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A Multicenter Phase I Trial of PX-866, an Oral Irreversible Phosphatidylinositol 3-Kinase Inhibitor, in Patients with Advanced Solid Tumors

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Abstract

Purpose: The objectives of the study were to evaluate the maximum tolerated dose (MTD), safety, pharmacodynamics, pharmacokinetics, and antitumor activity of PX-866 in patients with incurable cancers.

Experimental Design: This was a phase I, open-label, dose-escalation study. Drug was administered orally once per day either on an intermittent (arm 1; days 1–5 and 8–12 of a 28-day cycle) or continuous (arm 2; days 1–28 of a 28-day cycle) schedule. Additional patients were treated at the arm 2 MTD in a food effects substudy.

Results: Eighty-four patients were treated in the arm 1 ($n = 51$), arm 2 ($n = 20$), and food effects ($n = 13$) cohorts. The most frequent study drug–related adverse events were gastrointestinal disorders (69.0%), with diarrhea being the most common (48.8%). The MTD was 12 and 8 mg for arm 1 and 2, respectively. The dose-limiting toxicities (DLT) consisted of grade III diarrhea ($n = 3$) and grade III elevated aspartate aminotransferase (AST; $n = 1$). The pharmacokinetics profile was dose proportional, with no evidence of drug accumulation. PX-866–associated inhibition of platelet pAKTSER473 was observed at the arm 2 MTD. The best response per Response Evaluation Criteria in Solid Tumors (RECIST) was stable disease in 22% of evaluable patients in arm 1, 53% in arm 2, and 11% in the food effects cohort. Eight patients were on study for 4 or more months.

Conclusions: This first-in-human study shows that PX-866, an irreversible small-molecule inhibitor of phosphatidylinositol 3-kinase (PI3K), was well tolerated and was associated with prolonged stable disease, particularly when using a continuous dosing schedule. *Clin Cancer Res; 18(15); 4173–82. ©2012 AACR.*

Introduction

The phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway is deregulated in many human cancers, leading to decreased expression of proapoptotic genes and increased expression of cell proliferation and cell survival genes, making it an attractive cancer target (1). PI3K and AKT are oncogenes overexpressed or activated by mutation in many human cancers (2–6). *PIK3CA*, the gene encoding PI3K, is mutated in several tumor types including glioblastomas (27%) and gastric (25%), breast (18%), cervical (33%), and endometrial (39%) cancers and is one of the most common activating mutations in head and neck squamous cell carcinoma (HNSCC, 6%–8%; refs. 7–13). The PTEN (phosphatase and tensin homologue) tumor suppressor gene, which negatively regulates PI3K signaling, may be lost via deletion (25% of melanoma, breast, and prostate cancers), mutation, or epigenetic suppression (14–18). Finally, upstream growth factor receptors with increased activity in some cancers, such as EGF receptor (EGFR), activate downstream PI3K signaling (19).

There are 8 mammalian PI3K enzymes that are divided into 3 main classes based on sequence homology and substrate preference (20, 21). The class IA enzymes, which are most commonly related to cancer biology, include the p110α, p110β, and p110δ catalytic subunits (the latter restricted to leukocytes). Mutations that activate p110α result in greater signaling by PI3K and oncogenicity (7). Mutations of the p85 regulatory subunit are also oncogenic (7, 22) and increase p110α signaling (23).

PX-866 (acetic acid 4-diallylaminomethylene-6-hydroxy-1-α 12-methoxymethyl-10β,13β-dimethyl-3,7,17-trioxo-

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Translational Relevance

The phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway is dysregulated in a variety of solid tumors and is proposed to provide key growth and survival signals to tumor cells. Therefore, inhibitors of the PI3K protein represent a promising class of therapeutic agents with several small-molecule PI3K inhibitors in clinical development. This article reports data from the phase I, first-in-human study of PX-866, an oral, selective, irreversible inhibitor of PI3K. Results from this trial show that PX-866 may be administered with a tolerable toxicity profile in patients with advanced solid tumors. Evidence of antitumor activity supports development as a single agent or in combination with other therapies.

1,3,4,7,10,11β,12,13,14α,15,16,17-dodecahydro-2-oxacyclopenta[a]phenanthren-11-yl ester) is a synthetic derivative of wortmannin, a natural furanosteroid metabolite product isolated from a strain of *Penicillium Wortmannii*. The mechanism of action of PX-866 is consistent with irreversible inhibition of PI3K as the 21 position of the agent interacts with the lysine-802 residue in the ATP catalytic site of PI3K (24). PX-866 displays increased stability and activity, improved pharmacologic profile, and reduced toxicity in mice compared with wortmannin (24). PX-866 is a potent, pan-isoform inhibitor of PI3K with IC_{50}s of 39 ± 21, 88 ± 27, 124 ± 26 nmol/L and 183 ± 25 against PI3Kα, PI3Kβ, PI3Kδ, and PI3Kγ, respectively. 17-OH PX-866 is an active metabolite with more potency against PI3Kα (IC_{50} = 14 ± 6 nmol/L) and PI3Kβ (IC_{50} = 57 ± 7 nmol/L) than the parent compound (25).

