Clinical Trials: Targeted Therapy

Clinical Cancer Research

Phase II Study of Taselisib (GDC-0032) in Combination with Fulvestrant in Patients with HER2-Negative, Hormone Receptor–Positive Advanced Breast Cancer

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Abstract

Purpose: This single-arm, open-label phase II study evaluated the safety and efficacy of taselisib (GDC-0032) plus fulvestrant in postmenopausal women with locally advanced or metastatic HER2-negative, hormone receptor (HR)-positive breast cancer.

Patients and Methods: Patients received 6-mg oral taselisib capsules daily plus intramuscular fulvestrant (500 mg) until disease progression or unacceptable toxicity. Tumor tissue (if available) was centrally evaluated for *PIK3CA* mutations. Adverse events (AE) were recorded using NCI-CTCAE v4.0. Tumor response was investigator-determined using RECIST v1.1.

Results: Median treatment duration was 4.6 (range: 0.9–40.5) months. All patients experienced ≥1 AE, 30 (50.0%) had grade ≥3 AEs, and 19 (31.7%) experienced 35 serious AEs. Forty-seven of 60 patients had evaluable tissue for central *PIK3CA* mutation testing [20 had mutations, 27 had no mutation detected (MND)]. In patients with baseline measurable disease, clinical activity was observed in tumors with *PIK3CA* mutations [best confirmed response rate: 38.5% (5/13; 95% CI, 13.9–68.4); clinical benefit rate (CBR): 38.5% (5/13; 95% CI, 13.9–68.4)], *PIK3CA*-MND [best confirmed response rate: 14.3% (3/21; 95% CI, 3.0–36.3); CBR: 23.8% (5/21; 95% CI, 8.2–47.2)], and unknown *PIK3CA* mutation status [best confirmed response rate: 20.0% (2/10; 95% CI, 2.5–55.6); CBR: 30.0% (3/10; 95% CI, 6.7–65.2)].

Conclusions: Taselisib plus fulvestrant had clinical activity irrespective of *PIK3CA* mutation status, with numerically higher objective response rate and CBR in patients with *PIK3CA*-mutated (vs. -MND) locally advanced or metastatic HER2-negative, HR-positive breast cancer. No new safety signals were reported. A confirmatory phase III trial is ongoing.
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Introduction

The PI3K pathway is essential for normal cell growth and is implicated in many cancers (1, 2), including hormone receptor (HR)-positive breast cancer (3, 4). The gene encoding phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit-alpha (*PIK3CA*) is a commonly mutated human oncogene in breast cancer (5). Activating mutations in *PIK3CA* have been detected in approximately 40% of patients with HR-positive breast cancer (6, 7). Thus, the PI3K pathway is an attractive target for drug development.

Taselisib (GDC-0032) is a potent and selective PI3K inhibitor, with enhanced efficacy in cell lines that harbor a *PIK3CA* (p110α) somatic mutation (8–11). Clinical studies demonstrated that taselisib, when administered as an oral capsule formulation at doses of 3–16 mg once daily to patients with locally advanced or metastatic solid tumors in a phase Ia dose-escalation trial, had a linear exposure profile and an elimination half-life of approximately 40 hours (12). Taselisib was well tolerated and had clinical activity over the dosage range evaluated (12). Hyperglycemia,

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Translational Relevance

The PI3K pathway is essential for normal cell function and is implicated in the pathogenesis of hormone receptor (HR)-positive breast cancer. Taselisib (GDC-0032) is a potent and selective PI3K inhibitor with greater efficacy against mutant than wild-type phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit-alpha (*PIK3CA*). Inhibition of PI3K signaling in HR-positive breast cancer results in upregulation of estrogen receptor (ER)-dependent function. The combination of PI3K inhibition and ER inhibition with fulvestrant produces marked tumor regression in breast cancer models, providing a rationale for dual PI3K and ER inhibition in breast cancer. In this trial, women with advanced HR-positive breast cancer received oral taselisib plus intramuscular injections of fulvestrant. The adverse event profile was typical of that previously reported with PI3K inhibitors, and objective responses were obtained in women with *PIK3CA*-mutated and -mutation-not-detected tumors. On this basis, taselisib plus fulvestrant is being evaluated in a phase III study.

diarrhea, rash, and stomatitis were common adverse events (AE) observed in the trial, consistent with toxicities observed with other PI3K inhibitors (12).

Inhibition of PI3K signaling in HR-positive breast cancer results in upregulation of estrogen receptor (ER)-dependent function (13, 14). The mechanism by which this occurs has been recently elucidated and involves increased KMT2D activity, which in turn stimulates ER-dependent transcription (14). The combination of PI3K inhibition using BYL719 (alpelisib) and ER inhibition using fulvestrant resulted in marked tumor regression in a xenograft model that was more robust than either agent alone (13). Importantly, in a proof-of-concept study in patients with ER-positive breast cancer, the combination of anti-estrogen therapy using exemestane with inhibition of mTOR, a downstream target of PI3K, with everolimus significantly increased progression-free survival (PFS) compared with everolimus plus placebo (15). Collectively, these observations provide a rationale for dual PI3K and ER inhibition in patients with breast cancer.

