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A multicenter phase 1 study of PX-866 in combination with docetaxel in patients with advanced solid tumours

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Background: This phase I, dose-finding study determined the safety, maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D), pharmacokinetics, and antitumour activity of PX-866, a phosphatidylinositol 3-kinase inhibitor, combined with docetaxel in patients with incurable solid tumours.

Methods: PX-866 was administered at escalating doses (4–8 mg daily) with docetaxel 75 mg m^{-2} intravenously every 21 days. Archived tumour tissue was assessed for potential predictive biomarkers.

Results: Forty-three patients were enrolled. Most adverse events (AEs) were grade 1 or 2. The most frequent study drug-related AE was diarrhoea (76.7%), with gastrointestinal disorders occurring in 79.1% (docetaxel-related) and 83.7% (PX-866-related). No dose-limiting toxicities were observed. The RP2D was 8 mg, the same as the single-agent MTD. Co-administration of PX-866 and docetaxel did not affect either drug's PKs. Best responses in 35 evaluable patients were: 2 partial responses (6%), 22 stable disease (63%), and 11 disease progression (31%). Eleven patients remained on study for >180 days, including 8 who maintained disease control on single-agent PX-866. Overall median progression-free survival (PFS) was 73.5 days (range: 1–569). A non-significant association between longer PFS for *PIK3CA*-MUT/*KRAS*-WT *vs* *PIK3CA*-WT/*KRAS*-WT was observed.

Conclusion: Treatment with PX-866 and docetaxel was well tolerated, without evidence of overlapping/cumulative toxicity. Further investigation with this combination is justified.

The PI3K/serine-threonine kinase (AKT)/mammalian target of rapamycin (mTOR) signalling pathway is often altered in human cancers, leading to increased expression of cell proliferation and survival genes and decreased expression of pro-apoptotic signals (Nicholson and Anderson, 2002; Courtney *et al*, 2010). PI3K is an intracellular kinase consisted of the p110α, p110β, or p110δ

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catalytic subunits, and a p85 regulatory subunit; mutations to p110α and p85 can be oncogenic (Samuels and Ericson, 2006; Jaiswal *et al*, 2009). Activating mutations to *PIK3CA*, the gene encoding the p110α catalytic subunit of PI3K, are found in several tumour types, including glioblastoma (27%), breast (18%), colorectal (16% of non-hypermutated tumours), cervical (33%), endometrial (39%), squamous cell carcinoma of the head and neck (SCCHN; 6–8%), and non-small cell lung cancer (NSCLC; 2–6%) (Levine *et al*, 2005; Hayes *et al*, 2006; Samuels and Ericson, 2006; Miyake *et al*, 2008; Agrawal *et al*, 2011; Stransky *et al*, 2011; Cancer Genome Atlas Network, 2012). Increased *PIK3CA* copy numbers are seen in prostate cancer (28%), squamous histology NSCLC (33%), and SCCHN (45%) (Yamamoto *et al*, 2008; Agell *et al*, 2011; Morris *et al*, 2011). The phosphatase and tensin homolog (*PTEN*) tumour suppressor gene, which inhibits PI3K signalling, may be lost via deletion (25% of melanoma, breast, and prostate cancers), mutation, or epigenetic suppression (Pesche *et al*, 1998; Tokunaga *et al*, 2007; Cancer Genome Atlas Research Network, 2008; Carracedo and Pandolfi, 2008). Lastly, upstream growth factor receptors that activate PI3K signalling, such as epidermal growth factor receptor and insulin-like growth factor receptor, are often overexpressed (Bowles and Jimeno, 2011; Zhang *et al*, 2011).

PX-866 is a potent, pan-isoform inhibitor of PI3K that is a synthetic derivative of wortmannin. PX-866 irreversibly inhibits PI3K by binding covalently to lysine-802 in the ATP catalytic site (Wipf *et al*, 2004). PX-866 and its active metabolite, 17-OH-PX-866, demonstrate potent inhibition of PI3K, with respective IC_{50}s of 39 ± 21 and 14 ± 6 nM against PI3Kα, and 88 ± 27 and 57 ± 7 nM against PI-3K*β* (Wipf *et al*, 2004). Single-agent PX-866 delays tumour growth in A-549 NSCLC, OvCar-3 ovarian cancer, HT29 colon cancer, and U87 glioma xenografts, with an association between antitumour activity and the presence of *PIK3CA*-activating mutations or reduced *PTEN* expression (Ihle *et al*, 2005; Koul *et al*, 2010).