PX-866 blunts cell growth and decreases activation of PI3K downstream targets *in vitro* and *in vivo*, including p-AKT (26), pS6, and p-mTOR (27). In preclinical studies, inhibition of p-AKT (S473) and p-S6 (S235/236) occur with IC_{50}s of 60 and 74 nmol/L, respectively, in A549 non–small cell lung carcinoma (NSCLC) cells *in vitro* (Oncothyreon, unpublished data). Inhibition of p-AKT (S473) was observed for up to 48 hours after PX-866 dosing in HT29 tumor models (25). PX-866 delayed tumor growth in OvCar-3 ovarian cancer (25), HT29 colon cancer (25), A-549 NSCLC (28), and U87 glioma (27) xenografts with an association between antitumor activity and the presence of *PIK3CA*-activating mutations or PTEN loss.

The observation that PI3K inhibition persists for several days following drug administration suggested that an intermittent dosing schedule might provide sufficient target inhibition with less toxicity than a daily dosing schedule. Therefore, this phase I study had 2 sequential arms: arm 1 sought to identify the maximum tolerated dose (MTD) for an intermittent dosing schedule and arm 2 identified the MTD for continuous daily dosing. The study objectives were to determine the MTD, toxicity profile, pharmacodynamics, pharmacokinetics, and antitumor activity of PX-866 in patients with advanced cancers. A food effects substudy evaluated the impact of food on the pharmacokinetic profile of PX-866.

Patients and Methods

Study design

This was a phase I, open-label, dose-escalation study with 2 arms conducted at the University of Texas MD Anderson Cancer Center (Houston, TX) and the University of Colorado Cancer Center (Aurora, CO) after approval by the Institutional Review Boards of both centers.

In arm 1, patients received drug orally once daily on days 1 to 5 and 8 to 12 of a 28-day cycle. Once the MTD in arm 1 had been determined and confirmed with an expansion MTD arm 1 cohort, the daily dosing cohort of arm 2 started enrollment, with drug administered orally once daily on days 1 to 28 of a 28-day cycle. The starting dose for arm 1 was 0.5 mg once daily (one tenth of the severely toxic dose identified in GLP toxicity studies). The starting dose for arm 2 was 2 dose levels below the MTD for arm 1. Dose escalation in both arms followed a 3 + 3 design, with expansion to 6 patients if one dose-limiting toxicity (DLT) was observed. Dose escalation was stopped when 2 or more DLTs occurred. Patients received repeated cycles in the absence of unacceptable toxicity or disease progression.

A food effects cohort was enrolled once the MTD in arm 2 was declared. The patients in the food effects substudy were randomly assigned to one of 2 groups (group A or B). Each group consisted of approximately 5 patients. Each patient in the substudy received PX-866 administered orally at the dose determined to be the MTD in the dose-escalation portion of arm 2 (continuous daily dosing) of the protocol. For patients assigned to group A (first dose-fasted treatment), PX-866 was administered orally on cycle 1 day −7 on an empty stomach. Following a 2-day washout period, PX-866 was administered orally on cycle 1 day −4 with food. For patients assigned to group B (first dose fed treatment), PX-866 was administered orally on cycle 1 day −7 with food. Following a 2-day washout period, PX-866 was administered orally on cycle 1 day −4 on an empty stomach. After a 3-day washout period, patients in both groups then began the expansion phase (arm 2) of the protocol.

For the fasting treatment day, patients fasted overnight for approximately 10 hours. PX-866 was then administered with approximately 240 mL (8 ounces) of water. No food was permitted for at least 4 hours postdose administration. Water was permitted as desired except for 1 hour before and after drug administration. For the fed treatment day, following an overnight fast of approximately 10 hours, patients began the recommended meal approximately 30 minutes before administration of PX-866. The recommended meal consisted of a standard high-fat breakfast, consisting of 2 fried eggs, 2 slices toasted white bread, 1 tablespoon butter, 1 tablespoon jam, 3 strips fried bacon, 4 ounces of hash brown potatoes, and 8 fluid ounces of whole milk (total caloric content of the breakfast was 951 kcals,

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with distribution of calories being 52% from fat, 33% from carbohydrates, and 15% from protein). Patients had to consume the entire meal in 30 minutes or less; however, PX-866 was administered 30 minutes after the start of the meal. If the patient could not complete the meal, an approximate percentage of the consumed meal was documented. PX-866 was administered with approximately 240 mL (8 ounces) of water. No food was permitted for at least 4 hours after administration of PX-866. Water was permitted as desired except for 1 hour before and after drug administration.

Definition of DLT and MTD

Using Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 DLT was defined as: grade III or IV neutropenia accompanied by fever; grade III–IV thrombocytopenia; grade III–IV nausea, vomiting, or diarrhea that persisted despite optimal antiemetic or antidiarrheal therapy; any other grade III–IV gastrointestinal toxicity; grade III elevation of transaminases for >7 days; any other grade III–IV hepatic toxicity; grade III–IV increase in serum glucose that persisted despite optimal therapy including insulin based therapy; or any other grade III–IV toxicity, unless clearly related to an intercurrent illness or disease progression.

