus FUL in two separate cohorts according to the *PIK3CA* mutational status of their tumors (**Figure 1**)

ABC, advanced breast cancer; ALP, alpelisib; FUL, fulvestrant; HR+, hormone receptor positive; HER2-, human epidermal growth receptor 2-negative; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

# Methods (2 of 5)

## Figure 1. Study Design



<sup>a</sup> Randomized 1:1 within each cohort. <sup>b</sup> FUL given on day 1 of each 28-day cycle, with an additional administration on day 15 of cycle 1.

AI, aromatase inhibitor; ALP, alpelisib; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; FUL, fulvestrant; ORR, overall response rate; OS, overall survival; PBO, placebo; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression-free survival; QD, once daily; R, randomization.



# Methods (3 of 5)

## Monitoring of Glycemic Status

- According to the protocol, glycemic status was assessed at baseline and over time using fasting plasma glucose and glycated hemoglobin
- Hyperglycemia was regularly assessed as per the National Cancer Institute CTCAE, v4.03
- In addition to concomitant medications for hyperglycemia, dose interruptions or reductions by one level were recommended for both G3 and G4 hyperglycemia, per protocol (**Table 1**)

CTCAE, common terminology criteria for adverse event; G, grade.

# Methods (4 of 5)

## Table 1. ALP/PBO Dose Modifications and Interventions in SOLAR-1

Grade 1	<p><b>Maintain dose level</b> and remind patient of lifestyle changes (dietary advice and exercise):</p> <ul style="list-style-type: none"> <li>• If FPG &lt; 140 mg/dL, consider adding metformin</li> <li>• If FPG 140-160 mg/dL, start/intensify metformin</li> </ul>
Grade 2	<p><b>Maintain dose level</b> and remind patient of lifestyle changes:</p> <ul style="list-style-type: none"> <li>• If FPG is still increasing on maximum tolerated dose of metformin or is persistently &gt;160 mg/dL, add an insulin sensitizer (eg, pioglitazone 30 mg [maximum dose])</li> <li>• If FPG not <math>G \leq 1</math> within 21 days, reduce ALP/PBO by 1 dose level</li> </ul>
Grade 3	<p><b>Omit ALP/PBO</b> and confirm fasting status of the assessment:</p> <ul style="list-style-type: none"> <li>• Follow G2 recommendations for metformin and pioglitazone</li> <li>• Insulin may be used for 1-2 days until hyperglycemia resolves</li> <li>• If FPG <math>G \leq 1</math> within 3-5 days while off study treatment and on metformin, restart ALP/PBO and reduce by 1 dose level; continue antihyperglycemics               <ul style="list-style-type: none"> <li>– If no resolution within 3-5 days, consult a diabetologist</li> <li>– If no resolution within 21 days, permanently discontinue ALP/PBO</li> </ul> </li> </ul>
Grade 4	<p><b>Omit ALP/PBO</b> and confirm fasting status of the assessment:</p> <ul style="list-style-type: none"> <li>• Consider cooperation with diabetologist, initiate or intensify medication with appropriate antihyperglycemic treatment (see G3), recheck within 24 hours</li> <li>• If grade improves, follow specific grade recommendations</li> <li>• If FPG confirmed at G4 and confounding factors not excluded, permanently discontinue ALP/PBO</li> </ul>

ALP, alpelisib; FPG, fasting plasma glucose; G, grade; PBO, placebo.

# Methods (5 of 5)

## Case Selection

- Cases were selected on the basis of hyperglycemia events of interest to the community: (1) not well controlled on metformin alone; (2) required hospitalization; (3) no risk factors for hyperglycemia at baseline; (4) no action taken at initial presentation of hyperglycemia

# Results (1 of 7)

## ALP-Induced Hyperglycemia, Interventions, and Outcomes in SOLAR-1

### Table 2. ALP-Induced Hyperglycemia in SOLAR-1

- At the data cutoff of June 12, 2018, the incidence of all-G and G3/4 hyperglycemia in SOLAR-1 was 66% and 38%, respectively (**Table 2**)

