A Randomized, Phase 2 Trial of Docetaxel with or without PX-866, an Irreversible Oral Phosphatidylinositol 3-Kinase Inhibitor, in Patients with Relapsed or Metastatic Non–Small-Cell Lung Cancer

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Introduction: The phosphotidylinositol-3 kinase/serine-threonine kinase (AKT)/mammalian target of rapamycin signaling pathway is frequently altered in non–small-cell lung cancer (NSCLC). PX-866 is an oral, irreversible, pan-isoform inhibitor of phosphotidylinositol-3 kinase. Preclinical models revealed synergy with docetaxel and a phase 1 trial demonstrated tolerability of this combination. This randomized phase 2 study evaluated PX-866 combined with docetaxel in patients with advanced, refractory NSCLC.

Methods: Patients with locally advanced, recurrent, or metastatic NSCLC who had received at least one and no more than two prior systemic treatment regimens were randomized (1:1) to a combination of docetaxel (75 mg/m^2 intravenous every 21 days) with or without PX-866 (8 mg orally daily; arms A and B, respectively). The primary end point was progression-free survival (PFS). Secondary end points included objective response rate, overall survival (OS), toxicity, and correlation of biomarker analyses with efficacy outcomes.

Results: A total of 95 patients were enrolled. Median PFS was 2 months in arm A and 2.9 months in arm B ($p = 0.65$). Objective response rates were 6% and 0% in arms A and B, respectively ($p = 0.4$). There was no difference in OS between the two arms (7.0 versus 9.2 months; $p = 0.9$). Grade 3 or higher adverse events were infrequent, but more common in the combination arm with respect to diarrhea (7% versus 2%), nausea (4% versus 0%), and vomiting (7% versus 0%). *PIK3CA* mutations or *PTEN* loss were infrequently observed.

Conclusion: The addition of PX-866 to docetaxel did not improve PFS, response rate, or OS in patients with advanced, refractory NSCLC without molecular preselection.

Key Words: *PIK3CA*, Phosphotidylinositol-3 kinase, Docetaxel, Combination therapy, Non–small-cell lung cancer.

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The phosphotidylinositol-3 kinase (PI3K)/serine-threonine kinase (AKT)/mammalian target of rapamycin signaling pathway is frequently altered in human cancers, leading to cell proliferation, increased expression of survival genes, and decreased expression of proapoptotic signals.[1] In non–small-cell lung cancer (NSCLC), the PI3K pathway may play a role in cancer proliferation and response to therapy, particularly in squamous cell carcinomas.[2] This can occur by means of *PIK3CA* activation, mutation, or amplification; *PTEN* loss; or up-regulation of upstream tyrosine kinases.[3] PX-866 is a novel oral, pan-isoform inhibitor of PI3K.[4] In a phase 1 study, both PX-866 and docetaxel were given at their single-agent maximal tolerated doses in patients with advanced cancers.[5] The majority of adverse events (AEs) were gastrointestinal and grade 2 or lower similar to the single-agent PX-866 trial.[6] Therefore, we conducted an open-label, randomized, phase 2 trial comparing docetaxel alone versus docetaxel plus PX-866

in patients with relapsed/metastatic (R/M) NSCLC in the second- or third-line setting.

MATERIALS AND METHODS

Eligibility Criteria

Subjects had R/M NSCLC for which they had received one to two prior systemic therapies, including up to one platinum-based chemotherapy regimen. Other key inclusion criteria were age 18 years or older, measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria,[7] Eastern Cooperative Oncology Group performance status 0 to 1, life expectancy 3 months or more, and adequate hematologic, hepatic, and renal function. Treatment with any systemic anticancer or radiation therapy was prohibited within 4 weeks of study drug dosing. Patients with adequately treated and stable brain metastases were eligible. Salient exclusion criteria included known HIV infection; medical, social, or psychological factors affecting safety or compliance; grade 2 or higher neuropathy; history of hypersensitivity to docetaxel or other drugs formulated with polysorbate; pregnant/breastfeeding; prior docetaxel for R/M NSCLC or within 6 months of enrollment in the curative setting; or any prior treatment with a PI3K inhibitor. Each center's institutional review board granted approval and written informed consent was mandatory.

