original reports

Combined PIK3CA and FGFR Inhibition With Alpelisib and Infigratinib in Patients With PIK3CA-Mutant Solid Tumors, With or Without FGFR Alterations

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abstract

PURPOSE Concurrent PIK3CA mutations and fibroblast growth factor receptor (FGFR) alterations occur in multiple cancer types, including estrogen receptor–positive breast cancer, bladder cancer, and endometrial cancer. In this first-in-human combination trial, we explored safety and preliminary efficacy of combining the PI3Kα selective inhibitor alpelisib with the FGFR1-4 selective inhibitor infigratinib.

PATIENTS AND METHODS Patients with PIK3CA-mutant advanced solid tumors, with or without FGFR1-3 alterations, were enrolled in the dose escalation or one of three molecular-defined dose-expansion cohorts. The primary end point was the maximum tolerated dose. Secondary end points included safety, pharmacokinetics, and response. Archival tumor samples were sequenced to explore genomic correlates of response.

RESULTS In combination, both agents were escalated to full, single-agent recommended doses (alpelisib, 300 mg per day continuously; infigratinib, 125 mg per day 3 weeks on followed by 1 week off). The toxicity profile of the combination was consistent with the established safety profile of each agent, although 71% of all patients required at least one treatment interruption or dose reduction. Molecularly selected dose expansions in breast cancer and other solid tumors harboring *PIK3CA* mutations, alone or in combination with *FGFR* alterations, identified sporadic responses, predominately in tumor types and genotypes previously defined to have sensitivity to these agents.

CONCLUSION The combination of alpelisib and infigratinib can be administered at full single-agent doses, although the high rate of dose interruption or reduction suggests long-term tolerability may be challenging. In exploratory signal-seeking cohorts of patients harboring dual PIK3CA and FGFR1-3 alterations, no clear evidence of synergistic activity was observed.

INTRODUCTION

Genome-driven oncology has been focused primarily, to date, on the targeting of individual genomic alterations present in each tumor.[1] Although this approach has led to the development of many highly effective therapies,[2-6] we now understand that most oncogenes exist within a complex genomic landscape characterized by additional alterations that may, themselves, be targetable or modify sensitivity to therapy.[7] Even in instances in which the paradigm of targeting an individual genomic alteration has been successful, adaptation of the tumor eventually leading to acquired resistance ultimately limits effectiveness. One potential strategy to manage both acquired and intrinsic resistance has been the use of targeted therapy combinations. The combination of multiple targeted therapies has already been shown to sometimes prolong the duration of this benefit.[8,9] In instances where tumors demonstrate intrinsic resistance to a single agent, use of targeted drug combinations has also overcome this resistance and induced responses in some scenarios, with the potential cost of additional toxicity.[10]

PIK3CA is commonly mutated in a variety of tumor types, including breast, endometrial, and colon cancers, among others.[11,12] Similarly, the fibroblast growth factor receptor (FGFR) family of receptor tyrosine kinases, which consists of four members, is the target of recurrent mutation, amplification, and fusion events across a wide variety of solid tumors.[13] Preclinical data

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CONTEXT

Key Objective

To determine if the α-elective PI3K inhibitor alpelisib can be combined safely with the selective fibroblast growth factor receptor (FGFR) inhibitor infigratinib.

Knowledge Generated

Alpelisib and infigratinib were successfully escalated in combination to full single-agent doses; however, high rates of treatment interruption and dose reduction suggest long-term tolerability may be challenging. In exploratory signal-seeking cohorts of patients harboring dual PIK3CA and FGFR1-3 alterations, no clear evidence of synergistic activity was observed.

Relevance

Additional studies are necessary to determine the potential role of combined PI3K and FGFR inhibition in treatment of various advanced solid tumors with alterations in PIK3CA and/or FGFR1-3.

suggested that the combined inhibition of these oncogenes might be beneficial.[14] Moreover, in breast cancer, *PIK3CA* mutations often co-occur with *FGFR1* gene amplifications, indicating *PIK3CA* and *FGFR1* could cooperate as potential dual oncogenic drivers in this tumor type.[12,15] Similarly, concurrent activating *PIK3CA* and *FGFR2* mutations have been observed in endometrial carcinomas, with 90% or more *FGFR2*-mutant endometrial cancers also exhibiting genomic activation of the PI3K pathway.[16-18] Taken together, these data provided a rationale for evaluating the feasibility and preliminary activity of combined FGFR and PIK3CA inhibition in the clinic.

To evaluate this therapeutic strategy, we studied the combination of alpelisib (BYL719) and infigratinib (BGJ398). Alpelisib is a selective class I PI3Kα inhibitor that recently demonstrated a statistically significant and clinically relevant improvement in progression-free survival in a phase III study (SOLAR-1) of patients with PIK3CA-mutant, ER+ metastatic breast cancer.[19] Infigratinib is an orally bioavailable, selective pan-FGFR kinase inhibitor that has demonstrated single-agent activity in *FGFR2/3*-altered bladder cancers and *FGFR2* fusion-positive cholangiocarcinomas.[20,21] We hypothesized that the combination of a selective FGFR and PIK3CA inhibitors would be safe and would synergize in tumors with concurrent alteration of these oncogenes. Here, we present results from a phase IB dose escalation and expansion study in which we assessed the safety and preliminary efficacy of the combination of alpelisib and infigratinib in solid tumors with *PIK3CA* mutation either alone or in the presence of concurrent *FGFR1*, *FGFR2*, or *FGFR3* genetic alterations.