	ALP + FUL (n = 284)
Incidence of all-grade hyperglycemia, n (%)	187 (66)
Incidence of grade 3/4 hyperglycemia, n (%)	108 (38)
Time to onset of grade 3/4 hyperglycemia, median (range), days <sup>a,b</sup>	15 (5-395)
Time to improvement of grade 3/4 hyperglycemia, median (range), days <sup>a,b</sup>	6 (4-7)
Risk factors for hyperglycemia, n (%) <sup>c</sup>	
Prediabetic or diabetic glycemic status	171 (60)
BMI ≥ 30	74 (26)
Age ≥ 75 years	34 (12)
Received antihyperglycemic medication, n (%) <sup>d</sup>	163 (87)
Most common antihyperglycemic medications, n (%) <sup>e</sup>	
Metformin	142 (87)
Insulin	52 (32)

<sup>a</sup> Based on FPG values. <sup>b</sup> Observed in 110 patients. <sup>c</sup> Patients could have more than one risk factor. <sup>d</sup> Denominator is based on the 187 patients who developed hyperglycemia.

<sup>e</sup> Denominator is based on the 163 patients who received antihyperglycemic medications.

ALP, alpelisib; BMI, body-mass index; FUL, fulvestrant; G, grade.

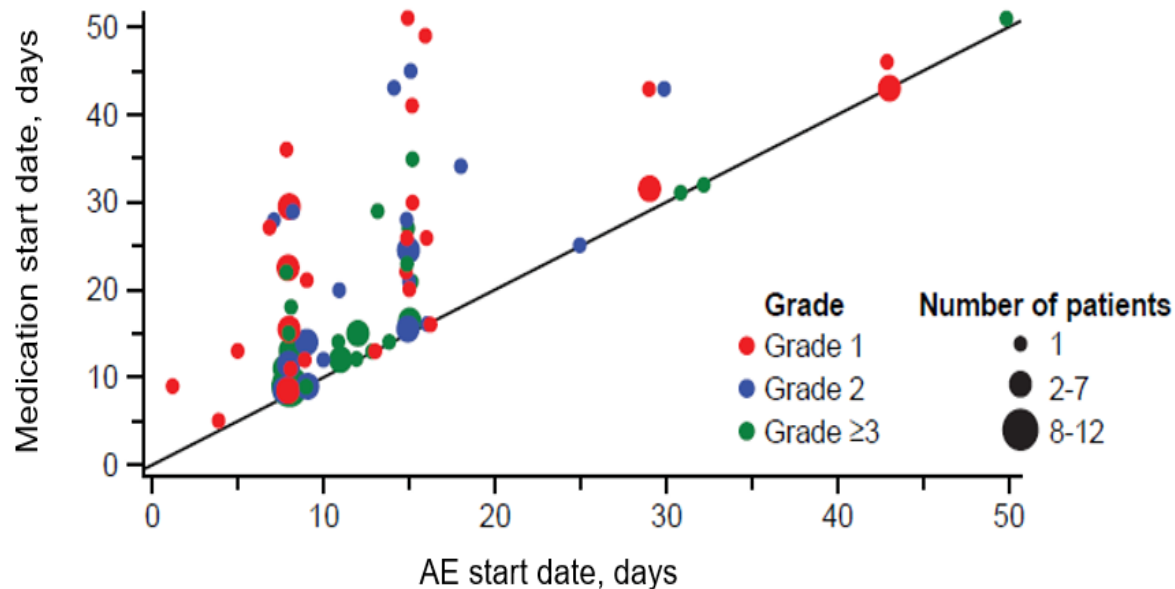
# Results (2 of 7)

- The median time to onset of grade 3/4 hyperglycemia was 15 days and median time to improvement of grade 3/4 hyperglycemia was 6 days
- Metformin was the most common antihyperglycemic medication used (87%)
- Only one antihyperglycemic medication was required in 36% of patients who developed hyperglycemia, two were required in 26% of patients, and three or more in 25% of patients
- Comparing the time to first hyperglycemia event with the time to first antihyperglycemic medication used, many patients experienced early intervention, where the time to receiving concomitant medications after initial hyperglycemia was short. Those farther from the 45-degree line indicate a delay antihyperglycemic medications after initial presentation **(Figure 2)**

ALP, alpelisib.

