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A randomized phase II non-comparative study of PF-04691502 and gedatolisib (PF-05212384) in patients with recurrent endometrial cancer

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HIGHLIGHTS

- Two PI3K/mTOR inhibitors were evaluated in recurrent endometrial cancer patients.
- Gedatolisib demonstrated activity in stathmin-low expressing endometrial cancers.
- Appropriate biomarkers to direct gedatolisib therapy were not confirmed in the study.

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ABSTRACT

Objective. PF-04691502 and gedatolisib (PF-05212384) are potent, dual PI3K/mTOR inhibitors. This phase II study (B1271004) was conducted in patients with recurrent endometrial cancer following platinum-containing chemotherapy. The primary endpoint was to assess clinical benefit response (complete or partial response, or stable disease for ≥16 weeks) following treatment with PF-04691502 or gedatolisib.

Methods. The main study consisted of four independent arms based on a Simon two-stage design. Patients were assigned to putative PI3K-basal (PF-04691502 or gedatolisib) or PI3K-activated (PF-04691502 or gedatolisib) arms based on stathmin-low or stathmin-high tumor expression, respectively. Japanese patients were also enrolled in a separate lead-in cohort.

Results. In stage 1 (main study), eighteen patients were randomized to PF-04691502 and 40 to gedatolisib. The two PF-04691502 arms were discontinued early due to unacceptable toxicity, including pneumonia and pneumonitis. The most common treatment-related adverse events associated with gedatolisib were nausea (53%), mucosal inflammation (50%), decreased appetite (40%), diarrhea (38%), fatigue (35%), and dysgeusia and vomiting (each 30%). Clinical benefit response rate was 53% (10/19) in the gedatolisib/stathmin-low arm and 26% (5/19) in the gedatolisib/stathmin-high arm. Safety profile and pharmacokinetic characteristics of both drugs in the Japanese lead-in cohort were comparable to the Western population.

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Conclusions. Gedatolisib administered by weekly intravenous infusion demonstrated acceptable tolerability and moderate activity in patients with recurrent endometrial cancer. PF-04691502 daily oral dosing was not well tolerated. Clinical benefit response criteria for proceeding to stage 2 were only met in the gedatolisib/stathmin-low arm. Stathmin-high expression did not correlate with greater treatment efficacy.
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1. Introduction

Endometrial cancer affects an estimated 52,630 women in the United States, accounting for >8000 deaths each year [1]. It is the most common gynecologic malignancy, and represents ~6% of all cancers in women [1,2]. The prognosis is poor for patients with recurrent disease or Stage IV endometrial cancer typically treated with a platinum-containing regimen. To date, chemotherapy regimens or currently available targeted agents have not improved clinical outcomes for patients with recurrent or metastatic disease and there is no standard of care for these patients, particularly after platinum-based chemotherapy [3–6].

Phosphatidylinositol 3-kinases (PI3K) constitute a lipid kinase family involved in the regulation of diverse cellular processes, including cell proliferation [7]. Activation of the PI3K pathway has been implicated in a wide variety of human cancers and is prevalent in both type 1 and 2 endometrial cancers. Pathway aberrations can present as mutations in *PIK3CA*, the gene encoding the catalytic subunit of PI3K, and they have been observed in ~30% of type 1 and 20% of type 2 endometrial cancers [8].

Stathmin has been considered a potential marker of PI3K pathway activation in solid tumors and its protein expression can be assessed by immunohistochemistry (IHC) [9–11]. Salvesen and colleagues reported that stathmin-high correlated with a PI3K signature, 3q26.32 chromosomal amplification, and PI3K protein overexpression in endometrial cancer specimens [10,11]. Trovik and colleagues reported that stathmin is readily detectable in endometrial cancer, with high levels of stathmin in 35% of endometrioid cancers and 50% to 55% of non-endometrioid curettage specimens by IHC [9].

PF-04691502 is a potent dual inhibitor of PI3K and mTOR [TOR complex (TORC)1 and TORC2] kinase activity intended for once-daily oral dosing [12]. In the first-in-patient study (B1271001), 37 patients with advanced solid tumors received PF-04691502 at doses ranging from 2 to 11 mg daily [13]. The maximum tolerated dose (MTD) was determined to be 8 mg. The most frequent treatment-related adverse events (AEs) at the MTD were fatigue (41%), decreased appetite (35%), nausea (35%), hyperglycemia (27%), rash (27%), and vomiting (27%). There was one treatment-related grade 4 AE of hypotension (8-mg dose level). One case each of acute respiratory distress syndrome and pneumonitis were reported, but not considered related to study treatment [13].

Gedatolisib (PF-05212384) is a potent inhibitor of PI3K and mTOR (TORC1 and TORC2) kinase activity intended for once-weekly intravenous infusion [14]. The safety and pharmacokinetic profile of gedatolisib were initially evaluated in patients with advanced solid tumors [15]. In that initial clinical study, 77 patients received gedatolisib at doses ranging from 10 to 319 mg. The MTD was determined to be 154 mg weekly. The most frequent treatment-related AEs at the MTD were mucosal inflammation (43%), nausea (41%), hyperglycemia (26%), and vomiting (24%). There were no grade 4 or higher treatment-related AEs [15].

The purpose of this phase II study was to evaluate single-agent treatment with PF-04691502 or gedatolisib in Western and Japanese patients with recurrent endometrial cancer. This study also tested the hypothesis that elevated stathmin expression in tumors, as a biomarker of PI3K/mTOR pathway activation, would predict response to treatment.

2. Patients and methods

2.1. Patients

Study B1271004 enrolled adult women with a confirmed diagnosis of recurrent endometrial cancer with disease progression following one or more platinum-containing regimen (adjuvant or metastatic setting). Patients also had to have at least one measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1, an Eastern Cooperative Oncology Group performance status of 0 or 1, and screening laboratory values within normal limits.

Patients were excluded if they had active central nervous system metastases or uncontrolled diabetes mellitus; or had received prior treatment with PI3K-, mTOR- or AKT-targeting agents, or >2 prior cytotoxic chemotherapy regimens (adjuvant or metastatic setting). Patients enrolled in the Japanese lead-in cohort (LIC) were not required to have measurable disease per RECIST.

Approval from the institutional review board or independent ethics committee of each participating center was required; all patients gave informed consent. The study followed the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. The study was sponsored by Pfizer and registered at ClinicalTrials.gov (NCT01420081).