Data from a phase Ib trial in patients with HR-positive breast cancer demonstrate that there is no pharmacokinetic drug–drug interaction between taselisib and fulvestrant, and suggest that the combination has clinical activity and acceptable tolerability (16). On this basis, we designed the present phase II study to evaluate the clinical efficacy and safety of taselisib plus fulvestrant in postmenopausal women with locally advanced or metastatic HER2-negative, HR-positive breast cancer.

Patients and Methods

Patients

Eligible patients were postmenopausal women with locally advanced or metastatic HER2-negative, HR-positive breast cancer who had progressed or failed to respond to $\geq$1 prior endocrine therapy in the adjuvant or metastatic setting. Patients were also required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, a fasting plasma glucose level $\leq$120 mg/dL, granulocyte count $\geq$1,500/μL, platelet count $\geq$100,000/μL, hemoglobin concentration $\geq$9 g/dL, serum albumin concentration $\geq$2.5 g/dL, and both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels $\leq$1.5 times the upper limit of normal. As an exception, patients with documented liver metastases were eligible if their AST and/or ALT levels were $\leq$5.0 times the upper limit of normal. The presence of measurable or evaluable disease, defined by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria, was required. Prior treatment with everolimus was allowed.

Patients were excluded if they had received: prior therapy with fulvestrant; >1 cytotoxic chemotherapy regimen for breast cancer in the metastatic setting; prior therapy with a PI3K inhibitor, or oral endocrine therapy within 2 weeks prior to initiation of study treatment. Patients with active inflammatory diseases requiring immunosuppressant agents, including Crohn disease or ulcerative colitis; known and untreated, or active central nervous system metastases (progressing or requiring anticonvulsants for symptomatic control); and/or type I or II diabetes mellitus requiring antidiabetic medication, were also excluded.

The study was performed after approval by an institutional review board and conducted in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonisation Guidelines, and the laws and regulations of the countries in which it was conducted. All patients provided written informed consent before undergoing any study procedures.

Study design and treatment

This was a phase II, open-label, multicenter, single-arm study (clinicaltrials.gov: NCT01296555). Patients received 6 mg oral taselisib capsules once daily in combination with fulvestrant until the occurrence of disease progression or unacceptable toxicity. Fulvestrant was administered as a 500 mg intramuscular injection on days 1 and 15 during cycle 1 and thereafter on day 1 of each 28-day cycle.

Dosing with taselisib or fulvestrant could be interrupted for up to 28 days in the event of toxicity or unanticipated medical events not associated with study drug toxicity or disease progression. Step-wise reductions in the dose of taselisib were permitted to manage study drug-related toxicity (first reduction: 3 mg every day; second reduction: 3 mg every other day). Dose reductions were not allowed for fulvestrant, although patients were allowed to temporarily suspend treatment with fulvestrant for $\leq$28 days. Study treatment was discontinued in patients who experienced disease progression or unacceptable toxicity.

Safety assessment

Safety was assessed by monitoring and recording protocol-defined AEs and serious AEs (SAE), and by monitoring protocol-specified laboratory parameters and vital signs. AEs were graded according to the National Cancer Institute–Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.0; ref. 17).

The protocol-defined AEs of special interest (AESI) for taselisib were hyperglycemia, colitis, diarrhea, rash, and pneumonitis. The search strategy for AESIs was based on Sponsor-specific AE group terms, based on the Medical Dictionary for Regulatory Activities (MedDRA; Supplementary Methods).

PIK3CA mutation testing

Patients were enrolled on the basis of *PIK3CA* mutation status by local or central testing, with central *PIK3CA* mutation testing performed retrospectively on all available samples. Formalin-

fixed paraffin-embedded tumor tissue samples (blocks or slides) either from prior tumor excisions or fresh biopsies, if available, were requested for all patients for central mutation testing, although availability of archival tissue was not required for enrollment. Tumors were classified as being *PIK3CA*-mutated if a positive result was obtained from central analysis of archival tumor tissue using the Cobas PIK3CA Mutation Test (Roche Molecular Diagnostics; ref. 4), which uses real-time PCR to detect frequent hotspot mutations in exons 1, 4, 7, 9, and 20. The following substitution mutations were included: E542K, E545X (A, D, G, or K), Q546X (K, R, E, or L), N345K, C420R, R88Q, H1047X (L, R, or Y), G1049R, and M1043I. Helical domain mutations were defined as E542K, E545X (A, D, G, or K), and Q546X (K, R, E, or L). Kinase domain mutations were defined as H1047X (L, R, or Y), G1049R, and M1043I. Tumors were classified as *PIK3CA*-mutation-not-detected (MND) if no mutations were detected by the Cobas test, and *PIK3CA* mutation status unknown if there was no tissue available or assay failure.