# Results (3 of 7)

## Figure 2. Time to First Hyperglycemia Event and First Antihyperglycemic in Patients Who Developed Hyperglycemia



AE, adverse events.

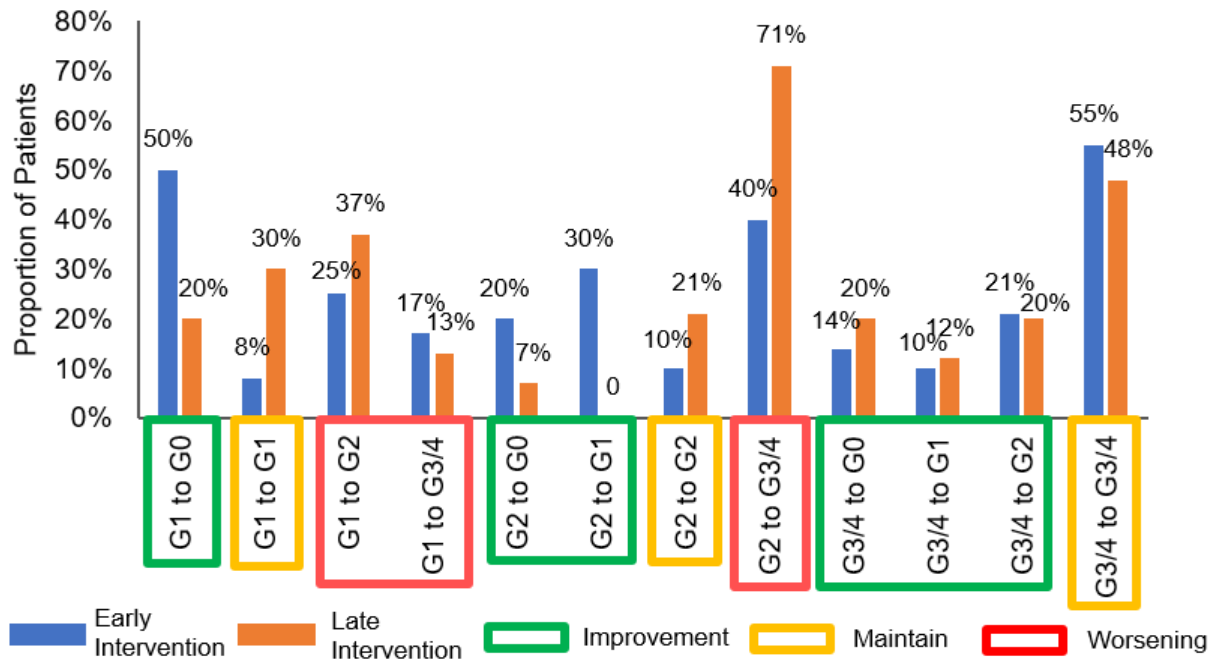
# Results (4 of 7)

- Early intervention was defined as follows: grade 1: starting medication within 4 days of onset of hyperglycemia (n = 12); grade 2: within 2 days (n = 10); grade 3/4: within 1 day (n = 29)
- Late intervention was defined as follows: grade 1: starting medication after 4 weeks of onset of hyperglycemia (n = 30); grade 2: after 3 weeks (n = 14); grade 3/4: after 4 days (n = 25)
  - For patients presenting with grade 1 or 2 hyperglycemia, delay in intervention resulted in a higher chance of hyperglycemia not improving or becoming more severe (**Figure 3**)

ALP, alpelisib.

# Results (5 of 7)

## Figure 3. Subsequent Grade by Early or Late Intervention of ALP-Induced Hyperglycemia in SOLAR-1



ALP, alpelisib; G, grade.