In the first-in-human, phase 1, single-agent study of PX-866, the recommended phase 2 dose (RP2D) was 8 mg daily (Hong *et al*, 2012). The most common adverse events (AEs) were diarrhoea, nausea, and vomiting. Best response per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 (Eisenhauer *et al*, 2009) was stable disease (SD) in over 50% of evaluable patients at week 6. As with other investigational PI3K inhibitors, *PIK3CA* mutations were associated with longer duration of SD, but this was not statistically significant (Bendell *et al*, 2012; Hong *et al*, 2012). Given the drug's favourable toxicity profile and the importance of PI3K/AKT/mTOR pathway signalling in numerous malignancies, PX-866 was deemed a good candidate for combination chemotherapy studies. Docetaxel is an effective cytotoxic chemotherapeutic agent for many tumours where PI3K signalling is important, including NSCLC, SCCHN, breast, and prostate cancer (Dreyfuss *et al*, 1996; Shepherd *et al*, 2000; Tannock *et al*, 2004; Harvey *et al*, 2006). The only significant overlapping toxicities between single-agent PX-866 and single-agent docetaxel are diarrhoea, nausea, and vomiting. Patient-derived SCCHN xenografts show enhanced tumour suppression when treated with PX-866 and docetaxel compared with either agent alone (Bowles *et al*, 2011). We conducted a phase 1 study of the combination of PX-866 and docetaxel to determine the maximum tolerated dose (MTD)/RP2D, toxicity profile, PK, antitumour activity, and predictive biomarkers of response for the combination in patients with advanced cancers.

PATIENTS AND METHODS

Patients. Inclusion criteria included patients with: incurable, locally advanced, or metastatic cancer for which docetaxel administered at a dose of $75\ mg\ m^{-2}$ IV every 21 days is approved, considered standard of care, or is compendia listed; measurable disease per RECIST 1.1 or, for metastatic castrate resistant prostate cancer (mCRPC), evaluable for response or progression based on prostate-specific antigen (PSA) or bone scan; life expectancy >3 months; adequate hepatic, haematological, and renal function; Eastern Cooperative Oncology Group performance status of $\leqslant 1$; and completed previous treatment >4 weeks. Exclusion criteria included: presence of any medical/social factors impacting patient safety; pregnancy or breastfeeding; previous treatment with docetaxel (except in CRPC) or a PI3K inhibitor; known human immunodeficiency virus; known or suspected clinically active brain metastases; grade $\geqslant 2$ peripheral neuropathy; and/or history of hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate. The institutional review board of all participating centres granted approval and written informed consent was mandatory.

Design. This was an open-label, dose-escalation study of orally administered daily PX-866 in combination with docetaxel $75\ mg\ m^{-2}$ IV once every 21 days. In cycle 1 only, to allow for assessment of the effect of PX-866 on docetaxel PK, docetaxel was administered on day 1 followed by initiation of treatment with daily oral PX-866 on day 8. In all subsequent cycles, PX-866 was administered in a fasting state daily throughout the cycle. Prophylactic and therapeutic use of filgrastim or pegfilgrastim was permitted in any cycle. Patients with CRPC received dexamethasone 8 mg PO at 12, 3, and 1 h before docetaxel administration, and also received prednisone 5 mg twice daily (BID) throughout treatment; all other patients received dexamethasone 8 mg PO BID for 3 days starting the day before docetaxel. Prophylactic anti-emetics were allowed per institutional guidelines. At the investigator's discretion, patients experiencing toxicity attributable to docetaxel were permitted to continue to receive single-agent PX-866 after receiving at least two cycles of combination treatment with PX-866 and docetaxel, and achieving SD or better.