Tumor response assessments and criteria

Measurable or evaluable disease was documented at screening and at each subsequent tumor evaluation on the basis of physical examinations, imaging studies, and laboratory results. The same radiographic procedure used at baseline was used throughout the study for each patient. Postbaseline tumor assessments were conducted at the end of cycles 2, 4, 6, and 8 and every 12 weeks thereafter. Bone scans and brain scans were performed if clinically indicated. Tumor response was determined by investigators using RECIST v1.1 criteria (18).

Outcomes

The primary endpoints were clinical benefit rate (CBR), defined as confirmed complete response, confirmed partial response, or stable disease lasting for $\geq$6 months in all patients, and objective response rate (ORR) in all patients and in patients with *PIK3CA*-mutated breast cancer per central Cobas test. The secondary endpoints, in all patients and in patients with *PIK3CA*-mutated breast cancer, included safety (all treated patients), duration of objective response (DoR), PFS, and overall survival (OS).

Statistical considerations

The planned enrollment was 60 patients, including a minimum of 30 patients with *PIK3CA*-mutated breast cancer as determined by local or central testing.

The study was designed to estimate the ORR and CBR of the combination of taselisib and fulvestrant and to allow for a comparison with historical studies of fulvestrant [ORR: 7%–10%; CBR: 32%–46% (19, 20)]. Assuming that 30% of patients (9 of 30) had nonmeasurable, bone-only disease, an observed ORR of $\geq$30% in the remaining 21 patients with *PIK3CA*-mutated tumors was estimated to have a lower bound of the 95% confidence interval (CI) $\geq$14.6%, excluding an ORR of 10%. An observed CBR of 67% ($n = 30$) was estimated to have a 95% CI of 47.2–82.7, excluding a CBR of 46%.

All safety and efficacy analyses were based on the safety-evaluable population, defined as all patients who received at least one dose of study drug (taselisib or fulvestrant).

95% CIs were estimated for ORR and DoR, with DoR estimated by Kaplan–Meier methodology.

Results

Patient characteristics

Overall, 60 patients were enrolled between July 9, 2013 and May 8, 2014 and treated with taselisib plus fulvestrant. The data-analysis cutoff was December 1, 2016. Baseline demographic and patient characteristics are shown by *PIK3CA* mutation status in Table 1. Patient demographics were well balanced between *PIK3CA* mutation status groups. The median age of women enrolled in the trial was 61.5 years (range: 31–82), the median time from initial diagnosis was 64.2 months (range: 6.7–315.3), and 56.7% of women had an ECOG PS of 0 (Table 1).

Among the 60 patients included in the analysis, 47 had evaluable tumor tissue for central *PIK3CA* mutation testing (25 from metastatic tissue and 22 from primary tissue; Supplementary Fig. S1). On the basis of central testing, 20 patients (33.3%) were *PIK3CA*-mutated, 27 (45.0%) were *PIK3CA*-MND, and 13 (21.7%) had an unknown *PIK3CA* mutation status (12 samples without sufficient evaluable tumor tissue and one assay failure). A numerically higher number of patients with an unknown *PIK3CA* mutation status had an ECOG PS of 0 [10/13 (76.9%)] versus patients with a known mutation status [24/47 (51.1%)].

The disposition of patients is shown in Supplementary Table S1. At the data cutoff, 42 patients (70.0%) had been discontinued from the study: 36 (60.0%) had died, 4 (6.7%) were lost to follow-up, and 2 (3.3%) had withdrawn from the study. The remaining patients were being followed for OS.

Safety

Treatment with taselisib and fulvestrant was generally well tolerated (Table 2). Sixty patients (100.0%) experienced $\geq$1 AE (Tables 2 and 3). The most common AEs, regardless of attribution, were diarrhea [42 patients (70.0%)], nausea [27 patients (45.0%)], fatigue [25 patients (41.7%)], and decreased appetite [19 patients (31.7%)] (Table 3). Thirty patients (50.0%) experienced grade $\geq$3 AEs (Tables 2 and 3), and the most common were colitis [8 patients (13.3%); median onset of grade $\geq$3 AEs was 4.5 months (range: 3.7–8.2)], diarrhea [7 patients (11.7%); median onset of grade $\geq$3 AE was 4.7 months (range: 3.7–12.2)], and hyperglycemia [4 patients (6.7%); median onset of grade $\geq$3 AE was 4.2 months (range: 1.9–5.3)] (Table 3). Overall, a total of 35 SAEs were observed in 19 patients (31.7%; Supplementary Table S2). SAEs that occurred in more than 1 patient included colitis in 6 patients (10.0%) and pneumonia in 3 patients (5.0%; Supplementary Table S2).

AESIs in the safety population were reported in 48 patients (80.0%; Supplementary Table S3). AESIs included diarrhea [42 patients (70.0%)], colitis [14 patients (23.3%)], stomatitis [25 patients (41.7%)], rash [18 patients (30.0%)], hyperglycemia [13 patients (21.7%)], and pneumonitis [1 patient (1.7%)] (Supplementary Table S3).

