Alpelisib Plus Fulvestrant in *PIK3CA*-Mutated, Hormone Receptor-Positive, Advanced Breast Cancer (BYLieve): Prior CDK4/6 Inhibitor Cohort in a Phase 2, Multicohort, Multicentre, Open-Label, Non-Comparative Study

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Research in Context

Evidence before this study

We searched PubMed between date of inception and June of 2020 for clinical trials or studies published in public medical databases assessing targeted therapies used for the treatment of advanced breast cancer (ABC) after progression on treatments including cyclin-dependent kinases 4 and 6 inhibitors (CDK4/6i). Terms used in this search included 'CDK4/6 inhibitor' and 'targeted therapies for advanced breast cancer.' We did not identify any trials evaluating a phosphatidylinositol-3-kinase inhibitor in ABC focusing solely in the post CDK4/6i setting. International guidelines recommend endocrine therapy plus CDK4/6i as first-line treatment in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) ABC; however, resistance develops in the majority of patients. Alpelisib plus fulvestrant demonstrated efficacy versus placebo plus fulvestrant in patients with *PIK3CA*-mutated HR+, HER2– ABC in the SOLAR-1 trial, but at the time that this trial was enrolling, CDK4/6i were not available in many regions, and only a small portion of patients who had progressed on CDK4/6i were enrolled.

Added value of this study

To our knowledge, BYLieve is the first prospective clinical study to examine the use of alpelisib plus fulvestrant for HR+, HER2–, *PIK3CA*-mutated ABC solely in the post-CDK4/6i setting. The primary endpoint of the study, evaluating proportion of patients alive and without disease progression at 6 months, was met. Side effects were manageable, with diarrhoea and hyperglycaemia the most common all-grade adverse events observed.

Implications of all the available evidence

BYLieve results presented in this manuscript demonstrate efficacy of alpelisib plus fulvestrant in 121 patients who previously received CDK4/6i plus any aromatase inhibitor immediately prior and had centrally confirmed *PIK3CA* mutation, with a manageable safety profile. These results support use of alpelisib plus

fulvestrant for treatment of HR+, HER2–, *PIK3CA*-mutated ABC in the post-CDK4/6i setting. To our knowledge, these data provide the first evidence for patients following progression on CDK4/6i-based treatment.

ABSTRACT

Background: Alpelisib, a PI3Kα-selective inhibitor and degrader, plus fulvestrant demonstrated efficacy in HR+, HER2–, *PIK3CA*-mutated advanced breast cancer (ABC) in SOLAR-1; limited data are available in the post-cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) setting. BYLieve aimed to assess alpelisib plus endocrine therapy in this setting; here, we report results from Cohort A.

Methods: This ongoing phase 2, multicentre, open-label, noncomparative study (NCT03056755) evaluates alpelisib plus fulvestrant or letrozole in patients with HR+, HER2–, ABC with tumour *PIK3CA* mutation, following progression on/after prior therapy including CDK4/6i. Participants aged ≥18 years with ECOG PS ≤2, with ≤2 prior anticancer and ≤1 prior chemotherapy regimens, were enrolled in three cohorts per immediate prior treatment. In Cohort A, patients with progression on/after CDK4/6i plus aromatase inhibitor (AI) received oral alpelisib 300 mg/day (continuous) plus fulvestrant 500 mg intramuscularly. Primary endpoint was proportion of patients alive without disease progression at 6 months per local assessment using Response Evaluation Criteria in Solid Tumors (RECIST) in patients with centrally confirmed *PIK3CA* mutation.

Findings: Between 14 Aug 2017 and 17 Dec 2019 (data cut-off), 127 patients with ≥6 months' follow-up were enrolled; 121 had centrally confirmed *PIK3CA* mutation. At data cut-off, median follow-up was 11·7 months (IQR 8·5-15·9). The primary endpoint was met: 50·4% (95% CI, 41·2-59·6) of patients were alive without disease progression at 6 months. Median progression-free survival (PFS) was 7·3 months (95% CI, 5·6-8·3), with numerically longer PFS versus standard real-world treatments. The most frequent grade 3/4 adverse events (AEs) were hyperglycaemia in 36 patients (28·3%) and rash and rash maculopapular (12

patients, 9·4% each). Serious AEs occurred in 33 patients (26·0%). No treatment-related deaths were reported.

Interpretation: BYLieve supports efficacy with manageable tolerability of alpelisib plus fulvestrant in patients with *PIK3CA*-mutated HR+, HER2– ABC, post-progression on CDK4/6i plus AI.

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INTRODUCTION

Hormone receptor-positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) disease accounts for >70% of incident breast cancer cases.[1,2] For patients with HR+, HER2– advanced breast cancer (ABC), first-line treatments recommended by expert guidelines include endocrine therapy (ET) plus a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i).[3,4] Resistance to endocrine-based therapies is common and can result from hyperactivated phosphatidylinositol-3-kinase (PI3K) pathway signaling, which can arise from mutations in the *PIK3CA* gene.[5] *PIK3CA* encodes the alpha isoform of PI3K (p110α), and mutations in this gene have been observed in about 40% of HR+, HER2– ABC.[1,6,7] Patients with *PIK3CA*-mutated HR+, HER2– ABC face a worse prognosis than those with wild-type disease.[8] Thus, there is a need for therapies that address the effects of the *PIK3CA* mutation and provide optimal treatment after progression on ET plus CDK4/6i.

Alpelisib is an orally bioavailable, α-selective PI3K inhibitor and degrader that demonstrated efficacy and a manageable safety profile in combination with fulvestrant in the phase 3 SOLAR-1 study of patients with *PIK3CA*-mutated disease that progressed on/after prior aromatase inhibitor (AI).[1,9,10] SOLAR-1 focused on an endocrine-resistant patient population, including those whose disease relapsed on or within 12 months from completing adjuvant ET. The study completed enrolment prior to implementation of CDK4/6i-based treatment as the standard of care in the first-line setting, although in a small proportion of patients with *PIK3CA*-mutated disease in SOLAR-1 who received prior CDK4/6i (n=20, 5·9%), median progression-free survival (PFS) in the alpelisib plus fulvestrant arm (n=9) was 5·5 months, compared with 1·8 months in the placebo plus fulvestrant arm (n=11; HR 0·48; 95% CI, 0·17-1·36).[1,11]

BYLieve is an ongoing phase 2, open-label, multicentre, noncomparative, three-cohort trial (NCT03056755) assessing the safety and efficacy of alpelisib plus letrozole or fulvestrant in patients with *PIK3CA*-mutated HR+, HER2– ABC who progressed on/after prior therapy, including CDK4/6i. To our knowledge, it is the first and only study that prospectively evaluates a PI3Kα inhibitor in patients who

progressed on treatment with a CDK4/6i in combination with ET in a substantial number of patients. Here, we present results from Cohort A of BYLieve: patients who previously received CDK4/6i plus AI.

