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ORIGINAL REPORT

Phosphatidylinositol 3-Kinase α–Selective Inhibition With Alpelisib (BYL719) in *PIK3CA*-Altered Solid Tumors: Results From the First-in-Human Study

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ABSTRACT

Purpose

We report the first-in-human phase Ia study to our knowledge (ClinicalTrials.gov identifier: NCT01219699) identifying the maximum tolerated dose and assessing safety and preliminary efficacy of single-agent alpelisib (BYL719), an oral phosphatidylinositol 3-kinase α (PI3Kα)–selective inhibitor.

Patients and Methods

In the dose-escalation phase, patients with *PIK3CA*-altered advanced solid tumors received once-daily or twice-daily oral alpelisib on a continuous schedule. In the dose-expansion phase, patients with *PIK3CA*-altered solid tumors and *PIK3CA*-wild-type, estrogen receptor–positive/human epidermal growth factor receptor 2–negative breast cancer received alpelisib 400 mg once daily.

Results

One hundred thirty-four patients received treatment. Alpelisib maximum tolerated doses were established as 400 mg once daily and 150 mg twice daily. Nine patients (13.2%) in the dose-escalation phase had dose-limiting toxicities of hyperglycemia (n = 6), nausea (n = 2), and both hyperglycemia and hypophosphatemia (n = 1). Frequent all-grade, treatment-related adverse events included hyperglycemia (51.5%), nausea (50.0%), decreased appetite (41.8%), diarrhea (40.3%), and vomiting (31.3%). Alpelisib was rapidly absorbed; half-life was 7.6 hours at 400 mg once daily with minimal accumulation. Objective tumor responses were observed at doses ≥ 270 mg once daily; overall response rate was 6.0% (n = 8; one patient with endometrial cancer had a complete response, and seven patients with cervical, breast, endometrial, colon, and rectal cancers had partial responses). Stable disease was achieved in 70 (52.2%) patients and was maintained > 24 weeks in 13 (9.7%) patients; disease control rate (complete and partial responses and stable disease) was 58.2%. In patients with estrogen receptor–positive/human epidermal growth factor receptor 2–negative breast cancer, median progression-free survival was 5.5 months. Frequently mutated genes (≥ 10% tumors) included *TP53* (51.3%), *APC* (23.7%), *KRAS* (22.4%), *ARID1A* (13.2%), and *FBXW7* (10.5%).

Conclusion

Alpelisib demonstrated a tolerable safety profile and encouraging preliminary activity in patients with *PIK3CA*-altered solid tumors, supporting the rationale for selective PI3Kα inhibition in combination with other agents for the treatment of *PIK3CA*-mutant tumors.

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ASSOCIATED CONTENT

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INTRODUCTION

The phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway is frequently dysregulated in cancer, often because of activating mutations or amplification of *PIK3CA* (encoding the catalytic p110α subunit of PI3K).[1] *PIK3CA* mutations are among the most frequent alterations in solid tumors, identified in 42% to 55% of endometrial,[2] 42% of cervical,[3] 27% to 36% of breast,[4,5] 18% of colorectal,[6] 13% of head and neck,[7] and 12% of ovarian cancers.[8]

Targeting the PI3K/mTOR pathway may be particularly effective in cancers that signal heavily through PI3Kα, such as those harboring *PIK3CA*

alterations.[9-12] The clinical development of pan-PI3K and dual PI3K/mTOR inhibitors has been limited by off-target toxicities (including GI toxicities, hepatotoxicity, and mood alterations) and modest clinical activity.[13-15] Isoform-specific inhibitors could permit administration at higher, pharmacologically active doses, with fewer off-target effects.[12,16]

Alpelisib (BYL719; Novartis Pharma AG, Basel, Switzerland) is an oral, selective inhibitor of p110α, with half-maximum inhibitory concentrations (in vitro biochemical assay) for p110α, β, γ, and δ of 4.6, 1,156, 250, and 290 nM, respectively.[12] Alpelisib has demonstrated antitumor activity in multiple cancer cell lines and tumor xenograft models, particularly those harboring *PIK3CA* mutations or amplifications,[12,17] highlighting the potential for enhanced clinical activity in patients with *PIK3CA*-altered tumors. We report final results from a first-in-human dose-escalation and dose-expansion study, to our knowledge, of single-agent alpelisib in patients with *PIK3CA*-altered advanced solid tumors and *PIK3CA*-altered and *PIK3CA*-wild-type estrogen receptor (ER)–positive/human epidermal growth factor receptor 2 (HER2)–negative breast cancer.

PATIENTS AND METHODS

Patient Population

This study (ClinicalTrials.gov identifier: NCT01219699) enrolled patients with tumors harboring *PIK3CA* mutation and/or amplification, assessed locally or centrally. To explore whether tumors harboring *PIK3CA* alterations were more sensitive to alpelisib than *PIK3CA*-wild-type tumors, the dose-expansion phase also included patients with *PIK3CA*-wild-type, ER-positive/HER2-negative, locally advanced or metastatic breast cancer.

Patients age ≥ 18 years and with Eastern Cooperative Oncology Group performance status ≤ 2, with histologically confirmed, unresectable, advanced solid tumors, who had progression of disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 on their last line of therapy within 3 months of screening, or for whom no standard anticancer therapy existed, were eligible. Patients had at least one measurable or nonmeasurable lesion per RECIST v1.0 and fasting plasma glucose (FPG) < 140 mg/dL (7.8 mmol/L). Key exclusion criteria included diabetes mellitus (treated and/or symptomatic, or with FPG ≥ 140 mg/dL [7.8 mmol/L]), a history of gestational diabetes mellitus, or documented steroid-induced diabetes mellitus; and failure to benefit from a prior PI3K, AKT (Protein Kinase B), or mTOR inhibitor.

