Alpelisib (ALP) + Fulvestrant (FUL) for Advanced Breast Cancer (ABC): Phase 3 SOLAR-1 Trial Results

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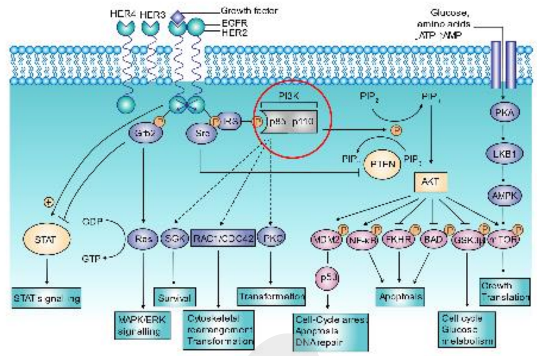
The Importance of the PI3K Pathway in HR+ Breast Cancer

- The PI3K pathway is frequently altered in HR+ breast cancer and has been implicated in resistance to endocrine therapies[1,2]
- Approximately 40% of HR+ breast cancers harbor a *PIK3CA* mutation, leading to hyperactivation of the PI3K pathway[3-5]
- PI3K signaling has been shown to promote estrogen-independent growth of ER+ breast cancer cells,[6,7] and this growth is inhibited by the addition of PI3K inhibitors to antiestrogens[8]



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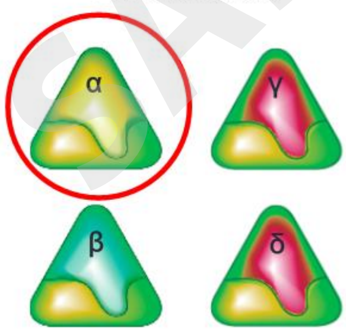
ER+, estrogen receptor-positive; HR+, hormone receptor-positive; PI3K, phosphatidylinositol 3-kinase.

1. Mi[illegible] *Clin Oncol* [illegible] *Transl Med*. 2015;7(283):283ra51. 3. Mayer IA, et al. *Clin Cancer Res*. 2017;23(1):26-34. 4. Loi S, et al. *Proc Natl Acad Sci U S A*. 2010;107(22):10208-10213.
5. Ste[illegible] al. *J Clin Invest*. 2010;120(7):2406-2413. 7. Crowder RJ, et al. *Cancer Res*. 2009;69(9):3955-3962. 8. Miller TW, et al. *Cancer Discovery*. 2011;1(4):338-351.

Selective Inhibition of PI3K-alpha Is a Promising Strategy in *PIK3CA*-Mutated Cancers

PI3K isoforms[1]

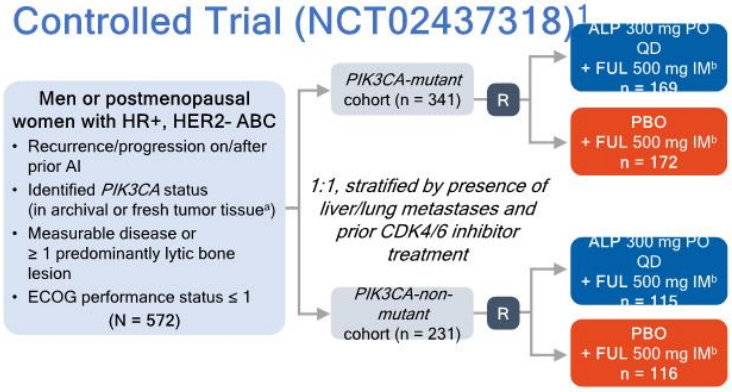


- While pan-PI3K and β-sparing inhibitors target multiple isoforms, alpelisib (BYL719) specifically targets the α-isoform[2]
- Alpelisib has demonstrated antitumor activity in preclinical models harboring *PIK3CA* alterations[2]
- In a phase 1b trial, alpelisib + fulvestrant provided a 9.1-mo median PFS in heavily pretreated patients with ER+ ABC and positive *PIK3CA* mutation status[3]

ABC, advanced breast cancer; ER+, estrogen receptor-positive; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase.