PX-866 dose escalation. PX-866 was administered at 4, 6, or 8 mg daily to cohorts of 6–9 patients each. The 4-mg starting dose of PX-866 was chosen as representing 50% of the previously determined single-agent MTD of 8 mg. Each cohort initially enrolled up to three patients; once at least two patients completed therapy through day 21 without experiencing a DLT, the remaining patients in the cohort were allowed to enrol. Patients were considered evaluable if they received at least 75% of the planned doses of PX-866 in cycles 1 and 2, unless the reason for not doing so was a DLT or other PX-866-related toxicity. If not more than one of the first six evaluable patients experienced a DLT, then the dose of PX-866 was escalated. A dose was considered not tolerated if the observed rate of DLT in 15 patients was 33%. After identification of the MTD/RP2D, 17 additional patients were treated in an expansion cohort. If $\geqslant 33\%$ of the patients in the expansion cohort experienced a DLT, enrollment was to have been halted pending review by the study Safety Monitoring Committee.

Patients were evaluated for efficacy approximately every 6 weeks. Patients with SD or better received repeat cycles of treatment until PD, unacceptable toxicity, or withdrawal of consent. Efficacy assessments were performed following RECIST 1.1, except in mCRPC patients who could have been evaluated for PSA response per the Prostate Cancer Clinical Trials Working Group recommendations.

Safety monitoring. Safety assessments included: vital signs, laboratory assessments, and physical exams. AEs were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.02. Dose-limiting toxicities included: $\geqslant$grade 3 events considered possibly, probably, or definitely

related to the combination study drug treatment, with the exception of nausea, vomiting, or diarrhoea without maximal anti-emetic or antidiarrhoeal therapy; >2-week delay in the start of cycle 2 or 3 as result of PX-866-related toxicity; grade 3 or 4 neutropenia with fever; platelets <25 000 per μl; absolute neutrophil count <500 per μl for >7 days; grade 3 transaminitis >7 days; grade 4 transaminitis; or >grade 3 increase in serum glucose despite optimal therapy. Patients who experienced a DLT were allowed to continue in the study at a reduced dose level.

Pharmacokinetic and biomarker measurements. Pharmacokinetics assessments included plasma measurements for: PX-866, metabolites of PX-866, and docetaxel. See Supplementary Data for additional details. Samples were collected to assess: docetaxel PK on cycle 1 day 1 and 2; PX-866 PK on cycle 1 days 8, 9, and 15 and cycle 2 day 15; and PK of both drugs on cycle 2 days 1 and 2. Optional archival tumour tissue blocks were evaluated for mutations in *PIK3CA* (G1624A, A1634G, A1633A, A3140G, and A3140T) and *KRAS* (codons 12 and 13) using the shifted termination assay (TrimGen Corporation, Sparks, MD, USA) (Hong *et al*, 2012), and expression of PTEN using immunohistochemistry (IHC) of archival biopsy samples was performed using the monoclonal antibody 6H2.1 (Al-Zaid *et al*, 2012). PTEN intensity in the tumour cells was scored relative to internal positive controls (0, completely absent; 1, markedly reduced; 2, mildly reduced; and 3, normal or increased). Only complete loss (score = 0) in >90% of the tumour cellularity assessed was considered significant.

Statistics. The planned enrollment for phase 1 was up to 36 evaluable patients, including up to 27 evaluable patients in three dose cohorts during dose escalation and approximately 9 evaluable patients in a safety expansion cohort at the MTD/RP2D. The sample size allowed for an approximately 33% early discontinuation rate due to non-PX-866-related events. With a sample size of 15 patients, if the true incidence of DLT was 10%, there would be a 79% probability of observing at least one DLT and a 45% probability of observing two or more DLTs. Progression-free survival (PFS) was measured from the time of consent to the date of progression or until death from any cause, or if unknown, the date that the patient was last known to be alive and progression-free.

RESULTS

Demographics and baseline characteristics. Patient demographics, baseline characteristics, and disposition are described in Table 1 and Figure 1. Forty-four patients were enrolled, with 43 patients receiving study treatment ($N = 10$ (4 mg), $N = 10$ (6 mg), and $N = 23$ (8 mg)). Of these, two patients in the 8-mg group did not receive PX-866, one because of early disease progression and another because of withdrawal of consent. Overall, the median number of prior treatments was 2 (range: 1–11). The most common tumour types were SCCHN ($N = 6$ out of 43; 14%), NSCLC ($N = 5$ out of 43; 12%), ovarian cancer ($N = 5$ out of 43; 12%), and prostate cancer ($N = 5$ out of 43; 12%).