Treatment and Efficacy Assessments

Patients were randomized to PX-866 8 mg by mouth daily with docetaxel 75 mg/m^2 intravenous once every 21 days or docetaxel 75 mg/m^2 intravenous once every 21 days alone in a 1:1 manner without stratification factors. Colony-stimulating factors and antiemetics were permitted in any cycle according to institutional guidelines. All patients received dexamethasone 8 mg orally twice daily for 3 days starting the day before docetaxel administration. Patients were evaluated for progression every two cycles. Patients continued therapy as long as they had stable disease or better per RECIST 1.1 criteria and lacked unacceptable toxicity or withdrawal of consent. Patients in the combination arm were allowed to continue PX-866 alone after discontinuation of docetaxel.

Safety Assessment

Safety assessments included vital signs, laboratory assessments, and physical examinations. AEs were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.02. Up to two dose reductions were allowed for docetaxel (60 and 45 mg/m^2) and three dose reductions for PX-866 (6, 4, and 2 mg/day). Subjects requiring additional dose reductions of PX-866 were removed from study. Study drugs were discontinued if treatment needed to be delayed by more than 2 weeks.

Biomarker Measurements

Optional archival tumor specimens were evaluated for *PIK3CA* and *KRAS* mutations and *PTEN* expression by immunohistochemistry as previously described.[5,6]

Statistics

The primary end point of this study was progression-free survival (PFS) and secondary end points were objective response rate (ORR), incidence and severity of AEs, overall survival (OS), and exploratory end points of biomarker correlations with efficacy. A docetaxel-alone control of median PFS of 3 months was assumed for the NSCLC study population. With a one-sided 0.20 false-positive error rate, a projected 1-year enrollment period with an additional 0.5 years of follow-up before analysis and a control over experimental hazard ratio of 1.5, a total of 80 patients were required for the log-rank test with 0.80 power to detect a statistically significant benefit of the combination arm of PX-866 plus docetaxel versus docetaxel alone. Assuming a drop-off rate of 10%, a total of 88 patients (44 per arm) with NSCLC were targeted to enroll.

RESULTS

Patient Characteristics

Ninety-five patients were enrolled between November 2011 and July 2012. Of these, 48 and 47 patients were randomized to the PX-866 plus docetaxel (arm A) and docetaxel-alone group (arm B), respectively. Baseline characteristics were well balanced between the two arms excluding histology (χ^2 test, $p = 0.04$) and sex (χ^2 test, $p = 0.08$; Table 1). The

TABLE 1. Patient Demographics

	PX-866 + Docetaxel ($n = 48$)	Docetaxel ($n = 47$)
Median age (range)	65 (44–84)	60 (35–84)
Sex		
Female	15 (31%)	23 (49%)
Male	33 (69%)	24 (51%)
Ethnicity		
Caucasian	39 (81%)	34 (72%)
African American	5 (10%)	3 (6%)
Other	4 (8%)	10 (21%)
ECOG		
0	14 (29%)	12 (26%)
1	34 (71%)	35 (75%)
Histology		
Adenocarcinoma	34 (71%)	24 (51%)
Squamous	8 (17%)	12 (26%)
Other	6 (13%)	11 (23%)
Stage at diagnosis, % I/II/III/IV	2/2/25/71	2/4/23/70
Stage at baseline, III/IV, N (%)	3 (6%)/45 (94%)	2 (4%)/45 (96%)
Prior anticancer therapy	47 (98%)	47 (100%)
Systemic therapy	39 (81%)	41 (87%)
Radiotherapy	10 (21%)	11 (23%)
Systemic/radiotherapy	17 (35%)	11 (23%)
No. of prior systemic therapies, mean/range	1.8 (1–7)	1.5 (1–5)
Median time since diagnosis, months	10.8	10.9

ECOG, Eastern Cooperative Oncology Group.