PATIENTS AND METHODS

Patients

Eligibility patients were at least 18 years of age and had advanced solid tumors with *PIK3CA* mutation with or without *FGFR* genetic alteration in which standard therapy was unsuccessful. Patients were required to have measurable disease by RECIST, version 1.1, and Eastern Cooperative Oncology Group performance status of 2 or less. Key exclusion criteria included prior FGFR or PI3K inhibitor therapy. Colorectal cancers were excluded on the basis of prior clinical experience demonstrating refractoriness to PI3K inhibition.

The protocol was approved by an institutional review board for each participating center. Written informed consent was obtained from all patients. The study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The study was designed by the sponsor (Novartis Pharmaceuticals, Basel, Switzerland) in collaboration with investigators and registered with ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT01928459).

Study Design

The study design is shown in the Data Supplement. Dose escalation was guided by a Bayesian logistic regression model with escalation with overdose control.[22] In total, three arms in the expansion cohort were planned: dual PIK3CA-mutant and FGFR-altered breast (arm 1) and nonbreast (arm 2) cancers and PIK3CA-mutant solid tumors (arm 3). Because of the slow rate of accrual and overall safety profile, the study was closed before the target enrollment was completed.

The primary objective was to determine the maximum tolerated dose and/or recommended dose for expansion of the combination of infigratinib and alpelisib. The secondary objectives included assessment of safety and tolerability of the combination, characterization of pharmacokinetic (PK) profiles, assessment of preliminary antitumor activity as measured by overall response rate (ORR), and progression-free survival (PFS), per RECIST, version 1.1.

Study Drug Administration

Alpelisib tablets were administered orally (300 mg or 400 mg once per day) over a 28-day cycle. Infigratinib capsules were administered at doses ranging from 20 to 125 mg once per day for the first 21 days of the treatment

cycle, followed by a 7-day break. Patients remained in the study until disease progression, unacceptable adverse events (AEs), or withdrawal at patient or investigator discretion.

Study Assessments

Tumor responses were measured by RECIST, version 1.1 (investigator assessed), using computed tomography or magnetic resonance imaging.[23] Assessments were performed at screening and every 8 weeks after first treatment until disease progression. Safety was monitored throughout the study according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.[24] ECGs were assessed and independently reviewed by a central laboratory.

Pharmacokinetic Analysis

During dose escalation, blood samples were collected to measure alpelisib and infigratinib plasma concentrations. Samples were collected predose and 0.5, 1, 2, 3, 4, 6, 8, and 24 hours postdose on cycle 1 day 1, cycle 1 day 15, and cycle 2 day 1. Predose samples were also collected on cycle 1 days 1, 8, 15, and 21, and during cycles 2, 3, and 4 on days 1 and 15, and then during cycles 5 through 10 on day 1. Drug plasma concentrations (and active metabolites) were measured using validated liquid chromatography-tandem mass spectrometry with a lower limit of quantification of 1 ng/mL.

Genomic Sequencing

Genomic alterations potentially associated with FGFR and PIK3CA signaling were assessed from archival tumor specimens of fresh, pretreatment tumor biopsy specimens. For samples with sufficient tissue material (n = 41), next-generation sequencing (NGS) analysis was performed in a Clinical Laboratory Improvement Amendments–certified laboratory (Foundation Medicine, Cambridge, MA) using previously published methods.[25]

Statistical Analysis

The data cutoff for all statistical analyses was August 23, 2016. Overall response rate was defined as the proportion of patients with a best overall response of complete or partial response (PR) with confirmation. Median PFS was estimated using a 95% CI with Kaplan-Meier estimates at prespecified time points. PK parameters were determined for all PK-evaluable patients using noncompartmental or compartmental methods by Phoenix WinNonlin (Pharsight, Mountainview, CA). The sample size for each expansion cohort was selected primarily for continued safety evaluation and was not powered for any specific efficacy end point.

RESULTS

Patient Demographics

A total of 62 patients were enrolled in the study between October 2013 and August 2016 across 22 clinical centers in 12 countries. The median age of patients at the time of study entry was 60 (range, 30 to 78) years, and all patients had an Eastern Cooperative Oncology Group performance status of 1 or less. Baseline patient characteristics are listed in Table 1. The most common tumor types were breast (30.6%), colorectal (17.7%), endometrial (9.7%), and ovary (8.1%). Patients were heavily pretreated, having received a median of three prior lines of systemic therapy.