Overall, 14 patients (23.3%) had AEs leading to taselisib dose reduction. AEs that led to taselisib dose reductions included colitis in 4 patients (6.7%); diarrhea in 4 patients (6.7%); mucosal inflammation in 3 patients (5.0%); and asthenia, decreased appetite, rash, and stomatitis, each in 1 patient (1.7%). In the 4 patients who had a dose reduction of taselisib due to diarrhea, all experienced a subsequent episode of diarrhea following the initial dose reduction. In the 3 patients who had a dose reduction due to mucosal inflammation, 1 patient experienced

Table 1. Baseline demographics and patient characteristics by *PIK3CA* mutation status

Characteristic	***PIK3CA*-mutated ($n = 20$)**	***PIK3CA*-MND ($n = 27$)**	***PIK3CA* mutation status unknown ($n = 13$)**	**All patients ($N = 60$)**
Median age, years (range)	61.0 (41–78)	57.0 (31–82)	63.0 (44–75)	61.5 (31–82)
ECOG PS, *n* (%)				
0	9 (45.0)	15 (55.6)	10 (76.9)	34 (56.7)
1	11 (55.0)	12 (44.4)	3 (23.1)	26 (43.3)
Median time from primary diagnosis, months (range)	$n = 17$; 65.3 (6.7–183.1)	$n = 23$; 56.7 (11.6–315.3)	$n = 12$; 81.7 (16.0–167.7)	$n = 52$; 64.2 (6.7–315.3)
Bone-only disease, *n* (%)				
Yes	1 (5.0)	4 (14.8)	2 (15.4)	7 (11.7)
No	19 (95.0)	23 (85.2)	11 (84.6)	53 (88.3)
Visceral disease, *n* (%)				
Yes	14 (70.0)	17 (63.0)	8 (61.5)	39 (65.0)
No	6 (30.0)	10 (37.0)	5 (38.5)	21 (35.0)
Endocrine sensitivity, *n* (%)[a]				
Yes	7 (35.0)	9 (33.3)	1 (7.7)	17 (28.3)
No	13 (65.0)	18 (66.7)	12 (92.3)	43 (71.7)
Median number of prior hormonal therapies, (range)	$n = 20$; 2.0 (1.0–5.0)	$n = 26$; 2.0 (1.0–4.0)	$n = 13$; 2.0 (1.0–5.0)	$n = 59$; 2.0 (1.0–5.0)
Prior treatment, *n* (%)[b]				
Aromatase inhibitor	18 (90.0)	21 (77.8)	13 (100.0)	52 (86.7)
Everolimus	4 (20.0)	3 (11.1)	3 (23.1)	10 (16.7)
Letrozole	13 (65.0)	14 (51.9)	8 (61.5)	35 (58.3)
Anastrozole	6 (30.0)	7 (25.9)	6 (46.2)	19 (31.7)
Exemestane	10 (50.0)	6 (22.2)	8 (61.5)	24 (40.0)
Tamoxifen	10 (50.0)	19 (70.4)	7 (53.8)	36 (60.0)
Prior chemotherapy, *n* (%)				
Adjuvant setting	8 (40.0)	15 (55.6)	6 (46.2)	29 (48.3)
Metastatic setting	4 (20.0)	8 (29.6)	4 (30.8)	16 (26.7)
Prior hormonal therapy, *n* (%)				
Adjuvant setting	12 (60.0)	21 (77.8)	9 (69.2)	42 (70.0)
Metastatic setting	14 (70.0)	12 (44.4)	11 (84.6)	37 (61.7)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MND, mutation-not-detected; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit-alpha.

[a]Endocrine sensitivity was defined based on a positive response to either of the following: (i) In patients with at least one hormonal treatment in the metastatic setting: treatment duration was ≥24 weeks from the most recent hormonal therapy in the metastatic setting, if the best response was missing. Documented complete/partial response or stable disease ≥24 weeks from the most recent hormonal therapy in the metastatic setting, if the best response was available. (ii) In patients without hormonal therapy in the metastatic setting, but who received hormonal treatment in the adjuvant setting: treatment duration of the most recent hormonal treatment in the adjuvant setting was ≥24 months.

[b]Patients received prior treatment in the adjuvant or metastatic setting. For the "median time from primary diagnosis" and "median number of prior hormonal therapies" categories, the number of patients for whom data were available is presented.

an additional event of mucositis following the initial dose reduction. In the patient who had a dose reduction of taselisib due to asthenia, this patient had one more reported event of asthenia following resolution of the first event. Overall, 7 of the 14 patients who had a dose reduction of taselisib did not experience another episode of the event that initially led to the dose reduction, including the 4 patients with colitis.

Taselisib treatment was discontinued due to 16 AEs in 12 patients (20.0%) for the following: colitis in 5 patients (8.3%); diarrhea in 3 patients (5.0%); and increased ALT (1.7%), increased AST (1.7%), atrial fibrillation (1.7%), enterocolitis (1.7%), fatigue (1.7%), nausea (1.7%), pneumonitis (1.7%), and maculopapular rash (1.7%), each in 1 patient.