Patients who experienced a DLT could continue in the study, at the dose level below after recovery of the toxicity. Patients who required more than 2 weeks for recovery from a DLT were withdrawn. The highest dose level at which 0 to 1 of 6 patients experienced DLT was declared the MTD. In the first cycle of arm 1, all patients who received 10 daily doses of PX-866 were evaluable for MTD determination. In arm 2, all patients who received 21 daily doses of PX-866 were evaluable for MTD determination.

Patients

Inclusion criteria were written signed informed consent; histologically confirmed advanced solid tumor untreatable by standard therapy; age $\geq$18 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) <2; life expectancy $\geq$12 weeks; discontinuation of anticancer therapy for $\geq$3 weeks (6 weeks for mitomycin C, nitrosureas, vaccines, or antibody therapy); recovery of previous therapy-related toxicities to baseline or $\leq$grade I; adequate hematologic, hepatic, and renal function. Exclusion criteria were active infection; diabetes or fasting blood glucose >160 mg/dL; significant concomitant disorders; surgery within 4 weeks; untreated or symptomatic brain metastasis; gastrointestinal conditions interfering with absorption. Patient safety was monitored by periodic physical exams, hematology and chemistry laboratory studies, and adverse events assessment. Patients had radiographic tumor assessment at baseline and after every second cycle. Tumor response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 (29).

Pharmacokinetics

Levels of PX-866 and the metabolite 17-OH PX-866 were analyzed in samples collected during cycle 1 for both arms 1 and 2. For arm 1, pharmacokinetic samples were collected at baseline, and then on cycle 1 days 1, 5, and 12 at 20, 40, 60, and 120 minutes postdosing. For arm 2, pharmacokinetic samples were collected at the same time points just on cycle 1 day 1. The pharmacokinetic profile was also evaluated in the food effects substudy. Samples for pharmacokinetic analyses were collected from patients on days -7 and -4 at baseline before PX-866 administration and at 10, 20, 40 minutes, 1, 2, 4, 6, and 24 hours after PX-866 administration.

Pharmacodynamic and biomarker testing

To noninvasively monitor PX-866 pharmacodynamics, assays were developed using platelets to quantify PI3K pathway inhibition using an ELISA to quantify total and phosphorylated AKT (p-AKT) protein in the fasted state (see Supplementary Methods). Optional, archival tumor tissue blocks were assessed for the presence of mutations in *PIK3CA* (G1624A, A1634G, A1633A, A3140G, A3140T) and KRAS (codons 12 and 13) using the shifted termination assay (TrimGen Corp.; ref. 30).

Statistics

Sample size was determined empirically, based upon a 3+3 escalation design. Descriptive statistics were used for analyses of safety, tumor response, pharmacokinetics, and pharmacodynamic measurements.

Results

Patient characteristics

Eighty-four patients were enrolled and treated with at least one dose of PX-866 while on the study across the intermittent (arm 1, $n = 51$), continuous (arm 2, $n = 20$), and food effects ($n = 13$) cohorts (Table 1). The median age was 61 years (range, 29–83). Several tumor types were represented in the patient population, with the most common being colorectal cancer ($n = 21$, 25.0%). Previous anticancer treatments included chemotherapy (90%), other therapy (33%), immune therapy (10%), and hormone therapy (10%). The majority (65%) of patients had received 3 or more anticancer therapies. Patient characteristics were comparable for the 3 arms of the study, although the overall percentage of patients with an ECOG PS of 1 was higher for the food effects cohort (77%) than for arm 1 (70%) or arm 2 (60%).

Dose escalation and MTD determination

PX-866 dose escalation started at 0.5 mg in arm 1 (intermittent schedule), then explored 1, 2, 3, 4.5, 6, 8, 10, 12, and 16 mg (Table 2). DLTs on the intermittent dosing schedule were grade III diarrhea ($n = 1$) and grade III elevated aspartate aminotransferase (AST; $n = 1$) in 2 of 5 patients receiving 16 mg of PX-866. The MTD for PX-866 was determined to be 12 mg for the intermittent schedule. Arm 1 was expanded to a total of 16 patients with no further DLTs.