Safety and Tolerability

Dose-limiting toxicities were reported in three patients (10.7%) who were included in the dose-escalation cohort (n = 38) during the first 28 days of treatment. Dose-limiting toxicities included grade 4 hyperglycemia in one patient receiving alpelisib 300 mg and infigratinib 40 mg; and grade 3 stomatitis in two patients (one receiving alpelisib 300 mg and infigratinib 75 mg; and the other receiving alpelisib 300 mg and infigratinib 100 mg). The recommended dose for expansion was determined to be alpelisib 300 mg once per day (administered continuously) and infigratinib 125 mg once per day (administered on a schedule of 3 weeks on followed by 1 week off).

Overall, the safety profile of alpelisib and infigratinib was similar to the known safety profiles of each agent; no new major AEs were noted (Table 2). The most common related AEs of any grade were diarrhea (n = 29; 46.8%); decreased appetite (n = 27; 43.5%); stomatitis (n = 26; 41.9%); nausea (n = 25; 40.3%); fatigue, hyperglycemia, and hyperphosphatemia (n = 24 each; 38.7%); dry mouth (n = 17; 27.4%); dysgeusia (n = 16; 25.8%); and vomiting (n = 14; 22.6%).

In total, grade 3/4 AEs suspected to be study-treatment related were reported in 37 patients (59.7%). The most frequent treatment-related grade 3/4 AEs (observed in ≥ 5% of patients) were hyperglycemia (n = 11; 17.7%), stomatitis (n = 8; 12.9%), and increase in alanine aminotransferase level and diarrhea (n = 5 each; 8.1%). Treatment-related grade 4 AEs were observed in three patients: hyperglycemia (n = 2; 3.2%) and hyponatremia (n = 1; 1.6%). Serious AEs suspected to be drug related were reported in 12.9% of patients (n = 8 of 62) overall and 16.1% (n = 5 of 31) treated at the recommended dose for expansion. These serious AEs included stomatitis (n = 2; 3.2%), maculopapular rash, nausea, diarrhea, dyspnea, hypersensitivity (ie, allergic reaction), hyponatremia, and hyperglycemia (n = 1 each; 1.6%). A total of 13 deaths (21%) were reported during the study, including three (4.8%) deaths resulting from disease progression while the patient was receiving study treatment. No drug-related deaths were reported.

As previously described, hyperphosphatemia was observed in a majority of patients treated with infigratinib at doses of 100 mg or higher.[20] Phosphate elevation is an established biomarker of on-target FGFR pathway inhibition, because of its role in mediating renal tubular

TABLE 1. Patient Demographics and Disease Characteristics

Characteristic	Dose Escalation (n = 38)	Dose Expansion (n = 24)	All Patients (N = 62)
Age (median), years	60.0	59.5	60.0
Sex, male	14 (36.8)	9 (37.5)	23 (37.1)
ECOG PS			
0	12 (31.6)	15 (62.5)	27 (43.5)
1	26 (68.4)	9 (37.5)	35 (56.5)
Primary site of tumor			
Breast	12 (31.6)	7 (29.2)	19 (30.6)
Colorectal	11 (28.9)	0	11 (17.7)
Endometrium	3 (7.9)	3 (12.5)	6 (9.7)
Ovary	1 (2.6)	4 (16.7)	5 (8.1)
Lung	4 (10.5)	0	4 (6.5)
Melanoma	2 (5.3)	0	2 (3.2)
Bladder	0	2 (8.3)	2 (3.2)
Head and neck	1 (2.6)	1 (4.2)	2 (3.2)
Other*	4 (10.5)	7 (29.2)	11 (17.7)
No. of prior therapies			
0	1 (2.6)	2 (8.3)	3 (4.8)
1	2 (5.3)	3 (12.5)	5 (8.1)
2	11 (28.9)	9 (37.5)	20 (32.3)
3	3 (7.9)	4 (16.7)	7 (11.3)
≥ 4	21 (55.3)	6 (25.0)	27 (43.5)
Mutation type			
PIK3CA†	37 (97.4)	23 (95.8)	60 (96.8)
FGFR1 status‡	—	0	0
SNV/indel	—	0	0
Translocation	—	5 (20.8)	5 (8.1)
Amplification	—	0	0
FGFR2 status‡	—	4 (16.7)	4§ (6.5)
SNV/indel	—	0	0
Translocation	—	1 (4.2)	1§ (1.6)
Amplification	—	1 (4.2)	1 (1.6)
FGFR3 status‡	—	1 (4.2)	1‖ (1.6)
SNV/indel	—	1 (4.2)	1‖ (1.6)
Translocation	—	1 (4.2)	1‖ (1.6)
Amplification	—	1 (4.2)	1‖ (1.6)

NOTE. Data reported at No. (%) unless otherwise indicated.

Abbreviations: —, no data; ECOG, Eastern Cooperative Oncology Group; indel, insertion and/or deletion; PS, performance status; SNV, single nuclear variant.

*Includes one patient each with primary site of cancer at anal canal, esophagus, kidney, nasopharynx, oral cavity, testis, uterus, pelvic region, gastroesophageal junction, and two other patients.