1. Andre F, et al. ESMO 2018. Abstract LBA3 [oral]. 2. Fritsch C, et al. *Mol Cancer Ther*. 2014;13(5):1117-1129. 3. Juric D, et al. *JAMA Oncol*. 2018;In press.

SOLAR-1: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial (NCT02437318)[1]



Primary endpoint
- PFS in *PIK3CA*-mutant cohort (locally assessed)

Secondary endpoints include
- OS (*PIK3CA*-mutant cohort)
- PFS (*PIK3CA*-non-mutant cohort)
- PFS (*PIK3CA* mutation in ctDNA)
- PFS (*PIK3CA*-non-mutant in ctDNA)
- ORR/CBR (both cohorts)
- Safety

- The primary endpoint included all randomized patients in the *PIK3CA*-mutant cohort; PFS was analyzed in the *PIK3CA*-non-mutant cohort as a proof of concept
- Safety was analyzed for all patients who received ≥ 1 dose of study treatment, in both cohorts

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; IM, intramuscular; ORR, overall response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; PO, oral; QD, once daily; R, randomization.
[a] More than 90% of patients had mutational status identified from archival tissue.
[b] Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.
1. Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

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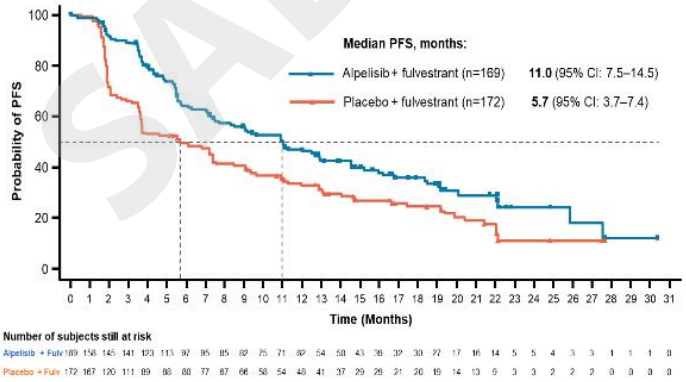
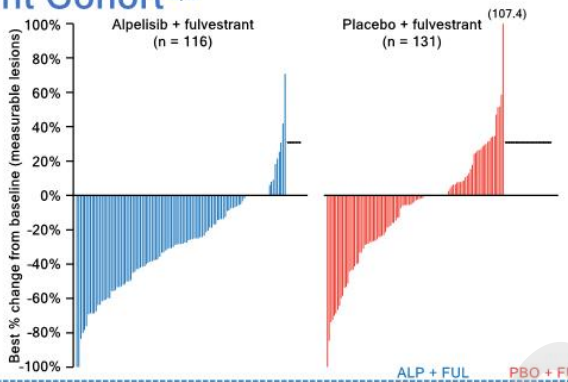
Primary Endpoint: Locally Assessed PFS in the *PIK3CA*-mutant Cohort[1,a]



Data cut-off: Jun 12, 2018	ALP + FUL (n = 169)	PBO + FUL (n = 172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5-14.5)	5.7 (3.7-7.4)
HR (95% CI)	0.65 (0.50-0.85)	
One-sided *P* value	0.00065	

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
At final PFS analysis, superiority was declared if one-sided, stratified log-rank test *P* value was ≤ 0.0199 (Haybittle-Peto boundary).
[a] Mutation status determined from tissue biopsy.
1. Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

Best Percentage Change in Sum of Target Lesion Diameters Based on Local Investigator Assessment in *PIK3CA*-mutant Cohort[a,b]



	ALP + FUL	PBO + FUL
Decrease in best percentage change from baseline	75.86%	43.51%
Increase/zero change in best percentage change from baseline	18.10%	35.88%
Percent change in target lesion contradicted by overall lesion response = PD	6.03%	20.61%

PD, progressive disease; UNK, unknown.
Patients for whom the best % change in target lesions was not available and patients for whom the best % change in target lesions was contradicted by overall lesion response = UNK were excluded from the analysis, percentages above
use n as denominator. Only patients with measurable disease at baseline are presented.
[a] Mutation status determined from tissue biopsy. [b] Change from baseline in sum of target lesion diameters.

