Effectiveness of Alpelisib + Fulvestrant Compared with Real-World Standard Treatment Among Patients with HR+, HER2–, *PIK3CA*-Mutated Breast Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

ABSTRACT

Background. The BYLieve trial (NCT03056755) confirmed efficacy and safety of alpelisib with fulvestrant for hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2−), *PIK3CA*-mutated advanced breast cancer (ABC), after cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) with an aromatase inhibitor (AI) as immediate prior therapy. Further analyses were performed to compare efficacy from BYLieve with effectiveness of standard treatment in the real-world setting.

Materials and Methods. Patients who progressed on a CDK4/6i plus AI and were treated with alpelisib with fulvestrant in BYLieve were matched with a real-world patient cohort who received standard-of-care from a deidentified clinico-genomics database (CGDB). Primary and secondary endpoints were to compare progression-free survival (PFS), estimated by the Kaplan-Meier method, and the proportion of patients remaining progression-free at 6 months, respectively, between the two cohorts.

Results. A total of 855 patients with *PIK3CA*-mutant disease who had prior CDK4/6i plus hormone therapy were selected from the CGDB; further matching to 120 patients from BYLieve selected 95 patients without exposure to HER2-targeting agents, clinical study drug, or alpelisib. In unadjusted and postmatching results, primary and secondary endpoints favored treatment with alpelisib with fulvestrant in BYLieve more than standard treatments in the real-world cohort. Postadjustment, median PFS for patients treated with alpelisib in BYLieve was 7.3 versus 3.7 months in the real-world cohort, and 6-month PFS was 54.6% versus 40.1%, respectively.

Conclusion. Matched/weighted analysis comparing BYLieve with the real-world setting further supports the clinical benefit of alpelisib with fulvestrant for treatment of HR+, HER2−, *PIK3CA*-mutant ABC after CDK4/6i treatment. *The Oncologist* 2021;26:e1133–e1142

Implications for Practice: Approximately 40% of patients with hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2−) advanced breast cancer (ABC) have *PIK3CA*-mutated tumors, which have been associated with endocrine therapy resistance. Alpelisib, an α-selective phosphatidylinositol-3-kinase inhibitor, demonstrated significantly improved progression-free survival in SOLAR-1 and demonstrated clinical efficacy in BYLieve when combined with fulvestrant. Data are limited in comparing the efficacy of alpelisib combined with fulvestrant with effectiveness of standard therapy after CDK4/6i treatment. Using real-world data, this is the first analysis comparing alpelisib combined with fulvestrant with standard treatments for HR+, HER2−, *PIK3CA*-mutant ABC in the post-CDK4/6i setting.

INTRODUCTION

Hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) is the most frequently occurring breast cancer subtype, comprising >70% of cases [1, 2]. First-line treatment options in the advanced setting for patients with HR+, HER2– advanced breast cancer (ABC) recommended by international expert guidelines include endocrine therapy (ET) combined with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) [3–5]. ET resistance is a common therapeutic challenge and can arise from hyperactivated phosphatidylinositol-3-kinase (PI3K) pathway signaling because of mutations in the *PIK3CA* gene [6]. *PIK3CA* encodes the alpha isoform of PI3K (p110α) [7]; such mutations are present in approximately 40% of cases of HR+, HER2– ABC [8–12].

Alpelisib is an α-selective inhibitor and degrader of PI3K that targets the effects of *PIK3CA* mutations [1]. In preclinical models, alpelisib demonstrated a dual mechanism of action by dose-dependent inhibition of PI3K and degradation of p110α [13]. Alpelisib has demonstrated efficacy in combination with fulvestrant in treating men and postmenopausal women with HR+, HER2–, *PIK3CA*-mutated ABC that progressed on/after ET [1, 14, 15]. The SOLAR-1 study, on which the initial approval of alpelisib was based, was initiated before CDK4/6i treatment became the standard-of-care (SoC) in the first-line setting. The few patients who did receive prior treatment with a CDK4/6i combined with an aromatase inhibitor (AI; $n = 20$) showed improvement in progression-free survival (PFS) in the alpelisib plus fulvestrant arm ($n = 9$) compared with the placebo plus fulvestrant arm ($n = 11$; median PFS, 5.5 vs. 1.8 months, respectively; hazard ratio, 0.48; 95% confidence interval [CI], 0.17–1.36) [15].