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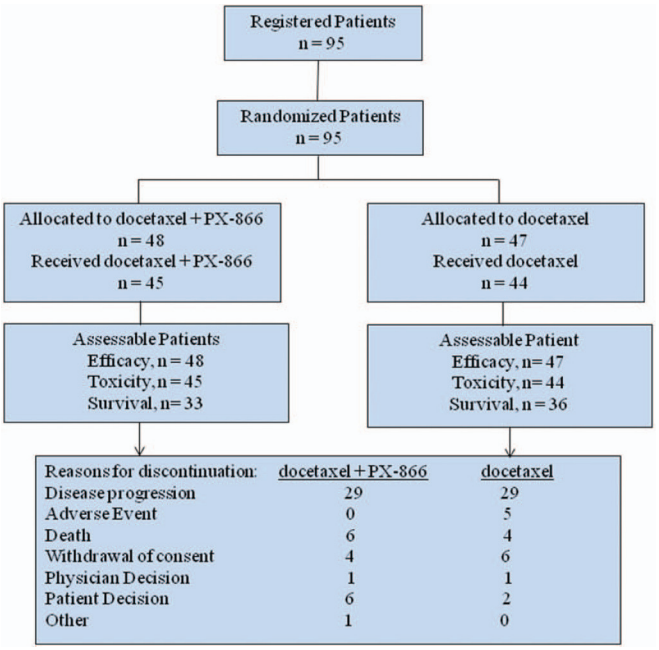

FIGURE 1. CONSORT diagram showing the progress of patients though the trial, adapted from Begg et al, Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996;276:637–639.

groups were similar with respect to numbers of prior systemic therapies and median time since diagnosis.

Treatment Delivered

In arm A, 45 patients (94%) received at least one dose of PX-866 and/or docetaxel, whereas 47 patients (94%) in arm B received at least one dose of docetaxel (Fig. 1). The median number of docetaxel cycles administered was 2 (range, 1–16) and 3.5 (range, 1–16) in arms A and B, respectively. Ten patients experienced docetaxel dose interruptions or modifications (3 in arm A and 7 in arm B). Twenty-seven patients (60%) experienced a total of 52 dose interruptions or modifications of PX-866, with 35 (67%) disruptions due to AEs. The most common reasons for dose disruptions include diarrhea ($n = 6$) and pneumonia ($n = 3$). A total of 58 patients (29 in each arm) were taken off study because of disease progression.

TABLE 2. Response Rate

	PX-866 + Docetaxel ($n = 48$)	Docetaxel ($n = 47$)
CR	0	0
PR	3 (6%)	0 (0%)
SD	14 (29%)	25 (53%)
Progressive disease	17 (35%)	9 (19%)
Not evaluable	14 (29%)	13 (28%)
Disease control rate (CR/PR/SD)	17 (35%)	25 (53%)

Response rate represent best overall response rate (investigator).
CR, complete response; PR, partial response; SD, stable disease.

Efficacy Evaluation

Seventy patients (74%) were evaluable for response as measured by RECIST 1.1 (34 in arm A and 36 in arm B). There was no difference in ORR (complete response plus partial responses; $p = 0.12$) or disease control rate (complete response + partial response + stable disease after 2 cycles; $p = 0.97$) between the two arms (Table 2). Median PFS was 2 months (95% confidence interval [CI], 1.6–2.9) for arm A and 2.9 months (95% CI, 1.6–4.8) for arm B ($p = 0.65$; Fig. 2). Median OS was 7.9 months in arm A (95% CI, 4.5–11.1) and 9.4 months in arm B (95% CI, 6.1 to not reached; $p = 0.9$; Fig. 3). Of the 50 patients whose archival tumors were analyzed, four patients had *PIK3CA* mutations (3 in arm A and 1 in arm B), whereas seven patients had *KRAS* mutations (4 in arm A and 3 in arm B). *PTEN* expression was reduced or absent in nine patients (3 in arm A and 6 in arm B). *PIK3CA* mutation, *KRAS* mutation, and *PTEN* immunohistochemistry could not be correlated with PFS, ORR, or OS because of their rarity.