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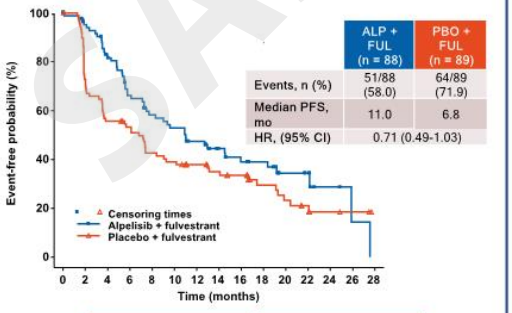
PFS by Line of Therapy in the *PIK3CA*-mutant Cohort[a]

First-line (n = 177)

Defined as patients whose disease progressed ≤ 1 year after (neo)adjuvant ET (endocrine resistant) or whose disease progressed > 1 year after (neo)adjuvant ET (endocrine sensitive) (later excluded after protocol amendment)

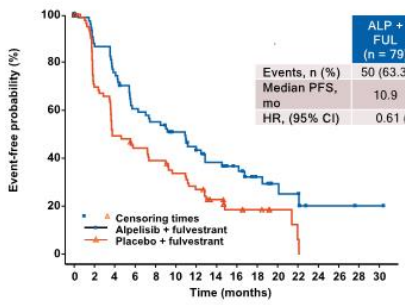


	ALP + FUL (n = 88)	PBO + FUL (n = 89)
Events, n (%)	51/88 (58.0)	64/89 (71.9)
Median PFS, mo	11.0	6.8
HR, (95% CI)	0.71 (0.49-1.03)	

	Endocrine sensitive patients		Endocrine resistant patients	
	ALP + FUL (n = 20)	PBO + FUL (n = 19)	ALP + FUL (n = 68)	PBO + FUL (n = 70)
Events, n (%)	11 (55.0)	9 (47.4)	40 (58.8)	55 (78.6)
Median PFS, mo	22.1	19.1	9.0	4.7

Second-line (n = 161)

Defined as patients whose disease progressed > 1 year after (neo)adjuvant ET and while on or after 1 line of ET for ABC or patients with newly diagnosed ABC whose disease progressed while on or after 1 line of ET

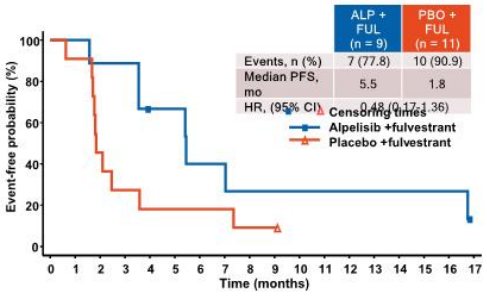


	ALP + FUL (n = 79)	PBO + FUL (n = 82)
Events, n (%)	50 (63.3)	65 (79.3)
Median PFS, mo	10.9	3.7
HR, (95% CI)	0.61 (0.42-0.89)	

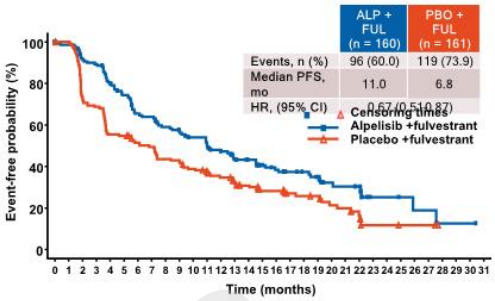
ABC, advanced breast cancer; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; PFS, progression-free survival.
[a] Mutation status determined from tissue biopsy.

PFS by Prior CDK4/6 Inhibitor Treatment in the *PIK3CA*-mutant Cohort[a]

With Prior CDK4/6 inhibitor therapy



Without Prior CDK4/6 inhibitor therapy

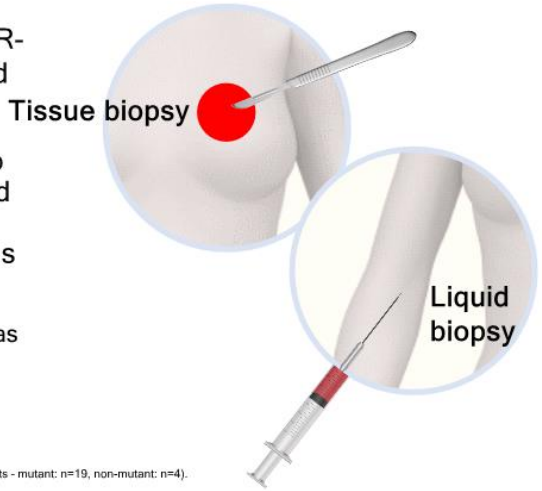


- Previous treatment with any CDK4/6 inhibitor was a stratification factor, however the number of patients enrolled who had received prior CDK4/6 inhibitor therapy was small
- Treatment benefit with alpelisib was observed regardless of prior use with a CDK4/6 inhibitor