†Two patients (one each in the dose escalation part and dose expansion part) were enrolled on the basis of locally reported PIK3CA mutations, but later data were not recorded correctly in the database.

‡FGFR alterations are only reported for patients treated in the dose expansion (n = 24).

§A patient had co-occurring FGFR2 amplification and FGFR2 mutation.

‖A patient had co-occurring FGFR3 amplification and FGFR3 arrangement.

TABLE 2. Adverse Events Suspected to be Related to Study

	All Patients (N = 62), No. (%)		
Preferred Adverse Effect Term	**Grades 1/2**	**Grades 3/4**	**All Grades**
Total*	24 (38.7)	37 (59.7)	61 (98.4)
Diarrhea	24 (38.7)	5 (8.1)	29 (46.8)
Decreased appetite	27 (43.5)	0	27 (43.5)
Stomatitis	18 (29.0)	8 (12.9)	26 (41.9)
Nausea	22 (35.4)	3 (4.8)	25 (40.3)
Hyperphosphatemia†	24 (38.7)	0	24 (38.7)
Hyperglycemia	13 (20.9)	11 (17.7)	24 (38.7)
Fatigue	22 (35.4)	2 (3.2)	24 (38.7)
Dry mouth	17 (27.4)	0	17 (27.4)
Dysgeusia	16 (25.8)	0	16 (25.8)
Vomiting	13 (20.9)	1 (1.6)	14 (22.6)
Mucosal inflammation	9 (14.5)	3 (4.8)	12 (19.4)
Blood creatinine level increased	11 (17.7)	0	11 (17.7)
Alopecia	11 (17.7)	0	11 (17.7)
Asthenia	8 (12.9)	2 (3.2)	10 (16.1)
Dry skin	9 (14.5)	0	9 (14.5)
Maculopapular rash	5 (8.1)	3 (4.8)	8 (12.9)
Palmar-plantar erythrodysesthesia syndrome	5 (8.1)	2 (3.2)	7 (11.3)
Alanine aminotransferase level increased	2 (3.2)	5 (8.1)	7 (11.3)
Dry eye	6 (9.7)	1 (1.6)	7 (11.3)
Lipase level increased	5 (8.1)	2 (3.2)	7 (11.3)
Rash	5 (8.1)	2 (3.2)	7 (11.3)
Anemia	4 (6.5)	2 (3.2)	6 (9.7)
Aspartate aminotransferase level increased	5 (8.1)	1 (1.6)	6 (9.7)
Constipation	4 (6.5)	1 (1.6)	5 (8.1)
Vision blurred	5 (8.1)	0	5 (8.1)
Weight decreased	5 (8.1)	0	5 (8.1)
Amylase level increased	4 (6.5)	0	4 (6.5)
Pyrexia	4 (6.5)	0	4 (6.5)
Thrombocytopenia	4 (6.5)	0	4 (6.5)

*Any grade occurring in ≥ 5% of patients.
†Hyperphosphatemia graded according to protocol-defined criteria not included in Common Terminology Criteria for Adverse Events, version 4.

phosphate secretion and reabsorbtion.[26] Clinically significant complications as a result of hyperphosphatemia did not develop in any patient. Similarly, hyperglycemia, which is a biomarker of on-target PI3K α inhibition, was also observed in 38.7% of all patients treated with alpelisib 200 mg or 300 mg, consistent with prior experience with this agent.[27]

For infigratinib, 37 patients (59.7%) reported at least one dose interruption and 23 patients (37.1%) reported at least one dose reduction. For alpelisib, 44 patients (71.0%) reported at least one dose interruption and 30 patients (48.4%) reported at least one dose reduction. The median duration of treatment of alpelisib with infigratinib across all dose levels was 68 (range, 7 to 491) days.

Pharmacokinetics

Exposure of infigratinib, as assessed by median area under concentration versus time curve (0 to 24 hours) on cycle 1 day 15 in combination with alpelisib 300 mg, increased marginally more than proportionately to the dose after the first dose as well as repeated dosing (Fig 1).

The median time to reach maximum concentration and terminal half-life of infigratinib ranged from 2.05 to 4.08 hours and 2.5 to 20.05 hours, respectively. A moderate