METHODS

Study Design and Participants

Participants were women and men aged ≥18 years with ECOG performance status ≤2 with HR+, HER2– ABC not amenable to curative therapy, with a confirmed *PIK3CA* mutation determined by local or central laboratory testing of tumour tissue or plasma (*therascreen*® PIK3CA RGQ PCR Kit[12]; additional details in appendix, p 1). Patients with documented evidence of progression per RECIST v1.1 criteria were assigned to one of three cohorts per most recent therapy and received alpelisib plus fulvestrant or letrozole across 114 study locations and 18 countries (appendix p 5). Patients in Cohort A must have received a CDK4/6i plus AI as immediate prior therapy. Enrolment in each cohort continued until at least 112 patients with a centrally confirmed *PIK3CA* mutation were enrolled; only patients with centrally confirmed *PIK3CA* mutation and one dose of study treatment were included in the primary efficacy analysis (modified full analysis set, mFAS; appendix p 1).

Patients could have had ≤2 prior anticancer therapies and ≤1 prior chemotherapy regimen in the advanced or metastatic setting and had fasting plasma glucose levels ≤140 mg/dL (7·7 mmol/L) and haemoglobin A1c (HbA1c) levels ≤6·4%, including patients with well-controlled type II diabetes. Key exclusion criteria were known hypersensitivity to alpelisib, fulvestrant, letrozole, goserelin, or leuprolide; prior treatment with a PI3K inhibitor; or established diagnosis of diabetes mellitus type I or uncontrolled type II diabetes.

BYLieve was conducted in accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent. Approval of the protocol and any modifications was obtained from an independent ethics committee or institutional review board. A steering committee comprising participating investigators and Novartis personnel ensured management of the trial according to protocol. A Novartis safety management team evaluated data for potential safety signal assessment.

Procedures

In Cohort A, 300 mg alpelisib orally once daily and fulvestrant 500 mg intramuscularly on Day 1 of each 28-day cycle plus Day 15 of Cycle 1 were administered. Treatment continued until disease progression, unacceptable toxicity, death, or discontinuation from study treatment due to any other reason. For patients unable to tolerate alpelisib due to adverse events (AEs), a maximum of two dose reductions of alpelisib was allowed (dose level –1: 250 mg/day; dose level –2: 200 mg/day). Tumour response was assessed locally via CT or MRI per Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) at screening and every 8 weeks in the first 6 months and every 12 weeks thereafter. Following approval of a protocol amendment (30 January 2019), assessments occurred every 12 weeks per standard of care throughout the entire study until disease progression, death, withdrawal of consent, loss to follow-up, patient/guardian decision, or end of study. AEs were assessed at screening, during treatment, and up to 30 days after the last dose of study treatment according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Analyses of fasting or random blood glucose were performed on Days 8 and 15 of Cycle 1, Days 1 and 15 of Cycle 2, and Day 1 of subsequent cycles.

Outcomes

The primary endpoint, or the proportion of patients alive without disease progression at 6 months, based on local investigator assessment using RECIST v1.1, was assessed separately in each cohort; secondary endpoints included PFS, overall response rate (ORR), clinical benefit rate (CBR), duration of response (DOR), overall survival (OS), and safety and tolerability. As follow-up for this trial is still ongoing, only Cohort A results are reported; similarly, the prespecified secondary endpoint of PFS on next-line therapy (PFS2) in Cohort A is not yet available.

Statistical Analysis

The mFAS was the primary analysis set for efficacy endpoints. The primary endpoint was calculated with a one-sided 2·5% level of significance (two-sided 95% CIs) using Clopper and Pearson (1934)[13] exact method for each cohort separately to reject the null hypothesis of no treatment effect, or $p \leq 0 \cdot 30$ where p is the proportion of patients alive and without progression at 6 months. Thus, the primary endpoint was considered clinically meaningful if the lower bound of the 95% CI was >30%. Patients who progressed, died, or discontinued study before 6 months were counted as 'failure' in the analysis. To have a power of >90% when the true $p \geq 0 \cdot 45$, the required sample size in each cohort was 112 patients (increased from 80 upon approval of protocol amendment dated 30 January 2019). The ORR and CBR were calculated based on the mFAS and are summarised using descriptive statistics (N, %) along with two-sided exact binomial 95% CIs.[13] PFS and time to response were estimated using the Kaplan-Meier method with 95% CI. DOR (time from first documented response of confirmed CR or PR, to first documented progression or death due to underlying cancer) was calculated using Kaplan-Meier estimation. Safety analyses were conducted on the safety set. Primary analysis was planned to be performed 6 months after the last patient started treatment or discontinued early for each cohort separately. Interim analysis was also planned after ≥170 patients were treated (regardless of cohort) and had ≥6 months of follow-up. Sensitivity analyses were planned for the primary endpoint analyses using the FAS and mFAS, and the mFAS population compliant to protocol requirements.

Post-hoc analyses compared PFS with alpelisib plus fulvestrant in Cohort A with a similar group of patients with *PIK3CA*-mutated ABC treated with standard post-CDK4/6i treatments in the real-world setting. This study used the de-identified electronic health record-derived nationwide US-based Flatiron Health-Foundation Medicine advanced breast cancer Clinico-genomic Database (CGDB) for patients who met relevant inclusion criteria consistent with those of BYLieve Cohort A (*PIK3CA* mutation, ≤2 prior lines for ABC, and ≤1 prior line of chemotherapy for ABC; prior exposure to CDK4/6i; and no fulvestrant exposure). Patients selected from the CGDB were matched to BYLieve Cohort A via three approaches: weighting by

odds, 1:1 greedy nearest neighbour matching, and 1:1 exact matching.[14] Expanded methodological details can be found in the appendix.

Statistical analyses were performed using SAS software, version 9.4. The BYLieve trial is registered with ClinialTrials.gov (NCT03056755).

Role of the Funding Source

The funders sponsored the study design and conduct, data collection by the investigators, and statistical analysis, and provided funding for medical writing and editorial support. All authors—including representatives of the study sponsor—had access to the data, and contributed to development of, and approved, the manuscript. The corresponding author had full access to the data and final responsibility to submit for publication.