The study was approved by ethics committees and institutional review boards of participating institutions and appropriate regulatory authorities; all patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and guidelines for Good Clinical Practice, as defined by the International Conference on Harmonization.

Study Design

This was a phase Ia, multicenter, open-label, dose-escalation study of single-agent alpelisib with a dose-expansion arm at the maximum tolerated dose (MTD). The primary objective was to determine the MTD or recommended phase II dose of oral alpelisib administered in once-daily and twice-daily regimens. Secondary objectives included assessment of safety and tolerability, pharmacokinetics (PK), and preliminary efficacy. Exploratory objectives included characterization of pharmacodynamic activity and biomarkers of response to alpelisib.

Patients received oral alpelisib 30 to 450 mg once daily or 120 to 200 mg twice daily on a continuous schedule in 28-day cycles until disease progression, unacceptable toxicity, withdrawal of consent, or investigator's decision. After MTD/recommended phase II dose determination for the once-daily schedule, an expansion arm was opened to further characterize safety and assess preliminary efficacy at this dose.

The MTD was defined as the highest dose of alpelisib not causing a dose-limiting toxicity (DLT) in > 33% of patients during the first treatment cycle. Dose escalation was guided by an adaptive Bayesian logistic regression model incorporating the escalation with overdose control (EWOC) principle.[18] Under EWOC, the dose selected as the MTD must have a < 25% chance that the true DLT rate exceeds 33%, given the available DLT information. The study data (including DLTs during cycle 1 and other safety and PK data) were reviewed by the sponsor and trial investigators at each dose level. Intrapatient dose escalation was not permitted during the first four treatment cycles.

DLTs were defined as adverse events (AEs) or laboratory abnormalities possibly related to study treatment (and unrelated to the underlying disease) occurring during the first treatment cycle. DLTs included: grade ≥ 2 hyperglycemia (see safety and efficacy assessments for grading); grade ≥ 2 photosensitivity; specified grade ≥ 3 hematologic, renal, hepatic, metabolic, or subcutaneous AEs lasting for > 7 days; or any other grade ≥ 3 toxicity.

Safety and Efficacy Assessments

Routine clinical and laboratory assessments, including hematology and biochemistry, were conducted at baseline, weekly until cycle 2 day 28, and then every 2 weeks. Glucose monitoring and other safety assessments were performed at baseline and regularly throughout the study. AEs were assessed continuously according to Common Terminology Criteria for Adverse Events version 4.0; hyperglycemia grading was based on modified American Diabetes Association criteria: grade 0 (FPG < 140 mg/dL [< 7.8 mmol/L]); grade 1 (FPG 140 to 199 mg/dL [7.8 to 11.1 mmol/L]); grade 2 (FPG 200 to 249 mg/dL [11.2 to 13.8 mmol/L], confirmed with a repeat FPG measurement within 24 hours, and not resolving to grade 0 within 14 days despite intervention with antidiabetic medication such as glimepiride, glibenclamide, or metformin); grade 3 (FPG 250 to 399 mg/dL [13.9 to 22.2 mmol/L] confirmed within 24 hours); grade 4 (FPG ≥ 400 mg/dL [≥ 22.3 mmol/L], confirmed within 24 hours). Serious AEs were defined as any medical or life-threatening AE resulting in hospitalization or significant disability. Radiologic tumor response assessments were performed by computerized tomography or magnetic resonance imaging at screening, cycle 2 day 28, every 8 weeks thereafter, and at end of treatment. Overall response rate (ORR), clinical benefit rate (CBR), and disease control rate (DCR) will be determined. See Data Supplement for pharmacokinetic profiling.

Biomarker and Pharmacodynamic Assessments

PIK3CA status was assessed by next-generation sequencing (NGS) using archival or fresh biopsy tissue collected before study start (Data Supplement). Blood samples for evaluation of glucose metabolism markers (plasma glucose, insulin, and C-peptide) were collected at baseline; predose and 2 and 4 hours postdose on cycle 1 day 2, cycle 1 day 9, and cycle 2 day 2; and 4 to 6 hours postdose on cycle 2 day 28. Metabolic response was assessed in a subset of patients by [^{18}F]-fluorodeoxyglucose positron emission tomography.

RESULTS

Patient Characteristics and Disposition

Between October 2010 and March 2014, 134 patients were enrolled across 11 sites. These included 76 patients in the dose-escalation phase and 51 patients in the dose-expansion phase with *PIK3CA*-altered advanced solid tumors (including two patients with unconfirmed *PIK3CA* mutation). There were seven patients with *PIK3CA*-wild-type tumors, including five patients with ER-positive/HER2-negative breast cancer (one in the dose-escalation phase and four in the dose-expansion phase). The most common primary cancer sites were breast (n = 36; 26.9%), colorectal (n = 35; 26.1%), and head

Table 1. Patient Characteristics at Baseline

Characteristic	All Patients (N = 134)
Age, years, median (range)	59 (21-82)
Female	98 (73.1)
ECOG performance status	
0	51 (38.1)
1	77 (57.5)
2	6 (4.5)
Primary cancer site	
Breast	36 (26.9)
Head and neck	19 (14.2)
Colorectal	35 (26.1)
Ovarian	14 (10.4)
Other*	30 (22.4)
Prior antineoplastic regimens	
≤ 3	57 (42.5)
4-6	63 (47.0)
≥ 7	14 (10.4)
Median (range)	4 (1-19)
PIK3CA alteration status	
Altered	125 (93.3)
Wild-type	7 (5.2)
Unknown†	2 (1.5)