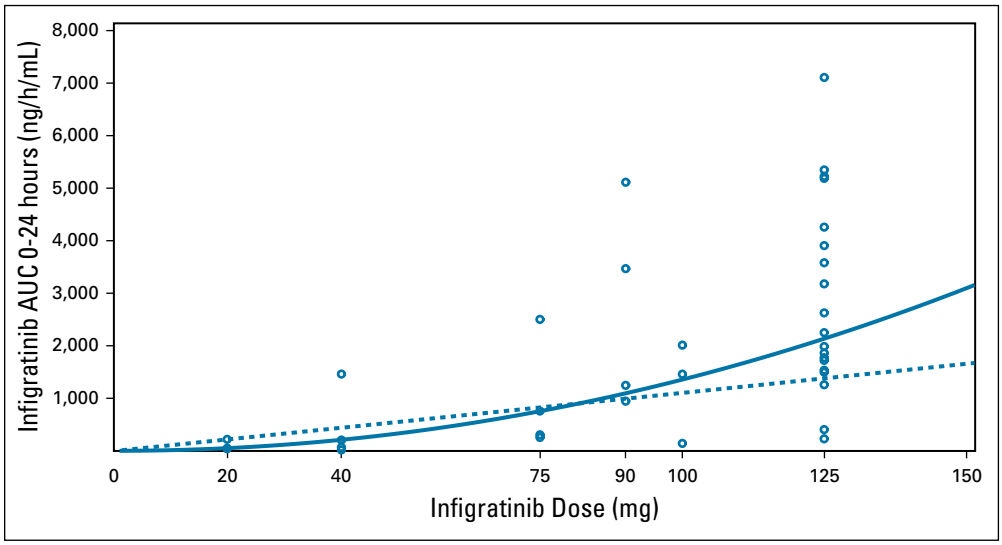

FIG 1. Infigratinib pharmacokinetics show dose proportional increases in the infigratinib area under the curve (AUC) when combined with alpelisib 300 mg on cycle 1 day 15. The solid line is modeled by the AUC 0-24 hours = exp (α) × dose × β, which denotes the actual exposure dose relationship. The dotted reference line is modeled by AUC 0-24 hours = exp (α 2) × dose, which is the reference line under the assumption of strict linear exposure dose relationship.

drug accumulation ratio on cycle 1 day 15 and cycle 2 day 1 ranging from 1.02 to 10.1 was observed.

The median time to reach maximum concentration and terminal half-life of alpelisib ranged from 1.61 to 4.04 hours and 5.72 to 9.86 hours, respectively. A moderate drug accumulation ratio on cycle 1 day 15 ranged from 0.961 to 2.01 and from 0.865 to 2.15 on cycle 2 day 1.

The PK properties of infigratinib and alpelisib administered in combination are similar to that observed in monotherapy. There was no or negligible PK interaction between infigratinib and alpelisib.

Antitumor Efficacy

In total, 52 patients were evaluable for response and 10 (n = 6 in the dose escalation study; n = 4 in the dose expansion study) were nonevaluable on the basis of discontinuing therapy before the first disease assessment (Table 3). For the purposes of efficacy analyses, nonevaluable patients were considered nonresponders. Among all 62 treated patients, PRs were observed in six patients (9.7%). Thirty-four patients (54.8%) demonstrated disease control (ie, PR and stable disease) at the first disease assessment performed at week 6. Among all 31 patients treated at the recommended dose for expansion, four patients (12.9%) achieved PR, and 19 patients (61.3%) demonstrated disease control. Patients with PR included one patient with cutaneous melanoma treated with infigratinib 75 mg and alpelisib 300 mg, one patient with squamous cell carcinoma of the anal canal treated with infigratinib 90 mg and alpelisib 300 mg, and four patients treated at the recommended dose for expansion (one *PIK3CA*-mutant only oral cavity adenocarcinoma, one *PIK3CA*-mutant and *FGFR3*-translocated bladder cancer, one *PIK3CA*-mutant undifferentiated nasopharynx carcinoma, and one *PIK3CA* and *FGFR2* dual-mutant endometrioid ovarian cancer). The median PFS for all patients treated at the recommended dose for expansion was 3.7 months (95% CI, 2.1 to 5.4). The median PFS for each arm (1, 2, and 3) of the expansion cohort was 4.0, 4.2, and 3.7 months, respectively (Fig 2).

Genomic Correlates of Response

Targeted NGS of 411 key cancer genes was successfully performed centrally on 41 patients (66%) with available tissue, including four of the six patients who achieved a PR. To explore the potential link between genetic alterations in the FGFR and PI3K pathway and treatment outcomes, alterations in key genes in both pathways were investigated for correlation with observed efficacy (Fig 3). Among 60 patients with a locally annotated *PIK3CA* mutation reported, sequencing with high confidence coverage was obtained centrally in 35 samples and the locally reported *PIK3CA* variant confirmed in 80% patients (n = 28 of 35). For two of the seven unconfirmed cases, a different *PIK3CA* variant than that reported locally was identified centrally. Among 11 patients who had locally reported *FGFR* alterations, central sequencing data were available for six patients and the *FGFR* alteration was confirmed in each case.