The phase II, open-label, multicenter, noncomparative, 3-cohort BYLieve trial (NCT03056755) is the first study designed to assess the safety and efficacy of alpelisib combined with ET in patients with *PIK3CA*-mutated, HR+, HER2– ABC and who progressed on/after prior CDK4/6i-based therapy. BYLieve confirmed efficacy and safety of alpelisib combined with fulvestrant in patients with confirmed *PIK3CA*-mutated disease who received a CDK4/6i with AI as immediate prior therapy (cohort A) [16, 17]. The primary endpoint of the trial was met, as 50.4% (95% CI, 41.2%–59.6%) of patients in cohort A were alive without disease progression at 6 months, with the lower bound of the CI being greater than the prespecified threshold of 30%. Median PFS was 7.3 months (59.5% of patients with events; 95% CI, 5.6–8.3 months). The safety profile in this cohort was consistent with the known safety profile of alpelisib [1, 18]; the most commonly experienced all-grade adverse events (AEs) were diarrhea (59.8%), hyperglycemia (58.3%), nausea (45.7%), fatigue (29.1%), decreased appetite (28.3%), rash (28.3%), and stomatitis (26.8%), with no new safety signals observed. Overall AE-related discontinuations in this cohort were 20.5% [16, 17].

Although BYLieve consists of three parallel cohorts, each is analyzed separately, and the study is designed as noncomparative. As more patients are treated with CDK4/6i combined with ET in the first-line setting, it is possible to use an external control group and compare data from BYLieve with data from the real world. With careful data abstraction, collection, and standardization, and with appropriate statistical analysis, real-world data may be used to address the lack of comparative evidence in the clinical trial setting [16, 17].

In this study, we assess the efficacy of treatment with alpelisib combined with fulvestrant in a cohort of patients with *PIK3CA*-mutated disease, whose most recent treatment was with a CDK4/6i combined with AI, compared with the effectiveness of real-world standard treatments in the post-CDK4/6i setting using data from the deidentified clinico-genomics database (CGDB) [16, 17].

MATERIALS AND METHODS

Study Overview and CGDB for Real-World Setting Analysis of PFS with Standard Therapy in the CDK4/6i Setting

This noninterventional, retrospective, observational, two-cohort study compared clinical outcomes among patients treated with alpelisib combined with fulvestrant in the phase II BYLieve trial with those among patients treated with standard treatments in the real world. Data for the real-world cohort were retrieved from the deidentified nationwide (U.S.-based) CGDB for patients who met relevant inclusion criteria consistent with those in BYLieve. Following application of sample selection criteria, the real-world cohort included 95 patients from the CGDB. As chemotherapy may not directly follow CDK4/6i-based treatment for many patients, a sensitivity analysis was performed that excluded patients who received chemotherapy after progressing on treatment with a CDK4/6i ($n = 65$).

This study was designed and implemented in accordance with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology, the Strengthening the Reporting of Observational Studies in Epidemiology guidelines, and with the ethical principles espoused in the Declaration of Helsinki. The BYLieve protocol and informed consent were reviewed and approved by an institutional review board/independent ethics committee/research ethics board before study start. Informed consent was obtained from all participants in the BYLieve cohort; consent was not required from patients in the real-world cohort, as the CGDB is a Health Insurance Portability and Accountability Act–compliant, deidentified dataset.

Inclusion and Exclusion Criteria

All patients from cohort A of the BYLieve trial with a *PIK3CA* mutation confirmed by tissue sample and received alpelisib with fulvestrant (the modified full analysis set [mFAS]) satisfying prespecified eligibility criteria were included in this comparison. Based on prespecified analytic guidance for real-world analysis that suggests that progression or death observed ≤14 days of treatment initiation may not be

directly associated with the real-world effectiveness of therapies, patients who died ≤14 days of treatment initiation were excluded, consistent with exclusion criteria of the real-world group. This resulted in one patient being removed from both BYLieve and real-world cohort populations prior to matching. PFS in this analysis was defined based on observed progression or death events >14 days after index date.

To be included in the real-world cohort, patients must have met key inclusion criteria from the BYLieve study that were feasible to apply to the CGDB: women and men with confirmed ABC, age ≥18 years, whose disease progressed on to the next line of therapy after treatment with a CDK4/6i (start date of this next line of therapy is defined as the index date) on or before January 31, 2019, and must have had documented medical care ≤90 days following initial ABC diagnosis. Patients must also have had a confirmed PIK3CA mutation from their first solid tissue biopsy through next-generation sequencing testing. Prior treatment with a CDK4/6i combined with ET, excluding fulvestrant, for advanced disease was required for inclusion [17]. Retrospective longitudinal clinical data were derived from electronic health record (EHR) data, comprising patient-level structured and unstructured data, curated via technology-enabled abstraction, and were linked to genomic data derived from Foundation Medicine's comprehensive genomic profiling (CGP) tests in the CGDB by deidentified, deterministic matching [19, 20]. Genomic alterations were identified via CGP of >300 cancer-related genes on Foundation Medicine's next-generation sequencing-based FoundationOne panel (Foundation Medicine, Inc., Cambridge, MA) [21, 22]. Some patients may have had incomplete physician reports, but none were excluded from the study because of this criterion, having previously been excluded owing to other criteria.