ABC, advanced breast cancer; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; PFS, progression-free survival.
[a] Mutation status determined from tissue biopsy.

PIK3CA-mutational Analysis in SOLAR-1

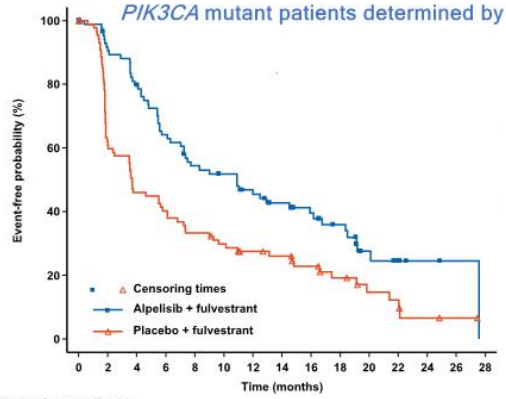
- For the primary analysis of SOLAR-1, mutation status was determined from a tumor tissue sample
- Plasma ctDNA samples were also collected at baseline and analyzed by PCR to retrospectively assess PFS by *PIK3CA* mutation status as a secondary endpoint[a]
  - Mutation status defined by ctDNA was also used to assess PFS in the population (positive vs negative)



[a] Not all patients had mutation status determined from blood samples (missing patients - mutant: n=19, non-mutant: n=4).
ctDNA, circulating tumor DNA; PFS, progression-free survival.

Locally Assessed PFS by Tissue or Plasma ctDNA-determined Mutation Status

PIK3CA mutant patients determined by ctDNA



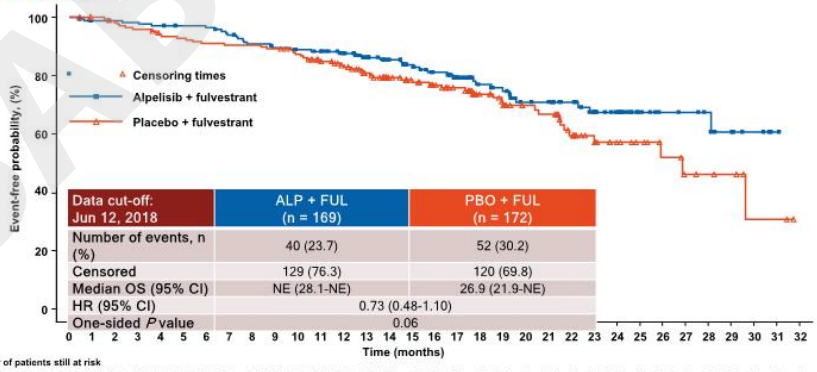
Number of patients still at risk

Alpelisib + ful	92	87	80	77	68	61	54	52	44	43	41	38	34	31	29	24	23	19	18	16	9	8	6	2	2	1	1	1	0
Placebo + ful	94	90	58	53	42	41	37	34	30	30	26	22	20	19	18	14	14	11	10	9	6	6	5	2	2	1	1	1	0

	ALP + FUL		PBO + FUL		
	Event n/N (%)	Median PFS	Event n/N (%)	Median PFS	HR
Patients with *PIK3CA* mutation: tissue	103/169 (60.9)	11.0	129/172 (75.0)	5.7	0.65
Patients with *PIK3CA* mutation: plasma	57/92 (62.0)	10.9	75/94 (79.8)	3.7	0.55
Patients without *PIK3CA* mutation: tissue	49/115 (42.6)	7.4	57/116 (49.1)	5.6	0.85
Patients without *PIK3CA* mutation: plasma	92/181 (50.8)	8.8	103/182 (56.6)	7.3	0.80

ctDNA, circulating tumor DNA; HR, hazard ratio; PFS, progression-free survival; QD, once daily.