Dose escalation and MTD/RP2D determination. PX-866 dosing started at 4 mg and was escalated to 6 mg, and then 8 mg (single-agent MTD). No DLTs were seen in the dose-escalation 3 cohorts, and the 8-mg cohort was expanded to a total of 23 patients with no DLTs documented.

Safety. Patients receiving at least one dose of either drug were evaluated for safety ($N = 43$). The most frequent treatment-emergent AEs were diarrhoea (77%), fatigue (61%), nausea (58%), vomiting (51%), neutropenia (40%), and peripheral oedema (40%) (Table 2). The majority (85%) of toxicities were grade 1/2

Table 1. Patient demographics and baseline characteristics

	PX-866 dose cohort			
Demographic or patient characteristic	**4 mg ($N = 10$)**	**6 mg ($N = 10$)**	**8 mg ($N = 23$)**	**Total ($N = 43$)(%)**
Age, median (years)	62	57	57	59
ECOG PS[a] = 0	3	0	6	9
ECOG PS[ab] = 1	7	10	16	33
Male	4	4	12	20 (47)
Female	6	6	11	23 (53)
White or Caucasian	9	10	21	40 (93)
Black of African American	1	0	1	2 (5)
Hispanic	0	0	1	1 (2)
Number of prior treatments	2.5 (range: 1–8)	3 (range: 1–11)	2 (range: 1–11)	2 (range: 1–11)
Number of patients with tumour type				
SCCHN	3	1	2	6 (14)
Ovarian	2	1	2	5 (12)
Prostate	0	1	4	5 (12)
NSCLC	1	1[c]	3	5 (12)
Other[d]	4	6	12	22 (51)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; PS = performance status; SCCHN = squamous cell carcinoma of the head and neck.
[a]ECOG PS was not available for one patient.
[b]One patient was an ECOG PS of 1 at screening but was an ECOG PS of 2 at the time of the first dose.
[c]One patient was enrolled but did not receive study treatment.
[d]Small cell lung ($N = 2$); adenoid cystic ($N = 2$); bladder ($N = 2$); pancreatic adenocarcinoma ($N = 2$); endometrial ($N = 2$); neurogenic lung ($N = 1$); pancreatic neuroendocrine ($N = 1$); melanoma ($N = 1$); cervical ($N = 1$); breast ($N = 1$); Merkel Cell ($N = 1$); gastroesophageal ($N = 1$); ureter ($N = 1$); rectal ($N = 1$); nasopharyngeal ($N = 1$); anal ($N = 1$); and gastric ($N = 1$).

(Table 2). Grade 3/4 AEs considered related to docetaxel and reported in 2 or more patients included the following: neutropenia ($N = 19$); leucopenia ($N = 4$); diarrhoea ($N = 3$); vomiting ($N = 3$); nausea ($N = 2$); and anaemia ($N = 2$). Grade 3/4 AEs that were considered related to PX-866 and reported in two or more patients included diarrhoea ($N = 3$) and nausea ($N = 2$). Two patients ($N = 1$ (6 mg) and $N = 1$ (8 mg)) discontinued study participation because of AEs (vomiting and abdominal pain).

Twenty patients experienced a total of 35 serious AEs (SAEs), of which 17 were considered related to study treatment. Most were considered related to docetaxel and included: ataxia ($N = 1$); febrile neutropenia ($N = 1$); pneumonia ($N = 1$); vomiting ($N = 3$); nausea ($N = 2$); and mental status changes ($N = 1$). Two SAEs of diarrhoea were considered related to PX-866 and docetaxel. There were three deaths on study. Two patients died after radiographic evidence of progressive disease and discontinuation of study drugs, and one patient died of pneumonia considered unrelated to either study drug.

PX-866 dose reductions were required in 4 out of 43 (9%) of patients (all in the 8 mg cohort), due to vomiting and/or diarrhoea. Docetaxel dose reduction was required in 18 out of 43 (42%) of patients. Fourteen of these patients required dose reduction due to neutropenia. At the investigator's discretion, docetaxel was discontinued in eight patients due to toxicity after achieving SD or better with combination therapy. These patients had received at least four (range: 4–11) cycles of combination treatment, and then continued to receive single-agent PX-866.