RESULTS

Between 14 August 2017 and data cut-off of 17 December 2019, a total of 127 patients (full analysis set, FAS) with at least 6 months' follow-up (on-treatment or posttreatment) were enrolled to Cohort A (Figure 1). Median follow-up (from enrolment to data cut-off) was 11·7 months (2-26). There were 121 patients in the mFAS. At data cut-off, treatment was ongoing in 33 patients (26%) and 94 (74%) of the 127 patients in the FAS had discontinued treatment. Primary reasons for discontinuation were progressive disease (64 [50%]) and AEs (18 [14%]; Figure 1).

Median age was 58 years (IQR 48·0-65·0), all patients were female (78% postmenopausal), and 64% were Caucasian. All 127 patients entered the study cohort with advanced disease following progression on/after prior CDK4/6i plus AI; and 98 (77%) had one prior line of ET in the metastatic setting. Eight patients (6%) received chemotherapy as first-line treatment in the metastatic setting; 76 (60%) had secondary endocrine resistance at baseline. The most frequent site of metastases was bone (108 [85%]), and 85 patients (67%) had visceral metastases. Median time since most recent recurrence or progression was 1·6 months (IQR 1·1-2·3; Table 1 and appendix p 8).[15]

Median duration of exposure in the safety set was 7·4 months for study treatment (alpelisib or fulvestrant; IQR 2·8-9·2), 5·1 months for alpelisib (IQR 1·8-8·6), and 6·5 months for fulvestrant (IQR 2·3-9·0). Median average daily dose of alpelisib was 299·1 mg (IQR 262·1-300·0; appendix p 9). Median duration of exposure to study treatment based on number of lines (0-3) of prior medication therapy in the metastatic setting ranged from 7·1 to 8·3 months.

In the mFAS, the proportion of patients alive and without disease progression at 6 months per local investigator assessment was 50·4% (n=61; 95% CI, 41·2%-59·6%; Table 2), with 72 events reported.[13] Thus, the study met its primary endpoint for this cohort.

Median PFS was 7·3 months (n=72; 95% CI, 5·6-8·3 months; IQR 3·6-13·6; Figure 2). Probability of PFS at 6 months was 54·1% (95% CI, 44·3%-62·9%). For the matched PFS analysis with standard treatments

(appendix p 11) in a real-world cohort per the CGDB (N=95), real-world PFS (rwPFS[16]) in the standard treatment group was 3·7 (95% CI, 2·2-5·3), 3·5 (95% CI, 3·0-5·4), and 3·4 (95% CI, 2·9-3·9) months for the weighting by odds, 1:1 greedy matching, and 1:1 exact matching approaches, respectively. (appendix p 12).

Median OS was 17·3 months (95% CI, 17·2-20·7; appendix p 7), with 25 events reported. A partial response was observed in 21 of 121 patients (17·4%) and stable disease in 55 patients (45·5%). ORR was 17·4% (95% CI, 11·1%-25·3%) and CBR was 45·5% (95% CI, 36·4%-54·8%). Median time to response among the 21 patients with a response was 1·84 months (range, 1·58-8·18; IQR 1·74-3·48). Median DOR was 6·6 months (nine events; 95% CI, 4·3 months to not estimable; Table 3 and appendix p 4).[17] Among the 100 patients with measurable disease at baseline, ORR was 21% (n=21; 95% CI, 13·5%-30·3%), CBR was 42·2% (n=42; 95% CI, 32·2%-52·3%), and 87 patients (70·1%) had negative best percentage change in tumour size from baseline (Figure 2). Efficacy was similar in the FAS (appendix p 13).

AEs were experienced by 126 patients (99·2%); all 126 had ≥1 AE considered to be treatment-related (Table 4). Grade ≥3 AEs were observed in 85 patients (66·9%), 79 of which (62·2%) were treatment-related. Serious AEs (SAEs) occurred in 33 patients (26·0%); 20 (15·7%) were treatment-related. One non-treatment-related SAE (0·8%) was fatal (Table 4). Most frequent (≥10%) all-grade AEs by preferred term included diarrhoea, hyperglycaemia, nausea, fatigue, decreased appetite, rash, and stomatitis. The most frequent (≥5%) grade ≥3 AEs were hyperglycaemia, rash, rash maculo-papular, and diarrhoea (appendix p 14). For AEs of special interest (AESIs), all-grade rash and grade ≥3 rash were observed in 58 (45·7%) and 26 (20·5%) patients, respectively. Of patients who had normal fasting plasma glucose and HbA1c at baseline, 33 (48·5%) and 11 (16·2%) experienced all-grade and grade ≥3 hyperglycaemia AESIs, respectively. Among the 48 patients who were prediabetic at baseline, 35 (72·9%) and 21 (43·8%) experienced all-grade and grade ≥3 hyperglycaemia AESIs, respectively. Of patients who were diabetic at baseline, three (100%) and one (33·3%) experienced all-grade and grade ≥3 hyperglycaemia AESIs,

respectively. Among the eight patients with unknown diabetic status at baseline, six (75%) and three (37·5%) experienced all-grade and grade ≥3 hyperglycaemia AESIs, respectively.

Of the 127 patients in the safety set, 82 (64·6%) experienced AEs requiring dose interruptions or adjustments. Thirty-seven (29·1%) required dose modifications/interruptions due to all-grade hyperglycaemia, 16 (12·6%) due to all-grade rash, 12 due to rash maculo-papular (9·4%), and ten due to diarrhoea (7·9%). AEs leading to treatment discontinuation occurred in 26 patients (20·5%), who were on therapy for a median of 38·5 days (IQR 15·0-113·0). These most frequently included rash in five patients (3·9%), and hyperglycaemia, colitis, urticaria, and vomiting in two patients (1·6%) each (Table 4).

Hyperglycaemia was medically managed in 55 of 74 patients (74·3%), with biguanides (different metformin formulations) used most frequently (n=52, 70·3%; appendix p 16).

Rash-preventive medication (prophylactic antihistamines) was administered to ten patients; three (30·0%) had at least one AESI rash event (grouped terms include rash, rash maculo-papular, rash macular, rash pruritic, dermatitis acneiform, rash erythematous, rash follicular, rash pustular, and rash morbilliform), of which two (20·0%) events were grade 1/2 and one (10·0%) was grade 1 (appendix p 17). Among 117 patients who did not receive prophylactic antihistamines, 55 (47·0%) experienced at least one AESI rash event, of which 30 (25·6%) were grade 1/2 and 25 (21·4%) were grade 3/4.