The median time to onset of any-grade colitis was 4.7 months (range: 3.2–8.2). Colitis was diagnosed by imaging studies and/or by endoscopy, and the observed pathology demonstrated ulcerations, and lymphocytic and/or eosinophilic infiltration. These events resolved or improved after interruption of study treatment, reduction of the taselisib dose, and/or initiation of corticosteroid therapy. In 13 patients with colitis, 5 (38.5%) were able to resume treatment following resolution of the event and either dose reduction (four) or interruption (one), without reoccurrence of colitis.

The median onset of any-grade diarrhea was 1.7 months (range: 0.1–8.3). All but two events of the 127 (98.4%) reports of diarrhea resolved after interruption of study treatment, reduction of the taselisib dose, and/or initiation of antidiarrheal and/or corticosteroid therapy.

Four patients (6.7%) experienced a total of five grade 5 AEs during study treatment (1 patient experienced grade 5 sepsis, 2 patients had grade 5 pneumonia, and 1 patient experienced both grade 5 device–related infection and grade 5 pericardial effusion). None of these events were related to taselisib treatment in the opinion of the investigator.

Time on treatment and exposure to taselisib

The duration of treatment with taselisib and fulvestrant is depicted by mutation status in Fig. 1. Twenty-two patients (37.0%) out of 60 received more than 6 months of treatment with taselisib. The overall median duration of treatment was 4.6 months (range: 0.9–40.5; Supplementary Table S4; Supplementary Fig. S2). The median dose intensity with taselisib was 97.1% (range: 42–100; Supplementary Table S4), and the median dose intensity of fulvestrant was 100% (range: 88–150).

Clinical activity

Among the subset of patients who had their *PIK3CA* mutation status evaluated by tumor tissue analysis, 44 patients had measurable disease at baseline; of these, 13 (29.5%) were *PIK3CA*-mutated, 21 (47.7%) had *PIK3CA*-MND, and 10 (22.7%) had unknown *PIK3CA* mutation status (Table 4). None had a complete

Table 2. Overview of AEs in the safety population

AE, *n* (%)	All patients (*N* = 60)
Any-grade AEs	60 (100.0)
Grade ≥3 AEs	30 (50.0)
Grade 5 AEs	4 (6.7)
Serious AEs	19 (31.7)
AEs leading to taselisib dose modifications	
AE leading to taselisib dose reduction	14 (23.3)
AE leading to taselisib dose interruption	27 (45.0)
AE leading to taselisib discontinuation	12 (20.0)

response. Confirmed partial responses were observed in 5 of 13 patients with *PIK3CA*-mutated tumors (38.5%; 95% CI, 13.9–68.4), in 3 of 21 patients with *PIK3CA*-MND tumors (14.3%; 95% CI, 3.0–36.3), and in 2 of 10 patients with unknown *PIK3CA* tumor mutation status (20.0%; 95% CI, 2.5–55.6; Fig. 2; Table 4).

In patients with measurable disease at baseline, the overall CBR was 29.5% (13/44; 95% CI, 16.8–45.2; Table 4). The CBR was 38.5% (5/13; 95% CI, 13.9–68.4) in patients with *PIK3CA* mutations, 23.8% (5/21; 95% CI, 8.2–47.2) in patients with *PIK3CA*-MND and 30.0% (3/10; 95% CI, 6.7–65.2) in patients with unknown *PIK3CA* mutation status (Table 4). Overall response rates and CBR for all 60 patients, including patients with and without measurable disease at baseline, are included in Supplementary Table S5.

Kaplan–Meier estimates of the median DoR in responders ($n = 10$), regardless of *PIK3CA* mutation status, was 19.6 months [range: 1.4 (censored)–36.1]. Median DoR was 8.8 months (range: 3.7–36.1) in the subgroup of responding patients with *PIK3CA*-mutated tumors ($n = 5$) and 18.5 months [range: 1.4 (censored)–19.6] in responding patients with *PIK3CA*-MND ($n = 3$).

Median PFS was 7.6 months in patients with *PIK3CA*-mutated tumors (95% CI, 4.9–13.7), 5.4 months in patients with *PIK3CA*-MND tumors (95% CI, 1.8–10.0), and 5.3 months [95% CI, 1.8–not evaluable (NE)] in patients with unknown *PIK3CA* mutation status. Median PFS was 6.5 months (95% CI, 4.9–7.8) in all patients, irrespective of *PIK3CA* status.

Median OS was 19.2 months (95% CI, 17.7–26.9) in 20 patients with *PIK3CA*-mutated tumors and 27.0 months (95% CI, 15.2–32.9) in 27 patients with *PIK3CA*-MND tumors. OS was NE (95% CI, 17.6–NE) in 13 patients with unknown *PIK3CA* mutation status.

Discussion

This phase II open-label study evaluated the efficacy and safety of taselisib plus fulvestrant in postmenopausal women with locally advanced or metastatic HER2-negative, HR-positive breast cancer. Overall, the combination of taselisib plus fulvestrant was generally well tolerated and clinical activity was observed. The safety profile of taselisib in combination with fulvestrant was consistent with previous reports (12, 16), with the most common AEs being diarrhea, nausea, fatigue, and decreased appetite. PI3K inhibitor class effects, as reported in other clinical trials of pan-PI3K inhibitors, also included AEs such as hyperglycemia, rash, stomatitis, and gastrointestinal toxicities (diarrhea), and these toxicities led to frequent dose modifications (21–24).