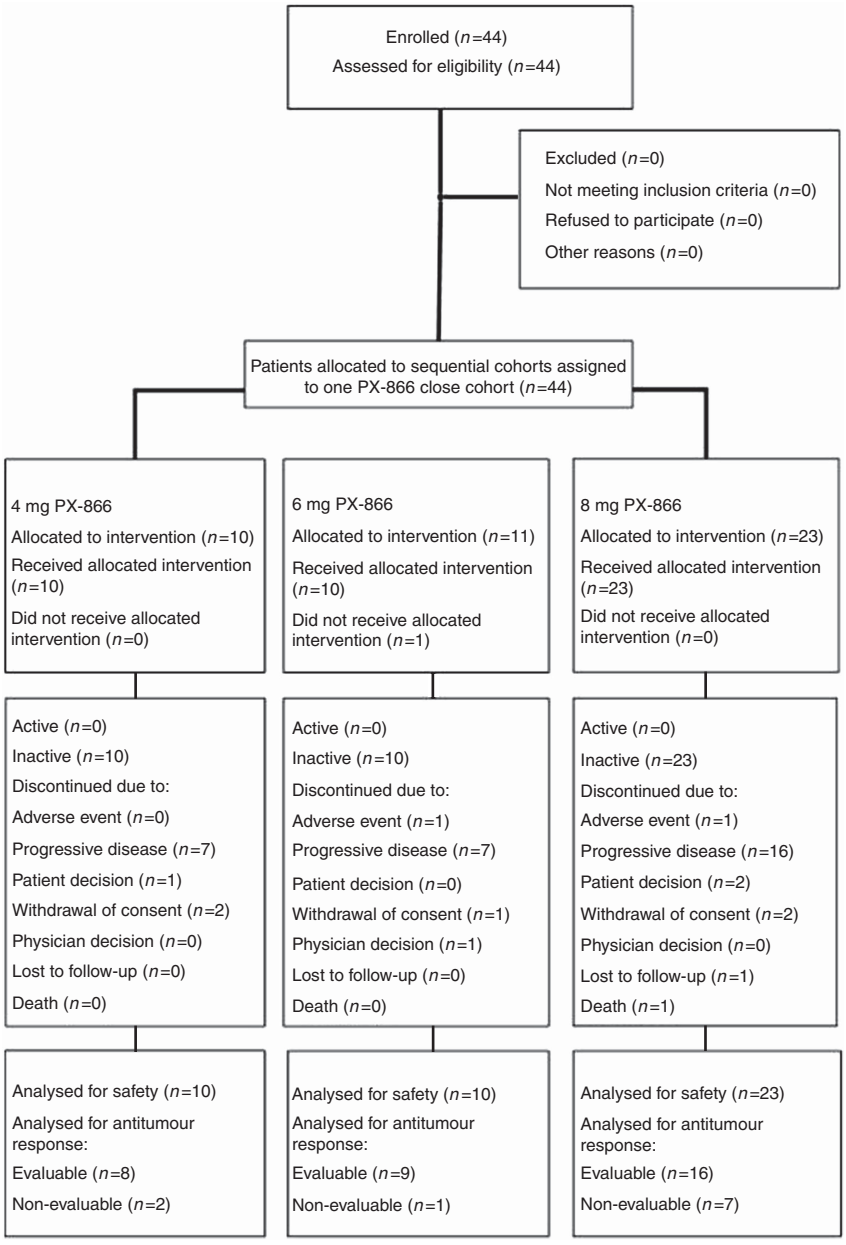

Figure 1. CONSORT diagram of the phase 1 portion of study PX-866-002. Enrollment and patient disposition in phase 1 of study PX-866-002. Forty-three patients were enrolled and treated with combination treatment (PX-866 and docetaxel), with 35 evaluable patients.