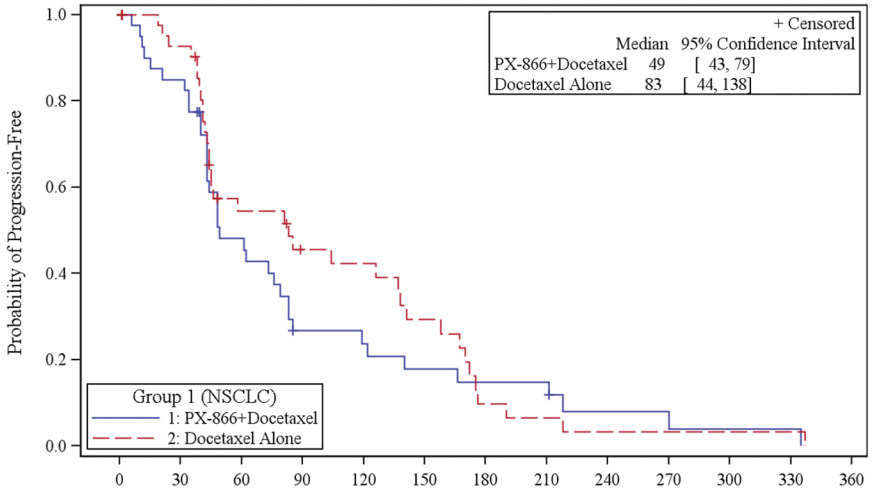

FIGURE 2. Kaplan–Meier curves for progression-free survival (days). NSCLC, non–small-cell lung cancer.

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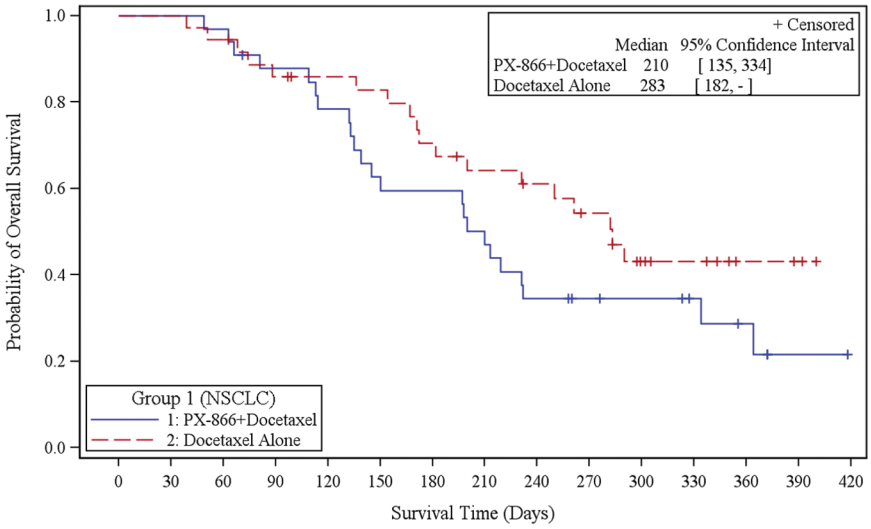

FIGURE 3. Kaplan–Meier curves for overall survival (days). NSCLC, non–small-cell lung cancer.

Safety and Tolerability

Eighty-nine enrolled patients received at least one treatment on protocol and were considered evaluable for safety. In both arms, most AEs were 2 or less (Table 3). There seemed to be more all-grade toxicity in arm A including diarrhea (76% versus 25%), nausea (56% versus 30%), vomiting (42% versus 21%), anorexia (40% versus 18%), and fatigue (62% versus 43%). However, there were few grade 3 or higher AEs in either arms excluding neutropenia (9% and 25% in arms A and B, respectively). No patients in arm A withdrew due to AEs, whereas five patients in arm B were taken off study because of toxicity.