2.2. Study design (main study)

Study B1271004 was an open-label, randomized, phase II, four-arm, optimal Simon two-stage, non-comparative, multicenter study designed to evaluate safety, efficacy, pharmacokinetics, and pharmacodynamics of PF-04691502 and gedatolisib. The planned starting doses for PF-04691502 and gedatolisib were oral 8 mg daily and intravenous 154 mg weekly, respectively, which were the MTDs established for these study drugs.

The primary endpoint was clinical benefit response (CBR), defined as complete response (CR), partial response (PR), or stable disease for ≥16 weeks. The study also included a separate LIC conducted at Japanese sites to explore safety and pharmacokinetics of each study drug in a Japanese patient population before including Japanese patients in the main study.

Eligible patients were stratified by putative PI3K pathway activation status (e.g. PI3K basal/stathmin-low or PI3K activated/stathmin-high status) and tumor histology (types 1 and 2), and randomly assigned within each stratum to receive either PF-04691502 or gedatolisib. Type 1 tumors included grade 1–2 endometrioid adenocarcinomas. Type 2 tumors included grade 3 endometrioid adenocarcinomas; serous, clear cell, and mucinous adenocarcinomas; squamous cell carcinomas; other mixed adenocarcinomas; and transitional, small cell, or undifferentiated carcinomas [7]. Putative PI3K pathway activation was characterized based on tumor stathmin expression by IHC. High (2+ and 3+) stathmin expression was hypothesized to be a marker of PI3K pathway activation and low (1+) expression to represent PI3K basal activity.

Stage 1 analysis for CBR and additional DNA- and protein-based biomarkers of PI3K pathway activation (e.g. *PIK3CA* amplification, PTEN loss) were planned after 20 response-evaluable patients had been enrolled and were assessable for CBR in each study arm.

2.3. Study design (LIC)

The LIC was designed to assess the tolerability and pharmacokinetics of PF-04691502 and gedatolisib in Japanese patients in order to allow them to be enrolled in the main study. In the LIC, patients received either PF-04691502 or gedatolisib at an oral starting dose of 4 mg daily or intravenous 89 mg weekly, respectively, which were both below the MTD established in non-Japanese patients in previous phase I trials (B1271001 and B2151001). Following one cycle of dosing, if no first-cycle unacceptable toxicity or one was observed among three patients at each dose level, the Japanese sites would join the main study. If two or more patients experienced unacceptable toxicity, the LIC would be discontinued and patients in Japan would not join the main study for that agent.

Unacceptable toxicity criteria for the LIC followed the dose reduction criteria for the main study and included grade 4 neutropenia ≥ 7 days, febrile neutropenia, or grade 4 thrombocytopenia; grade ≥ 3 gastrointestinal toxicity despite optimal treatment; grade ≥ 3 unmanageable hyperglycemia; mean corrected QT interval ≥ 500 ms; clinically significant interstitial lung disease or other respiratory toxicity interfering with daily living; and any other grade ≥ 3 toxicity or treatment delay of ≥2 weeks due to study drug–related toxicity.

2.4. Study assessments

Safety was assessed by physical examination, laboratory tests, and AE reporting. AEs were graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Tumor assessments were performed for all patients at screening, week 8, and every 8 weeks thereafter. Response was assessed by the investigator, based on RECIST version 1.1. PR and CR were confirmed by a repeat assessment after ≥4 weeks.

All patients were required to provide an archival or fresh tumor sample for biomarker analysis during the screening period. Formalin-fixed paraffin-embedded (FFPE) tumor tissues were analyzed for stathmin and PTEN expression status, *PIK3CA* amplification, and *KRAS* mutation status. Stathmin and PTEN protein expression were assessed in FFPE tumor tissues using IHC staining at Quintiles Inc. (Marietta, GA, USA). Stathmin IHC results were evaluated by a pathologist in central review and reported as H-scores based on staining intensity (1+, 2+, 3+), by CLIA [Clinical Laboratory Improvement Amendments] standards. Following initial screening, samples from all enrolled patients were re-scored in the central laboratory according to an updated threshold. PTEN IHC results were analyzed and reported as a manual pathologist score (0, 1+, 2+, 3+). *PIK3CA* gene was detected in FFPE tissues using a fluorescence in situ hybridization (FISH) assay at Quintiles Inc. The total number of *PIK3CA* gene copies was analyzed. A score > 2.2 was considered amplified. *KRAS* mutation analysis was performed using the Qiagen KRAS RGQ PCR assay (Qiagen, Manchester, UK), able to detect seven different *KRAS* single-nucleotide polymorphism mutations (G12A, G12D, G12R, G12C, G12S, G12V, and G13D) in DNA from FFPE tissue samples. Further biomarker analyses will be published in a future manuscript.

Blood was collected for pharmacokinetic sampling of gedatolisib on day 1 of cycle 1 at 0 h (pre-dose) and at 0.5 (after end of infusion), 1, 2, 4, 6, 24, 72, and 120 h; and pre-dose on day 1 of subsequent cycles, through cycle 4. Plasma samples were analyzed for gedatolisib concentrations at inVentiv Health Clinical, Inc. (Princeton, NJ, USA) using a validated analytical assay.

2.5. Statistical analyses

The optimal Simon two-stage design based on CBR was used for each of the four arms independently. For each arm, the study tested the null hypothesis, with a one-sided 10% significance level, that the CBR rate was ≤35% versus the alternative hypothesis that the CBR rate was ≥50%. Fifty-eight response-evaluable patients were required in each study arm to provide 80% power to reject the null hypothesis when the true response rate was 50%. Further details on progression to stage 2 are provided in Supplementary Text. The CBR rate was calculated as the proportion of patients with confirmed CR, PR, or stable disease for ≥16 weeks (from day 1 of cycle 1 to treatment failure) relative to the total number of response-evaluable patients.

Secondary efficacy endpoints included objective response rate (ORR), defined as the proportion of patients with CR and PR; progression-free survival (PFS); and overall survival. Due to early study termination, survival follow-up was discontinued. Response rates were presented with 95% confidence intervals (CIs). Time-to-event endpoints were analyzed using the Kaplan–Meier method; median values and corresponding 95% CIs were calculated. PFS was calculated from administration of first study drug dose to first documentation of recurrence/progression or death due to any cause.

3. Results

3.1. Patients (main study)

A total of 58 patients with recurrent endometrial cancer were enrolled. Fourteen patients received 8 mg and four patients received 6 mg as the starting oral dose of PF-04691502. Forty patients received 154 mg weekly as the starting intravenous dose of gedatolisib. Thirty-eight patients treated with gedatolisib and 15 treated with PF-04691502 were evaluable for efficacy (Fig. 1). Patient baseline demographic and disease characteristics are shown in Table 1.

