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COMPOUND NUMBER: PF-3512676

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: This drug is not marketed in the United States (US).

NATIONAL CLINICAL TRIAL NO.: NCT00254904

PROTOCOL NO.: A8501002

PROTOCOL TITLE: International, Randomized, Open-Label, Phase 3 Trial of Gemcitabine/Cisplatin Plus PF-3512676 Versus Gemcitabine/Cisplatin Alone as First-Line Treatment of Patients with Advanced Non-Small Cell Lung Cancer

Study Centers: The study was conducted at 115 centers in 24 countries (including 4 centers that did not randomize subjects) as follows: 1 center in Austria, 10 centers in Belgium (including 3 centers that did not randomize subjects); 4 centers in Brazil (including 1 center that did not randomize subjects), 6 centers in Canada, 5 centers in China, 3 centers in the Czech Republic, 6 centers in Germany, 2 centers in Hong Kong, 5 centers in Hungary, 6 centers in India, 2 centers in Israel, 5 centers in Italy, 4 centers in the Republic of Korea, 5 centers in the Netherlands, 8 centers in Poland, 5 centers in Portugal, 1 center in Singapore, 4 centers in Slovakia, 2 centers in South Africa, 7 centers in Spain, 4 centers in Taiwan, 3 centers in Turkey, 10 centers in the United Kingdom, and 7 centers in the US.

Study Initiation and Completion Dates: 29 November 2005 to 25 June 2008

Phase of Development: Phase 3

Study Objectives: The objectives were to assess the efficacy and safety of PF-3512676 administered in combination with gemcitabine/cisplatin chemotherapy as first-line treatment of subjects with locally advanced (Stage IIIB with pleural effusion) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) and to compare it to efficacy and safety of gemcitabine/cisplatin chemotherapy alone.

Primary Objective:

- To compare overall survival (OS) in subjects randomized to gemcitabine/cisplatin + PF-3512676 (Investigational Treatment Arm) versus that in subjects randomized to gemcitabine/cisplatin alone (Control Treatment Arm).

Secondary Objectives:

- To compare additional measures of efficacy, safety and health-related quality of life and disease/treatment-related symptoms in subjects randomized to gemcitabine/cisplatin + PF-3512676 versus subjects randomized to gemcitabine/cisplatin alone.

- To evaluate the effect of PF-3512676 on the pharmacokinetics (PK) of gemcitabine and cisplatin.

- To evaluate the PK of PF-3512676 when administered in combination with gemcitabine and cisplatin.

METHODS

Study Design: This was an international, multicenter, open-label, 2-arm, randomized Phase 3 study. It was planned to enroll at least 800 subjects (400 per arm) over approximately 13 months.

Subjects enrolled in the study were randomized (1:1) to either the investigational treatment arm (Arm A) or to the control treatment arm (Arm B):

- Subjects randomized to Arm A were to receive standard platinum-based doublet chemotherapy consisting of gemcitabine and cisplatin plus PF-3512676 administered in 3-week cycles. Chemotherapy treatment was to be continued for a maximum of 6 cycles. After completion or discontinuation of chemotherapy, for reasons other than disease progression, subjects were to have continued to receive weekly single agent PF-3512676 maintenance.

- Subjects randomized to Arm B were to receive standard platinum-based doublet chemotherapy consisting of gemcitabine and cisplatin administered in 3-week cycles. Chemotherapy treatment was to be continued for a maximum of 6 cycles.

Chemotherapy and/or PF-3512676 were to have been discontinued upon disease progression, unacceptable treatment-related toxicity, physician decision or subject refusal to continue study treatment.

PK assessments were planned for approximately 30 subjects enrolled in Arm A. PK assessments were only undertaken in appropriate subjects at designated study sites equipped to perform high quality PK sampling.

Number of Subjects (Planned and Analyzed): It was planned to enroll at least 800 subjects. Overall, 839 subjects were randomized and were included in the All Randomized as Randomized population; 819 of these subjects were treated and were included in the As Treated population.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were 18 years of age or older with a histologically or cytologically confirmed diagnosis of NSCLC (Stage IIIB with pleural effusion or Stage IV disease). Eligible subjects had measurable disease, defined by at least

1 lesion that could be accurately measured in at least 1 dimension as ≥20 mm with conventional techniques or ≥10 mm with spiral computed tomography scan within 28 days prior to the planned start of study treatment. Subjects were to have received no prior systemic treatment for NSCLC with chemotherapy, immunotherapy, biologic response modifiers or other investigational drugs. Subjects with any histological/cytological evidence of small cell or carcinoid lung cancer or known central nervous system metastasis were not eligible. Eligible subjects were to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, adequate organ function, no pre-existing autoimmune diseases, no chronic systemic corticosteroid therapy and a lack of serious medical or psychiatric condition.