Arm 2 (continuous schedule) started 2 dose levels below the MTD for arm 1, which corresponded to 8 mg. The DLT on the continuous dosing schedule was grade III diarrhea,

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Table 1. Baseline demographics and patient characteristics

Demographic/characteristic	Arm 1 ($N = 51$)	Arm 2 ($N = 20$)	Food effects ($N = 13$)	Total ($N = 84$)
Sex, *n* (%)				
Male	27 (52.9)	8 (40.0)	7 (53.8)	42 (50.0)
Female	24 (47.1)	12 (60.0)	6 (46.2)	42 (50.0)
Age, y				
Mean	61.7	60.4	60.1	61.1
Median	61.0	61.0	62.0	61.0
Range	41–83	29–76	43–74	29–83
Race/ethnicity, *n* (%)				
White	42 (82.4)	16 (80.0)	12 (92.3)	70 (83.3)
Hispanic/Latino	2 (3.9)	0 (0.0)	1 (7.7)	3 (3.6)
African-American	5 (9.8)	2 (10.0)	0	7 (8.3)
Asian	2 (3.9)	2 (10.0)	0	4 (4.8)
ECOG PS[a]				
0	15 (30.0)	8 (40.0)	3 (23.0)	26 (31.3)
1	35 (70.0)	12 (60.2)	10 (77.0)	57 (68.7)
Number of prior anticancer systemic treatments for metastatic disease, *n* (%)				
0	3 (5.9)	1 (5.0)	0 (0.0)	4 (4.8)
1	5 (2.0)	2 (10.0)	1 (7.7)	8 (9.5)
2	10 (19.6)	4 (20.0)	3 (23.1)	17 (20.2)
3	3 (5.9)	4 (20.0)	4 (30.8)	11 (13.1)
>3	30 (58.8)	9 (45.0)	5 (38.4)	44 (52.4)
Tumor type, *n* (%)				
CRC	9 (17.6)	7 (35.0)	4 (31.8)	20 (23.8)
Ovarian	6 (11.8)	5 (25.0)	1 (7.7)	12 (12.3)
Head and neck	8 (15.7)	1 (5.0)	0 (0.0)	9 (10.7)
NSCLC	4 (7.8)	0 (0.0)	2 (15.3)	6 (7.1)
Melanoma	3 (5.9)	1 (5.0)	2 (15.3)	6 (7.1)
Breast	3 (5.9)	0 (0.0)	0 (0.0)	3 (3.6)
Other[b]	16 (31.3)	4 (20.0)	4 (30.8)	24 (28.6)

Abbreviations: Arm 1, intermittent dosing; Arm 2, continuous dosing.

[a]ECOG PS was not available for 1 patient in arm 1.

[b]Other includes: 2 each of leiomyosarcoma, skin (squamous cell), prostate, small-cell lung, kidney, and anaplastic thyroid cancer; and 1 each of adenocystic, hepatoma, gastrointestinal stromal, chondrosarcoma, endometrial, salivary gland, pancreatic islet cell, pancreatic neuroendocrine, pancreatic, esophageal, sarcoma, cholangiocarcinoma, urothelial, and gastric cancers.

which occurred in 2 of 3 patients receiving 10 mg of PX-866. The MTD for PX-866 was determined to be 8 mg for the continuous dosing schedule. Arm 2 was expanded to a total of 17 patients with no further DLTs.

Safety

Patients who received at least one dose of PX-866 were evaluated for safety ($n = 84$). The most frequent toxicities considered likely related to study drug were gastrointestinal disorders (69%), with diarrhea being the most common (49%), followed by nausea (38%) and vomiting (25%; Table 3). The majority (91%) of study drug–related toxicities were grade I–II. Other study drug–related toxicities were grade III and were reported in patients treated at $\geq$8 mg. In arm 1, 7 grade III study drug–related toxicities were reported in 6 of 51 patients (12%), all treated at 12 or 16 mg. These included fatigue ($n = 2$), vomiting ($n = 1$), diarrhea ($n = 1$), hypertension ($n = 1$), elevated AST ($n = 1$), and dehydration ($n = 1$).

In arm 2, 5 grade III study drug–related toxicities were reported in 3 of 20 patients (15%), all in the 10 mg cohort and included nausea ($n = 1$), vomiting ($n = 1$), diarrhea ($n = 2$), and elevated alanine aminotransferase (ALT)/AST ($n = 1$). In the food effects cohort, 4 of 13 patients (31%), each treated at 8 mg, experienced grade III toxicities, including diarrhea ($n = 2$), anemia ($n = 1$), and elevated liver transaminases ($n = 1$). The incidence of ALT/AST elevations considered to be study drug–related was higher in patients on arm 2 than those on arm 1. Study drug–related hematologic toxicities were uncommon.

Outcome

Of the 84 patients treated, 28 discontinued before receiving a follow-up scan, including 20 patients (13 in arm 1, 3 in

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Table 2. Dose escalation and DLTs

Dose cohort, mg	No. of patients in dose cohort (*n*)	No. of patients with DLT[a] (*n*)	DLT
Arm 1			
0.5	3	0	
1	3	0	
2	3	0	
3	3	0	
4.5	4	0	
6	6	0	
8	4	0	
10	4	0	
12[b]	16	0	
16	5	2	One patient with grade III diarrhea and 1 patient with grade III AST elevation and grade II diarrhea
Arm 2			
8[b]	17	0	
10	3	2	Two patients with grade III diarrhea

Abbreviations: Arm 1, intermittent dosing; arm 2, continuous dosing.
[a]In patients during the first treatment cycle.
[b]Includes MTD expansion cohort.

arm 2, and 4 in the food effects cohort) who came off-study due to early progressive disease; 5 patients in arm 1 who withdrew due to adverse events (considered study drug related in only 1 patient who withdrew due to grade I nausea and diarrhea and grade II vomiting); and 3 patients (1 in arm 1 and 2 in arm 2) who withdrew consent. Across all study arms, the median duration of treatment was 51 days (range, 1–552 days). The median duration of treatment was 51 days (range, 1–229 days) for arm 1 (range, 1–229 days), 57 days for arm 2 (range, 3–552 days), and 46 days for the food effects arm (range, 6–98 days).