Patients from the CGDB must have had no more than two lines of anticancer therapy in the advanced setting, including CDK4/6i-based treatment, and no more than one line of chemotherapy in the locoregional or metastatic setting, prior to index date; treatment with alpelisib, an HER2-directed therapy, or a clinical trial drug also was not allowed. Owing to small sample size, the real-world cohort was not restricted to patients with known biomarker status; as the absence of HER2-positive (+) specific treatment was a proxy for HER2− status, patients receiving HER2+ treatment were excluded, whereas prior CDK4/6i treatment was a proxy for HR+, HER2− status. Real-world PFS (rwPFS) for patients in the CGDB was defined based on observed progression or death events >14 days after index date.

Objectives

The primary objective of this analysis was to assess PFS for patients with HR+, HER2−, PIK3CA-mutated ABC whose disease progressed on/after treatment with CDK4/6i combined with AI and who received alpelisib combined with fulvestrant in cohort A of the BYLieve trial, compared with a matched real-world cohort of patients who received SoC for their disease, from the CGDB.

Progression in BYLieve cohort A was defined locally per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1;

progression events in the CGDB cohort were abstracted retrospectively from EHRs of patients in the CGDB [23], using clinician assessment as primary evidence and radiology reports as confirmatory documentation. Because of differing definitions of PFS between cohorts, PFS was labeled in the real-world cohort as rwPFS. As rwPFS assessment is retrospectively provided through EHR documentation, physicians had no knowledge or involvement in this post hoc analysis, of which the BYLieve trial was conducted independently.

Statistical Analysis

Patients selected from the CGDB were matched to those in the BYLieve trial cohort by baseline covariates, including metastatic site, number of metastatic sites (<3, ≥3), age group, and time between initial diagnosis and index date. Number of prior lines of therapy was not used as a baseline covariate for weighting/matching because of the observation in BYLieve that approximately 10% of patients received a CDK4/6i in the adjuvant setting; in the CGDB, it is unlikely that an adjuvant CDK4/6i could be identified because it was likely masked as a clinical trial regimen, given the lack of approved CDK4/6i treatment in this setting. As it is likely correlated with the number of prior therapy lines, we attempted to account for the prognostic relevance of this by including time between initial diagnosis and index date. Success of the matching process was evaluated by comparing standardized mean differences (SMDs) between the two cohorts; <25% was considered balanced [24–26]. PFS results were evaluated separately for each approach.

Balancing Approaches on Observable Characteristics

Propensity score methods were used to reduce confounding because of systematic differences in observed baseline characteristics between real-world and trial cohorts when estimating the treatment effect. A propensity score is the probability of a patient being in one cohort or the other, conditional on covariates included for balancing.

Weighting by odds was the primary method used [17]. Patients were assigned weights; each patient in the BYLieve cohort was assigned a weight of 1, to calculate the average treatment effect on the treated (ATT). Those in the real-world cohort were assigned weights representing the odds of their presence in the trial depending on observed covariates. As this weight is equal to the propensity score (ρ_i), converted to the odds scale ($= \rho_i/(1 - \rho_i)$ [27], the effective sample size of a group can increase or decrease when applying this method. Weighting by odds allows retaining the full patient sample without restricting the common support region for propensity scores, if balance is achieved. This may offer the most representative estimate of ATT; doing so retains all patients, weighting them by odds of receiving treatment, helping to maintain statistical power to detect difference [28].

Two matching approaches, 1:1 greedy nearest neighbor matching and 1:1 exact matching, were used [17] as sensitivity analyses to test the assumption that the treatment effect remains the same in subsets of patients with overlapping propensity scores, ensuring that results from the analysis were robust [27]. The 1:1 greedy nearest neighbor

matching estimates ATT on a subset of patients included in the matched set. This method used the nearest neighbor matching algorithm with caliper of 0.2 and 0.1 of logit of propensity in the real-world group and subgroup of patients whose index treatment excluded chemotherapy, respectively, to produce 1:1 matched samples without replacement. Logistic regression was used to generate the propensity scores. The 1:1 exact matching also estimates ATT on a subset of patients. Each patient from BYLieve was matched to one from the real-world cohort based on an exact match on the same set of covariates used in propensity-score–based approaches. This method results in the smallest patient groups, as each patient in the BYLieve cohort was required to have at least one match in the real-world cohort based on the covariates considered.

Assessment of Treatment Effect

PFS was estimated by Kaplan-Meier analyses, and differences between groups were examined using p values from log-rank tests. Because matched patients can be considered drawn from the same multivariable normal distribution, the correlation among matched pairs was accounted for by conducting a stratified log-rank test for the two matching approaches. The secondary objective was to evaluate PFS at 6 months after starting treatment.

To avoid inappropriate variance calculation with a weighted sample, bootstrapping was applied to estimate the empirical standard error of treatment effect for the weighting approach for the primary and secondary endpoints. Two hundred bootstrap samples were drawn, and the 95% bootstrapped CI of the treatment effect was constructed as the estimated treatment $\pm 1.96 \times$ the bootstrap estimate of the standard error (SE) [29].