PFS and best response. Of the 43 patients treated, 12 discontinued treatment before progression for the following reasons, including 8 before a reassessment scan: AE ($N=2$), patient decision ($N=3$), withdrawal of consent ($N=5$), physician decision ($N=1$), or lost to follow-up ($N=1$). Of the 35 patients evaluable with at least one follow-up CT scan, best responses were 2 PR (6%), 22 SD (63%), and 11 PD (31%). The PRs were observed in patients with NSCLC and ovarian cancer. Ten patients (29%) had tumour shrinkage of $\geqslant 15\%$. Eleven patients had PFS of >180 days, including four patients with ovarian cancer, two patients with NSCLC, and one patient each with endometrial cancer, large cell neuroendocrine lung cancer, prostate cancer, nasopharyngeal carcinoma, and adenoid cystic carcinoma. Of the patients who discontinued docetaxel and continued on single-agent PX-866, disease control was maintained for up to 10 additional cycles, including a NSCLC patient with a *PIK3CA* mutation stable for 5 additional cycles on single-agent PX-866, and two patients with unknown mutational status who remained on single-agent PX-866 for 10 additional cycles.

Molecular correlation: PFS and best responses. We hypothesised that oncogenic *PIK3CA* mutation might be associated with improved response to PX-866, but that this effect could be overridden by mutant *KRAS*. Mutational status of *PIK3CA* and *KRAS* was obtained from archived tumour biopsies from 31 patients (Supplementary Table 1). Median PFS for *PIK3CA*-WT/*KRAS*-WT ($N=20$) was 49 days (range: 1–342) *vs* 175 days (range: 49–334) for *PIK3CA*-MUT/*KRAS*-WT ($N=6$) (two-tailed *t*-test; $P=0.23$). Patients whose mutational status ($N=12$) was unknown had a median PFS of 77.5 days (range: 1–569). There were a limited number of patients with *KRAS* mutation only (*PIK3CA*-WT/*KRAS*-MUT) ($N=3$) and dual mutations (*PIK3CA*-MUT/*KRAS*-MUT) ($N=2$).

Pharmacokinetics. Full PK data are available in Table 3, Table 4, and the Supplementary Data (Supplementary Figures 1 and 2). The exposure of PX-866 in the presence of docetaxel was similar to historical levels, and docetaxel exposure was not affected by the presence of PX-866.

Table 2. Treatment-emergent adverse events by severity and preferred term* occurring in ⩾15% of phase 1 patients

	PX-866 dose			
	4 mg (*N* = 10)	6 mg (*N* = 10)	8 mg (*N* = 23)	Total (*N* = 43)
Frequency by severity, *N* (%)				
Grade 1	32 (56)	36 (49)	84 (50)	152 (51)
Grade 2	10 (18)	30 (41)	62 (37)	102 (34)
Grade 3	8 (14)	5 (7)	15 (9)	28 (9)
Grade 4	7 (12)	3 (4)	8 (5)	18 (6)
Grade 5	0 (0)	0 (0)	0 (0)	0 (0)
Frequency by preferred term, *N* (%)				
Diarrhoea	7 (70)	8 (80)	18 (78)	33 (77)
Fatigue	6 (60)	7 (70)	13 (57)	26 (61)
Nausea	5 (50)	4 (40)	16 (70)	25 (58)
Vomiting	3 (30)	5 (50)	14 (61)	22 (51)
Neutropenia	6 (60)	5 (50)	6 (26)	17 (40)
Oedema peripheral	4 (40)	6 (60)	7 (30)	17 (40)
Decreased appetite	1 (10)	4 (40)	10 (44)	15 (35)
Dehydration	3 (30)	1 (10)	11 (48)	15 (35)
Anaemia	2 (20)	2 (20)	9 (39)	13 (30)
Constipation	2 (30)	3 (30)	8 (35)	13 (30)
Alopecia	2 (20)	6 (60)	4 (17)	12 (28)
Asthenia	1 (10)	4 (40)	6 (26)	11 (26)
Pyrexia	1 (10)	4 (40)	6 (26)	11 (26)
Cough	2 (20)	5 (50)	3 (13)	10 (23)
Bone pain	0 (0)	4 (40)	5 (22)	9 (21)
Hypokalemia	2 (20)	1 (10)	6 (26)	9 (21)
Stomatitis	1 (10)	4 (40)	4 (17)	9 (21)
Dysgeusia	2 (20)	3 (30)	3 (13)	8 (19)
Arthralgia	0 (0)	2 (20)	5 (22)	7 (16)
Dizziness	1 (10)	2 (20)	4 (17)	7 (16)
Epistaxis	1 (10)	2 (20)	4 (17)	7 (16)
Oropharyngeal pain	1 (10)	1 (10)	5 (22)	7 (16)

*Preferred terms were coded using Medical Dictionary for Regulatory Activities version 13.0.