Best response in the 56 evaluable subjects (defined as having a scan during or at the end of cycle 2) was stable disease in 7 of 32 patients (22%) in arm 1, stable disease in 8 of 15 patients (53%) in arm 2, and stable disease in 1 of 9 patients (11%) in the food effects cohort (Fig. 1). Several patients experienced prolonged stable disease, including 4 patients in arm 1 (melanoma, adenocystic carcinoma,

Table 3. Adverse events reported in the safety population following treatment with PX-866

AE type reported	Arm 1[a] *N* = 51, *n* (%)	Arm 2[b] *N* = 20, *n* (%)	Food effects *N* = 13, *n* (%)	Total population[c] *N* = 84, *n* (%)
Patients with AEs	50 (98.0)	19 (95.0)	13 (100.0)	82 (97.6)
Patients with treatment-related AEs	35 (68.6)	17 (85.0)	12 (92.3)	64 (76.2)
Treatment-related AEs by preferred term in ≥5% of patients				
Diarrhea	17 (33.3)	15 (75.0)	9 (69.2)	41 (48.8)
Nausea	18 (35.3)	8 (40.0)	6 (46.2)	32 (38.1)
Vomiting	10 (19.6)	7 (35.0)	4 (30.8)	21 (25.0)
Fatigue	6 (11.8)	5 (25.0)	3 (23.1)	14 (16.7)
Anorexia	2 (3.9)	4 (20.0)	2 (15.4)	8 (9.5)
AST increased	2 (3.9)	2 (10.0)	1 (7.7)	5 (6.0)
ALT increased	1 (2.0)	2 (10.0)	1 (7.7)	4 (4.8)

Abbreviation: AE, adverse event.
[a]Arm 1.
[b]Arm 2.
[c]Arm 1, arm 2, and food effects.

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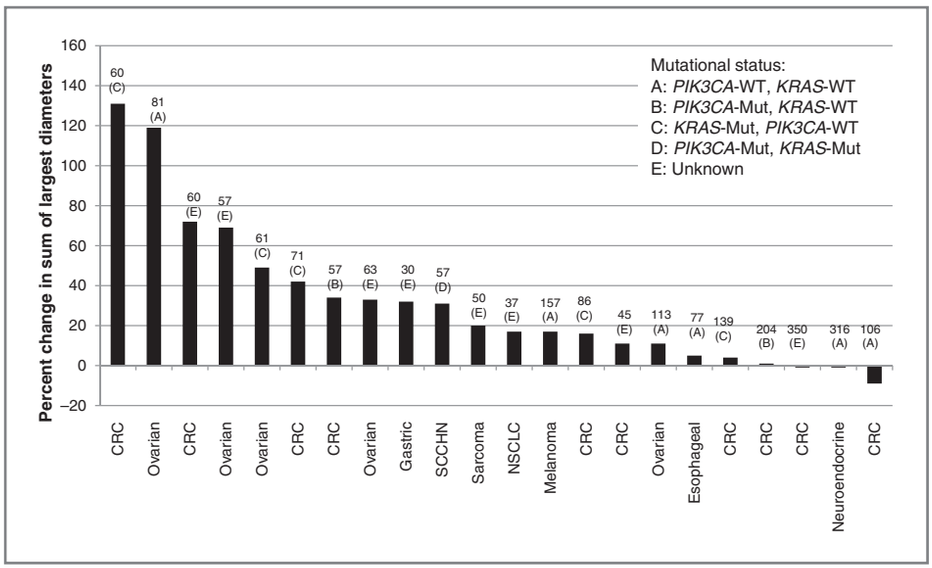

Figure 1. Best responses by time on study (days), mutational status, and tumor type for patients receiving continuous PX-866.

NSCLC, and chondrosarcoma) who received between 5 and 8 cycles, and 4 patients in arm 2 [colorectal carcinoma (CRC); $n = 2$; metastatic pancreatic neuroendocrine tumor, and castration-resistant prostate cancer (CRPC)], who received between 6 and 20 cycles.

The 3 patients in arm 2 who had the longest duration of stable disease had CRC, pancreatic neuroendocrine cancer, and CRPC. The patient with CRC had progressive disease on the regimen before enrollment and was on therapy for 6 cycles. The patient with pancreatic neuroendocrine carcinoma had documented progressive disease on study entry and experienced stable disease while receiving 10 cycles of PX-866 (8 mg) before developing progression. The patient with CRPC had a history of progression after hormonal therapy and chemotherapy and entered the study with a normal prostate-specific antigen (PSA) and bone metastases for which he received chronic pain medication. He initiated treatment at 10 mg per day and required 2 dose reductions to 8 and 6 mg due to a DLT (grade III diarrhea) first and recurrent grade I diarrhea later. The patient received 20 cycles before disease progression occurred and was able to discontinue all pain medications while on study.