In the four patients with PR with central targeted sequencing available, genomic activation of one or both pathways by central testing was observed for three patients: one with bladder cancer with FGFR3-TACC3 fusion, one with endometrioid ovarian cancer with concurrent PIK3CA E542V and FGFR2 N549K mutations, and one with

TABLE 3. Best Overall Response by Treatment Group

Response	Infigratinib 20 mg + Alpelisib 300 mg (n = 4)	Infigratinib 20 mg + Alpelisib 400 mg (n = 4)	Infigratinib 40 mg + Alpelisib 300 mg (n = 6)	Infigratinib 75 mg + Alpelisib 300 mg (n = 6)	Infigratinib 90 mg + Alpelisib 300 mg (n = 5)	Infigratinib 100 mg + Alpelisib 300 mg (n = 6)	Infigratinib 125 mg + Alpelisib 300 mg (n = 31)	All Patients (N = 62)
Overall response rate	0	0	0	1 (16.7)	1 (20.0)	0	4 (12.9)	6 (9.7)
Best overall response								
Complete response	0	0	0	0	0	0	0	0
Partial response	0	0	1 (6.7)	1 (20.0)	0	0	4 (12.9)	6 (9.7)
Non-CR/non-PD*	0	0	0	0	0	0	2 (6.5)	2 (3.2)
Stable disease	2 (50.0)	1 (25.0)	3 (50.0)	2 (33.3)	3 (60)	0	15 (48.4)	28 (45.2)
Progressive disease	2 (50.0)	1 (25.0)	3 (50.0)	1 (16.7)	1 (20.0)	4 (66.7)	9 (29.0)	21 (33.9)
Unknown†	0	0	0	2 (33.3)	0	2 (33.3)	1 (3.2)	5 (8.1)
Disease control rate‡	2 (50.0)	3 (75.0)	3 (50.0)	3 (50.0)	4 (80.0)	0	19 (61.3)	34 (54.8)

NOTE. Data reported as No. (%), except where n = 0.

Abbreviations: CR, complete response; PD, progressive disease.

*For patients who only had nontarget lesions at baseline and did not experience either a CR or PD, response is reported as non-CR/non-PD.

†Patient with unknown best overall response due to (1) no valid postbaseline assessment, or (2) stable disease occurred too early (< 6 weeks)

‡Defined as patients who have best overall response CR, partial response, or stable disease, in which stable disease needs to occur at least 6 weeks after the first dosing.

squamous anal cancer with PIK3CA E545K mutation. Interestingly, in the patient with melanoma who had a PR, the only genomic activation of either pathway identified by central sequencing was an FGFR2 M722I mutation, an alteration not known to be recurrent or of biologic significance.[27]

We also explored whether genetic alterations of the MAPK pathway co-occurred with mutations in the FGFR and/or PI3K pathways and may account for lack of response, at least partially, in those settings. However, MAPK pathway alterations, in particular *KRAS* mutations, were identified in both responder and nonresponder patients. Overall, NGS studies showed no clear association of alterations in the FGFR, PI3K, or MAPK pathways with response.

DISCUSSION

To our knowledge, this is the first study to evaluate the safety and preliminary efficacy of combined selective PI3K and FGFR inhibition in patients. We defined a recommended dose for expansion of alpelisib 300 mg once per day and infigratinib 125 mg once per day, 3 weeks on followed by 1 week off, which is the full single-agent dose and schedule of each drug. Although this combination did not raise new specific safety concerns, 71% of patients required a dose interruption of alpelisib and 60% of patients reported at least one dose interruption of infigratinib during the course of treatment. Of note, dose interruptions in the range of 50% to 70% have previously been reported with each agent when used individually, again suggesting that their combination may not be associated with significant additive toxicity over the component parts but that each drug alone can exhibit long-term tolerance issues.[20,28,29] No drug-drug interactions were reported between infigratinib and alpelisib.

This study does have some important limitations. First, the sample size for each expansion cohort was selected primarily for continued safety evaluation and was not powered for any specific efficacy end point. The relatively small number of patients treated with relevant concurrent alterations, as well as the heterogeneity of the population, do not permit a definitive assessment of synergistic efficacy. As such, any efficacy data presented from these expansions should be considered hypothesis generating only. Second, we note that in the subset of 58% of patients (n = 35 of 60) with tumor tissue in which successful central sequencing was completed, the *PIK3CA* mutations were centrally confirmed in 80% of patients. It is worth noting that this trial took place at a time when circulating free DNA NGS was still maturing, and thus plasma collection for central testing was not incorporated into the study design, further limiting the number of patients in whom central, broad profiling was available for biomarker analysis. As a result, some patients may have been enrolled on the basis of PIK3CA mutations characterized by subclonality, spatial or temporal heterogeneity, or even test failures, as has been observed in prior genome-driven studies.[7]

Finally, enrollment in the expansion cohorts for patients harboring concurrent *PIK3CA* and *FGFR1-3* alterations was not restricted to variants functionally characterized as activating but to regions of the affected genes that are recurrently the target of alteration. Similarly, any locally reported *FGFR* amplification was considered eligible without a specific fold-change required. Previous studies have suggested that responsiveness of tumors harboring