Treatment-emergent diarrhea was the most common AE in the present trial. The median time to onset of all-grade diarrhea was 1.7 months, and the median time to onset of grade ≥3 diarrhea was 4.7 months, suggesting that diarrhea with a higher grade had a longer latency. Diarrhea was manageable and reversible with antidiarrheal medications, corticosteroids, and/or taselisib dose interruption and reduction.

Treatment-emergent colitis was the most common grade ≥3 AE and SAE, and the most common AE leading to dose reduction and discontinuation of taselisib in the present trial. Colitis was observed in patients treated with a pan-PI3K inhibitor (22), as well as with the delta-isoform–specific inhibitor, idelalisib (25). Pathologic examination of tissue obtained from patients who experienced colitis showed that this AE was associated with infiltration of inflammatory cells and ulceration in some patients; similar to that reported with idelalisib (26). Our results, and those from a previous report (12), suggest that taselisib-associated treatment-emergent colitis can be managed by dose reductions and/or corticosteroid treatment, although some patients (5/60; 8.3%) discontinued therapy permanently due to this AE. In addition, therapy was reinitiated after resolution of colitis in some patients, without subsequent additional events of colitis. As such, it is recommended that early patient reporting, close monitoring, and early intervention may lead to reduced severity of

Table 3. AEs occurring in ≥10% of patients or grade ≥3 AEs occurring in ≥2% of patients regardless of attribution in the safety population

AE, *n* (%)	All-grade AEs (*N* = 60)	Grade ≥3 AEs (*N* = 60)
Total number of patients with at least one AE	60 (100.0)	30 (50.0)
Total number of AEs	901	69
Diarrhea	42 (70.0)	7 (11.7)
Nausea	27 (45.0)	
Fatigue	25 (41.7)	
Decreased appetite	19 (31.7)	1 (1.7)
Mucosal inflammation	17 (28.3)	2 (3.3)
Dry skin	16 (26.7)	
Rash	15 (25.0)	1 (1.7)
Dyspepsia	14 (23.3)	
Colitis	13 (21.7)	8 (13.3)
Hyperglycemia	13 (21.7)	4 (6.7)
Asthenia	12 (20.0)	2 (3.3)
Abdominal pain	11 (18.3)	
Stomatitis	11 (18.3)	
Back pain	10 (16.7)	1 (1.7)
Cough	10 (16.7)	
Headache	10 (16.7)	
Arthralgia	9 (15.0)	
Insomnia	9 (15.0)	
Dyspnea	8 (13.3)	
Urinary tract infection	8 (13.3)	
Alopecia	7 (11.7)	
Dizziness	7 (11.7)	
Dysgeusia	7 (11.7)	
Muscle spasms	7 (11.7)	
Constipation	6 (10.0)	
Dry mouth	6 (10.0)	
Gastroesophageal reflux disease	6 (10.0)	
Hypokalemia	6 (10.0)	1 (1.7)
Musculoskeletal pain	6 (10.0)	
Pyrexia	6 (10.0)	
Vomiting	6 (10.0)	
Weight decreased	6 (10.0)	
Aspartate aminotransferase increased	5 (8.3)	2 (3.3)
Rash maculopapular	5 (8.3)	2 (3.3)
Pneumonia	4 (6.7)	3 (5.0)
Hyponatremia	2 (3.3)	2 (3.3)

NOTE: All AE categories are preferred terms, encoded using MedDRA version 20.0. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted once. For the total number of events, multiple occurrences of the same AE in an individual were counted separately.

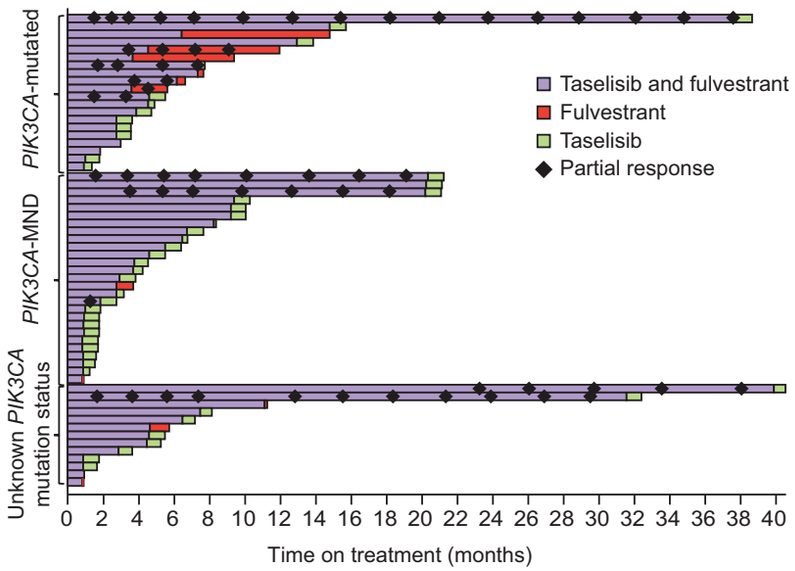

Figure 1.
Time on treatment by *PIK3CA* mutation status. Many patients are shown as having received taselisib alone after their last dose of fulvestrant treatment. This is because they stopped taselisib treatment mid-cycle (typically for progression) and fulvestrant was received on days 1 and 15 of cycle 1, then on day 1 of each 28-day cycle.

treatment-related toxicities, particularly diarrhea and colitis, thereby maintaining greater duration of therapy.