Mutational status of *PIK3CA* and KRAS was obtained from archival tumor specimens from 45 patients (Supplementary Tables S1 and S2). No differences in mean time on study based on mutational status were observed for arm 1 patients, which may reflect conservative initial dosing and a lack of antitumor effects in the intermittent dosing arm. Mutational status and time on study for patients treated with continuous dosing are represented in Fig. 2. While not statistically significant, an association with longer time on study was observed in patients with a *PIK3CA* mutation (*PIK3CA*-mut) versus wild-type (*PIK3CA*-WT). The mean time on study for *PIK3CA*-mut patients ($n = 4$) was 204 days (range, 57–552 - time on treatment) versus 115 days (range, 24–316) for *PIK3CA*-WT patients ($n = 8$; 2-tailed t-test; $P = 0.28$). Two of the 3 patients with the longest duration of stable disease in arm 2 had dual *PIK3CA* point mutations, including the patients with CRPC and CRC. The patient with pancreatic neuroendocrine tumor was *PIK3CA*-WT.

Pharmacokinetics

Plasma levels of PX-866 were undetected. Consequently, pharmacokinetics parameters were determined using an active metabolite of PX-866 (17-OH PX-866), which was identified in preclinical models (data on file, Oncothyreon, Inc.). Pharmacokinetic parameters from the arm 1, arm 2, and the food effect cohorts are reported in Table 4. A mean plasma concentration–time curve for 17-OH PX-866 in a representative dose level is shown in Fig. 3. The AUC for 17-OH PX-866 appears to be dose proportional from 4.5 to 16 mg ($R^2 = 0.973$), and C_{max} is dose proportional across all dose levels ($R^2 = 0.78$). No evidence of drug accumulation or drug reduction was seen with repeat dosing.

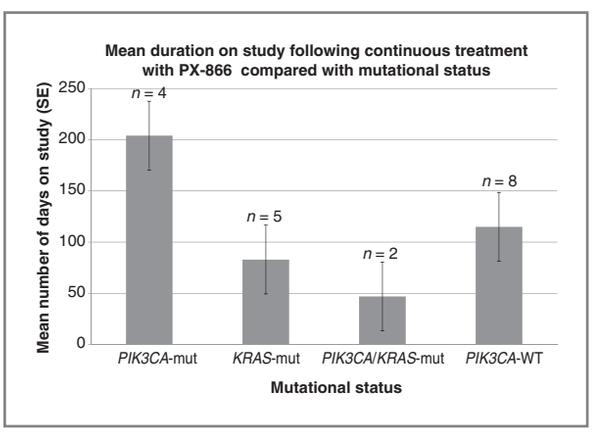

Figure 2. Duration of clinical benefit by mutational status.

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Table 4. Pharmacokinetics

Study arm	Dose level, mg	Patient (*n*)	C_{max}, ng/mL (mean ± SD)	T_{max}, h (mean ± SD)	Vz/F (L)	Cl/F, L/h	$T_{1/2}$, h	AUC_{inf} (h × ng/mL ± SD)
1	0.5	3	0.16 ± 0.08	0.63 ± 0.13				0.35 ± 0.12
	1	3	0.07 ± 0.01	0.93 ± 0.23				
	2	3	0.96 ± 0.04	0.82 ± 0.28				1.82 ± 0.31
	3	3	1.36 ± 0.07	1.11 ± 0.19				3.86 ± 2.54
	4.5	4	0.95 ± 0.68	0.83 ± 0.65				1.42 ± 0.63
	6	6	0.97 ± 0.38	0.67 ± 0.21				1.46 ± 0.11
	8	4	4.02 ± 0.75	1.07 ± 0.21				8.77 ± 4.32
	10	4	2.86 ± 0.33	0.94 ± 0.28				5.53 ± 0.30
	12	16	2.84 ± 0.57	0.88 ± 0.22				6.82 ± 0.42
	16	5	2.44 ± 1.14	0.95 ± 0.19				7.91 ± 3.72
2	8	17	1.21 ± 0.18	1.10 ± 0.21	11,180 ± 2,078	3,346 ± 730	3.88 ± 0.99	4.88 ± 1.03
	10	3	0.76 ± 0.12	0.89 ± 0.11	14,209 ± 4,027	4,574 ± 1,527	2.22 ± 0.33	2.7 ± 0.81
FE fast[a]	8	6	2.39 ± 1.28	0.94 ± 0.22				6.47 ± 3.15
FE fed[b]	8	6	0.73 ± 0.17	1.27 ± 0.31				3.21 ± 0.85

NOTE: In arm 1, both interpatient and intrapatient variability (CV%) was calculated for C_{max}, T_{max}, and AUC parameters for all patients on all dose levels for each of the 3 pharmacokinetic sampling days. Median composite variability was calculated for all 3 days. The composite CV% for both interpatient and intrapatient variability for C_{max} was 70% versus 47% and for AUC, 80% versus 45%, respectively. T_{max} was similar between the 2 groups with a CV% of 40%.