DISCUSSION

The addition of PX-866 to docetaxel failed to improve PFS, ORR, or OS in patients with R/M NSCLC. Both clinical

TABLE 3. Selected Adverse Events

	PX-866 ± Docetaxel (n = 45)		Docetaxel Alone (n = 44)	
Adverse Event	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Hematological				
Anemia	7 (16%)	2 (4%)	10 (23%)	3 (7%)
Neutropenia	14 (31%)	4 (9%)	15 (34%)	11 (25%)
Thrombocytopenia	2 (4%)	1 (2%)	0 (0%)	0 (0%)
Febrile neutropenia	4 (9%)	4 (9%)	4 (9%)	4 (9%)
Nonhematological				
Abdominal pain	8 (18%)	2 (4%)	3 (17%)	1 (2%)
Diarrhea	34 (76%)	3 (7%)	12 (25%)	1 (2%)
Constipation	10 (22%)	0 (0%)	10 (22%)	1 (2%)
Nausea	25 (56%)	2 (4%)	13 (30%)	0 (0%)
Stomatitis	5 (11%)	0 (0%)	7 (16%)	1 (2%)
Vomiting	19 (42%)	3 (7%)	9 (21%)	0 (0%)
Fatigue	28 (62%)	2 (4%)	19 (43%)	1 (2%)
Anorexia	18 (40%)	0 (0%)	8 (18%)	0 (0%)
Peripheral edema	9 (20%)	1 (2%)	9 (20%)	0 (0%)
Arthralgia	7 (15%)	0 (0%)	9 (18%)	0 (0%)
Peripheral neuropathy	4 (9%)	1 (2%)	2 (5%)	0 (0%)
Cough	9 (20%)	0 (0%)	6 (14%)	1 (2%)
Dyspnea	10 (22%)	4 (9%)	3 (7%)	1 (2%)
Alopecia	8 (18%)	0 (0%)	8 (18%)	0 (0%)
Rash	9 (20%)	0 (0%)	2 (5%)	0 (0%)
Transaminitis	5 (11%)	0 (0%)	0 (0%)	0 (0%)
Hyperglycemia	1 (2%)	0 (0%)	2 (5%)	1 (2%)

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and biological reasons may account for the lack of benefit. The imbalance between adenocarcinoma histology and female sex, both favorable prognostic factors, may have confounded the results[8,9]; however, each arm had an increased proportion of one of these favorable factors, so it is difficult to fully explain the study findings based on these imbalances. Perhaps a more compelling explanation for the lack of clinical benefit rests in the patients' tumor biology which revealed very few genetic alterations (*PIK3CA* mutations, *PTEN* loss) thought to predict sensitivity to PI3K inhibitors. Although it has been difficult to identify predictive biomarkers across all tumor types for this class of drugs, preclinical data suggest that PI3K pathway activation may correlate with sensitivity to PI3K inhibitors.[10–13] Given that the frequencies of these alterations are influenced by the underlying histology and are more common in squamous cell carcinoma, under-representation of patients with squamous cancers may have contributed to the negative outcome.

Although the addition of PX-866 to docetaxel was reasonably well tolerated, all-grade toxicity seemed to be more pronounced in the combination arm. Many of AEs are consistent with other phase 1/2 studies evaluating PI3K inhibitors including our own phase 1 study.[5] Of note, there are few studies with reported safety outcomes evaluating PI3K inhibitors in combination with docetaxel, and our study adds substantial experience with this combination. To date, rash, hyperglycemia, and transaminase elevations seem to be class effects of PI3K/AKT/mammalian target of rapamycin inhibition, although gastrointestinal side effects have been reported in studies as well.[14] Interestingly, despite more frequent AEs in the combination arm, no patients were taken off study because of toxicity in this arm suggesting that the toxicity was manageable.

In summary, the addition of PX-866 to docetaxel did not improve clinical outcomes over docetaxel alone for a molecularly unselected population of patients with R/M NSCLC. Despite these negative results, the scientific rationale in a target-selected population remains compelling, and further studies investigating inhibition of this pathway in NSCLC should be carried out. Investigations should focus on appropriate biomarker or histology selection to optimize clinical benefit.

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