As of this analysis, all patients treated with PF-04691502 (n = 18) and 93% (n = 37) of patients treated with gedatolisib had discontinued study treatment. Patients discontinued PF-04,691,502 due to disease progression (39%), AEs (56%; e.g., treatment-related urticaria, diarrhea, pneumonia, pneumonitis, stomatitis, spontaneous pneumothorax, and hyperglycemia), or death (6%). Patients discontinued gedatolisib due to disease progression (75%) and AEs (15%; e.g. treatment-related fatigue, pulmonary embolism, and infusion reaction; and non-treatment-related new primary gastric cancer, acute renal failure, and back pain/withdrawn consent). Median treatment duration and total dose received are summarized for both agents in Supplementary Table S1.

3.2. Safety and tolerability

Treatment-related AEs of any grade observed in ≥20% of patients treated with PF-04691502 (n = 18) included diarrhea (67%); fatigue (61%); hyperglycemia (56%); nausea (56%); decreased appetite (39%); dry mouth, hypokalemia, mucosal inflammation, and stomatitis (each 33%); and dysgeusia, dyspnea, pneumonitis, and rash (each 22%). The most common grade 3–4 treatment-related AEs in patients treated with PF-04691502 were hyperglycemia (28%); stomatitis (22%); and diarrhea, pneumonia, and pneumonitis (each 17%; Table 2). Treatment-related serious AEs (SAEs) observed in more than one patient included grade 2–3 pneumonitis (n = 4), grade 3–4 pneumonia (n = 3), grade 3 diarrhea (n = 3), and grade 3–4 stomatitis (n = 2). One patient experienced a grade 4 SAE of hyperglycemia.

Due to the high incidence of pneumonia and pneumonitis, the starting dose of PF-04691502 was reduced from 8 (n = 14) to 6 mg (n = 4) in August 2012, ~7 months after study initiation. Dose reductions were required in 14 (78%) patients treated with PF-04691502; two (11%) patients experienced a dose delay. Nine deaths occurred in patients treated with PF-04,691,502 during the course of the study. Of these 9 deaths, one was due to treatment-related aspiration pneumonia within 28 days of final dose and eight during the follow-up period were due to disease progression. Enrollment to the PF-04691502 study arms was stopped in October 2012, after review of safety data from this and another phase IB/II study (B1271003).

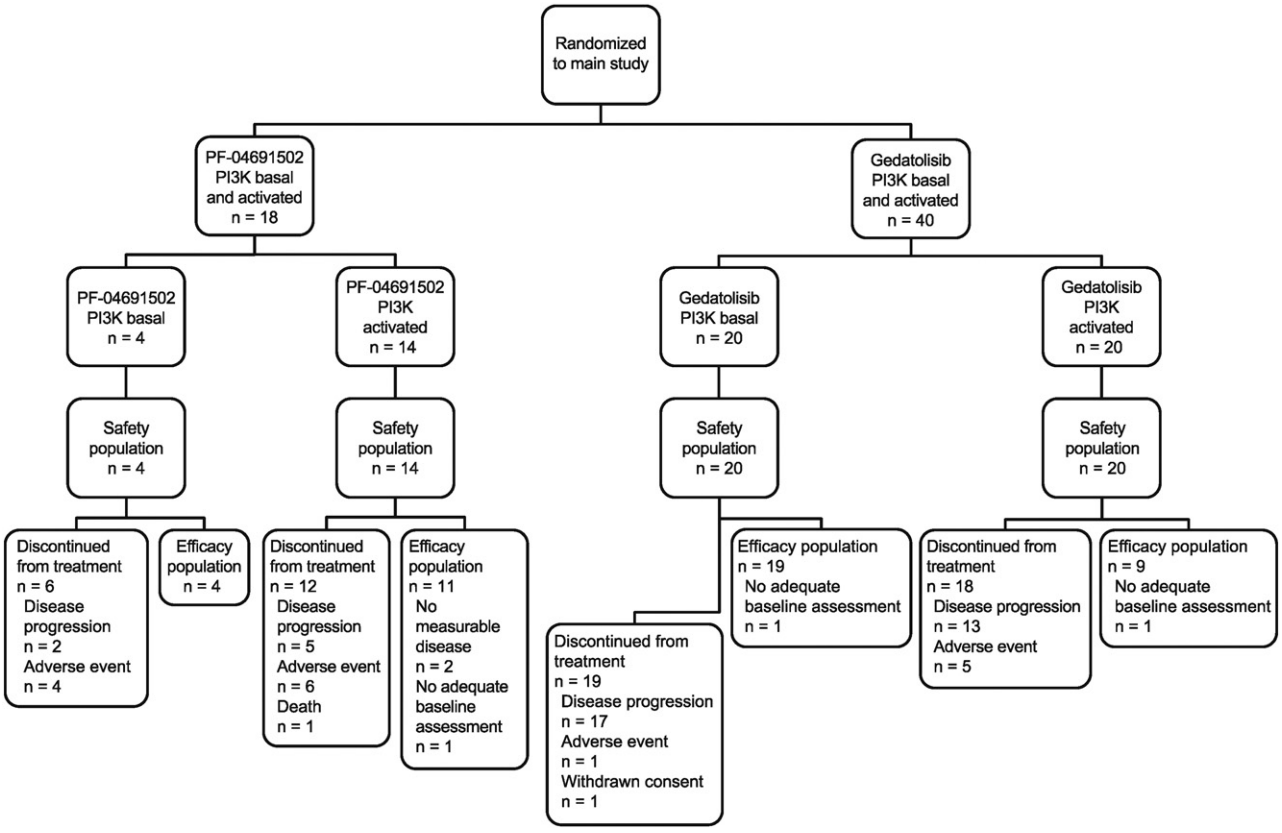

Fig. 1. Flow of patients through the main study. All patients in the main study were evaluable for safety. One patient treated with PF-04691502 and two treated with gedatolisib were not evaluable for efficacy due to lack of adequate baseline assessment. Two patients treated with PF-04691502 were not evaluable for efficacy due to lack of measurable disease.

In the gedatolisib arms (n = 40), treatment-related AEs of any grade observed in ≥20% of patients included nausea (53%), mucosal inflammation (50%), decreased appetite (40%), diarrhea (38%), fatigue (35%), dysgeusia and vomiting (each 30%), rash (23%), and stomatitis (20%). Asthenia, dry mouth, and hyperglycemia were each noted in 18% of patients. The most common grade 3–4 treatment-related AEs in patients treated with gedatolisib were fatigue (10%), hypertension (8%), and asthenia and pulmonary embolism (each 5%; Table 2). Treatment-related SAEs were reported for three patients; the events were grade 3–4 pulmonary embolism (n = 2) and grade 2 chills (n = 1).