# Results (6 of 7)

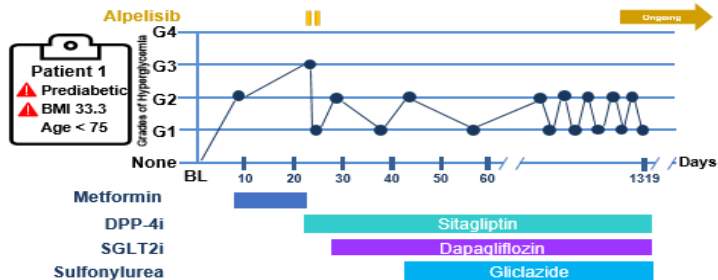
- Case studies presenting different clinically relevant scenarios of early intervention (data cutoff, September 30, 2019) are represented by patients 1 through 3 (**Figure 4A-C**), and an example of late intervention is represented by patient 4 (**Figure 4D**)

ALP, alpelisib.

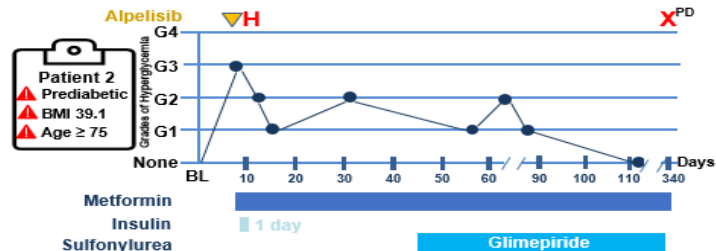
# Results (7 of 7)

## Figure 4. Case Studies of Four Patients in the SOLAR-1 Trial

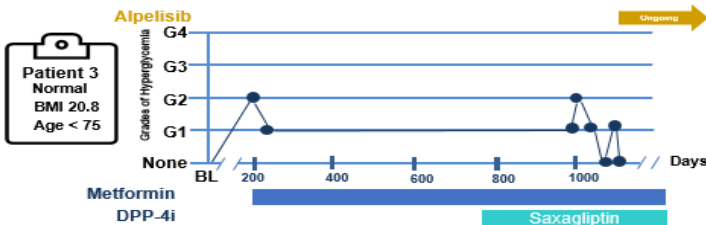
A. Not Well Controlled on Metformin Alone



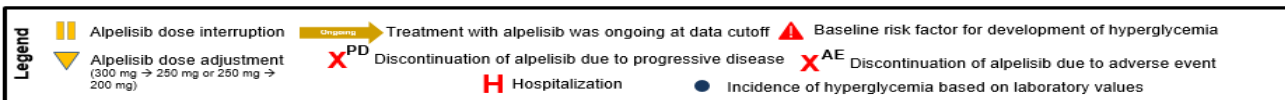
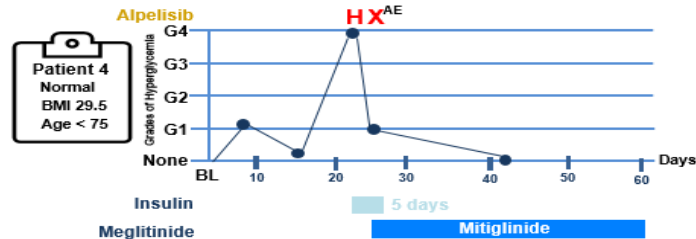
B. Required Hospitalization



C. No Risk Factors for Hyperglycemia at Baseline



D. Late Intervention



AE, adverse event; BL, baseline; BMI, body-mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; H, hospitalization; PD, progressive disease; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

# Conclusions

- Hyperglycemia was the most common grade 3/4 adverse event in the SOLAR-1 trial, and recommended antihyperglycemic treatments were outlined in the protocol
- The majority of patients required more than one antihyperglycemic medication to manage hyperglycemia
- Patients presenting with grade 1 and 2 hyperglycemia who had delayed intervention with antihyperglycemic medication were more likely to not improve or have a worsening grade than those who had early intervention
  - These cases should be interpreted with caution due to the limited number and type of patients who were included as examples
- These data and cases from SOLAR-1 confirm that ALP-induced hyperglycemia is manageable with identification of baseline risk factors, close monitoring, early detection and intervention, including concomitant medications and dose modifications where appropriate

ALP, alpelisib.

# References

1. André F, et al. *N Engl J Med*. 2019;380(20):1929-1940.
2. Rugo HS, et al. *Ann Oncol*. 2020;31(8):1001-1010.

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# Disclosures

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