Study Treatment: *Treatment Arm A*: Standard platinum-based doublet chemotherapy consisting of gemcitabine (1250 mg/m^2, intravenously over 30 minutes) followed by cisplatin (75 mg/m^2 intravenously over 1-2 hours) administered on Day 1 of a 3-week cycle. In addition, subjects received gemcitabine (1250 mg/m^2, intravenously over 30 minutes) followed by PF-3512676 (0.20 mg/kg, subcutaneously) on Day 8 of each cycle and PF-3512676 (0.20 mg/kg, subcutaneously) on Day 15 of each cycle. Chemotherapy was continued for a maximum of 6 cycles. After completion or discontinuation of chemotherapy, for reasons other than disease progression, subjects continued to receive weekly single agent PF-3512676 (0.2 mg/kg) maintenance starting 3 weeks after Day 1 of the final cycle of chemotherapy.

Treatment Arm B: Standard platinum-based doublet chemotherapy consisting of gemcitabine (1250 mg/m^2, intravenously over 30 minutes) followed by cisplatin (75 mg/m^2 intravenously over 1-2 hours) administered on Day 1 and gemcitabine (1250 mg/m^2, intravenously over 30 minutes) on Day 8 of a 3-week cycle. Chemotherapy was continued for a maximum of 6 cycles. Subjects in Treatment Arm B were not permitted to crossover to receive PF-3512676.

Efficacy Evaluations: Baseline imaging tumor assessments were to be performed within 28 days prior to commencing study treatment. Post-baseline tumor assessments were performed in all subjects at the end of every other cycle, while receiving chemotherapy and every 8 weeks thereafter, until radiological disease progression was documented or the subject commenced a subsequent anticancer therapy. All subjects with responding tumors (complete response [CR] or partial response [PR]) were to have the response confirmed no sooner than 4 weeks after the initial documentation of response. Objective tumor response was measured using the Response Evaluation Criteria in Solid Tumors. Efficacy endpoints included OS, overall confirmed objective response rate (ORR), progression-free survival (PFS), and time to tumor progression (TTP).

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: A subset of subjects in Arm A had blood samples collected for determination of plasma PK of PF-3512676 given in combination with gemcitabine and cisplatin and for the evaluation of the effect of PF-3512676 on the PK of gemcitabine and cisplatin. Only concentration listings were presented.

Changes in health-related quality of life (HQoL) and disease/treatment-related symptoms were assessed in each subject using the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-LC13. Subjects completed the self-administered questionnaire at baseline, on Day 1 of each chemotherapy cycle (prior to having any tests or receiving any chemotherapy and prior to any discussion of the subject's progress with their physician) and at the end of chemotherapy (either when the subject completed or discontinued chemotherapy).

Safety Evaluations: Post-baseline safety evaluations included adverse events (AEs), safety laboratory tests, weight and assessment of ECOG PS**.** Blood samples for assessment of immunopathology (including antinuclear antibody, anti-double stranded [ds] DNA, anti-single stranded [ss] DNA, antineutrophil cytoplasmic antibody [ANCA] and rheumatoid factor [RF]) were collected in Arm A subjects only at baseline and final study visit and analyzed following study completion.

Statistical Methods: For OS, treatment arms were compared by a two-sided stratified log rank test accounting for the stratification factors of disease stage (IIIB with pleural effusion vs IV), smoking history (smoked vs never smoked), and sex (male vs female) (those factors used in randomization as collected at randomization). Kaplan-Meier curves by treatment arms were produced. Kaplan-Meier plots were also prepared for each of the 8 combinations of strata. Median survival was evaluated based on Kaplan-Meier methods for each treatment. Brookmeyer Crowley method was used for 95% confidence interval (CI) for the median OS. PFS and TTP were analyzed in the same manner. ORR rates for the 2 treatment arms were compared using Pearson's chi square test adjusted for stratification factors.

HQoL subscales and single item subscores were summarized by the mean and median for each arm. The change from baseline for all domains was examined by treatment arm.