Antitumor activity was observed in this trial and the confirmed response rate of 22.7% (95% CI, 11.5–37.8) and CBR of 29.5% (95% CI, 16.8–45.2) in patients with baseline measurable disease were promising, although the sample size was small. Among patients with baseline measurable disease, there was a numerically higher ORR and CBR in patients with *PIK3CA*-mutated tumors [ORR: 38.5% (95% CI, 13.9–68.4); CBR: 38.5% (95% CI, 13.9–68.4)] compared with patients with *PIK3CA*-MND tumors [ORR: 14.3% (95% CI, 3.0–36.3); CBR: 23.8% (95% CI, 8.2–47.2)]. The response rate of 38.5% (95% CI, 13.9–68.4) in patients with *PIK3CA* mutations is promising given that the lower limit of the 95% CI exceeds the historical response rate achieved with fulvestrant alone (~7%–10%) in a similar patient population, including an ORR of 8.2% in patients with PI3K pathway–activated tumors treated with fulvestrant plus placebo in the BELLE-2 trial (19, 20, 24).

In the phase Ia study of single-agent taselisib, objective responses were observed only in patients with *PIK3CA*-mutated tumors (12). In contrast, responses were reported in patients with both *PIK3CA*-mutated and *PIK3CA*-MND when treated with taselisib in combination with fulvestrant in the present study. It is difficult, however, to draw conclusions regarding the magnitude of benefit conferred by taselisib in patients with *PIK3CA*-MND tumors as, in the present study, patients also received fulvestrant. Potential activity of combined PI3K and ER inhibition in both *PIK3CA*-mutated and -wild-type tumors may reflect the cross-talk between these two pathways in breast cancer.

As an open-label, single-arm phase II trial, this study has several limitations. No comparator group was included and the cohort was highly selected. While the study enrolled 60 patients, only 47 patients had suitable tissue samples for *PIK3CA* mutation testing. The absence of information regarding the *PIK3CA* mutation status in 13 patients limits the power of the mutation analysis. Tissue samples were tested using the Cobas test that detects 17 *PIK3CA* hotspot mutations, potentially missing some tumors with non-hotspot rare *PIK3CA* mutations. Archival tumor samples were tested for *PIK3CA* mutations, with samples provided from primary tumor tissue or a metastatic site. In our study, approximately half of the samples submitted for testing were from metastatic tissue; however, primary tissue may be used as a surrogate for absent or unavailable metastatic tissue as there is generally a high

Table 4. Clinical activity in patients with measurable disease at baseline

n (%)	***PIK3CA*-mutated** (***n*** = 13)	***PIK3CA*-MND** (***n*** = 21)	***PIK3CA* mutation status unknown[a]** (***n*** = 10)	**All patients** (***N*** = 44)
Best confirmed response				
Responders	5 (38.5)	3 (14.3)	2 (20.0)	10 (22.7)
95% CI for response rate	13.9–68.4	3.0–36.3	2.5–55.6	11.5–37.8
Nonresponders	8 (61.5)	18 (85.7)	8 (80.0)	34 (77.3)
Complete response	0	0	0	0
95% CI	0.00–24.7	0.0–16.1	0.0–30.8	0.0–8.0
Partial response	5 (38.5)	3 (14.3)	2 (20.0)	10 (22.7)
95% CI	13.9–68.4	3.0–36.3	2.5–55.6	11.5–37.8
Clinical benefit rate	5 (38.5)	5 (23.8)	3 (30.0)	13 (29.5)
95% CI	13.9–68.4	8.2–47.2	6.7–65.2	16.8–45.2
Median duration of response, months	8.8	18.5	30.5	19.6
95% CI	3.7–36.1	17.4–19.6	NE	8.8–31.4
Patients with disease progression	2 (15.4)	8 (38.1)	2 (20.0)	12 (27.3)

[a]One patient had missing or unavailable response data; this patient died before receiving a postbaseline tumor assessment, as a result of pericardial effusion related to study disease and device-related infection. 95% CI for median duration of response was calculated using the method of Brookmeyer and Crowley; all others used the Clopper–Pearson method. Patients were classified as missing or NE if no post–baseline response assessments were available or all post–baseline response assessments were unevaluable. Clinical benefit was defined as an objective response or stable disease lasting for ≥24 weeks since first study treatment.