Results

Patients

In BYLieve, 121 patients were used in the mFAS to assess efficacy; as one patient died ≤14 days after treatment initiation and was thus excluded (per CGDB eligibility criteria above, death after ≤14 days may not be directly associated with the effectiveness of treatment), 120 were included in this analysis. Eligibility criteria were initially applied to 855 patients in the CGDB whose disease progressed on/after treatment with CDK4/6i combined with ET; after applying eligibility criteria, 95 patients were selected from the CGDB (Table 1) for comparison with 120 from BYLieve; after weighting by odds, the effective sample size of the real-world cohort was 116 patients (Table 2).

Index Treatments in the Real-World Cohort

Index treatments received by the patients in the real-world cohort were varied. Frequent components of post-CDK4/6i treatment regimens included fulvestrant (45.3%, $n = 43$), CDK4/6i (33.7%, $n = 32$), chemotherapy (31.6%, $n = 30$), everolimus (17.9%, $n = 17$), and letrozole (15.8%, $n = 15$) (Fig. 1). Top treatment regimens included capecitabine monotherapy (14.7%, $n = 14$), fulvestrant monotherapy (14.7%, $n = 14$), palbociclib combined with fulvestrant

(13.7%, $n = 13$), everolimus combined with exemestane (11.6%, $n = 11$), and palbociclib combined with fulvestrant and letrozole (5.3%, $n = 5$); a complete listing of treatment regimens is included in supplemental online Table 1 [17].

Patient Characteristics

Of patients in the BYLieve cohort ($n = 120$), 45.0% were 50–65 years of age, compared with 51.6% of patients in the real-world group, including those who received prior chemotherapy (SMD from BYLieve, −13.1%), before weighting and matching. Seventy percent in the BYLieve cohort had less than three metastatic sites, compared with 60% in the real-world cohort (SMD, 21.0%). A proportion of 18.3% of BYLieve patients had bone-only metastases, compared with 21.1% in the real-world cohort (SMD, −6.8%), and 66.7% of patients from BYLieve had lung and/or liver metastases, compared with 59.0% of patients from the real-world cohort (SMD, 15.9%; Table 2; preweighted).

Time from initial diagnosis to index date was distributed into four quartiles: <27 months (25.8% of patients in the BYLieve cohort), 27 to <60 months (25.0%), 60 to <128 months (25.8%), and ≥ 128 months (23.3%). Among the real-world cohort, 23.2% of patients were diagnosed <27 months before indexing, 25.3% were diagnosed between 27 and <60 months, 25.3% were indexed 60 to <128 months following initial diagnosis, and 26.3% of patients were diagnosed ≥128 months before indexing.

Postweighting by odds, 48.1% of patients in the real-world cohort were 50–65 years of age (SMD: −6.1%), 68.2% had less than three metastatic sites (SMD, 3.8%), 20.5% had bone-only disease, and 63.0% had lung and/or liver metastases (SMDs, −5.4% and 7.6%, respectively). The populations were balanced, as SMDs were < 25%. SMD plots are shown in supplemental online Figure 1.

With matching methods used for the sensitivity analysis, 55.3% of patients were aged 50–65 years (SMD, 5.3%), 63.2% had less than three metastatic sites (SMD, 5.5%), 18.4% had bone-only disease, and 61.8% had lung and/or liver metastases (SMDs, 9.9% and −5.4%, respectively), after greedy nearest neighbor matching. SMDs indicated that the populations were balanced. After 1:1 exact matching, 60.7% of patients were 50–65 years of age, 67.2% had less than three metastatic sites, 21.3% had bone-only disease, and 59.0% had lung and/or liver metastases. Standardized mean differences were 0.0% for all covariates; therefore, 1:1 exact matching was considered to provide successful balance, although there was a reduction in sample size that could reduce the ability to extrapolate conclusions or declare statistical significance.

Baseline characteristics for the real-world group patients who did not receive prior chemotherapy, evaluated in the sensitivity analysis, are reported in supplemental online Table 2, and corresponding plots of postmatching SMDs are shown in supplemental online Figure 2.

Primary Objective: Evaluation and Comparison of PFS

Alpelisib combined with fulvestrant demonstrated higher PFS treatment effect compared with SoC. The unadjusted median PFS (mPFS) was 7.3 months (95% CI, 5.6–8.3 months) in patients in the BYLieve cohort compared

Table 1. Cohort selection of eligible real-world patients—CGDB: Stepwise patient selection