There were seven deaths (5·5%) during treatment: four from complications of their cancer (3·1%), one respiratory failure (0·8%; only fatal SAE), one superior vena cava occlusion (0·8%), and one due to unspecified reason (0·8%; appendix p 18). None were treatment related.

DISCUSSION

To our knowledge, BYLieve establishes the first benchmark in an underexplored population, as the first and only prospective study explicitly designed to investigate the efficacy of a PI3Kα-selective inhibitor in a large number of patients with HR+, HER2–, *PIK3CA*-mutated ABC in the post-CDK4/6i setting. The primary endpoint was met in this cohort of patients whose immediate prior treatment was CDK4/6i plus AI.

Thus far, studies assessing efficacy of post-CDK4/6i treatment have been mostly retrospective.[18-23] The phase 3 SOLAR-1 trial is the only other prospective study investigating alpelisib in patients with prior CDK4/6i treatments; however, these data comprise only a small subgroup.[1] In the overall population, PFS in the *PIK3CA*-mutant cohort was significantly prolonged with the addition of alpelisib to fulvestrant (HR 0·65; 95% CI, 0·50-0·85; one-sided $P<0·001$.)[1] Furthermore, adding alpelisib to fulvestrant numerically improved median OS by 7·9 months, although the pre-specified O'Brien-Fleming efficacy boundary was not crossed (HR 0·86; 95% CI, 0·64-1·15, one-sided $P\leq0·0161$).[24] Among patients in the *PIK3CA*-mutant cohort who received prior CDK4/6i in SOLAR-1 (n=20, 5·9% of study population), median PFS was 5·5 months in the alpelisib arm and 1·8 months in the placebo arm (HR 0·48; CI, 0·17-1·36).[11] Although this subgroup was small, the PFS treatment effect was consistent with that in the overall population of SOLAR-1. Notably, only one prior line of therapy was permitted in the metastatic setting prior to enrolment in SOLAR-1, and approximately 50% of patients across the two treatment arms received study treatment in the first-line setting.

As there are few data in the post-CDK4/6i setting, selection of a time-driven rather than an event-driven endpoint in BYLieve allowed for observation of any clinically meaningful effects of alpelisib treatment. A proportion of 30% of patients was defined as a clinically meaningful threshold, consistent with comparative trials and considered clinically relevant. Additional investigations of tissue and liquid biopsy specimens from BYLieve and other trials in the post-CDK4/6i setting are needed to characterise this observation further. Despite patients being more heavily pretreated in BYLieve than SOLAR-1, the proportion of

patients with negative best percentage change from baseline in BYLieve was similar between the two trials,[11] although ORR among patients with measurable disease at baseline in BYLieve was lower compared with SOLAR-1 (21·0% and 35·7%, respectively).[1] In addition, the median relative dose intensity of alpelisib in BYLieve (89·9%) was greater than in SOLAR-1 (82·7%).

Due to lack of a comparator arm, rwPFS with standard treatments was evaluated. These results should be interpreted with caution, as real-world progression data are not RECIST-based and can be subjective to multiple factors, such as the physician's clinical interpretation of available radiology, laboratory, and pathology reports, and variability in assessment schedule. These limitations are not present in a clinical trial.

However, *PIK3CA* mutations have been shown to confer a poor response and prognosis to therapy in patients with HR+, HER2– ABC. Results from the SAFIR02 trial demonstrated that patients with *PIK3CA*-mutated HR+, HER2– ABC had worse median OS compared with those without *PIK3CA*-mutated ABC (19·6 months versus 23·5 months, respectively; P=0·04).[8] In a meta-analysis of 11 unique trials that assessed the prognostic value of a *PIK3CA* mutation in HR+, HER2– ABC, excluding patients who received PI3K-targeted therapies, median PFS was 5·4 months (95% CI, 1·4-19·0).[25] Together with the patient population in BYLieve, wherein all patients were considered endocrine resistant and most received one to two lines of prior therapy for metastatic disease, the low PFS observed in the comparator arm is not unexpected. Further details of these external comparison analyses will be presented separately.

Collectively, these data illustrate that alpelisib plus fulvestrant is an effective treatment option in a large population of patients with HR+, HER2–, *PIK3CA*-mutated ABC that progressed on or after prior CDK4/6i. Brandão and colleagues reported that the combination of a CDK4/6i with fulvestrant was the optimal treatment for endocrine-sensitive and -resistant patients with HR+, HER2– ABC, although a meta-analysis of PFS in subgroups with *PIK3CA* mutations was not performed.[26] The recent 5th ESO-ESMO guidelines added alpelisib plus fulvestrant as a treatment option following progression on CDK4/6i plus ET with *PIK3CA*-mutated disease.[3] These findings further support the use of alpelisib plus fulvestrant as a potential

treatment option for patients harbouring a *PIK3CA* mutation who progress on first-line CDK4/6i-based therapy. Notably, the addition of alpelisib to fulvestrant did not adversely affect overall health-related quality of life.[27]

AEs in BYLieve were consistent with the reported safety profile of alpelisib.[1,28] Overall, fewer treatment discontinuations due to AEs were observed in BYLieve than in SOLAR-1 (20·5% and 25·0%, respectively). A notable decrease in treatment discontinuations due to hyperglycaemia was reported in BYLieve compared with SOLAR-1 (1·6% and 6·3%, respectively, a difference of ~fourfold), along with a reduction in all-grade hyperglycaemia events (58·3% and 63·7%, respectively). These data suggest that hyperglycaemia was monitored and managed more effectively in BYLieve. Similar to SOLAR-1,[29] fewer rash events were observed in patients who received prophylactic antihistamines compared with those who did not; small patient numbers limit further interpretation. A retrospective analysis involving patients with ABC from four clinical trials receiving alpelisib showed an association between prophylactic nonsedating antihistamines and grade 1/2 rash onset reduction (n=43) and recommended their use for the first 8 weeks of alpelisib treatment.[30] Considering these data, we encourage healthcare practitioners to consider prophylactic use of antihistamines in patients receiving alpelisib. Overall, the safety profile observed in BYLieve suggests that the additional management and monitoring measures for these AEs are effective in improving tolerability. Continued education and implementation of management strategies can help support optimisation of therapy with alpelisib plus fulvestrant.