Dose reductions were required in 24 (60%) patients treated with gedatolisib; 18 (45%) patients experienced a dose delay. Nineteen patients receiving gedatolisib died during the course of the study. Two deaths due to disease progression occurred within 28 days of final dose. Of the 17 deaths that occurred during the follow-up period, 16 were due to disease progression and one to other, unspecified reason.

3.3. Antitumor activity (main study)

Antitumor activity is only reported for patients treated with gedatolisib, as the PF-04691502 arms were stopped early for safety reasons. Best overall responses based on investigator review of radiographic and clinical data are summarized in Table 3. Data are presented for patients as randomized; however, one patient treated with gedatolisib had stathmin status changed from high to low after randomization, following a re-evaluation in central review of the threshold used to distinguish high versus low expression.

Overall, 15 (40%; 95% CI: 24–57%) patients treated with gedatolisib experienced CBR: 10 (53%; 95% CI: 29–76%) patients randomized to the gedatolisib/stathmin-low arm and five (26%; 95% CI: 9–51%) patients randomized to the gedatolisib/stathmin-high arm. The ORR for all gedatolisib-treated patients was 16% (95% CI: 6–31%); 16% (95% CI: 3–40%) for patients in the stathmin-low arm and 16% (95% CI: 3–40%) in the stathmin-high arm, including one patient with CR. An additional 37% and 11% of patients in the gedatolisib/stathmin-low and -high arms, respectively, achieved stable disease and maintained it for ≥16 weeks (Table 3 and Fig. 2).

Median PFS was 112 (95% CI: 59–167) days and 89 (95% CI: 56–172) days in the gedatolisib/stathmin-low and -high arms, respectively. The overall median PFS for all patients treated with gedatolisib was 108 (95% CI: 62–149) days. In the gedatolisib/stathmin low arm, four of the 19 patients had PFS beyond 6 months ranging from 226 to 336 days. In the gedatolisib/stathmin high arm, four of the 19 patients had PFS beyond 6 months ranging from 220 to 404 days.

3.4. Japanese LIC

In the Japanese LIC, three patients received PF-04691502 4 mg daily and six patients received gedatolisib 89 mg (n = 3) or 154 mg (n = 3) weekly. Baseline demographic and disease characteristics are shown in Table 1. One patient treated with PF-04691502 discontinued treatment due to disease progression and two due to AEs (pneumonia and rash). All six patients treated with gedatolisib discontinued treatment due to disease progression or relapse (n = 5) or other, non-AE-related reason (n = 1). Median treatment durations are summarized for both agents in Supplementary Table S1.

Treatment-related AEs of any grade observed in more than one patient treated with PF-04691502 (n = 3) included rash (n = 3), hyperglycemia (n = 2), and malaise (n = 2). Rash was the only grade 3–4 AE occurring in more than one patient in this group (n = 2). Treatment-related SAEs were reported in one patient, including *Pneumocystis jirovecii* pneumonia and lymphopenia. Dose reductions were required in all three PF-04691502-treated patients and dose

Table 1
Baseline patient characteristics.

Parameter	Main study[a]						Japanese lead-in cohort[a]			
	PF-502 (putative PI3K basal) n = 4	PF-502 (putative PI3K activated) n = 14	PF-502 (putative PI3K activated + basal) n = 18	Gedatolisib (putative PI3K basal) n = 20	Gedatolisib (putative PI3K activated) n = 20	Gedatolisib (putative PI3K activated + basal) n = 40	PF-502 (4 mg) n = 3	Gedatolisib (89 mg) n = 3	Gedatolisib (154 mg) n = 3	Gedatolisib (89 mg + 154 mg) n = 6
Mean age, years (range)	59.8 (54–65)	65.1 (52–85)	63.9 (52–85)	65.7 (58–82)	69.6 (50–80)	67.6 (50–82)	64.3 (61–70)	56.7 (40–69)	62.7 (57–71)	59.7 (40–71)
<65 years, n (%)	3 (75)	7 (50)	10 (56)	9 (45)	4 (20)	13 (33)	2 (67)	2 (67)	2 (67)	4 (67)
≥65 years, n (%)	1 (25)	7 (50)	8 (44)	11 (55)	16 (80)	27 (68)	1 (33)	1 (33)	1 (33)	2 (33)
Race, n (%)										
White	3 (75)	10 (71)	13 (72)	17 (85)	16 (80)	33 (83)	0	0	0	0
Black	0	0	0	0	1 (5)	1 (3)	0	0	0	0
Asian	1 (25)	2 (14)	3 (17)	3 (15)	1 (5)	4 (10)	3 (100)	3 (100)	3 (100)	6 (100)
Japanese	0	0	0	2 (10)	1 (5)	3 (8)	3 (100)	3 (100)	3 (100)	6 (100)
Other	1 (25)	2 (14)	3 (17)	1 (5)	0	1 (3)	0	0	0	0
Other	0	2 (14)	2 (11)	0	2 (10)	2 (5)	0	0	0	0
ECOG PS, n (%)										
0	2 (50)	8 (57)	10 (56)	9 (45)	10 (50)	19 (48)	2 (67)	1 (33)	2 (67)	3 (50)
1	2 (50)	6 (43)	8 (44)	10 (50)	10 (50)	20 (50)	0	2 (67)	1 (33)	3 (50)
Not evaluated	0	0	0	1 (5)	0	1 (3)	1 (33)	0	0	0
Histology										
Type 1	2 (50)	8 (57)	10 (56)	14 (70)	10 (50)	24 (60)	2 (67)	2 (67)	2 (67)	4 (67)
Type 2	2 (50)	6 (43)	8 (44)	6 (30)	10 (50)	16 (40)	1 (33)	1 (33)	1 (33)	2 (33)
Prior radiation therapy, n (%)	3 (75)	9 (64)	12 (67)	12 (60)	9 (45)	21 (53)	1 (33)	0	0	0
Prior systemic therapy, n (%)										
1	2 (50)	8 (57)	10 (56)	12 (60)	9 (45)	21 (53)	3 (100)	1 (33)	0	1 (17)
2	2 (50)	6 (43)	8 (44)	6 (30)	9 (45)	15 (38)	0	1 (33)	1 (33)	2 (33)
3	0	0	0	2 (10)	1 (5)	3 (8)[b]	0	1 (33)	2 (67)	3 (50)[b]
4	0	0	0	0	1 (5)	1 (3)[b]	0	0	0	0

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PF-502, PF-04691502; PI3K, phosphatidylinositol 3-kinases.
[a] Percentages for subcategories may not add to 100% due to rounding.
[b] One patient had received 3 prior cytotoxic chemotherapy regimens and was considered a protocol violation. The other patients with >2 prior regimens had received non-cytotoxic agents (hormonal treatments) in prior regimens and thus they were eligible for the study.

delays occurred in one (33%) patient. No deaths occurred on study or during follow-up in patients treated with PF-04691502.