AEs were summarized by treatment and by the frequency of subjects experiencing treatment emergent AEs corresponding to body systems and preferred term. AEs were summarized by worst Common Terminology Criteria for Adverse Events (CTCAE) grade. AEs were summarized by cycle and by relatedness to study treatment.

Hematological and chemistry laboratory data were summarized by treatment and by cycle (Cycle 1, Cycle >1), and by cycles during chemotherapy and cycles post-chemotherapy. Each subject was summarized by the worst severity grade observed for a particular laboratory parameter. Immunopathology data were summarized using shift tables.

RESULTS

Subject Disposition and Demography: Subject evaluation groups are summarized in Table 1.

Overall, approximately 70% of subjects completed the study (died) and approximately 30% of subjects discontinued or were still alive when data collection stopped.

Table 1. Subject Evaluation Groups

Number (%) of Subjects	Arm A	Arm B	Overall
As Randomized			
Randomized			839
Treated	404	415	819
Completed[a]	285 (68.5)	288 (68.1)	573 (68.3)
Discontinued[a]	131 (31.5)	135 (31.9)	266 (31.7)
As Treated			
Randomized			839
Treated	393	426	819
Completed	273 (69.5)	297 (69.7)	570 (69.6)
Discontinued	120 (30.5)	129 (30.3)	249 (30.4)
Analyzed for Safety[b]			
Adverse Events	393 (100.0)	426 (100.0)	819 (100.0)
Laboratory Data	393 (100.0)	412 (96.7)	805 (98.3)

Subjects were considered to be a study completer if they died.
[a] For the percentage of subjects, the denominator was the number of subjects randomized (416 on Arm A, 423 on Arm B, 839 overall)
[b] For the percentage of subjects, the denominator was the number of subjects treated in the As Treated population (393 on Arm A, 426 on Arm B, 819 overall).

Overall, 249 treated subjects were discontinued from the study; 120 subjects who received gemcitabine/cisplatin plus PF-3512676 and 129 subjects who received gemcitabine/cisplatin. The most common reason for discontinuation was study terminated by the sponsor (ie, the subject was still alive when data collection stopped): 94 subjects who received gemcitabine/cisplatin plus PF-3512676 and 98 subjects who received gemcitabine/cisplatin were discontinued for this reason.

Demographic and baseline characteristics are summarized in Table 2.

Table 2. Demographic and Baseline Characteristics - All Randomized as Randomized

	Arm A (N=416)	Arm B (N=423)
Sex, number (%) of subjects		
Male	294 (70.7)	297 (70.2)
Female	122 (29.3)	126 (29.8)
Age, years		
Mean (standard deviation)	59.9 (9.1)	59.9 (9.6)
Median (range)	60 (28-84)	60 (32-85)
Race		
White	312 (75.0)	321 (75.9)
Black	4 (1.0)	4 (0.9)
Asian	98 (23.6)	96 (22.7)
Other	2 (0.5)	2 (0.5)
Current Disease Stage		
Stage IIIB with effusion	41 (9.9)	45 (10.6)
Stage IV	375 (90.1)	378 (89.4)
Histological Classification		
Squamous cell carcinoma	131 (31.5)	133 (31.4)
Adrenocarcinoma	185 (44.5)	204 (48.2)
Large cell	31 (7.5)	29 (6.9)
Other	71 (17.1)	67 (15.8)
ECOG Performance Status		
0	123 (29.6)	127 (30.0)
1	272 (65.4)	287 (67.8)
Smoking Status		
Smoked	352 (84.6)	353 (83.5)
Never smoked	64 (15.4)	70 (16.5)
Prior Weight Loss[a]		
Yes	63 (15.1)	57 (13.5)
No	353 (84.9)	366 (86.5)
Lactate Dehydrogenase, number (%) of subjects		
Normal	245 (58.9)	225 (53.2)
Abnormal	142 (34.1)	163 (38.5)

N=number of subjects; ECOG = Eastern Cooperative Oncology Group
[a] Weight loss >5% during the previous 6 months which was captured as an adverse event with preferred term 'weight decreased'.

Efficacy Results: Overall, 573/839 subjects (68.3%) had an event (died) and 266/839 subjects (31.7%) were censored, primarily because they were alive at the time when data collection ceased (191/266 censored subjects, 71.8%) (Table 3). The percentage of subjects with an event was similar for both arms. There were no significant treatment

differences in terms of the Kaplan Meier plots, median survival, approximately 11 months for both arms, or in the percentage of subjects achieving 1-year survival, approximately 45% for both arms.