NOTE. Data presented as No. (%) unless otherwise noted.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Primary cancer sites classed as other include: cervix (n = 5), lung (n = 5), uterus (n = 3), bladder, gall bladder, kidney, liver, stomach, pancreas, peritoneum, thymus (n = 1 each), and other (n = 9).
†Two patients were enrolled who did not have *PIK3CA* status confirmed by local or central assessment.

and neck (n = 19; 14.2%; Table 1). At initial diagnosis, 86 patients (64.2%) had stage III or IV cancer, and all patients had received prior antineoplastic therapy.

In total, 108 patients received alpelisib once daily at doses of 30 to 450 mg, including 65 patients at 400 mg once daily; and 26 patients received alpelisib twice daily at doses of 120 to 200 mg, including 15 patients at 150 mg twice daily. As of February 5, 2015, 130 (97.0%) patients had discontinued treatment: 105 (78.4%) because of disease progression, 18 (13.4%) because of AEs, three (2.2%) because of withdrawal of consent, three (2.2%) because of death (all considered unrelated to study treatment by the investigator), and one (0.7%) because of administrative problems.

Dose Escalation and Dose-Limiting Toxicities

In the dose-escalation phase, nine of 68 evaluable patients experienced DLTs. At the highest dose (450 mg once daily), four of nine patients experienced DLTs of grade 3 nausea or grade 3 hyperglycemia (n = 2 each). No patients treated at ≤ 400 mg once daily experienced DLTs. At 200 mg twice daily, four of five patients had dose-limiting hyperglycemia (n = 1 grade 3; n = 3 grade 4). At 150 mg twice daily, one of 10 patients reported hyperglycemia and hypophosphatemia (both grade 3). The 400 mg once-daily and 150 mg once-daily dose levels met the requirements of the Bayesian logistic regression model–EWOC, having probabilities of 48.4% and 56.9%, respectively, that the true DLT rate was within the target toxicity range of 16% to 33% and probabilities of 4.5% and 16.0%, respectively, that the DLT rate exceeded 33%. Alpelisib single-agent MTDs were established as 400 mg once daily and 150 mg twice daily.

DLTs were monitored in the dose-expansion phase to support the MTD determined by dose escalation. In total, four of 58 evaluable patients receiving alpelisib 400 mg once daily experienced DLTs of grade 4 hyperglycemia (n = 2), grade 3 diarrhea (n = 1), and grade 3 nausea and grade 3 vomiting (n = 1).

Safety and Tolerability

The most frequent treatment-related AE was hyperglycemia, an on-target effect of PI3K inhibition,[19] reported in 69 (51.5%) patients across both dosing regimens (32 [23.9%] patients at grade 3 or 4; Table 2). Other treatment-related, all-grade AEs (≥ 15% of patients, any grade) were nausea (50.0%), skin toxicities (42.5%),

Table 2. Adverse Events (≥ 15% of patients) Suspected to be Related to Study Treatment

		Once-Daily Doses					Twice-Daily Doses			
Adverse Event	Grade	≤ 270 mg* (n = 20)	300 mg (n = 8)	350 mg (n = 6)	400 mg (n = 65)	450 mg (n = 9)	120 mg (n = 5)	150 mg (n = 15)	200 mg (n = 6)	All Patients (N = 134)
Total	All	17 (85.0)	7 (87.5)	6 (100)	64 (98.5)	9 (100)	5 (100)	15 (100)	6 (100)	129 (96.3)
	3 and 4	2 (10.0)	1 (12.5)	3 (50.0)	33 (50.8)	6 (66.7)	2 (40.0)	6 (40.0)	6 (100)	59 (44.0)
Hyperglycemia	All	5 (25.0)	1 (12.5)	2 (33.3)	39 (60.0)	6 (66.7)	2 (40.0)	8 (53.3)	6 (100)	69 (51.5)
	3 and 4	0	1 (12.5)	0	17 (26.2)	3 (33.3)	1 (20.0)	5 (33.3)	5 (83.3)	32 (23.9)
Nausea	All	6 (30.0)	3 (37.5)	5 (83.3)	35 (53.8)	6 (66.7)	0	8 (53.3)	4 (66.7)	67 (50.0)
	3 and 4	0	0	0	1 (1.5)	2 (22.2)	0	0	0	3 (2.2)
Decreased appetite	All	4 (20.0)	4 (50.0)	3 (50.0)	29 (44.6)	5 (55.6)	1 (20.0)	6 (40.0)	4 (66.7)	56 (41.8)
	3 and 4	0	0	1 (16.7)	2 (3.1)	0	0	0	0	3 (2.2)
Diarrhea	All	3 (15.0)	2 (25.0)	3 (50.0)	30 (46.2)	5 (55.6)	2 (40.0)	6 (40.0)	3 (50.0)	54 (40.3)
	3 and 4	0	0	0	3 (4.6)	0	0	0	1 (16.7)	4 (3.0)
Vomiting	All	6 (30.0)	2 (25.0)	2 (33.3)	24 (36.9)	3 (33.3)	0	2 (13.3)	3 (50.0)	42 (31.3)
	3 and 4	0	0	0	3 (4.6)	0	0	0	0	3 (2.2)
Fatigue	All	5 (25.0)	2 (25.0)	1 (16.7)	23 (35.4)	3 (33.3)	0	5 (33.3)	1 (16.7)	40 (29.9)
	3 and 4	1 (5.0)	0	0	2 (3.1)	1 (11.1)	0	0	0	4 (3.0)
Stomatitis	All	0	3 (37.5)	1 (16.7)	13 (20.0)	2 (22.2)	1 (20.0)	5 (33.3)	2 (33.3)	27 (20.1)
	3 and 4	0	0	0	1 (1.5)	0	0	0	0	1 (0.7)