Step	Description	n	Remaining from previous step, %
0	CDK4/6i in combination with HT (excluding fulvestrant) combination therapy at any time	855	100
1	Progressed to next line of therapy after CDK4/6i in combination with HT combination therapy (start of this next therapy is index date)	637	74.5
2	No more than two lines of prior anticancer regimens for advanced breast cancer	370	58.1
3	No more than one line of prior chemotherapy regimen in the advanced/metastatic setting	368	99.5
4	Patients with advanced breast cancer prior to the start of index treatment	362	98.4
6	Patients having documented medical care within 90 days of advanced diagnosis	288	79.6
7	Patients ≥18 years of age at index	288	100.0
8	Patients having a confirmed *PIK3CA* mutation	126	43.8
9	Initiated treatment on or prior to January 31, 2019, to allow for a minimum of 6 months of observation time (data extraction end date in the CGDB is June 30, 2019)	112	88.9
10	Patients available for rwPFS analysis	111	99.1
11	Exclude patients with HER2+ drugs, clinical study drug, or alpelisib as part of the index regimen	95	85.6
	Exclude patients with HER2+ drugs, clinical study drug, alpelisib, or chemotherapy as part of the index regimen (sensitivity analysis)	65	58.6[a]

[a]The number of patients in sensitivity analysis was not derived from that of the final real-world cohort; therefore, the denominator used to calculate this percentage is the number of patients in step 10 (n = 111).
Abbreviations: CDK4/6i, cyclin-dependent kinases 4 and 6 inhibitor; CGDB, clinico-genomics database; HER2+, human epidermal growth factor receptor 2–positive; HT, hormone therapy; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; rwPFS, real-world progression-free survival.

with a median rwPFS of 3.6 months (95% CI, 3.1–6.1 months) among those in the real-world group ($p = .005$). After weighting by odds, mPFS for patients in the BYLieve cohort compared with rwPFS in the real-world cohort was 7.3 months (95% CI, 5.3–9.2 months) versus 3.7 months (95% CI, 2.2–5.3 months), respectively ($p = .004$; Table 3, Fig. 2) [17].

In the sensitivity analyses using additional matching approaches, mPFS in patients in the BYLieve cohort was 8.0 months (95% CI, 5.6–8.6 months) compared with a median rwPFS of 3.5 months (95% CI, 3.0–5.4 months) in the real-world cohort ($p = .004$), by 1:1 greedy nearest neighbor matching. After 1:1 exact matching, mPFS/median rwPFS was 6.5 months (95% CI, 5.3–8.3 months) compared with 3.4 months (95% CI, 2.9–3.9 months) in the BYLieve and real-world cohorts, respectively ($p = .008$).

In the sensitivity analysis with patients who had not received prior chemotherapy, the combination of alpelisib and fulvestrant also demonstrated prolonged PFS compared with SoC treatments. Unadjusted mPFS for patients in BYLieve compared with rwPFS in the real-world cohort was 7.3 months (95% CI, 5.6–8.3 months) versus 3.4 months (95% CI, 2.9–3.9 months; $p < .01$) and 7.3 months (95% CI, 5.2–9.3 months) versus 3.4 months (95% CI, 2.4–4.5 months) after weighting by odds ($p < .01$). Full results

are reported in supplemental online Table 3 and supplemental online Figure 3.

Secondary Objective: PFS at the 6-Month Milestone Time Point
Patients in the BYLieve cohort had greater probability of being alive without progression after 6 months compared with real-world patients receiving index treatment including chemotherapy. Unadjusted 6-month PFS was 54.6% (95% CI, 44.8%–63.4%) in the BYLieve cohort versus a 6-month rwPFS of 40.5% (95% CI, 30.6%–50.2%) in the real-world cohort ($p = .009$). Adjusted 6-month PFS/rwPFS rates were 54.6% (95% CI, 45.4%–63.8%) versus 40.1% (95% CI, 28.8%–51.4%) in the BYLieve and real-world cohorts, respectively ($p = .009$).

Sensitivity analyses revealed 58.7% (95% CI, 46.0%–69.5%) of patients in the BYLieve cohort were alive and progression free after 6 months, versus 37.4% (95% CI, 26.6%–48.2%) of real-world patients, by 1:1 greedy nearest neighbor matching ($p = .013$). These PFS/rwPFS rates were 54.4% (95% CI, 40.3%–66.6%) versus 34.4% (95% CI, 22.9%–46.3%) following 1:1 exact matching ($p = .064$; Table 3).

Six-month PFS/rwPFS results were similar with the sensitivity analysis of patients without prior chemotherapy in the real-world cohort; in the unadjusted analysis, 54.6% of

Table 2. Patient characteristics and baseline disposition: BYLieve versus real-world cohort with standard treatment post-CDK4/6i