Limitations

Study limitations are that a comparator arm was not included, and cross-comparisons cannot be made; therefore, real-world retrospective data were analysed as a virtual external control arm. Further data are still awaited from the other two cohorts and will provide more complete evidence on the efficacy and safety of alpelisib plus ET in patients who progressed on/after prior therapies. Additional analyses, including indirect analyses that may account for differences in populations, are warranted to better understand how these data

compare with other data in the second-line setting and beyond, particularly in patients who progressed on CDK4/6i.

Conclusions

Consistent with observations in SOLAR-1, BYLieve demonstrates that alpelisib plus fulvestrant is an effective treatment option with manageable tolerability for patients with HR+, HER2–, *PIK3CA*-mutated ABC in the post-CDK4/6i plus AI setting. The improved safety outcomes observed in BYLieve support that prior CDK4/6i exposure is unlikely to impact the safety profile of alpelisib plus fulvestrant, and that AEs are generally manageable with current guidance. Additional follow-up from SOLAR-1 and Cohort A of BYLieve, along with data from Cohorts B and C, will further guide the use of alpelisib for the treatment of HR+, HER2–, *PIK3CA*-mutated ABC.

DATA SHARING

The authors declare that all data supporting the findings of this analysis, including the redacted study protocol, are available within the Article and its appendix at publication. Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymised to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com. The real-world data have been originated by Flatiron Health, Inc., and Foundation Medicine, Inc. These de-identified data may be made available upon request and are subject to a license agreement with Flatiron Health and Foundation Medicine; interested researchers should contact cgdb-fmi@flatiron.com to determine licensing terms.

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CONTRIBUTORS

HR, EC, DJ, NT, CA, Y-MS, and SC were responsible for study conception or design. HR, EC, DJ, NT, CA, Y-MS, and SC were responsible for development of methodology, and HR, NS, JPZ, and CA for study supervision. All authors were responsible for acquiring, analyzing/interpreting the data. Y-MS, HK, and W-CH verified the raw data. All authors wrote, reviewed, and/or revised the draft and approved the final versions of the manuscript. All authors had unrestricted access to the final study data upon request and were responsible for data interpretation, manuscript preparation, and submission for publication; all authors attest to the accuracy of the data and data analysis.

DECLARATION OF INTERESTS

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FIGURES

Figure 1. Patient enrolment and disposition at data cut-off

All patients were enrolled by 17 June 2019, except one patient who was inadvertently enrolled in August 2019, discontinued a few weeks after, but was included in the analyses and coded as failure due to less than 6 months of study observation. For this patient, progression-free survival was censored with no event at cut-off date. Data cut-off was 17 December 2019 for analysis of the prior CDK4/6i plus AI cohort. AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy.

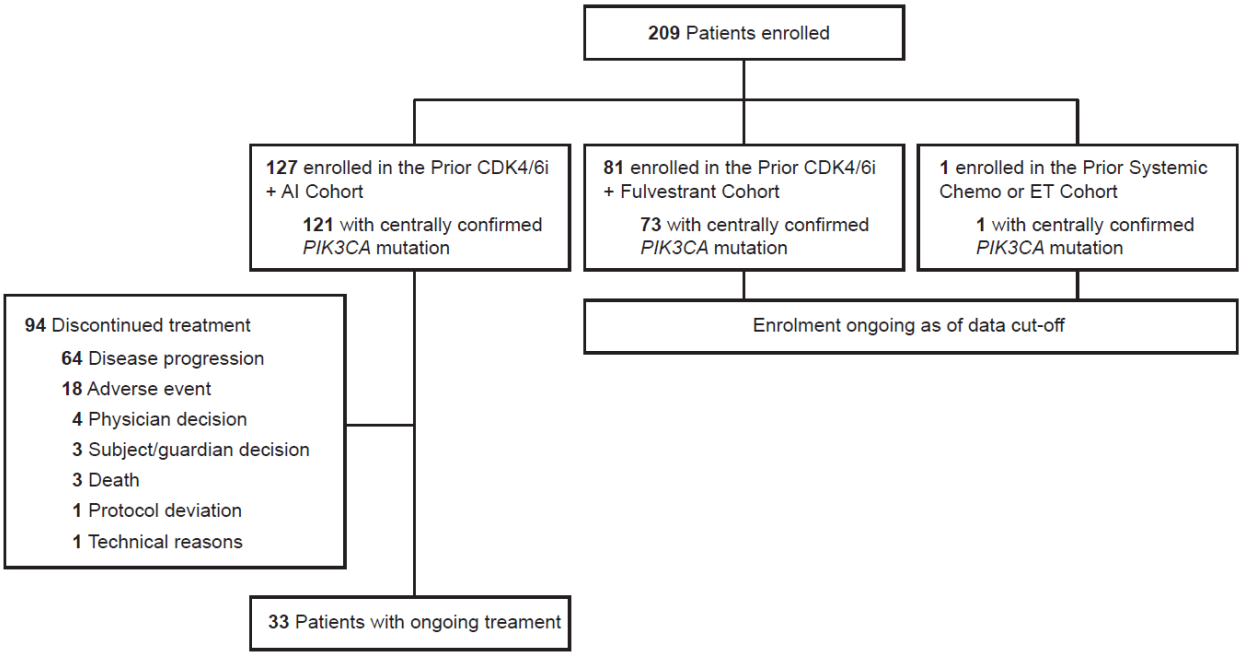
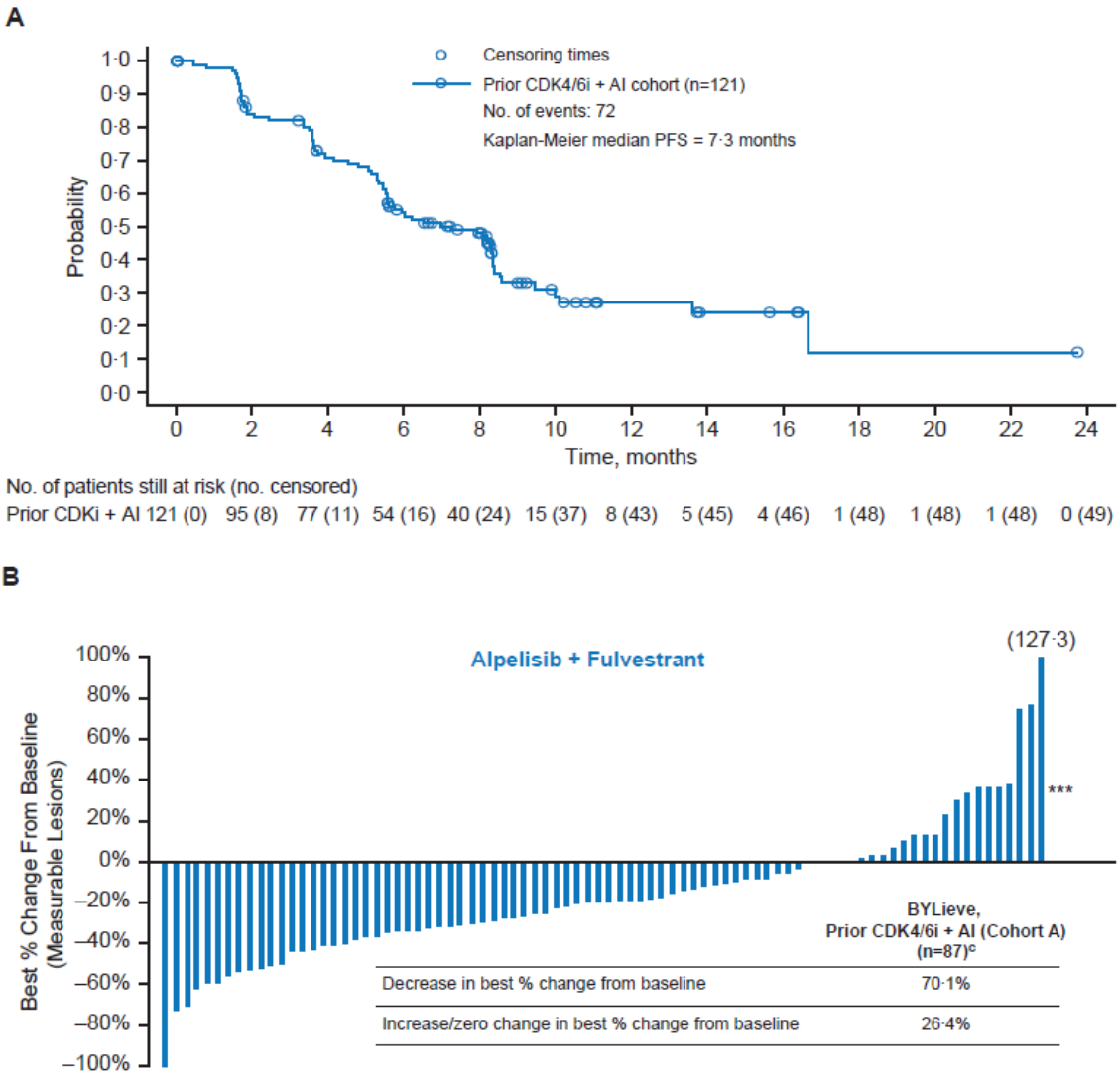