NOTE. Data presented as No. (%). All adverse events were characterized and graded per Common Terminology Criteria for Adverse Events v4.0, except for hyperglycemia, which was graded on the basis of a modified version of the American Diabetes Association accepted criteria.
*≤ 270 mg group includes patients treated with alpelisib 30, 60, 90, 180, and 270 mg once daily.

decreased appetite (41.8%), diarrhea (40.3%), vomiting (31.3%), fatigue (29.9%), and stomatitis (20.1%). Overall, the frequency of AEs, including fatigue, GI toxicities, weight loss, and dyspnea, increased slightly with prolonged treatment. The rate of grade 3 or 4 hyperglycemia, rash, and liver toxicities was stable between cycle 1 and later cycles, and the AE profile was consistent throughout the study (Data Supplement).

Hyperglycemia increased in a dose-dependent manner but was effectively managed, by dose interruption/reduction or by concomitant oral antidiabetic medication (metformin), and in some cases with the addition of insulin; only six (4.5%) patients permanently discontinued study treatment because of hyperglycemia. Treatment-related skin toxicities mainly comprised mild to moderate erythematous or maculopapular rash. Rash was dose dependent and typically occurred during the first 2 weeks of treatment. Skin toxicities were managed by concomitant antihistamines or corticosteroids; 12 (9.0%) patients required dose interruption/reduction because of skin toxicities, and one (0.7%) patient permanently discontinued treatment because of hypersensitivity.

In total, 51 (38.1%) patients had at least one dose reduction; most were in line with protocol-specified guidelines due to AEs. At the MTDs, dose reductions occurred in 27 of 65 (41.5%) patients starting at 400 mg once daily and nine of 15 (60.0%) patients starting at 150 mg twice daily. Dose interruptions were required by 78 (58.2%) patients, of which 63 (47.0%) were due to AEs; dose interruptions occurred in 40 of 65 (61.5%) patients at 400 mg once daily and 11 of 15 (73.3%) patients at 150 mg twice daily. Median exposure to alpelisib was 11.9 (0.4 to 145.4) weeks; 9.6 (1.0 to 145.4) weeks at 400 mg once daily and 13.0 (4.0 to 108.3) weeks at 150 mg twice daily.

Fourteen (10.4%) patients experienced treatment-related serious AEs; those reported in ≥ 4% of patients (regardless of study treatment relationship) were nausea, vomiting, abdominal pain, dyspnea, hyperglycemia, and pyrexia. None of the 13 (9.7%) on-treatment deaths were suspected to be treatment-related, and all were attributed to underlying disease progression (including one death due to hypoxia).

Pharmacokinetic and Pharmacodynamics Analyses

Alpelisib was rapidly absorbed, with median time to peak plasma concentrations on cycle 1 day 1 of approximately 2 hours at both MTDs. The median half-life of alpelisib was 7.6 (4.6 to 27.1) hours at 400 mg once daily. Alpelisib PK profiles and exposure were consistent on cycle 1 day 1, cycle 1 day 8, and cycle 2 day 1, suggesting minimal drug accumulation with repeated dosing (Fig 1; Data Supplement). Systemic exposure to alpelisib at both dosing schedules seemed to be dose-proportional within the range tested (Data Supplement). Interpatient variability at steady state for the once-daily dosing schedule was moderate, with mean coefficient of variation 17% to 43% for peak serum concentration and 16% to 41% for total exposure (area under the curve 0 to 24 hours), and was higher with twice-daily dosing, with mean coefficient of variation 37% to 54% for peak serum concentration and 26% to 40% for area under the curve 0 to 12 hours.

Plasma glucose, insulin, and C-peptide levels were monitored as pharmacodynamic markers of glucose regulation, because cellular glucose uptake is tightly regulated by PI3Kα.[19] There was a dose-dependent increase in maximum fold change in FPG during cycle 1, starting from 180 mg once daily, with the most pronounced increase observed at doses higher than the MTDs (Fig 2A). Dose-limiting hyperglycemia was reported in seven patients. Similar increases were observed for insulin and C-peptide (Figs 2B and 2C). A decrease in glucose uptake measured by [^{18}F]-fluorodeoxyglucose positron emission tomography was observed at doses ≥ 180 mg once daily (Fig 2D), with the first partial metabolic response occurring on cycle 1 day 24.