DISCUSSION

This study demonstrates that PX-866, an oral, irreversible small-molecule PI3K inhibitor, can be safety combined with docetaxel 75 mg m^{-2} every 21 days at the maximal-tolerated single-agent dose of 8 mg daily. The most common AEs of all grades included gastrointestinal toxicities (diarrhoea, nausea, and vomiting) and fatigue. Overall, PX-866-related gastrointestinal AEs were dose related. Although the overall incidence of grade 2 AEs increased with PX-866 dose escalation, there was no increase in the frequency of grade 3 or 4 AEs. The pattern of AEs was similar to those described with either single-agent PX-866 or docetaxel, though the incidence of neutropenia was somewhat higher than seen with some second-line docetaxel trials (Schuette *et al*, 2005). Although PX-866 has not been associated with neutropenia as a single agent, a drug–drug interaction that enhances docetaxel's myelosuppressive effects cannot be ruled out. Unexpected increases in neutropenia have been seen in other docetaxel combination trials with agents thought not to be myelosuppressive (Janne *et al*, 2013; Marshall *et al*, 2013). This may have been compounded by PX-866's introduction at the neutrophil nadir on day 8 of cycle 1. PX-866 exposure in this study was similar to historical controls, and docetaxel exposure was not modified by PX-866 (Hong *et al*, 2012). PX-866 dose reductions were uncommon; docetaxel was reduced in less than half of patients. As combination therapies are most effective when all agents are given at their MTD, it is encouraging that PX-866 and docetaxel can be combined at the MTD of each single agent.

There were signs of anticancer activity in this phase 1 study. The partial response rate of 6% (2 out of 35) in evaluable patients, with a PR + SD rate of 69%, is consistent with what is expected in a heavily pretreated population and the second-line docetaxel responses in NSCLC (PR 13%, PR − SD 50%) (Roberts *et al*, 2004; Horstmann *et al*, 2005; Schuette *et al*, 2005). Overall, the median PFS for evaluable patients was 73.5 days (range: 1–569), including 31% (11 out of 35) of evaluable patients remaining on study in excess of 180 days, is encouraging and supports further investigation. It is noteworthy that several patients continued to experience SD on single-agent PX-866 after completing at least four cycles of concurrent docetaxel chemotherapy, including one patient with a *PIK3CA* mutation. One hypothesis is that PX-866 enhances the initial response to docetaxel, and then suppresses further growth through cell signalling inhibition without the cumulative toxicity of continued cytotoxic therapy. In prostate cancer xenografts, for instance, destruction of bulk tumour cells with docetaxel and cancer stem cell (CSC) suppression with a PI3K/mTOR inhibitor was more effective at suppressing growth

Table 3. Summary of docetaxel pharmacokinetics

Visit	Patient	T_{max} (h)	C_{max}(ng ml^{-1})	AUC_{last}(h*ng ml^{-1})	AUC_{INF}(h*ng ml^{-1})	Cl (L h^{-1})	Vz (L)	Half-life (h)	MRT_{INF} (h)
C1D1	*N*	43	43	43	43	43	43	43	43
	Mean	0.19	799.12	1203.79	1530.81	143.66	2993.46	14.89	15.23
	SE	0.02	146.59	235.49	270.84	10.98	273.91	1.12	1.65
	CV%	56.1	120.3	128.3	116	50.1	60	49.3	70.9
C2D1	N	35	35	35	35	35	35	35	35
	Mean	0.19	538.86	850.85	1106.26	154.1	2691.45	13.14	13.89
	SE	0.02	60.66	88.15	127.4	15.23	235.19	0.87	1.08
	CV%	48.1	66.6	61.3	68.1	58.5	51.7	39	46.1

Abbreviations: AUC = area under the curve; C = cycle; Cl = clearance; CV = coefficient of variance; INF = infinity; D = day; MRT = mean resonance time; SE = standard error; Vz = volume of distribution.