Table 3. Overall Survival - All Randomized as Randomized

Kaplan-Meier Estimate	Arm A (N=416)	Arm B (N=423)	p-value	Hazard Ratio[a]
Number (%) of Subjects with Events	286 (68.8)	287 (67.8)		
Cause of Death, number (%) of subjects[b]:				
Disease under study	247 (86.4)	254 (88.5)		
Adverse event	24 (8.4)	21 (7.3)		
Other	6 (2.1)	6 (2.1)		
Unknown	9 (3.1)	6 (2.1)		
Number (%) of Subjects Censored	130 (31.3)	136 (32.2)		
Median Survival, months (95% CI)[c]	11.04 (9.63, 12.58)	10.68 (9.20, 12.39)	0.9777[d]	0.9976 (0.8464, 1.1760)
% Subjects Achieving 1-Year Survival (95% CI)[e]	47.03% (42.08%, 52.00%)	45.67% (40.75%, 50.60%)	0.7024[f]	
Reason(s) for Censoring, number (%) of subjects[g]				
Lost to follow-up	18 (13.85)	17 (12.50)		
Withdrawal of consent	14 (10.77)	17 (12.50)		
Other withdrawal from study	5 (3.85)	4 (2.94)		
Still alive when data collection ceased	93 (71.54)	98 (72.06)		

N = number of subjects; CI = confidence interval
[a] A value >1 favors Arm A.
[b] Denominator is the number of events (deaths).
[c] Using Brookmeyer Crowley method.
[d] p-value from two-sided stratified log rank test accounting for the stratification factors of disease stage (IIIB with pleural effusion vs IV), smoking history (smoked vs never smoked), and sex (male vs female).
[e] Using the Greenwood formula
[f] p-value calculated by the normal approximation using the Kaplan-Meier estimates of 1-year survival rates and their standard error estimates based on the Greenwood formula.
[g] Denominator is number of subjects censored.

Overall, 700/839 subjects (83.4%) had an event (progression or death). The percentage of subjects with an event was similar for both arms. There were no significant treatment differences in terms of the Kaplan-Meier plots, median PFS, approximately 5 months for both arms, or in the percentage of subjects achieving 6 months PFS, approximately 40% for both arms.

Overall, 538/839 subjects (64.1%) had an event (progression). The percentage of subjects with an event was similar for both arms. There were no significant treatment differences in terms of the Kaplan-Meier plots, median TTP, approximately 5.9 months for both arms. The

percentage of subjects with tumor progression at 6 months was also similar for both arms, approximately 48%.

A total of 134/416 subjects (32.2%; 95% CI: 27.7%, 36.7%) in Arm A and 131/423 subjects (31.0%; 95% CI: 26.6%, 35.4%) in Arm B were considered to have experienced an objective response per investigator (CR or PR). This difference was not considered to be statistically significant (p=0.7542).

For the HQoL evaluations, only clinically relevant changes defined as 5 points or more (in absolute value) within each treatment at any cycle are considered important. Improvement or worsening was established if the 95% CI of the mean change did not include zero. Subjects in Arm A reported significant improvement in emotional functioning, insomnia and pain scores on the EORTC QLQ-C30. For subjects in Arm B, dyspnea, pain, and insomnia scores improved, but there were no improvements in any of the functional scores. On the QLQ-LC13, subjects in Arm A reported improvements in cough and chest pain, whereas subjects in Arm B reported improvements in cough, hemoptysis, chest pain and arm pain.

Global health status/QoL, physical, role, cognitive and social functioning scores and the symptom scores of fatigue, nausea/vomiting, dyspnea and appetite loss on the EORTC QLQ-C30 worsened for subjects in Arm A. In contrast, only physical, role, cognitive, and social functioning scores and the symptom scores of fatigue, nausea/vomiting, and appetite loss exhibited significant worsening for subjects in Arm B. On the QLQ-LC13, symptom scores for dyspnea, sore mouth, peripheral neuropathy, and alopecia worsened for subjects in Arm A. Relatively fewer symptom scores (ie, sore mouth, peripheral neuropathy, alopecia) worsened for subjects in Arm B.