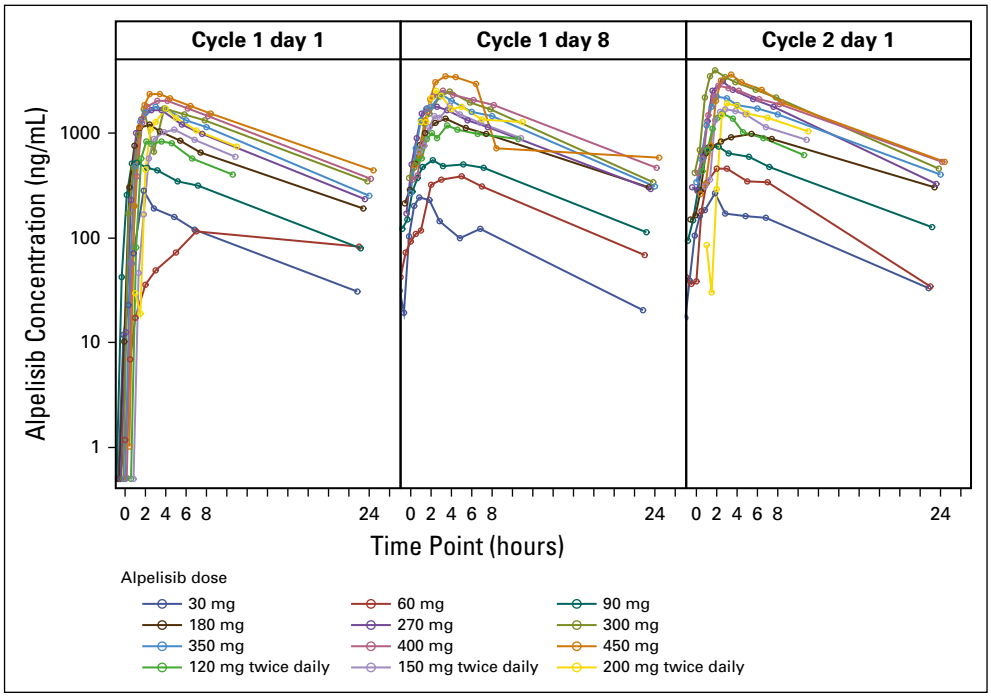

Fig 1. Alpelisib geometric mean plasma concentration–time profiles.

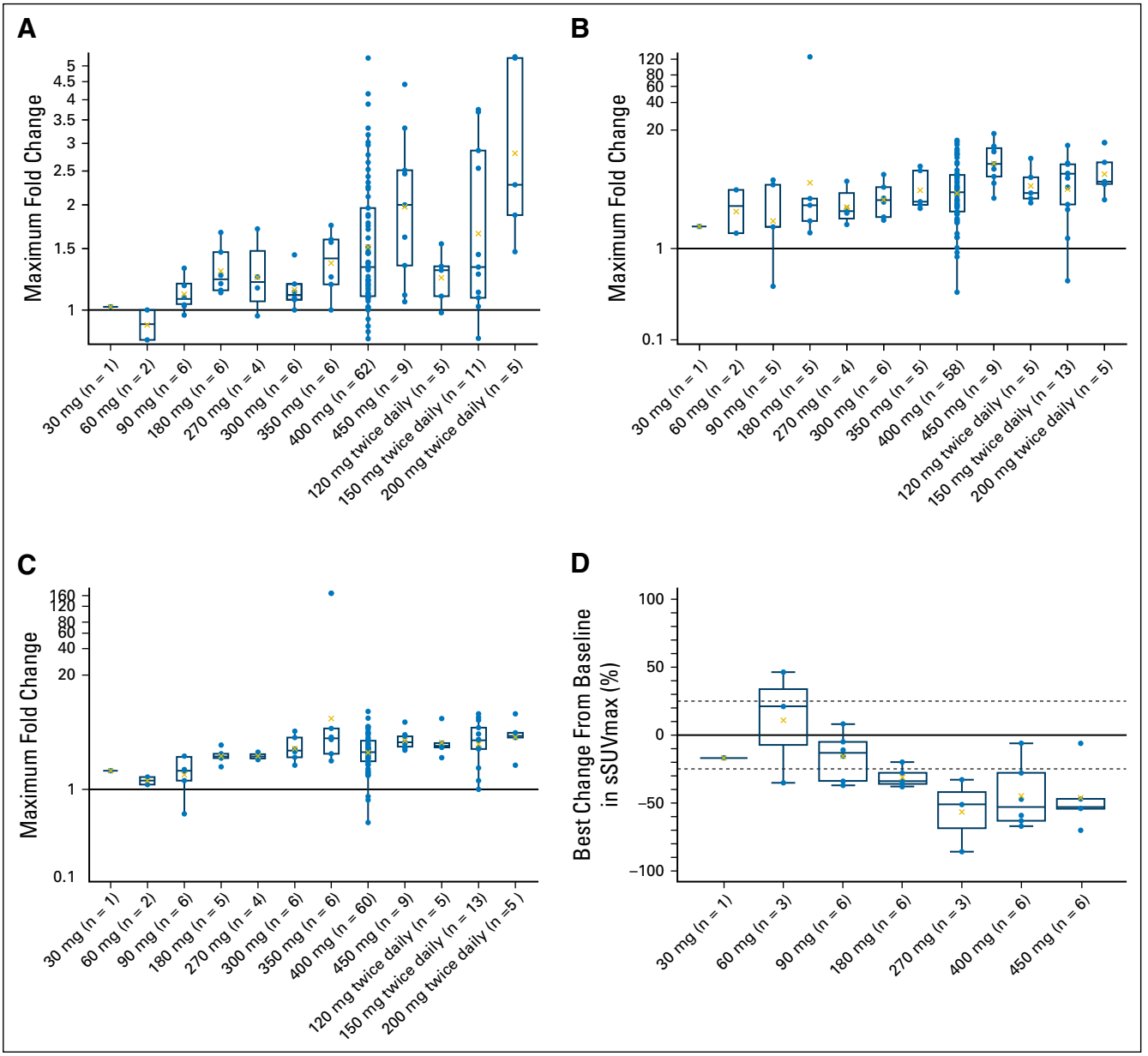

Fig 2. Maximum fold increase from baseline in (A) fasting plasma glucose, (B) fasting serum insulin, and (C) fasting serum C-peptide during cycle 1, and (D) best percentage change from baseline in sum of maximum standardized uptake values (sSUVmax) measured by [^{18}F]-fluorodeoxyglucose positron emission tomography. X represents the geometric mean value.