Patient characteristic	Preweighted			Postweighting by odds			Post-1:1 greedy nearest neighbor matching			Post-1:1 exact matching		
	CGDB (n = 95)	BYLieve (n = 120)	SMD, %	CGDB (n = 116)	BYLieve (n = 120)	SMD, %	CGDB (n = 76)	BYLieve (n = 76)	SMD, %	CGDB (n = 61)	BYLieve (n = 61)	SMD, %
Age at indexing, yr												
<50	13 (13.7)	35 (29.2)	38.2	30 (26.0)	35 (29.2)	7.9	13 (17.1)	13 (17.1)	0.0	7 (11.5)	7 (11.5)	0.0
50–<65	49 (51.6)	54 (45.0)	−13.1	56 (48.1)	54 (45.0)	−6.1	42 (55.3)	44 (57.9)	5.3	37 (60.7)	37 (60.7)	0.0
≥65	33 (34.7)	31 (25.8)	−19.4	30 (26.0)	31 (25.8)	−0.3	21 (27.6)	19 (25.0)	−5.7	17 (27.9)	17 (27.9)	0.0
Pooled number of metastatic sites												
<3	57 (60.0)	84 (70.0)	21.0	79 (68.2)	84 (70.0)	3.8	48 (63.2)	50 (65.8)	5.5	41 (67.2)	41 (67.2)	0.0
≥3	38 (40.0)	36 (30.0)	−21.0	37 (31.8)	36 (30.0)	−3.8	28 (36.8)	26 (34.2)	−5.5	20 (32.8)	20 (32.8)	0.0
Sites of metastases												
Bone only	20 (21.1)	22 (18.3)	−6.8	24 (20.5)	22 (18.3)	−5.4	14 (18.4)	17 (22.4)	9.9	13 (21.3)	13 (21.3)	0.0
Lung/liver	56 (59.0)	80 (66.7)	15.9	73 (63.0)	80 (66.7)	7.6	47 (61.8)	45 (59.2)	−5.4	36 (59.0)	36 (59.0)	0.0
Time from initial diagnosis to index date, mo												
<27	22 (23.2)	31 (25.8)	6.2	31 (26.3)	31 (25.8)	−1.1	18 (23.7)	18 (23.7)	0.0	15 (24.6)	15 (24.6)	0.0
27–<60	24 (25.3)	30 (25.0)	−0.6	29 (25.0)	30 (25.0)	0.0	17 (22.4)	16 (21.1)	−3.0	12 (19.7)	12 (19.7)	0.0
60–<128	24 (25.3)	31 (25.8)	1.3	31 (26.9)	31 (25.8)	−2.5	20 (26.3)	20 (26.3)	0.0	17 (27.9)	17 (27.9)	0.0
≥128	25 (26.3)	28 (23.3)	−6.9	25 (21.8)	28 (23.3)	3.6	21 (27.6)	22 (29.0)	3.0	17 (27.9)	17 (27.9)	0.0

Data are presented as n (%) unless otherwise noted.
Abbreviations: CDK4/6, cyclin-dependent kinases 4 and 6 inhibitor; CGDB, clinico-genomics database; SMD, standardized mean difference.

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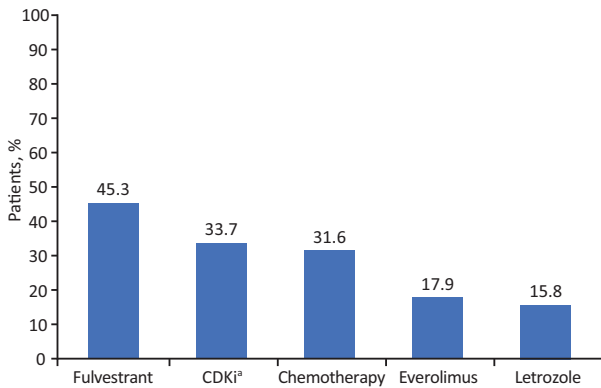
Figure 1. Most common components of post-CDK4/6i treatments in real-world cohort ($n = 95$). [a]CDK4/6i-based treatments given after disease progression may be due to a CDK4/6i rechallenge.
Abbreviations: CDK4/6i, cyclin-dependent kinases 4 and 6 inhibitor.

BYLieve patients (95% CI, 44.8%–63.4%) were alive without disease progression after 6 months compared with 32.9% (95% CI, 21.8%–44.4%) in the real-world cohort ($p < .001$). Adjusted PFS/rwPFS rates at 6 months were 54.6% (95% CI, 44.4%–64.7%) versus 28.8% (95% CI, 16.2%–41.4%) by weighting by odds ($p < .001$). Full results are available in supplemental online Table 3.

DISCUSSION

This analysis provided a comparator to a clinical trial result of alpelisib combined with fulvestrant as treatment for HR+, HER2−, *PIK3CA*-mutant ABC in the post-CDK4/6i setting, with patient-matched real-world data serving as an external control. Three weighting/matching methods were employed to account for differences in key baseline covariates, and propensity-score–based approaches were used to mimic a randomized study and estimate treatment effects. The data presented here demonstrate a favorable PFS treatment effect of alpelisib combined with fulvestrant versus standard treatments in the real-world setting in this patient population.