Treatment-related AEs of any grade observed in more than one patient treated with gedatolisib (n = 6) included nausea and stomatitis (n = 6 each); decreased appetite, malaise, oropharyngeal pain, pruritus, and rash (n = 3 each); and abdominal pain, cheilitis, conjunctivitis, paronychia, and vomiting (n = 2 each). Anemia and maculopapular rash were the only grade 3–4 AEs occurring in this group (n = 1 each). No treatment-related SAEs occurred in gedatolisib-treated patients (Table 2). Dose reductions were required in four of six (67%) gedatolisib-treated patients and dose delays occurred in four of six (67%) patients. Two deaths due to disease progression occurred during follow-up in patients treated with gedatolisib.

Patients treated with gedatolisib in the LIC were not evaluable for efficacy, as they were not required to have measurable lesions. As none of the patients treated at the 89-mg dose experienced unacceptable toxicities and the pharmacokinetic profile of gedatolisib in the Japanese LIC was comparable to the Western population, three patients received the 154-mg dose. Since also the patients treated at 154 mg did not experience any unacceptable toxicities and had comparable

Table 2
Treatment-related grade 3–4 AEs in ≥1 patient in any cohort (safety population[a]).

Event, n (%)	Main study						Japanese lead-in cohort			
	PF-502 (putative PI3K basal) n = 6	PF-502 (putative PI3K activated) n = 12	PF-502 (putative PI3K activated + basal) n = 18	Gedatolisib (putative PI3K basal) n = 21	Gedatolisib (putative PI3K activated) n = 19	Gedatolisib (putative PI3K activated + basal) n = 40	PF-502 (4 mg) n = 3	Gedatolisib (89 mg) n = 3	Gedatolisib (154 mg) n = 3	Gedatolisib (89 mg + 154 mg) n = 6
Any grade 3/4 AE	5 (83)	11 (92)	16 (89)	4 (19)	9 (47)	13 (33)	3 (100)	0	1 (33)	1 (17)
Asthenia	0	0	0	1 (5)	1 (5)	2 (5)	0	0	0	0
Diarrhea	1 (17)	2 (17)	3 (17)	0	1 (5)	1 (3)	0	0	0	0
Dyspnea	0	2 (17)	2 (11)	0	0	0	0	0	0	0
Fatigue	0	2 (17)	2 (11)	0	4 (21)	4 (10)	1 (33)	0	0	0
Hyperglycemia	0	5 (42)	5 (28)	0	0	0	0	0	0	0
Hypertension	0	0	0	3 (14)	0	3 (8)	0	0	0	0
Hypokalemia	1 (17)	1 (8)	2 (11)	0	1 (5)	1 (3)	0	0	0	0
Pneumonia	1 (17)	2 (17)	3 (17)	0	0	0	1 (33)	0	0	0
Pneumonitis	2 (33)	1 (8)	3 (17)	0	0	0	0	0	0	0
Pulmonary embolism	0	0	0	0	2 (11)	2 (5)	0	0	0	0
Rash	1 (17)	1 (8)	2 (11)	0	0	0	2 (67)	0	1 (33)	1 (17)
Stomatitis	1 (17)	3 (25)	4 (22)	0	1 (5)	1 (3)	0	0	0	0

Abbreviations: AE, adverse event; PF-502, PF-04691502; PI3K, phosphatidylinositol 3-kinases.
[a] Actual treatment group, by stathmin status, not per randomization.

Table 3
Best overall response to study treatment (main study evaluable population – randomized treatment group[a]).

Response	Gedatolisib (putative PI3K basal; stathmin low) n = 19	Gedatolisib (putative PI3K activated; stathmin high) n = 19	Gedatolisib (putative PI3K basal + activated) n = 38
Objective response[a], n (%)	3 (16)	3 (16)	6 (16)
95% CI	3–40	3–40	6–31
CR	0	1 (5)	1 (3)
PR	3 (16)	2 (11)	5 (13)
Stable disease, n (%)			
<16 weeks	3 (16)	3 (16)	6 (16)
≥16 weeks	7 (37)	2 (11)	9 (24)
CBR[b], n (%)	10 (53)	5 (26)	15 (40)
95% CI	29–76	9–51	24–57
Progressive disease, n (%)	6 (32)	8 (42)	14 (37)

Abbreviations: CBR, clinical benefit response; CI, confidence interval; CR, complete response; PI3K, phosphatidylinositol 3-kinases; PR, partial response.
[a] Objective response includes CR and PR.
[b] CBR includes CR, PR, and stable disease for ≥16 weeks.

pharmacokinetics, it was determined that Japanese patients could be randomized in the main study with the Western patients.

3.5. Pharmacogenomics, pharmacodynamics, and pharmacokinetics

Results of pharmacogenomic analyses performed in this study are summarized by best overall treatment response in Table 4. Pharmacodynamic and pharmacokinetic results are only reported for patients treated with gedatolisib, as the PF-04691502 arms were stopped early for safety reasons. Changes in glucose homeostasis consistent with PI3K blockade were observed following administration of gedatolisib. Increases in blood glucose levels were observed on day 15 of cycle 1, generally peaking in cycle 2 (gedatolisib/putative PI3K-basal arm) and cycle 3 (gedatolisib/putative PI3K-activated arm). Corresponding changes in insulin levels also were noted, lasting through cycle 4 (data not shown).