Clinical Activity and Biomarker Analysis

Best tumor response per RECIST v1.0 was available for 115 of 134 patients; 19 patients were not evaluable, mainly because of missing postbaseline assessments (for example, if patients discontinued before the first on-treatment scan or if they did not have measurable disease). Objective responses were observed after two to six treatment cycles at doses of ≥ 270 mg once daily, with signs of tumor growth suppression at doses ≥ 180 mg once daily. ORR was 6.0%. One patient with endometrial cancer achieved a complete response (CR) at 150 mg twice daily. Partial responses (PRs) were observed in seven patients: cervical (n = 3), breast, endometrial, colon, and rectal cancers (n = 1 each; Table 3). Stable disease (SD) was observed in more than half of patients (52%; n = 70); 13 patients (9.7%) had SD for > 24 weeks. No clinical benefit was observed in the four patients with *PIK3CA*-wild-type ER-positive/HER2-negative breast cancer in the dose-expansion arm.

Across all tumor types, the CBR (CR + PR + SD > 24 weeks) was 15.7%, and the DCR (CR + PR + SD) was 58.2%. DCR was highest in patients with ER-positive/HER2-negative breast cancer (14 of 23 [60.9%] patients), head and neck cancer (13 of 19 [68.4%]), and cervical cancer (five of five [100.0%]). CBR for patients with ER-positive/HER2-negative breast cancer was 17.4% (four of 23 patients). DCR and CBR in patients with colorectal cancer, where two of 35 patients had PR, was 34.3% and 8.6%, respectively.

Table 3. Summary of Best Overall Response per RECIST v1.0

Response	All Patients (N = 134)	ER-Positive/HER2-Negative Breast Cancer (n = 23)	Head and Neck Cancer (n = 19)	Colorectal Cancer (n = 35)
Best overall response				
CR*	1	0	0	0
PR†	7	1	0	2
SD	70	13	13	10
Progressive disease	37	6	3	19
Unknown	19	3	3	4
Overall response rate (CR + PR), No. (%)	8 (6.0)	1 (4.3)	0	2 (5.7)
95% CI	2.6 to 11.4	0.1 to 21.9		0.7 to 19.2
Disease control rate (CR + PR + SD), No. (%)	78 (58.2)	14 (60.9)	13 (68.4)	12 (34.3)
95% CI	49.4 to 66.7	38.5 to 80.3	43.4 to 87.4	19.1 to 52.2
Clinical benefit rate (CR + PR + SD > 24 weeks), No. (%)	21 (15.7)	4 (17.4)	2 (10.5)	3 (8.6)
95% CI	10.0 to 23.0	5.0 to 38.8	1.3 to 33.1	1.8 to 23.1

Abbreviations: CR, complete response; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
*CR was observed in one patient with endometrial cancer.
†Other PRs were observed in one patient with endometrial cancer and three patients with cervical cancer.

Of the 114 patients with tumor volume assessments, 55 (48.2%) patients achieved some degree of tumor shrinkage (Fig 3). Signs of increased activity were detected in patients with advanced breast cancer, with 15 of 27 (55.6%) achieving tumor shrinkage, mostly among those with *PIK3CA*-mutant ER-positive/HER2-negative disease, and two achieving tumor shrinkage of 25.0% and 23.5% (Data Supplement). Similarly, tumor shrinkage was observed in patients with ovarian (six of 14 [42.9%]) and head and neck tumors (seven of 17 [41.2%]). Among 22 patients with ER-positive/HER2-negative advanced breast cancer treated at ≥ 270 mg once daily, median progression-free survival was 5.5 months (95% CI, 3.0 to 7.0).

In addition to *PIK3CA* mutation status being measured locally during screening, tumor samples from 76 patients were also analyzed centrally by NGS (Data Supplement); *PIK3CA* mutations were confirmed in 64 of 76 (84.2%) tumors. Frequently mutated genes (≥ 10% of tumors) were *TP53* (51.3%), *APC* (23.7%), *KRAS* (22.4%), *ARID1A* (13.2%), and *FBXW7* (10.5%). *PTEN* mutations (which may contribute to PI3K inhibitor resistance)[20] were detected in five patients, including three whose disease progressed during the first two treatment cycles. Concomitant *KRAS* mutations were detected in 13 of 17 (76.5%) colorectal tumors, but none in breast tumors (Data Supplement). Because of the heterogeneous patient population, a robust analysis of NGS results and tumor response was not possible.

DISCUSSION

We report a first-in-human study, to our knowledge, evaluating the safety, MTD, and preliminary efficacy of single-agent alpelisib, a potent and highly specific p110α inhibitor, in patients with *PIK3CA*-altered tumors. Alpelisib demonstrated a favorable safety profile up to the MTDs of 400 mg once daily and 150 mg twice daily. At equivalent total daily doses (400 mg once daily and 200 mg twice daily), the once-daily regimen was better tolerated. Overall, single-agent alpelisib demonstrated a wide therapeutic window, with significant pharmacodynamic effects and disease stabilization at ≥ 180 mg once daily, and objective activity at ≥ 270 mg once daily, both well below the MTD of 400 mg once daily. On the basis of improved tolerability and similar efficacy compared with 400 mg once daily, 300 mg once daily was selected as the dose in the phase III trial of fulvestrant with or without alpelisib (SOLAR-1; ClinicalTrials.gov identifier: NCT02437318).