Figure 2. Progression-free survival (PFS) and best percentage change from baseline in Cohort A (modified full analysis set).

(A) Kaplan-Meier plot of time to PFS per local investigator assessment (modified full analysis set).[a] The Kaplan-Meier median PFS and event-free probability at 6 months only includes patients with disease progression or death. (B) Best percentage change from baseline (measurable lesions; data cut-off date: 17 December 2019).[b] AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase inhibitor.



[a]Censoring date was date of last adequate tumour assessment before the cut-off date.

[b]Best percentage change in sum of diameters per investigator assessment for patients with measurable disease at baseline.

[c]Patients with missing best percentage change or those with best percentage change in target lesion but overall response of Unknown are excluded.

*Percentage change in target lesion contradicted by overall lesion response = PD

TABLES

Table 1. Patient characteristics at baseline	
Characteristic	**Prior CDK4/6i Plus AI Cohort (N=127)**
Age, years	
N	127
Mean (SD)	56·7 (10·65)
Median (IQR)	58·0 (48·0-65·0)
Min-Max	33 - 83
Age category, No. (%)	
<50 years	39 (30·7)
≥50 years - <65 years	56 (44·1)
≥65 years	32 (25·2)
Sex, No. (%)	
Female	127 (100)
Race, No. (%)	
Asian	12 (9·4)
Black	6 (4·7)
Caucasian	81 (63·8)
Missing	1 (0·8)
Other	3 (2·4)
Pacific Islander	1 (0·8)
Unknown	23 (18·1)
Ethnicity, No. (%)	
East Asian	7 (5·5)
Hispanic or Latino	20 (15·7)
Mixed Ethnicity	1 (0·8)
Not Reported	32 (25·2)
Other	42 (33·1)
Russian	0
South Asian	3 (2·4)
Southeast Asian	3 (2·4)
Unknown	19 (15·0)
Body mass index, kg/m^2	
n	117
Mean (SD)	26·07 (5·473)
Median	25·34
Min-Max	16·1 - 46·6
Diabetic diagnosis status,[a] No. (%)	
Normal	68 (53·5)
Prediabetic	48 (37·8)
Diabetic	3 (2·4)
Missing	8 (6·3)
Menopausal status, No. (%)	
Premenopausal	28 (22·0)
Postmenopausal	99 (78·0)
ECOG performance status, No. (%)	
0	79 (62·2)
1	41 (32·3)
2	2 (1·6)
Missing	5 (3·9)
Stage at time of study entry, No. (%)	

Table 1. Patient characteristics at baseline	
Characteristic	**Prior CDK4/6i Plus AI Cohort (N=127)**
III	3 (2·4)
IV	124 (97·6)
Number of lines of prior medication therapy in the metastatic setting,[b] No. (%)	
0	15 (11·8)[c]
1	89 (70·1)
2	21 (16·5)
3	2 (1·6)
Lines of prior endocrine therapy in the metastatic setting, No. (%)	
0	15 (11·8)[c]
1	98 (77·2)
2	14 (11·0)
Endocrine status at study entry,[d] No. (%)	
Primary endocrine resistance	26 (20·5)
Secondary endocrine resistance	76 (59·8)
Endocrine sensitivity	1 (0·8)
Previous exposure to fulvestrant or chemotherapy as first-line treatment in the metastatic setting, No. (%)	
Fulvestrant	0
Chemotherapy	8 (6·3)
Current extent of disease, No. (%) (metastatic sites)	
Bone	108 (85·0)
Bone only	24 (18·9)
Visceral	85 (66·9)
Lung	43 (33·9)
Liver	59 (46·5)
Other visceral	8 (6·3)
Lymph nodes	37 (29·1)
Skin	4 (3·1)
Breast	5 (3·9)
Central nervous system	2 (1·6)
Other	12 (9·4)