Abbreviations: Arm 1, intermittent dosing; arm 2, continuous dosing; FE, food effects; SD, stable disease.

[a]PX-866 was administered while patients were fasting.

[b]PX-866 was administered with intake of food.

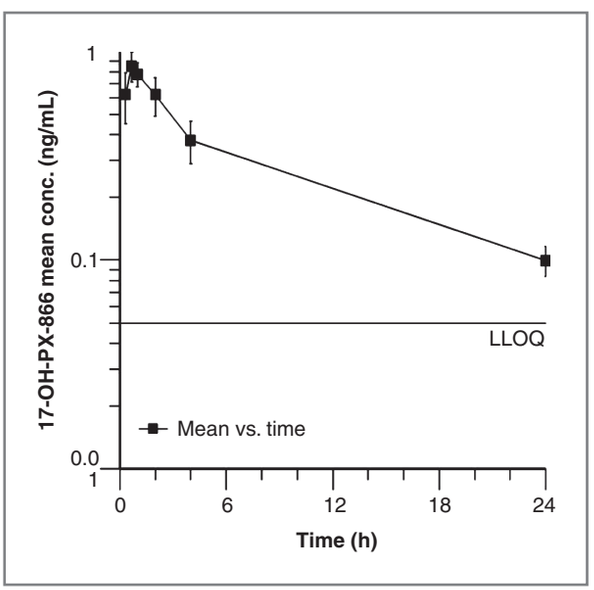

Figure 3. Pharmacokinetics. Mean plasma concentration–time pharmacokinetic profile of 17-OH PX-866 from arm 2 patients dosed with 10 ($n = 3$) and 8 mg ($n = 17$) PX-866. Data from the 2 arms were combined to increase statistical power. Samples were collected predose and at the following time points (±5 minutes) after the oral administration of PX-866: 10, 20, 40 minutes, 1, 2, 4, 6, and 24 hours. Mean concentration and stable disease are presented as log 17-OH PX-866 ng/mL. Horizontal line represents the lower limit of quantification (LLOQ) for 17-OH PX-866.

The effect of food intake on PX-866 pharmacokinetic parameters was evaluated in a food effects substudy. Thirteen patients were enrolled, with evaluable data available for 8. In this small number of patients, T_{max} was slightly delayed in the fed cohort and AUC and C_{max} were lower than the fasting state, although these differences were not significant ($P = 0.253$ for AUC and $P = 0.063$ for C_{max}). Significant variability was observed because of 2 patients who exhibited high fasting C_{max} values that were outside the normal distribution for the 8-mg dose and 1 patient who had drug levels below the limit of quantitation for all time points.

Pharmacodynamics

Pharmacodynamic assays evaluating quantitative changes in p-AKT and total AKT (T-AKT) in platelets was developed. Sampling was carried out in 10 patients enrolled in the food effects substudy who then went on to treatment with daily dosing using the arm 2 schedule at the MTD of 8 mg. Inhibition of p-AKT was observed within 4 hours in 7 patients with p-AKT/T-AKT ratio decreases of 13% to 94% (Supplementary Fig. S1), with 4 having p-AKT/T-AKT ratio decreases >80%. No correlation was established between p-AKT/T-AKT ratios and adverse events or antitumor activity.

Discussion

This first-in-human study shows that PX-866, an irreversible small-molecule PI3K inhibitor, is safe and well tolerated, with similar safety profiles when administered

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intermittently or continuously. The PX-866 MTD are 12 and 8 mg for the intermittent and continuous schedules, respectively.

The most common toxicity observed was diarrhea. This side effect was tolerable in most patients with the use of antidiarrheal medications and, if needed, dose reduction of PX-866. Nausea, vomiting, and diarrhea are common side effects seen with other PI3K inhibitors and were also tolerable with antiemetics and antidiarrheals. Interestingly, PX-866 was not associated with the significant hyperglycemia or skin toxicity reported with many other compounds targeting PI3K (19, 31). This is not entirely unique as GDC-0941 in a phase Ib combination with chemotherapy with or without bevacizumab showed no hyperglycemia and only a mild rash (32). In addition, while DLT associated with the α-specific inhibitor BYL719 included hyperglycemia, hyperglycemia was not reported at dose levels associated with disease stabilization (33). These results suggest that rash and hyperglycemia may not always be present with a PI3K inhibitor or may occur at levels of exposure greater than those needed for antitumor activity. Moreover, PX-866's unique mechanism of action as an irreversible PI3K inhibitor may make its toxicity profile different from reversible PI3K inhibitors. Because PI3K signaling has a well-established role in resistance to EGFR inhibitors (34), the lack of skin toxicity with PX-866 enables potential combinations of PI3K and EGFR inhibitors (12).