Key Secondary Endpoint: Overall Survival in the *PIK3CA*-mutant Cohort[a]



Data cut-off: Jun 12, 2018	ALP + FUL (n = 169)	PBO + FUL (n = 172)
Number of events, n (%)	40 (23.7)	52 (30.2)
Censored	129 (76.3)	120 (69.8)
Median OS (95% CI)	NE (28.1-NE)	26.9 (21.9-NE)
HR (95% CI)	0.73 (0.48-1.10)	
One-sided *P* value	0.06	

Number of patients still at risk

Alpelisib + fulv	169	163	162	161	159	157	156	151	145	142	139	137	129	117	107	97	88	79	67	63	53	52	44	35	28	17	13	12	10	7	4	1	0
Placebo + fulv	172	168	164	160	155	153	150	149	149	147	142	132	125	112	99	91	81	74	60	53	45	43	32	24	17	14	10	7	6	5	2	2	0

OS data at this first interim analysis were immature; as of the cut-off date, 52% of the planned number of events for the final OS analysis were included

Median OS follow-up time from randomization date to event/censoring date was 15.9 months (range 0.4-31.7 months).

[a] Mutation status determined from tissue biopsy.

CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; QD: daily

Adverse Events by *PIK3CA* Mutational Status[a]

AEs ≥ 20% in either arm, %	*PIK3CA*-mutant cohort						*PIK3CA*-non-mutant cohort					
	ALP + FUL (n = 169)			PBO + FUL (n = 171)			ALP + FUL (n = 115)			PBO + FUL (n = 116)		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any AE	168 (99.4)	116 (68.6)	20 (11.8)	152 (88.9)	46 (26.9)	11 (6.4)	114 (99.1)	67 (58.3)	13 (11.3)	112 (96.6)	41 (35.3)	4 (3.4)
Hyperglycemia	110 (65.1)	54 (32.0)	8 (4.7)	15 (8.8)	0	1 (0.6)	71 (61.7)	39 (33.9)	3 (2.6)	13 (11.2)	1 (0.9)	0
Diarrhea	92 (54.4)	13 (7.7)	0	19 (11.1)	1 (0.6)	0	72 (62.6)	6 (5.2)	0	26 (22.4)	0	0
Nausea	77 (45.6)	4 (2.4)	0	34 (19.9)	0	0	50 (43.5)	3 (2.6)	0	30 (25.9)	1 (0.9)	0
Rash	67 (39.6)	22 (13.0)	0	11 (6.4)	1 (0.6)	0	34 (29.6)	6 (5.2)	0	6 (5.2)	0	0
Decreased appetite	57 (33.7)	1 (0.6)	0	13 (7.6)	0	0	44 (38.3)	1 (0.9)	0	17 (14.7)	1 (0.9)	0
Stomatitis	45 (26.6)	5 (3.0)	0	11 (6.4)	0	0	25 (21.7)	2 (1.7)	0	7 (6.0)	0	0
Weight decreased	45 (26.6)	6 (3.6)	0	1 (0.6)	0	0	31 (27.0)	5 (4.3)	0	5 (4.3)	0	0
Vomiting	43 (25.4)	0	0	16 (9.4)	0	0	34 (29.6)	2 (1.7)	0	12 (10.3)	1 (0.9)	0
Fatigue	40 (23.7)	5 (3.0)	0	26 (15.2)	0	0	29 (25.2)	5 (4.3)	0	23 (19.8)	3 (2.6)	0

[a] Mutation status determined from tissue biopsy.