Hyperglycemia was the most frequent DLT and was an anticipated on-target effect related to the role of PI3Kα in insulin signaling and glucose homeostasis; it was managed per guidance provided by Busaidy et al[19,21] for this class of inhibitors. Indeed, serial monitoring of plasma glucose, insulin, and C-peptide levels revealed a dose-dependent increase in all three markers. Of 134 patients, only two permanently discontinued treatment during cycle 1 because of hyperglycemia (both grade 4), with a further four patients discontinuing during later cycles, reflecting effective management by dose interruptions and concomitant antidiabetic medications. Pretreatment patient characteristics and metabolic factors associated with hyperglycemia are under investigation. Other frequent AEs (including GI toxicities, fatigue, and rash) were effectively managed by standard supportive care and concomitant antihistamines or corticosteroids. Eight patients have received treatment of at least 1 year, demonstrating the long-term tolerability of alpelisib.

This study provides evidence of clinical activity of alpelisib in a subset of *PIK3CA*-altered tumors. The ORR in ER-positive/HER2-negative breast cancer was 4.3%, and these patients experienced the highest CBR (17.4%) and a high DCR (60.9%) compared with other cancer types. Although alpelisib single-agent activity was moderate in this group of patients, the combination of alpelisib with letrozole in patients with ER-positive/HER2-negative breast cancer resulted in an ORR of 19% and CBR of 35%[22]; CBR was higher in *PIK3CA*-altered versus *PIK3CA*-wild-type tumors (44% *v* 20%, respectively) in this study. In addition, translational research indicates the potential mechanistic synergy of combining PI3K inhibitors and endocrine therapies, particularly for patients with activating mutations of *PIK3CA*.[23,24] Taken together, these findings highlight potential treatment benefits of alpelisib, either as a single agent or in combination with endocrine therapy, in *PIK3CA*-altered ER-positive/HER2-negative breast cancer. Moreover, modest single-agent activity is not uncommon in early studies of targeted agents in a heterogeneous patient population with multiple prior lines of therapy.[25] Furthermore, *PIK3CA* mutation status at enrollment