The pharmacokinetic results indicate that the complex pharmacology of PX-866 is likely mediated by drug metabolites including, but not limited to, 17-OH PX-866. The half-life of PX-866 is short but daily dosing is supported by its irreversibility. On-target PI3K inhibition was documented in patient platelet samples; however, there was no clear correlation between PI3K pathway inhibition, drug pharmacokinetics, toxicity, or efficacy. This might be explained by interpatient variation in PX-866 metabolism as well as with the generation of other unidentified active metabolites. Further studies will examine the role of other metabolites in PI3K pathway inhibition, efficacy, and drug tolerability. Results from the food effect substudy suggest that food may decrease some of the variability observed in PX-866 pharmacokinetics. Although the C_{max} and AUC appear to be lower in the fed group, these differences were not statistically different. In addition, the food effect pharmacokinetics data are limited by a small sample size and substantial interpatient variability. Therefore, a food effect study in healthy volunteers is being conducted (NCT01408316).

While no objective responses were observed, stable disease occurred in 8 of 15 (53%) evaluable patients in arm 2, with 4 (26.6%) of these patients having stable disease >4 months. The difference in stable disease rates between the intermittent (22%) and continuous (53%) dosing schedules is likely multifactorial, but the constant drug exposure seen with continuous dosing may induce higher PI3K/AKT pathway signaling suppression. The 2 patients with the longest time on study (CRPC and pancreatic neuroendocine carcinoma) both had progression before enrollment, and the patient with CRPC was able to discontinue pain medications during PX-866 treatment. A patient harboring dual *PIK3CA* mutations had stable disease for over 6 months. These outcomes support a direct anticancer effect of PX-866 rather than variability in baseline tumors characteristics. The stable disease seen in this study is consistent with other exclusive inhibitors of PI3K, where responses are rare (19, 31). For instance, the response rate with BKM120 was less than 3% in unselected phase I patients (31). Our study is limited by a relatively high early discontinuation rate for clinical progression. This may have been driven by several factors. First, the majority of early discontinuations occurred in the intermittent dosing arm that was ultimately thought to be ineffective due to inadequate drug exposure. Second, the food cohort contributed the second highest percentage of early discontinuations. This group had the worst performance status of any cohort, and the time on study for this group was calculated from the time continuous dosing began on cycle 1 day 1 rather than the first day of dosing on day −7. Finally, the enrollees in this study represented a heavily pretreated population where more than 65% had received 3 or more previous lines of therapy.

An interesting finding was a possible association with longer time on PX-866 for *PIK3CA*-mut versus *PIK3CA*-wt patients, including 2 previously progressing patients with *PIK3CA*-mut CRC and prostate carcinoma on study for 6 and 20 months, respectively. While this association could be explained by a small sample size and an overall improved prognosis for patients with *PI3KCA* mutations, activation of the PI3K pathway is typically associated with worse prognosis in patients with ovarian or prostate cancer (35, 36). Moreover, substantial preclinical data suggest that PI3K inhibition may be more effective in tumors harboring an activated PI3K pathway. For instance, *PIK3CA* mutation or PTEN loss were predictors for response to PX-866 in human xenograft models of several tumors (37). Similarly increased antitumor activity has been seen in other preclinical *PIK3CA*-mut cancer models (38, 39). KRAS and p53 mutations may be indicators of resistance to PI3K inhibition (37, 40). Consistent with this, a recent analysis of gynecologic malignancies who harbored *PIK3CA* mutations treated on P13K/AKT/mTOR inhibitors showed a higher response rate than patients without mutations in the MD Anderson Cancer Center phase I clinic (41).

The correlation between PI3K/AKT pathway activation and outcome is limited as less than 50% of patients were tested for *PIK3CA* and *KRAS* mutations as the mutation analysis was not preplanned and other potential biomarkers of PI3K signaling (PTEN loss, *PIK3CA* amplification, or PI3K overexpression) were not evaluated. Future studies will further investigate biomarkers predictive of benefit following PX-866 administration.

In conclusion, this first-in-human study of PX-866 established the MTD for 2 dosing schedules that were well tolerated, and 8 mg of PX-866 daily is the recommended phase II dose. Tumor mutational analyses suggest an association with increased time on study in patients with

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PIK3CA-mut cancers, which will require prospective confirmation. Pharmacokinetic and pharmacodynamic analyses show rapid absorption and "on-target" pathway inhibition. The agent's favorable toxicity profile and antitumor activity support its further clinical development. PX-866 is currently in phase II trials for glioblastoma (NCT01259869) and CRPC (NCT01331083) and combination phase I–II studies with cetuximab (NCT01252628) or docetaxel (NCT01204099) for HNSCC/CRC and HNSCC/NSCLC, respectively.

Disclosure of Potential Conflicts of Interest

D.S. Hong, G.S. Falchook, and A. Jimeno have commercial research grant from Oncothyreon. S.G. Eckhardt is the consultant/advisory board member for Oncothyreon. S. Peterson and D.F. Hausman have ownership interest (including patents) for Oncothyreon. No potential conflicts of interest were disclosed by other authors.

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Clinical Cancer Research

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