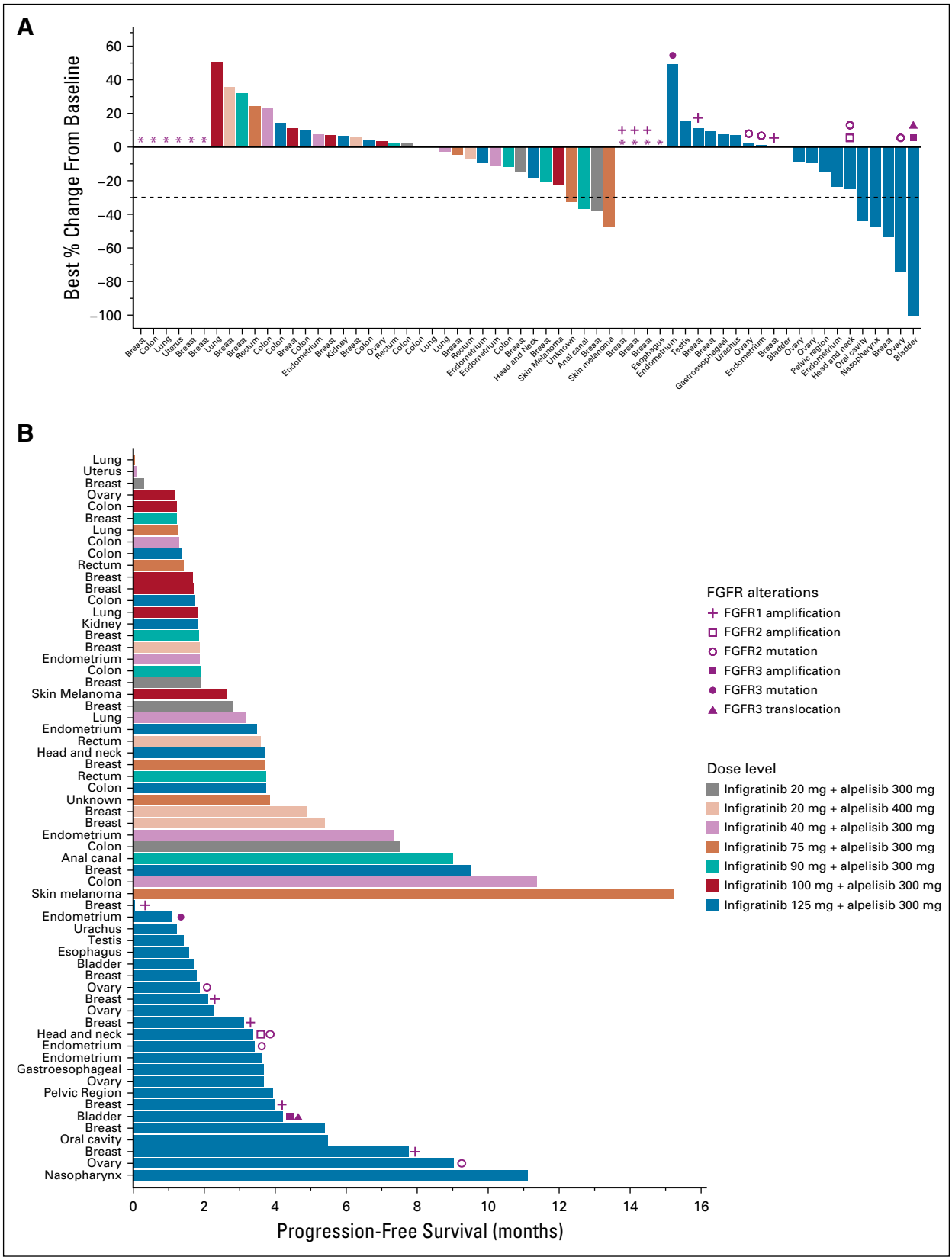

FIG 2. Efficacy by (A) a waterfall plot depicting best percent change in the target tumor burden from baseline according to cohort and (B) a swimmer plot depicting progression-free survival by patients according to cohort. (*) Missing best percent change in sum of diameters from baseline, as a result of evaluation based on only nontarget lesions, missing target lesion measurements, or discontinuation before first response assessment.