Table 1. Patient characteristics at baseline

Characteristic	Prior CDK4/6i Plus AI Cohort (N=127)

Patients in CDK4/6i plus AI cohort received alpelisib plus fulvestrant.
Metastatic sites and number of organs involved are derived from CRF page of diagnosis and extent of cancer if available. Otherwise, they will be derived.
No.: Number of patients who are at the corresponding category.
AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CRF, case report form; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.
[a]Diabetic diagnosis status at baseline is defined per American Diabetes Association 2017.[15] Diabetic: Fasting plasma glucose (FPG) ≥7·0 mmol/L or 126 mg/dL or haemoglobin A1c (HbA1c) ≥6·5 %; Prediabetic: FPG 5·6-<7·0 mmol/L or 100-125 mg/dL or HbA1c 5·7%-<6·5%; Normal: FPG <5·6 mmol/L or 100 mg/dL and HbA1c <5·7%.
[b]Protocol deviation: Two patients received three lines of therapy for advanced disease and were not eligible for the study.
[c]Ten patients received CDK4/6i in the adjuvant setting, three patients in the (neo)adjuvant setting, and one patient in the palliative setting. One patient received medication in the metastatic setting, but was classified as having received zero lines of prior medication therapy in the metastatic setting due to inappropriate regimen coding.
[d]Primary endocrine resistance is defined as relapse <24 months while on endocrine therapy in the adjuvant setting or progression <6 months while on endocrine therapy in the metastatic setting. Secondary endocrine resistance is defined as relapse ≥24 months while on endocrine therapy in the adjuvant setting, relapse <12 months after end of endocrine therapy in the adjuvant setting, or progression occurring ≥6 months while on endocrine therapy in the metastatic setting. Endocrine sensitivity is defined as relapse ≥12 months after the end of endocrine therapy in the adjuvant setting or progression occurring ≥12 months after the end of endocrine therapy in the metastatic setting. If sufficient data were not available to determine endocrine status, per these criteria, patients were not coded.

Table 2. Efficacy of alpelisib plus fulvestrant in the prior CDK4/6i plus AI cohort (mFAS)

Prior CDK4/6i Plus AI Cohort (n=121)	
Proportion of patients who were alive without disease progression at 6 months as assessed by local investigator,[a] % (95% CI)	50·4 (41·2-59·6)
Alive without PD/n	61/121
Patients with PD/n	47
Deaths/n	6
Withdrawal of informed consent/n	5
Lost to follow-up/n	2

Patients in CDK4/6i plus AI cohort received alpelisib plus fulvestrant.
n: The total number of patients in the cohort. It is the denominator for percentage (%) calculation.
AI, aromatase inhibitor; CDK4/6i, cyclin-dependent 4/6 inhibitor; mFAS, modified full analysis set; PD, progressive disease.
[a]Number of patients who were alive without disease progression at 6 months as assessed by local investigator. Patients who progressed, died, or discontinued study before 6 months were counted as 'failure.' The 95% confidence interval (CI) is calculated using Clopper and Pearson (1934)[13] exact method.

Table 3. Best overall response, according to local assessment, in the prior CDK4/6i plus AI cohort (mFAS)		
Prior CDK4/6i Plus AI Cohort (n=121)	**Patients, n (%)**	
Patients with measurable disease at baseline	100 (82·6)	
Patients with nonmeasurable disease only at baseline	19 (15·7)[a]	
	Best overall response	Best overall response (patients with measurable disease)
Complete response (CR)	0	0
Partial response (PR)	21 (17·4)	21 (21·0)
Neither CR nor PD (NCR/NPD)[b]	16 (13·2)	0
Stable disease (SD)	55 (45·5)	55 (55·5)
Progressive disease (PD)	14 (11·6)	11 (11·0)
Unknown (UNK)	15[c] (12·4)	13 (13·0)
Overall response rate (ORR: CR+PR)	21 (17·4) 95% CI (11·1-25·3)	21 (21·0) 95% CI (13·5-30·3)
Clinical benefit rate (CBR: CR+PR+SD+NCR/NPD≥24 weeks)[d]	55 (45·5) 95% CI (36·4-54·8)	42 (42·0) 95% CI (32·2-52·3)
Duration of response,[e] months		
Total number of events/total number of patients (%)	9/21 (42·9)	
50th percentile (95% CI)[f]	6·6 (4·3-NE)	

Patients in CDK4/6i plus AI cohort received alpelisib plus fulvestrant.
n: The total number of patients in the cohort. It is the denominator for percentage (%) calculation.
AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; mFAS, modified full analysis set; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]Measurability of lesions was recorded after first treatment administration in two patients; these patients were classified as missing measurable/nonmeasurable disease identification.
[b]Refers to presence of lesions not fulfilling criteria for target lesions at baseline or abnormal nodal lesions (ie, ≥10 mm), unless there is unequivocal progression of the non-target lesions (PD) or it is not possible to determine progression unequivocally (UNK).
[c]Eleven patients had no valid post-baseline tumour assessment; one patient was coded as SD by the investigator before 6 weeks after the start date of study treatment; two patients started the new antineoplastic treatment before first post-baseline tumour assessment; one patient was coded as PD too late by investigator since first tumour assessment was performed >12 weeks after start date of study treatment.
[d]Refers to the proportion of patients with a best overall response of CR or PR or an overall lesion response of stable disease (SD) or Non-CR/Non-PD lasting ≥24 weeks based on local investigator's assessment according to RECIST v1.1.
[e]The start date is the date of first documented response of CR or PR, and the end date is defined as the date of the first documented progression or death due to underlying cancer.
[f]Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).[16]