The analysis of the primary endpoint demonstrated a significantly longer mPFS in the BYLieve cohort compared with that of an odds-weighted real-world cohort of patients. Similar results were reached when applying 1:1 matching approaches for sensitivity analyses. The post-weighted 6-month PFS rate was also significantly higher for patients in the BYLieve cohort than for those in the real-world cohort, as was 6-month PFS following the 1:1 greedy nearest neighbor matching sensitivity analysis. Although statistical significance was not achieved in the secondary endpoint using exact matching, all matching methods showed consistent results favoring alpelisib combined with fulvestrant. This demonstrated that the results were robust to the variability associated with the choice of method used to account for differences in baseline characteristics between the BYLieve and real-world cohorts. Results from an additional sensitivity
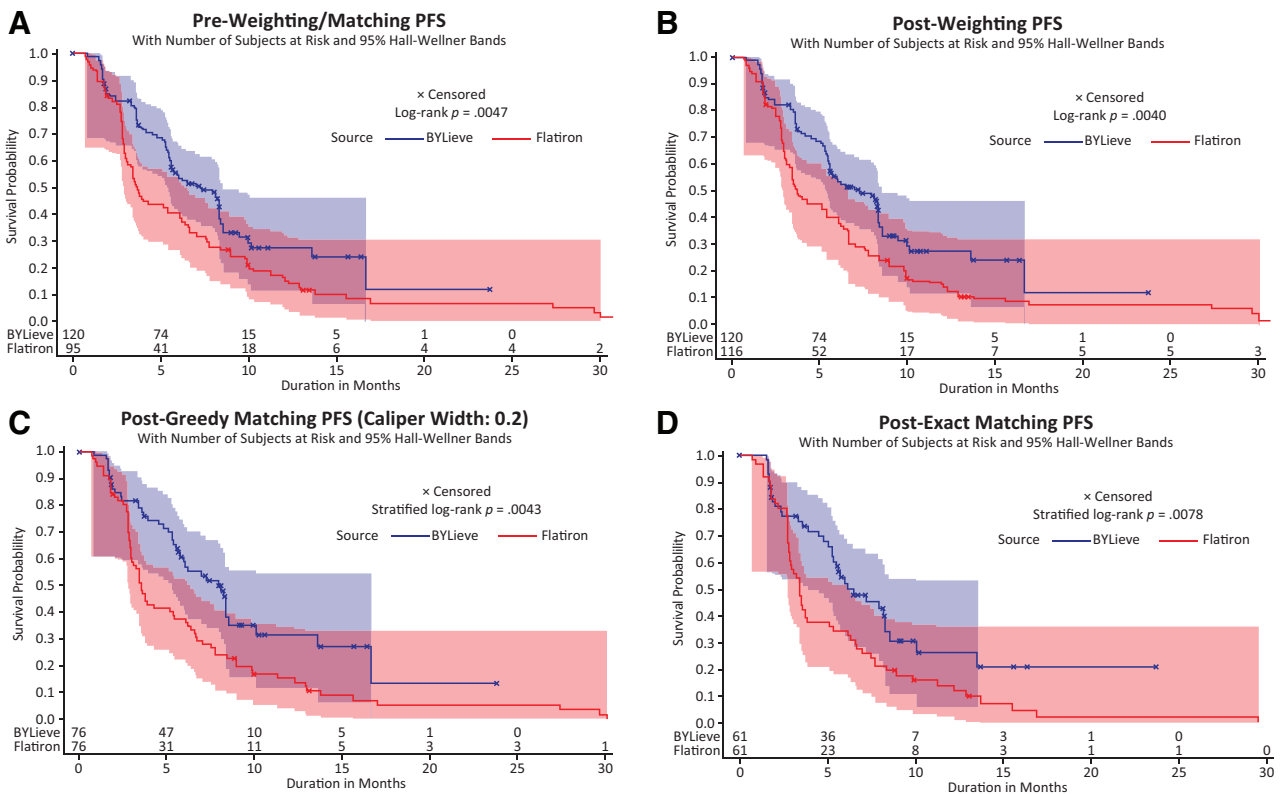
Figure 2. Kaplan-Meier analysis of PFS versus rwPFS: BYLieve versus real-world cohort with standard treatment post-CDK4/6i. **(A):** Preweighted PFS and rwPFS. **(B):** PFS and rwPFS, postweighting by odds. **(C):** PFS and rwPFS, post-greedy nearest neighbor matching. **(D):** PFS and rwPFS, post-exact matching.
Abbreviations: CDK4/6i, cyclin-dependent kinases 4 and 6 inhibitor; PFS, progression-free survival; rwPFS, real-world PFS.