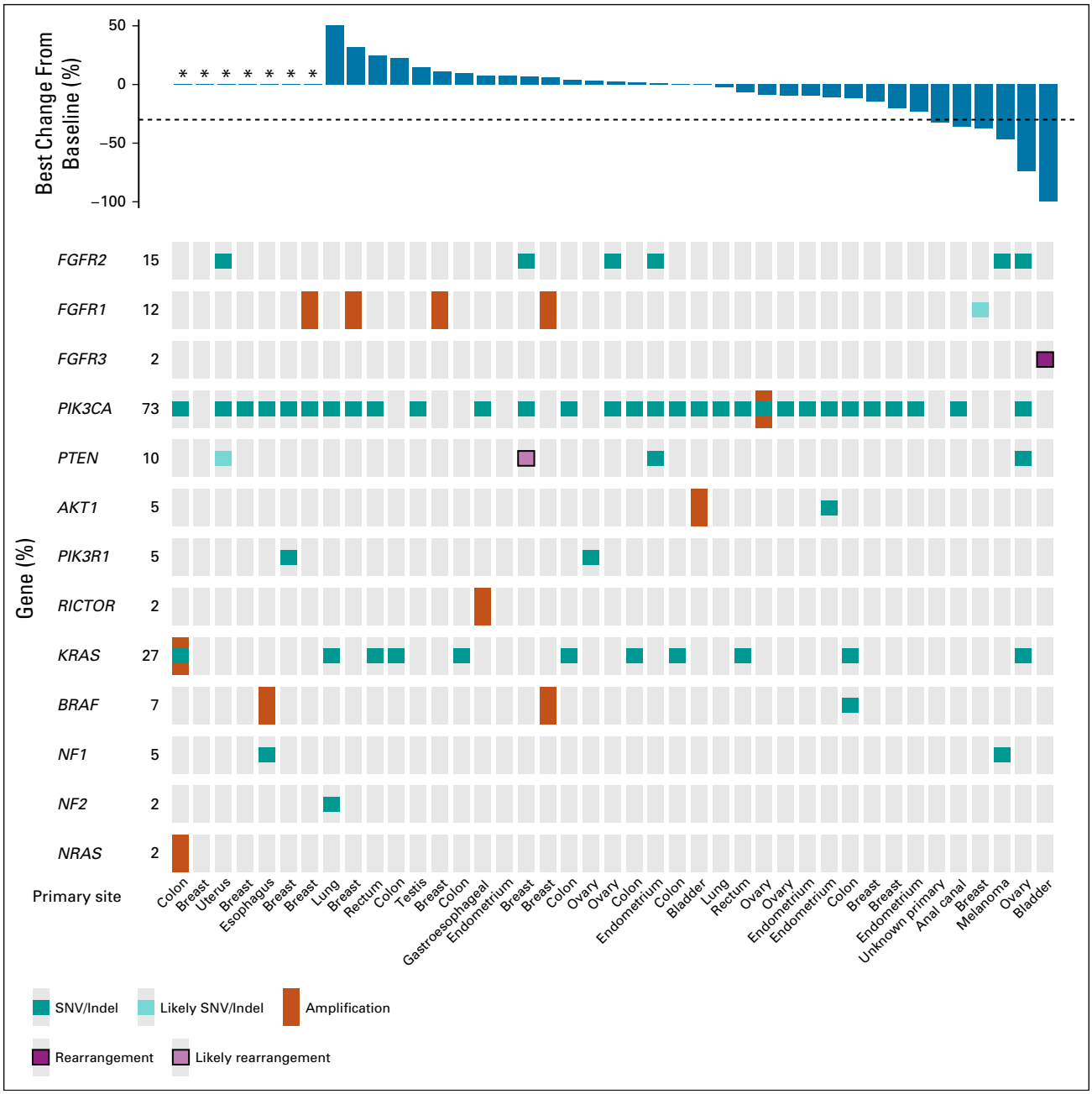

FIG 3. Integrated genomic analysis of efficacy according to mutations in the FGFR, PI3K, and MAPK pathways by central next-generation sequencing. (*) Missing response data, as a result of discontinuation before first response assessment. Indel, insertion and/or deletion.

FGFR amplification is partially dependent on the degree of amplification.[30] Both the inclusion of variants of unknown significance as well as copy number amplifications with a specific fold-change requirement may have adversely affected the observed ORR by enrolling tumors without true pathway dependency on FGFR.

Despite these important limitations, a relatively low ORR of only 9.7% across the entire study suggests that these two classes of agents may not provide synergistic activity. Moreover, responses were generally observed in tumors arising from anatomic sites and harboring genetic alterations previously described as sensitizing to either alpelisib or infigratinib. It is also noteworthy that a significant proportion of patients did not respond, or had stable disease as their best response, despite harboring PIK3CA mutations alone or in combination with FGFR alterations. These data are consistent with prior experience demonstrating that the presence of *PIK3CA* and most *FGFR* alterations alone are generally insufficient to predict tumor-agnostic response to alpelisib and infigratinib, respectively.[20,27]

Targeted therapy combinations have often been cited as a means of overcoming both intrinsic and acquired resistance, but a number of scientific, technical, and logistic impediments have made successful implementation challenging.[31,32] Perhaps the most difficult barrier to successful implementation has been identification of the right drug combinations. Enrichment for concurrent alterations of two oncogenes in one or multiple cancer types has served as one basis for selecting potential drug combinations and formed the basis of the hypothesis evaluated in this clinical study. Recently, findings were reported from two precision medicine studies, I-PREDICT and WINTHER, suggesting that a higher degree of molecular matching between somatic alterations detected at baseline and the therapy administered was associated with improved outcomes.[33,34] Although these results imply that targeting multiple oncogenic alterations with polytherapy may be a worthwhile strategy in select circumstances, the data presented here demonstrate that more rigorous evaluation of specific biomarker and drug combinations is required before the approach is more widely embraced.

In conclusion, the combination of PIK3CA and FGFR inhibition with alpelisib and infigratinib was feasible, although overall tolerability was limited by each agent. Although larger, potentially randomized studies would be needed to more definitively explore the synergy of combined PIK3CA and FGFR inhibition in tumors harboring genomic activation in one or both drug targets, overall, these efficacy data were not considered sufficiently promising to pursue additional clinical development.

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