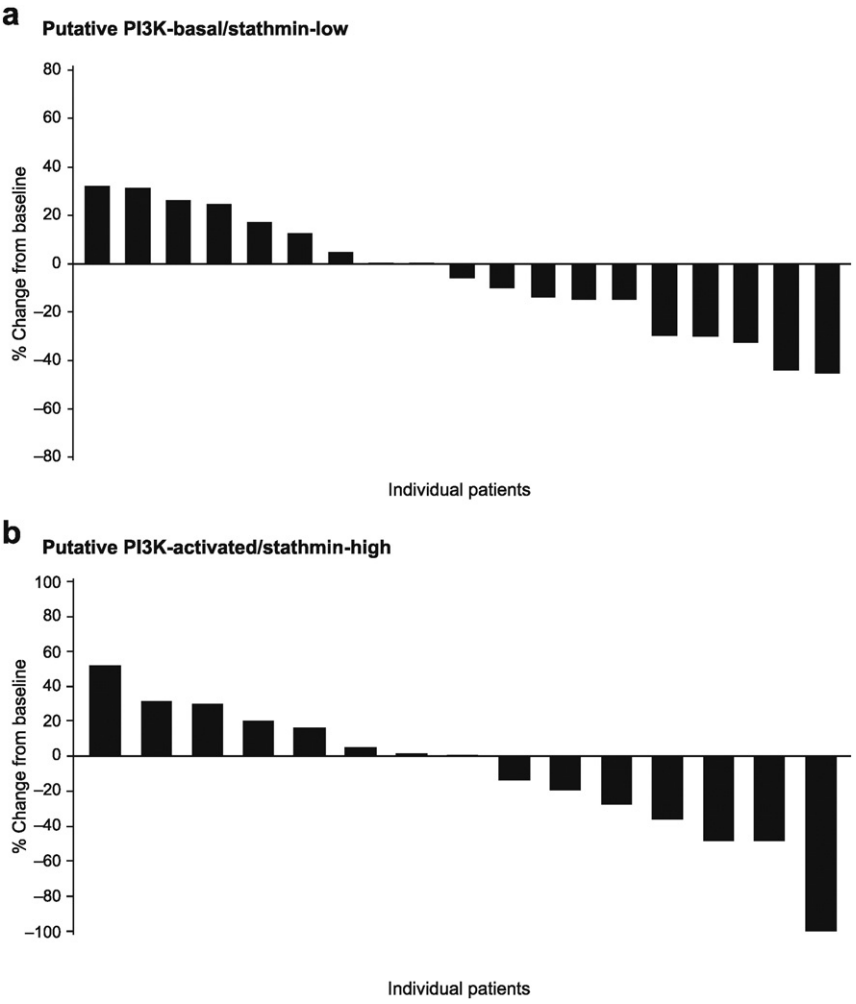

Fig. 2. Waterfall plot of best tumor response in patients treated with gedatolisib in (a) the putative PI3K-basal/stathmin-low arm and (b) the putative PI3K-activated/stathmin-high arm (per protocol analysis set, randomized treatment group). Maximum change (%) = (smallest tumor size after baseline − baseline tumor size) / baseline tumor size. Only patients with target lesion measurements after baseline were included in this analysis.

The pharmacokinetic profiles of gedatolisib following a single, intravenous 154-mg dose (day 1 of cycle 1) were comparable in the putative PI3K-basal and PI3K-activated arms (Supplementary Fig. S1). In addition, the pharmacokinetic profiles observed with gedatolisib in Japanese patients were consistent with those observed in Western patients, with the exception of one patient who had an approximately two-fold higher area under the serum concentration–time curve from 0 extrapolated to infinity (AUC_{inf}) compared with the other two patients treated in the 154-mg dose group. The terminal elimination half-life of gedatolisib was determined to be approximately 34 to 35 h and the systemic clearance 10 L/h (Supplementary Table S2).

4. Discussion

This phase II study investigated the safety and efficacy of two different PI3K/mTOR inhibitors, PF-04691502 and gedatolisib, in patients with recurrent endometrial cancer, and evaluated their safety and pharmacokinetics in Japanese patients.

PF-04691502 was administered orally on a daily basis. The starting dose was based on phase I studies previously conducted in adult patients with advanced solid tumors, which included men and women. Four of the 18 patients who received PF-04691502 in this study developed treatment-related pneumonitis. Non-infectious pneumonitis is a known class effect for mTOR inhibitors, which has been observed in ~30% of treated patients in retrospective studies [16–18]. Further, grade 3 skin toxicity was noted in 50% (n = 7) of treated patients in a phase IB/II (B1271003) study of PF-04691502 plus letrozole conducted in 14 women with endocrine receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer [19]. The severity of these pulmonary and skin toxicities contributed to the decision to discontinue patient enrollment to the PF-04691502 arms of this study and, subsequently, to terminate development of this molecule.

Gedatolisib is a potent dual PI3K/mTOR inhibitor administered intravenously weekly. The rate of grade 3–4 AEs considered by the investigators related to treatment with gedatolisib in this study was generally comparable to or lower than that observed with other PI3K, mTOR, or dual PI3K/mTOR inhibitors such as apitolisib (GDC-0980) or pilarasilib (XL-147) [20–22]. Grade 3–4 treatment-related AEs reported for apitolisib included hyperglycemia (46%), rash (30%), colitis (5%), and pneumonitis (4%); and for pilarasilib, rash (9%), diarrhea (4.5%), and increased alanine aminotransferase levels (4.5%) [21–22].

The 16% ORR observed with gedatolisib in each patient group studied was slightly higher than the ORRs reported with other dual inhibitors in similar patient populations [21–22]. The median PFS (108 days; 95% CI: 62–149) observed with gedatolisib was comparable to that reported with other agents in this setting [21–22]. An unconfirmed ORR of 9% and median PFS of 3.5 (95% CI: 2.7–3.7) months were observed for apitolisib [21]. A 6% ORR was reported for pilarasilib in patients who had received one prior regimen and 0% in those with two prior regimens. PFS > 6 months for pilarasilib-treated patients was 11.9%, mostly in the one-prior-regimen group [22]. Additionally, single-agent studies of other mTOR or PI3K inhibitors in second- or third-line recurrent endometrial cancer showed low response rates, with no CRs and few PRs (0–9%), along with stable disease lasting ≥8–12 weeks in generally <35% of patients [20].

The changes observed in this study in metabolic biomarkers indicate that gedatolisib affected glucose transport and/or metabolism, resulting in increased glucose levels and providing evidence of pharmacodynamics effects of gedatolisib in treated patients.

Prior reports had suggested that stathmin protein levels may correlate with deregulated PI3K signaling in cancers of the endometrium, breast, and other organs [9–11], and therefore response to PI3K inhibitors such as gedatolisib may be predicted by observation of higher stathmin protein levels. However, stathmin protein and RNA profiles do not always correlate precisely with genetic alterations in PI3K components or response to treatment. Further, different types of pathway alterations may promote different PI3K activation levels or have different effects on overall signaling [11]. The current study was designed to test the hypothesis that patients with high stathmin protein IHC scores in FFPE tumor tissues, as a biomarker for PI3K activation, would respond better to PI3K/mTOR inhibition. The study results do not support this hypothesis, suggesting that stathmin protein levels may not be correlated with tumor dependence on the PI3K pathway. It is recognized that the reliability of IHC scoring might have been limited by its subjective nature (pathologist assessment of staining intensity in tumor tissues). However, when stathmin expression re-scoring took place midway through the study, only one patient receiving gedatolisib required re-categorization for stathmin status.