Table 4. Safety of alpelisib plus fulvestrant in the prior CDK4/6i plus AI cohort (safety set)					
	Prior CDK4/6i Plus AI Cohort (N=127)				
	All Grades, No. (%)	Grade ≥3, No. (%)			
Adverse events	126 (99·2)	85 (66·9)			
Treatment-related	126 (99·2)	79 (62·2)			
SAEs	33 (26·0)	31 (24·4)			
Treatment-related	20 (15·7)	18 (14·2)			
Fatal SAEs[a]	1 (0·8)	1 (0·8)			
AEs leading to discontinuation	26 (20·5[b])	15 (11·8)			
Treatment-related[c]	23 (18·1)	13 (10·2)			
AEs leading to dose adjustment/interruption	82 (64·6)	68 (53·5)			
AEs requiring additional therapy	120 (94·5)	75 (59·1)			
Adverse events by preferred term (≥10%)	**All Grades, No. (%)**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
Diarrhoea	76 (59·8)	69 (54·3)	7 (5·5)	0	0
Hyperglycaemia	74 (58·3)	38 (29·9)	35 (27·6)	1 (0·8)	0
Nausea	58 (45·7)	58 (45·7)	0	0	0
Fatigue	37 (29·1)	36 (28·3)	1 (0·8)	0	0
Decreased appetite	36 (28·3)	35 (27·6)	1 (0·8)	0	0
Rash	36 (28·3)	24 (18·9)	11 (8·7)	1 (0·8)	0
Stomatitis	34 (26·8)	32 (25·2)	2 (1·6)	0	0
Vomiting	30 (23·6)	28 (22·0)	2 (1·6)	0	0
Asthenia	25 (19·7)	24 (18·9)	1 (0·8)	0	0
Headache	24 (18·9)	23 (18·1)	1 (0·8)	0	0
Dry skin	20 (15·7)	19 (15·0)	1 (0·8)	0	0
Pruritus	20 (15·7)	18 (14·2)	2 (1·6)	0	0
Dyspnoea	19 (15·0)	16 (12·6)	2 (1·6)	1 (0·8)	0
Dysgeusia	18 (14·2)	18 (14·2)	0	0	0
Rash maculopapular	18 (14·2)	6 (4·7)	12 (9·4)	0	0
Dyspepsia	18 (14·2)	18 (14·2)	0	0	0
Abdominal pain	17 (13·4)	15 (11·8)	2 (1·6)	0	0
Pyrexia	17 (13·4)	17 (13·4)	0	0	0
Alopecia	16 (12·6)	16 (12·6)	0	0	0
Weight decreased	16 (12·6)	14 (11·0)	2 (1·6)	0	0
Aspartate aminotransferase increased	15 (11·8)	11 (8·7)	4 (3·1)	0	0
Urinary tract infection	14 (11·0)	11 (8·7)	3 (2·4)	0	0
Abdominal pain upper	13 (10·2)	13 (10·2)	0	0	0
Muscle spasms	13 (10·2)	13 (10·2)	0	0	0
Cough	13 (10·2)	12 (9·4)	1 (0.8)	0	0
Alanine aminotransferase increased	13 (10·2)	9 (7·1)	4 (3·1)	0	0
Blood creatinine increased	13 (10·2)	12 (9·4)	1 (0·8)	0	0
Adverse events leading to treatment discontinuation[d]					
Rash	5 (3·9)	3 (2·4)			
Urticaria	2 (1·6)	2 (1·6)			
Colitis	2 (1·6)	1 (0·8)			
Hyperglycaemia	2 (1·6)	2 (1·6)			
Vomiting	2 (1·6)	1 (0·8)			
Adverse events leading to dose interruption/adjustment[e]					
Hyperglycaemia	37 (29·1)	32 (25·2)			

Table 4. Safety of alpelisib plus fulvestrant in the prior CDK4/6i plus AI cohort (safety set)

	Prior CDK4/6i Plus AI Cohort (N=127)	
	All Grades, No. (%)	**Grade ≥3, No. (%)**
Rash	16 (12·6)	10 (7·9)
Rash maculo-papular	12 (9·4)	11 (8·7)
Diarrhoea	10 (7·9)	6 (4·7)
Vomiting	5 (3·9)	1 (0·8)
Asthenia	4 (3·1)	1 (0·8)
Pruritus	4 (3·1)	2 (1·6)
Stomatitis	4 (3·1)	2 (1·6)
Hypokalaemia	3 (2·4)	3 (2·4)
Pyrexia	3 (2·4)	0
Weight decreased	3 (2·4)	1 (0·8)
Cough	2 (1·6)	1 (0·8)
Headache	2 (1·6)	0
Lipase increased	2 (1·6)	1 (0·8)
Neutrophil count decreased	2 (1·6)	2 (1·6)
Urticaria	2 (1·6)	2 (1·6)

Patients in CDK4/6i plus AI cohort received alpelisib plus fulvestrant.
No.: Number of patients who are at the corresponding category.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
Medical Dictionary for Regulatory Activities (MedDRA) version 22.1, Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
AE, adverse event; AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; GI, gastrointestinal; SAE, serious adverse event.
[a]Per investigator assessment, the fatal SAE in one patient was respiratory failure secondary to aspiration, not related to the study drug or pneumonitis. During the SAE, the patient concomitantly developed acute myocardial infarction, meningitis, and supraventricular tachycardia. The drug was discontinued at the start of management of the SAE.
[b]Patients who discontinued or withdrew study treatment due to an AE during a study cycle may have resumed study treatment at a later time.
[c]AEs leading to discontinuation included skin and subcutaneous tissue disorders (7), GI disorders (6), investigations (4), general disorders and administration site conditions (3), metabolism and nutrition disorders (2), infections and infestations (1), nervous system disorders (1), and respiratory, thoracic and mediastinal disorders (1).
[d]AEs that led to treatment discontinuation in one patient each are Alanine aminotransferase increased, Angular cheilitis, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood creatinine increased, Cerebrovascular accident, Discomfort, Fatigue, Gamma-glutamyltransferase increased, Hypoxia, Nausea, Paraesthesia, Pneumonia, Pneumonitis, Pneumothorax, Pyrexia, Stomatitis, and Weight decreased.
[e]AEs that led to dose interruption/adjustment in one patient each are Abdominal pain, Acute myocardial infarction, Alanine aminotransferase increased, Anaemia, Anaphylactic reaction, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood creatinine increased, Blood glucose increased, Dehydration, Dermatitis exfoliative generalised, Dry eye, Dyspnoea, Eczema, Fatigue, Febrile neutropaenia, Glycosylated haemoglobin increased, Haematemesis, Hypersensitivity, Hyperuricemia, Hypoesthesia, Hypocalcaemia, Hypoxia, Intestinal perforation, Liver function test increased, Muscle spasms, Myalgia, Nausea, Neutropaenia, Paraesthesia, Peripheral swelling, Pleural effusion, Pneumothorax, Rash macular, Rash pruritic, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Skin lesion, Skin toxicity, Subileus, Supraventricular tachycardia, Tachycardia, and Thrombocytopaenia.