Table 4. Pharmacokinetic parameters of PX-866 metabolites (17-OH-PX-866 and 17-diOH-PX-866) from patient plasma samples following treatment with 8 mg PX-866 at cycle 1 day 8

17-OH-PX-866						
Visit	**Patient**	**Half-life (h)**	**AUC_{last} (h*ng ml^{-1})**	**AUC_{INF} (h*ng ml^{-1})**	**T_{max} (h)**	**C_{max}(ng ml^{-1})**
C1D8	*N*	13	18	13	18	18
	Mean	1.93	5.12	5.77	2.19	2.39
	SE	0.26	1.04	1.22	1.29	0.6
	CV%	48.7	85.9	76.3	250	106.5
C2D1	*N*	14	18	14	18	18
	Mean	10.33	5.09	4.58	2.44	1.39
	SE	3.85	1.42	1.25	1.29	0.37
	CV%	139.5	118	102.1	224	111.9
11,17-diOH-PX-866						
C1D8	*N*	3	13	3	13	13
	Mean	1.58	1.58	2.47	1.44	0.48
	SE	0.3	0.47	0.79	0.25	0.12
	CV%	32.6	106.4	55.5	62.4	88.4
C2D1	*N*	1	8	1	8	8
	Mean	1.85	2.08	1.79	7.08	0.25
	SE	NA	0.66	NA	3.7	0.05
	CV%	NA	89.6	NA	147.6	56.3

Abbreviations: AUC = area under the curve; C = cycle; Cl = clearance; CV = coefficeint of variance; D = day; INF = infinity; NA = not available; SE = standard error.

and decreasing CSC populations than monotherapy with either agent alone (Dubrovska *et al*, 2010). In breast cancer *in vivo* and *in vitro* models, PI3K inhibition increased caspase-3-mediated apoptosis in cells in mitotic arrest from docetaxel therapy (Wallin *et al*, 2012). The ability to provide chronic tumour suppression with a PI3K inhibitor after initial induction of response would be of clinical value, because PX-866 may be given safely for over 1 year (Hong *et al*, 2012).

We did not identify a reliable predictive biomarker for response to therapy with PX-866 plus docetaxel. In this study, *PIK3CA* mutation, *KRAS* mutation, or PTEN level by IHC did not predict outcome. It has been difficult to correlate tumour mutations or protein expression profiles with responses to PI3K inhibitors. The presence of activating *PIK3CA* mutations did predict a higher response rate to PI3K/AKT/mTOR pathway inhibitors in a mixed phase 1 population, though this study included PI3K, AKT, mTOR, and combined inhibitors (Janku *et al*, 2011; Janku *et al*, 2012b). However, in the single-agent PX-866 phase 1 study there was a suggestion of longer time on study for patients with *PIK3CA* mutations that did not meet statistical significance (Hong *et al*, 2012). Similarly, in the phase 1 study of BKM120, an oral pan-PI3K inhibitor, no correlation was reported between antitumour activity and mutation status (*PIK3CA* or *KRAS*) or PTEN protein expression (Bendell *et al*, 2012). Moreover, alterations in PTEN level do not appear to predict responses to inhibitors of the PI3K/AKT/mTOR pathway, though this may reflect PTEN-deficient tumours' dependence on p110β rather than p110α (Jia *et al*, 2008; Wee *et al*, 2008; Janku *et al*, 2012a). At this point, an accurate predictor of benefit to PI3K/AKT/mTOR inhibition remains elusive.

In conclusion, this phase 1 combination study of PX-866 and docetaxel established the RP2D as 8 mg of PX-866 when given with docetaxel at full dose. Tumour mutational analysis and protein expression of PTEN did not correlate with outcome. PK analysis revealed no drug–drug interaction between PX-866 and docetaxel. The combination's favourable toxicity profile and antitumour activity support its further clinical development. A randomised phase 2 open-label study of docetaxel +/− PX-866 in second-line NSCLC and platinum-refractory SCCHN (NCT01204099) is ongoing.

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CONFLICT OF INTEREST

Alex A Vo, Scott Peterson, Luke Walker, and Diana Hausman are employees of Oncothyreon Inc. Antonio Jimeno has received laboratory research support from Oncothyreon Inc.; the University of Colorado holds intellectual property interests. The remaining authors declare no conflict of interest.

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