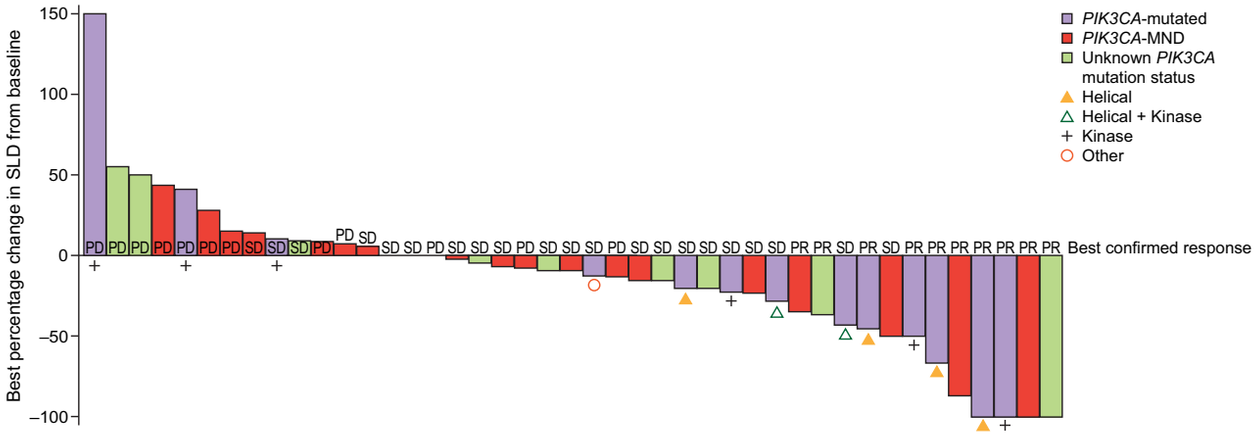

Figure 2.

Antitumor activity of taselisib plus fulvestrant in patients with measurable or evaluable disease at baseline (safety evaluable population). PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of the longest diameter.

concordance between *PIK3CA* mutation status from primary tumor samples compared with samples from metastatic sites or relapses (4, 27). Overall, 44 of 60 patients had baseline measurable disease, limiting the number of patients evaluable for objective response. Analysis by *PIK3CA* mutation status was retrospective and there were differences in baseline characteristics among subjects with different *PIK3CA* mutation status. This trial was also conducted prior to the approval of the cyclin-dependent kinase 4/6 inhibitors (palbociclib, ribociclib, abemaciclib) and, while this is not in itself a limitation of the study, these agents have been shown to increase PFS in patients with HR-positive, HER2-negative breast cancer (28–31). It remains to be seen how any new agent such as taselisib may be used either sequentially or in combination with cyclin-dependent kinase 4/6 inhibitors to further improve outcomes in this population.

Taselisib may offer an improved therapeutic window with a more favorable toxicity profile than pan-PI3K inhibitors, where higher rates of treatment discontinuations were reported in the pictilisib (22, 23) and buparlisib (24) treatment arms compared with the placebo arms. While preliminary activity of taselisib plus fulvestrant was observed in this single-arm trial, further study in a larger, randomized cohort study is required to determine whether taselisib has additive efficacy when combined with fulvestrant, and differential antitumor activity in *PIK3CA*-mutated versus *PIK3CA*-MND tumors. The efficacy and safety of the combination of taselisib plus fulvestrant is currently being evaluated in postmenopausal women with ER-positive, HER2-negative locally advanced or metastatic breast cancer in the phase III randomized SANDPIPER study (ClinicalTrials.gov: NCT02340221; ref. 32). The phase III trial is recruiting a population that is enriched with patients who have *PIK3CA*-mutated tumors as determined prior to enrollment by the centrally assessed Cobas PIK3CA Mutation Test in tumor tissue (32). Taselisib dosing for SANDPIPER (4 mg tablet daily) had an exposure equivalent to the 6 mg daily capsule used in this phase II trial (33).

In conclusion, the results of this phase II trial demonstrated that the combination of taselisib plus fulvestrant was tolerable in postmenopausal women with locally advanced or metastatic HER2-negative, HR-positive breast cancer. Preliminary clinical activity was observed; however, further study in a larger, ongoing randomized phase III study will determine whether taselisib has additive efficacy when combined with fulvestrant in *PIK3CA*-mutated tumors.

Disclosure of Potential Conflicts of Interest

M.N. Dickler is an employee of Eli Lilly and is a consultant/advisory board member for Novartis and Roche. I.E. Krop reports receiving commercial research grants, speakers bureau honoraria from, and is a consultant/advisory board member for Genentech. P.L. Bedard reports receiving other commercial research support from Roche/Genentech. M.R. Patel reports receiving speakers bureau honoraria from Exelixis and Genentech. M. Oliveira reports receiving other commercial research support from Roche/Genentech and is a consultant/advisory board member for PUMA Biotechnology and Roche/Genentech. J. Baselga is a consultant/advisory board member for Genentech. No potential conflicts of interest were disclosed by the other authors.

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