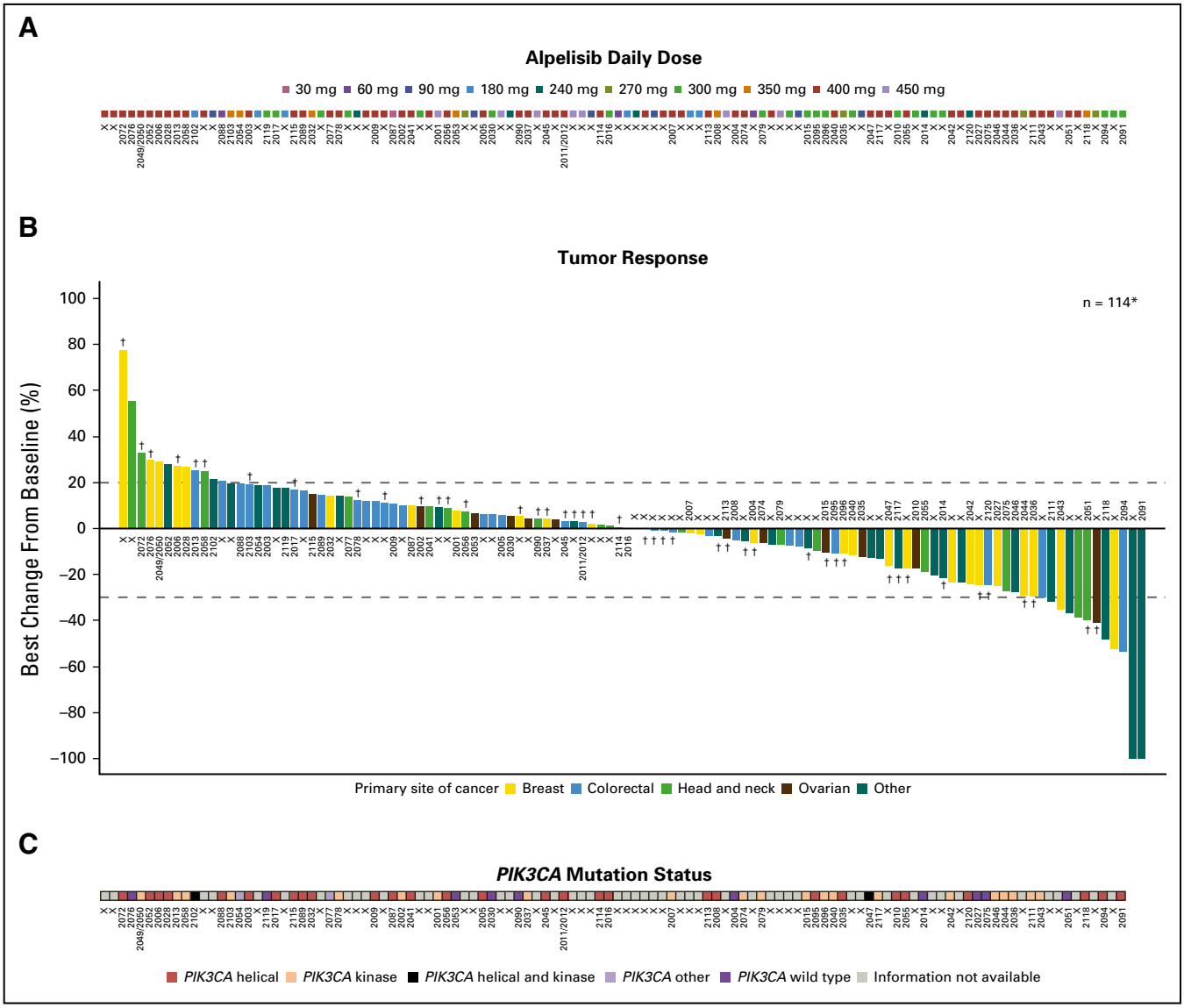

Fig 3. Best percentage change in sum of longest diameters according to (A) study treatment dose, (B) primary site of cancer and metformin treatment, and (C) centrally obtained next-generation sequencing results. Dummy sample numbers for each patient correspond with the next-generation sequencing results in the Data Supplement. Of 12 patients with ≥ 30% reduction in tumor size, complete response (demonstrated with two or more scans taken at least 1 month apart) was observed in one patient with endometrial cancer. However, overall response was lower because some patients experienced rapid disease progression. A partial response was observed in one patient with breast cancer, two patients with colorectal cancer, and four patients with other cancers (one patient with endometrial cancer and three patients with cervical cancer). Stable disease was observed in one patient with ovarian cancer, two patients with head and neck cancer, and one patient with breast cancer. (*) Patients with no postbaseline assessment for target lesions or patients with only nontarget lesions were excluded. (†) Patients receiving metformin for hyperglycemia.

was determined locally in archival tissue, which may not provide an accurate assessment of tumor molecular status because of the spatiotemporal heterogeneity of *PIK3CA* mutations in tumors.[26-28] Indeed, *PIK3CA* alterations were confirmed centrally by NGS in only 84.2% of locally positive samples, suggesting tumor heterogeneity or differences in sequencing methods. Interestingly, exploratory analyses of BELLE-2 (a phase III study of fulvestrant with or without the pan-PI3K inhibitor buparlisib) revealed a predictive value for *PIK3CA* status in circulating tumor DNA collected immediately before treatment start.[29] The ongoing SOLAR-1 trial includes biomarker analyses to evaluate circulating tumor DNA *PIK3CA* status as a tool to identify patients who might derive increased benefit from alpelisib combination treatment.

Our analysis of the overall genomic landscape reveals the frequent presence of multiple concomitant oncogenic alterations in addition to *PIK3CA*. Preclinical studies in ovarian cancer have shown that both *PIK3CA* mutation and loss of phosphatase and tensin homolog (PTEN) are required to drive tumor growth.[30] Moreover, clinical studies suggest that *KRAS* mutations might confer resistance to PI3K/mTOR pathway inhibitors in *PIK3CA*-mutant tumors.[31] Interestingly, we found that breast tumors exhibited fewer alterations with an absence of *KRAS* mutations and more promising clinical activity. Meanwhile, concomitant *KRAS* mutations were detected in > 76.5% of colorectal tumors, which points toward a potential mechanism of resistance to PI3K inhibitors, illustrated by the lesser clinical benefit in these patients.

Even in the absence of concomitant alterations at treatment initiation, *PIK3CA*-mutant breast tumors may develop resistance to PI3Kα inhibition via increased dependency on PI3Kβ,[32] upregulation of ER pathway signaling[23] or acquisition of a variety of alterations leading to PTEN loss.[20] In the future, sustained disease control might be achieved through further molecular characterization to identify *PIK3CA*-dependent tumors and avoid those with concomitant *KRAS* or *PTEN* alterations, or by combinatorial approaches, such as addition of alpelisib to endocrine therapies. Although the sample size was small, patients with *PIK3CA* helical domain mutations (E545K or E542K), unusual kinase mutations (eg T1052K), or PTEN loss had partial or complete response, whereas no responses were observed in patients with kinase mutations on H1047. However, differential activity of alpelisib in helical versus kinase mutants cannot be accurately determined in such a heterogeneous set of samples, because the analysis is heavily confounded by an unequal number of patients in each disease type, cell lineage effects, and/or concomitant mutations.

In summary, this first-in-human study, to our knowledge, demonstrates that alpelisib has a favorable safety profile with predictable PK characteristics. Encouraging signs of antitumor activity were observed in patients with *PIK3CA*-mutant, ER-positive/HER2-negative breast cancer and other *PIK3CA*-altered advanced solid tumors. MTD in this phase Ia study is determined on the basis of the tolerability profile of this agent during the first cycle of treatment, using widely accepted safety boundaries for single-agent dose-escalation studies. Since we observed single-agent activity at ≥ 270 mg, a subsequent phase Ib study tested both 300-mg and 400-mg doses in combination with fulvestrant, with special attention to long-term tolerability of this agent in patients with breast cancer.[33] This phase Ib study was used to inform the dose for subsequent phase III trials. Ongoing studies are evaluating alpelisib in combination with endocrine therapy and other targeted anticancer agents in a range of tumor types.

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Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phosphatidylinositol 3-Kinase α–Selective Inhibition With Alpelisib (BYL719) in *PIK3CA*-Altered Solid Tumors: Results From the First-in-Human Study

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