This study demonstrated that gedatolisib has a manageable toxicity profile and is active as a single agent in patients with advanced endometrial cancer. Nonetheless, this study was terminated early, before patient enrollment in stage 2, following a strategic decision based on the lack of sufficient efficacy of gedatolisib in patients with stathmin-high/putative PI3K–activated tumors, which disproved the initial hypothesis.

Table 4
Genetic biomarker analysis and best overall response in evaluable patients treated with gedatolisib.

Parameter	Best overall response	Gedatolisib (putative PI3K basal; stathmin low) n = 20	Gedatolisib (putative PI3K activated; stathmin high) n = 18	Gedatolisib (putative PI3K activated + basal) n = 38
KRAS mutation	n	20	17	37
Positive, n (%)	PR	2 (10)	0	2 (5)
	PD	2 (10)	0	2 (5)
	Indeterminate	0	1 (6)	1 (3)
Negative, n (%)	CR	0	1 (6)	1 (3)
	PR	1 (5)	2 (11)	3 (8)
	Stable disease ≥ 16 weeks	8 (40)	0	8 (21)
	Stable disease < 16 weeks	3 (15)	3 (17)	6 (16)
	PD	4 (20)	8 (44)	12 (32)
	Indeterminate	0	2 (11)	2 (5)
PIK3CA amplification	n	11	14	25
Amplified, n (%)	PD	0	1 (6)	1 (3)
Non-amplified, n (%)	CR	0	1 (6)	1 (3)
	PR	2 (10)	1 (6)	3 (8)
	Stable disease ≥ 16 weeks	3 (15)	1 (6)	4 (11)
	Stable disease < 16 weeks	1 (5)	3 (17)	4 (11)
	PD	5 (25)	6 (33)	11 (29)
	Indeterminate	0	1 (6)	1 (3)

Abbreviation: Cr, complete response; PD, progressive disease; PI3K, phosphatidylinositol 3-kinases; PR, partial response.

Gedatolisib appears to have activity in stathmin-low cancers and may be of benefit in selected patient populations; an appropriate biomarker to direct gedatolisib therapy was not confirmed in this study.

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Conflict of interest statement

JMdC, MB, MG, AGM, SL, CM, KM, AP, and AO have nothing to disclose related to this study. KF received research funding from Pfizer and honoraria from Chugai, Zeria, Nippon Kayaku, Kyowa, Eisai, Pfizer, Sanofi, and Kaken. CD, AG, BH, KP, MS, and JV were Pfizer employees during this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2016.04.019.

References

[1] American Cancer Society, Cancer Facts & Figures 2014, American Cancer Society, Atlanta, GA, 2014 (available from: http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf).
[2] American Cancer Society, Global Cancer Facts & Figures, second ed. American Cancer Society, Atlanta, GA, 2011 (available from: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-027766.pdf).
[3] K.C. Hancock, R.S. Freedman, C.L. Edwards, F.N. Rutledge, Use of cisplatin, doxorubicin, and cyclophosphamide to treat advanced and recurrent adenocarcinoma of the endometrium, Cancer Treat. Rep. 70 (1986) 789–791.
[4] J.C. Seski, C.L. Edwards, J. Herson, F.N. Rutledge, Cisplatin chemotherapy for disseminated endometrial cancer, Obstet. Gynecol. 59 (1982) 225–228.
[5] K.J. Dedes, D. Wetterskog, A. Ashworth, S.B. Kaye, J.S. Reis-Filho, Emerging therapeutic targets in endometrial cancer, Nat. Rev. Clin. Oncol. 8 (2011) 261–271.
[6] A. Bregar, K. Robison, D.S. Dizon, Update on the chemotherapeutic management of endometrial cancer, Clin. Adv. Hematol. 12 (2014) 659–665.
[7] D.A. Fruman, D.E. Meyers, L.C. Cantley, Phosphoinositide kinases, Annu. Rev. Biochem. 67 (1998) 481–507.
[8] A. Bardelli, V.E. Velculescu, Mutational analysis of gene families in human cancer, Curr. Opin. Genet. Dev. 15 (2005) 5–12.
[9] J. Trovik, E. Wik, I.M. Stefansson, J. Marcickiewicz, S. Tingulstad, A.C. Staff, et al., MoMaTec Study Group, Stathmin overexpression identifies high-risk patients and lymph node metastasis in endometrial cancer, Clin. Cancer Res. 17 (2011) 3368–3377.
[10] H.B. Salvesen, S.L. Carter, M. Mannelqvist, A. Dutt, G. Getz, I.M. Stefansson, et al., Integrated genomic profiling of endometrial carcinoma associates aggressive tumors with indicators of PI3 kinase activation, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 4834–4839.
[11] K. Stemke-Hale, A.M. Gonzalez-Angulo, A. Lluch, R.M. Neve, W.L. Kuo, M. Davies, et al., An integrative genomic and proteomic analysis of *PIK3CA*, *PTEN*, and *AKT* mutations in breast cancer, Cancer Res. 68 (2008) 6084–6091.
[12] J. Yuan, P.P. Mehta, M.J. Yin, S. Sun, A. Zou, J. Chen, et al., PF-04691502, a potent and selective oral inhibitor of PI3K and mTOR kinases with antitumor activity, Mol. Cancer Ther. 10 (2011) 2189–2199.
[13] C.D. Britten, A.A. Adjei, R. Millham, B.E. Houk, G. Borzillo, K. Pierce, et al., Phase I study of PF-04691502, a small-molecule, oral, dual inhibitor of PI3K and mTOR, in patients with advanced cancer, Investig. New Drugs 32 (2014) 510–517.
[14] R. Mallon, L.R. Feldberg, J. Lucas, I. Chaudhary, C. Dehnhardt, E.D. Santos, et al., Antitumor efficacy of PKI-587, a highly potent dual PI3K/mTOR kinase inhibitor, Clin. Cancer Res. 17 (2011) 3193–3203.
[15] G.I. Shapiro, K.M. Bell-McGuinn, J.R. Molina, J. Bendell, J. Spicer, E.L. Kwak, et al., First-in-human study of PF-05212384 (PKI-587), a small-molecule, intravenous, dual inhibitor of PI3K and mTOR in patients with advanced cancer, Clin. Cancer Res. 21 (2015) 1888–1895.
[16] D.A. Dabydeen, J.P. Jagannathan, N. Ramaiya, K. Krajewski, F.A. Schutz, D.C. Cho, et al., Pneumonitis associated with mTOR inhibitors therapy in patients with metastatic renal cell carcinoma: incidence, radiographic findings and correlation with clinical outcome, Eur. J. Cancer 48 (2012) 1519–1524.
[17] B.J. Atkinson, D.H. Cauley, C. Ng, R.E. Millikan, L. Xiao, P. Corn, et al., Mammalian target of rapamycin (mTOR) inhibitor-associated non-infectious pneumonitis in patients with renal cell cancer: predictors, management, and outcomes, BJU Int. 113 (2014) 376–382.
[18] S. Chia, S. Gandhi, A.A. Joy, S. Edwards, M. Gorr, S. Hopkins, et al., Novel agents and associated toxicities of inhibitors of the pi3k/Akt/mTOR pathway for the treatment of breast cancer, Curr. Oncol. 22 (2015) 33–48.
[19] Canon JL, Saura C, Oliveira M, de Braud F, Bergh J, Einbeigi Z, et al. Phase Ib/II study of an oral PI3K/mTOR inhibitor plus letrozole compared with letrozole in preoperative setting in patients with estrogen receptor-positive, HER2-negative early breast cancer (BC): phase Ib preliminary data. San Antonio Breast Cancer Symposium; December 4–8, 2012; San Antonio, TX. Abstract OT2-3-02.
[20] A.P. Myers, New strategies in endometrial cancer: targeting the PI3K/mTOR pathway—the devil is in the details, Clin. Cancer Res. 19 (2013) 5264–5274.
[21] V. Makker, F.O. Recio, L. Ma, U. Matulonis, J. O'Hara Lauchle, H. Parmar, et al., PIM4972g: MAGGIE Investigators, Phase II trial of GDC-0980 (dual PI3K/mTOR inhibitor) in patients with advanced endometrial carcinoma: final study results, J. Clin. Oncol. 32 (15 Suppl.) (2014) 5513.
[22] U. Matulonis, I. Vergote, F. Backes, L.P. Martin, S. McMeekin, M. Birrer, et al., Phase II study of the PI3K inhibitor pilaralisib (SAR245408; XL147) in patients with advanced or recurrent endometrial carcinoma, Gynecol. Oncol. 136 (2015) 246–253.