Table 3. Median PFS/rwPFS and PFS/rwPFS at 6 months: BYLieve versus real-world cohort with standard treatment post-CDK4/6i

Matching technique	Group	n	PFS (rwPFS for CGDB), mo (95% CI)	p value[a,b]	PFS (rwPFS for CGDB) at 6 months, % (95% CI)	p value[a,b]
Preweighted	CGDB	95	3.6 (3.1–6.1)	.005	40.5 (30.6–50.2)	.009
	BYLieve	120	7.3 (5.6–8.3)		54.6 (44.8–63.4)	
Weighting by odds	CGDB	116	3.7 (2.2–5.3)[c]	.004	40.1 (28.8–51.4)[c]	.009
	BYLieve	120	7.3 (5.3–9.2)[c]		54.6 (45.4–63.8)[c]	
Greedy matching	CGDB	76	3.5 (3.0–5.4)	.004	37.4 (26.6–48.2)	.013
	BYLieve	76	8.0 (5.6–8.6)		58.7 (46.0–69.5)	
Exact matching	CGDB	61	3.4 (2.9–3.9)	.008	34.4 (22.9–46.3)	.064
	BYLieve	61	6.5 (5.3–8.3)		54.4 (40.3–66.6)	

[a]No multiplicity adjustments were conducted.
[b]p values were obtained from stratified log-rank testing for greedy matching and exact matching approaches.
[c]95% CIs are based on bootstrapping.
Abbreviations CDK4/6i, cyclin-dependent kinases 4 and 6 inhibitor; CGDB, clinico-genomics database; CI, confidence interval; PFS, progression-free survival; rwPFS, real-world progression-free survival.

analysis comparing the BYLieve cohort with a subgroup of patients in the real-world cohort who were not treated with chemotherapy were generally consistent with those observed with the primary cohort.

Overall, following adjustment for baseline covariates through weighting by odds and sensitivity analyses, patients in the BYLieve cohort were associated with a favorable effect of treatment for both endpoints versus standard-of-care treatments for HR+, HER2−, *PIK3CA*-mutated ABC.

Limitations

There are notable differences between the prospectively collected data from the BYLieve trial and this analysis with retrospectively collected data from the CGDB; not all eligibility criteria of the BYLieve trial could be replicated in this analysis. Progression in routine care is not RECIST-based, as it was in the BYLieve trial; furthermore, patients in the real-world cohort were not required to have a documented progression event on/after CDK4/6i treatment, and subsequent lines of therapy following CDK4/6i-based treatment were used as a proxy for progression. Prior lines of therapy were not considered in the real-world cohort, and 10% of patients in BYLieve cohort A had no prior lines of therapy, which did not allow a strong match on covariates. Time since initial diagnosis was a proxy for how heavily pretreated patients were likely to be. Additionally, patients were not required to have laboratory-confirmed HR+ and HER2− status, so the absence of HER2-targeted therapies was used as an indicator of HER2− status; treatment compliance in the real-world population is also difficult to assess. As is common with all retrospective observational studies, generalizability, selection bias, and missing data were potential limitations.

Another important difference could be found in the method of progression assessment; progression events in BYLieve patients were assessed locally by study investigators using RECIST v1.1, whereas CGDB progression data were based on information included in electronic medical records. The CGDB data, which were generated from real-world clinical practice, could be subject to miscoding and

errors typically encountered in the clinic, the treating physician's opinion, and the availability and accuracy of relevant reports. Real-world assessments may also vary by interval of clinical visits. Information regarding patient treatment outside the specific cancer center may not have been captured in structured or unstructured EHR data in the CGDB.

The overall sample size is relatively small considering the high heterogeneity of the study population included in this analysis. All treatment regimens following CDK4/6i-based treatment were used as a single cohort, rather than selecting one regimen; however, this is supported by feasibility assessments that main regimens had similar mPFS and that there were a wide variety of treatment regimens used.

As matching approaches were implemented to balance on observable prognostic factors in the absence of a randomized, controlled clinical trial, it should be acknowledged that, despite best attempts, matching approaches can only account for measurable and feasible confounders that can be included in the model. Potential selection bias and unmeasured and residual confounding cannot therefore be ruled out.

Finally, standards of care differ between the U.S. and other major global regions. Such differences may affect the generalizability of this analysis, as the CGDB is limited to U.S. patients.

CONCLUSION

Owing to a lack of a comparator arm in the BYLieve study, matched analyses to a real-world cohort were performed to provide additional perspective to results. Irrespective of the method used, all three analytical approaches demonstrated a consistent benefit for alpelisib combined with fulvestrant in BYLieve cohort A compared with standard therapies for patients with *PIK3CA*-mutated, HR+, HER2− ABC and prior CDK4/6i-based therapy, with or without chemotherapy. This analysis illustrates use of real-world data to augment clinical trial data and reinforce informed decision making in the clinic.

In closing, the clinical benefit of alpelisib combined with fulvestrant observed in this comparator study is consistent with the results from the phase III SOLAR-1 study [1, 16, 17].

These results provide additional support for the use of alpelisib combined with fulvestrant in patients with HR+, HER2−, *PIK3CA*-mutated ABC, particularly in the post-CDK4/6i setting.

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