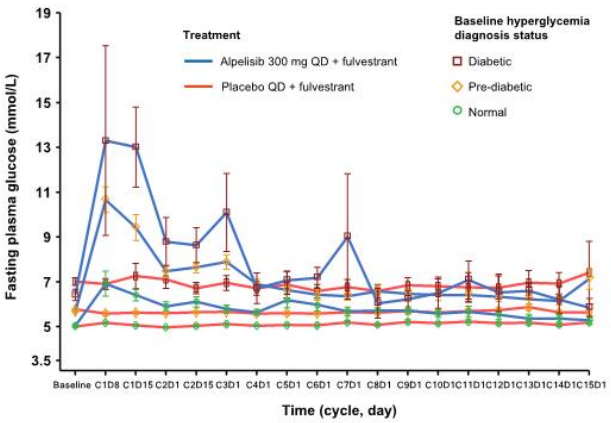
Hyperglycemia in Alpelisib-Treated Patients

- Hyperglycemia:
  - Is a reversible, on-target effect of PI3K inhibition
  - Is an easily identified AE
- Monitor blood glucose in first 2 weeks and then at least monthly thereafter
  - Glucose > 160 mg/dL was generally noted by Day 15 with a median duration of 10 days
  - Glucose > 500 mg/dL was uncommon, with improvement in 2-15 days; the majority of cases resolved in 2 days
- Hyperglycemia SAEs reported for 10.6% (n = 30) patients
  - Only two cases of ketoacidosis were reported; both resolved
- Among patients with hyperglycemia, the median duration of exposure to alpelisib was the same as the overall population (6.0 months versus 5.5 months)
- Due to hyperglycemia AEs
  - Dose interruptions occurred in 40.6% of patients (76/187) and dose adjustments in 43.9% of patients (82/187)
  - Treatment discontinuation occurred in 6.3% of patients treated with alpelisib plus fulvestrant

AE, adverse event; PI3K, phosphatidylinositol 3-kinase; SAE, serious adverse event.

No sustained induction of diabetic metabolism was observed after discontinuation of alpelisib treatment

Mean Fasting Plasma Glucose (FPG) Over Time, by Baseline Metabolic Diagnosis Status



- At baseline in the alpelisib arms, 56% of patients were pre-diabetic and 4% were diabetic, based on FPG and HbA1c levels[a]; patients with uncontrolled diabetes were excluded
- Increases in FPG and HbA1c were more pronounced in patients who were diabetic or pre-diabetic at baseline
  - Among the pre-diabetic patients, 74% experienced hyperglycemia during the treatment period
- 87% of patients with hyperglycemia were managed with anti-diabetic medication
  - 76% of patients were treated with metformin
- Mean FPG values peaked within the first 2 weeks, then decreased towards

FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; QD, once daily.
[a] Categories are those of the American Diabetes Association (2017).

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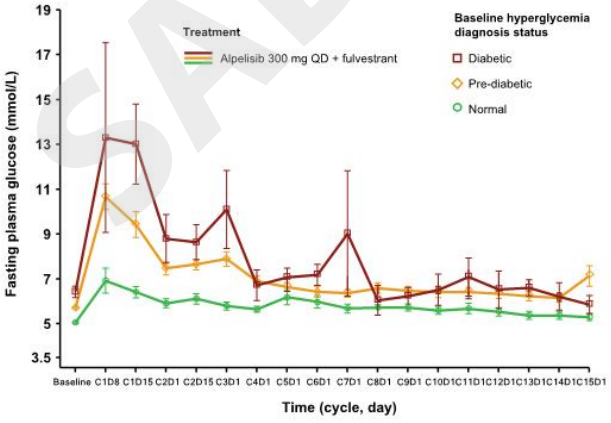

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Conclusions

- SOLAR-1 met its primary endpoint; a statistically significant and clinically meaningful prolongation of median PFS was observed with the addition of alpelisib to fulvestrant in patients with *PIK3CA*-mutant disease
- The majority of patients in the study were endocrine resistant; subgroup analyses demonstrated the benefit of alpelisib, regardless of line of therapy or prior CDK4/6 inhibitor treatment
- OS data at the first interim analysis in patients with a *PIK3CA* mutation were immature (52% of planned events); the median OS was not reached in the alpelisib arm
- Hyperglycemia, an on-target AE, can be easily identified (most commonly within the first 2 weeks of treatment) and managed with oral anti-diabetic agents
- PFS was significantly prolonged in patients with plasma ctDNA-determined mutational status, demonstrating the clinical utility of the ctDNA test in selecting patients with a *PIK3CA* mutation and confirming the robustness of the primary endpoint results

AE, adverse event; CDK4/6, cyclin-dependent kinase 4 and 6; ctDNA, circulating tumor DNA.

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- Members of the independent Data Monitoring Committee
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