Del Campo et al. SUPPLEMENTARY DATA

Supplementary Text: Methods

Supplementary Table S1. Treatment summary (safety population)

Supplementary Table S2. Summary of gedatolisib pharmacokinetic characteristics (day 1, cycle 1)

Supplementary Fig. S1. Median gedatolisib concentration-time profiles by treatment arm (cycle 1)

Supplementary Text: Methods

Statistical design

Decision rules that applied at the end of stages 1 and 2 were as follows: if ≥8 clinical benefit responders were observed among 20 (40%) response-evaluable patients at the end of stage 1, then that arm would proceed to stage 2. If there were ≥25 clinical benefit responders among 58 (43%) response-evaluable patients at the end of stage 2, then the null hypothesis would be rejected, and it would be concluded that the primary endpoint had been achieved. To ensure 58 response-evaluable patients, each arm that entered stage 2 was planned to enroll a total of 63 patients. In the event that exactly 20 patients were not evaluable, additional decision criteria were to be applied.

Supplementary Table S1. Treatment summary (safety population)

	Main study						Japanese lead-in cohort			
Parameter	**PF-502 (Putative PI3K basal) n = 4**	**PF-502 (Putative PI3K activated) n = 14**	**PF-502 (Putative PI3K activated + basal) n = 18**	**Gedatolisib (Putative PI3K basal) n = 20**	**Gedatolisib (Putative PI3K activated) n = 20**	**Gedatolisib (Putative PI3K activated + basal) n = 40**	**PF-502 (4 mg) n = 3**	**Gedatolisib (89 mg) n = 3**	**Gedatolisib (154 mg) n = 3**	**Gedatolisib (89 mg + 154 mg) n = 6**
Median treatment duration, d (range)	81 (34–169)	56 (21–71)	56 (21–169)	107 (29–345)	57 (1–400)	99 (1–400)	70 (21–83)	449 (29–547)	60 (50–105)	83 (29–547)
Treatment discontinuations,[a] *n* (%)	6 (100)	12 (100)	18 (100)	19 (91)	18 (95)	37 (93)	3 (100)	3 (100)	3 (100)	6 (100)
Study discontinuations, *n* (%)	4 (100)	14 (100)	18 (100)	18 (90)[b]	19 (95)[b]	37 (93)	3 (100)	3 (100)	3 (100)	6 (100)

Abbreviations: PF-502, PF-04691502; PI3K, phosphatidylinositol 3-kinase.

[a]Discontinuation from treatment dataset is based on actual treatment group rather than as randomized. Two patients receiving PF-04691502 changed stathmin status during the course of the study. This accounts for the difference between number of patients randomized to this arm and number of patients who have discontinued treatment.

[b]Three patients were still on study at the time of this analysis.

Supplementary Table S2. Summary of gedatolisib pharmacokinetic characteristics (day 1, cycle 1)

Parameter, units[a]	Gedatolisib (Putative PI3K basal)	Gedatolisib (Putative PI3K activated)
N, n	20, 19	19, 15[b]
AUC_{inf}, ng·h/mL	15,280 (24)	14,870 (40)
AUC_{last}, ng·h/mL	15,080 (24)[b]	15,890 (52)
C_{max}, ng/mL	9,078 (36)	7,057 (84)
T_{max}, h	0.525 (0.50–1.07)	0.650 (0.50–1.08)
$t_{½}$, h	35.02 ± 5.32	34.09 ± 8.87
CL, L/h	10.09 (24)	10.36 (40)
V_{ss}, L	165.6 (32)	174.9 (57)

Abbreviations: AUC_{inf}, area under the serum concentration-time profile from time 0 to infinity; AUC_{last}, area under the serum concentration-time profile from time 0 to the time of the last quantifiable concentration; CL, clearance; C_{max}, maximum plasma concentration; PI3K, phosphatidylinositol 3-kinase; $t_{½}$, terminal elimination half-life; T_{max}, time to reach maximum plasma concentration; V_{ss}, steady-state volume of distribution.

[a]Geometric mean (geometric % coefficient of variation) for all except median (range) for T_{max}; arithmetic mean ± SD for $t_{½}$.

[b]N = 19 (AUC_{last} was not reported for 1 patient with an incomplete concentration-time profile.)

Supplementary Figure S1. Median gedatolisib concentration-time profiles by treatment arm (cycle 1).