Pharmacokinetic, Pharmacodynamic, and/or Other Results: HQoL assessments showed improvements in functional and symptom scales that were similar in both treatment arms with worsening in more functional scales in the PF-3512676 arm, whereas more symptom scales showed worsening in the control arm.

Safety Results: An overall summary of AEs is presented in Table 4. Most AEs were considered to be related to PF-3512676 and/or chemotherapy.

Table 4. Overall Summary of Treatment-Emergent Adverse Events – As Treated

	All Causalities		PF-3512676 Related	PF-3512676 Related or Chemotherapy Related	
Number (%) of Subjects	**Gemcitabine/ Cisplatin + PF-3512676**	**Gemcitabine/ Cisplatin**	**Gemcitabine/ Cisplatin + PF-3512676[a]**	**Gemcitabine/ Cisplatin + PF-3512676**	**Gemcitabine/ Cisplatin**
Evaluable for AEs	393	426	393	393	426
Number of AEs	4362	3107	1078	3010	1945
With AEs	389 (99.0)	413 (96.9)	256 (65.1)	380 (96.7)	380 (89.2)
With SAEs	170 (43.3)	138 (32.4)	31 (7.9)	102 (26.0)	53 (12.4)
With Grade 3/4 AEs	331 (84.2)	295 (69.2)	94 (23.9)	292 (74.3)	228 (53.5)
With Grade 5 AEs	39 (9.9)	44 (10.3)	1 (0.3)	2 (0.5)	4 (0.9)
Discontinued due to AEs	130 (33.1)	93 (21.8)	30 (7.6)	86 (21.9)	44 (10.3)
Dose Reduced or Temporary Discontinuation due to AEs	277 (70.5)	220 (51.6)	69 (17.6)	255 (64.9)	188 (44.1)

AE = adverse event; SAE = serious adverse event
[a] Two subjects who received gemcitabine and cisplatin alone also had an AE reported that was considered to be related to PF-3512676.

The most frequently reported Grade 3/4/5 AEs (>2% of subjects in either group) are summarized in Table 5. The most common AEs were hematological disorders: neutropenia, thrombocytopenia and anemia, all of which were more frequently reported for subjects receiving gemcitabine/cisplatin and PF-3512676 compared to subjects receiving gemcitabine/cisplatin alone. The most frequently reported non-hematological Grade 3/4/5 AEs were fatigue and dyspnea.

Table 5. Summary of Most Frequent Grade 3/4/5 Adverse Events by Preferred Term – As Treated

	All Causalities		PF-3512676 Related	PF-3512676 Related or Chemotherapy Related	
Number (%) of Subjects with Preferred Term Adverse Event:	**Gemcitabine/ Cisplatin + PF-3512676 (N=393)**	**Gemcitabine/ Cisplatin (N=426)**	**Gemcitabine/ Cisplatin + PF-3512676 (N=393)**	**Gemcitabine/ Cisplatin + PF-3512676 (N=393)**	**Gemcitabine/ Cisplatin (N=426)**
Any adverse event	**343 (87.3)**	**312 (73.2)**	**95 (24.2)**	**297 (75.6)**	**231 (54.2)**
Neutropenia	174 (44.3)	123 (28.9)	27 (6.9)	174 (44.3)	123 (8.9)
Thrombocytopenia	157 (39.9)	68 (16.0)	30 (7.6)	156 (39.7)	68 (16.0)
Anemia	95 (24.2)	44 (10.3)	10 (2.5)	89 (22.6)	40 (9.4)
Leukopenia	48 (12.2)	25 (5.9)	9 (2.3)	48 (12.2)	25 (5.9)
Fatigue	31 (7.9)	32 (7.5)	7 (1.8)	21 (5.3)	22 (5.2)
Dyspnea	30 (7.6)	23 (5.4)	1 (0.3)	4 (1.0)	4 (0.9)
Vomiting	25 (6.4)	13 (3.1)	3 (0.8)	23 (5.9)	13 (3.1)
Nausea	17 (4.3)	14 (3.3)	1 (0.3)	16 (4.1)	14 (3.3)
Asthenia	16 (4.1)	14 (3.3)	4 (1.0)	14 (3.6)	10 (2.3)
Disease progression	15 (3.8)	13 (3.1)	0	0	0
Febrile neutropenia	15 (3.8)	6 (1.4)	2 (0.5)	15 (3.8)	6 (1.4)
Anorexia	14 (3.6)	9 (2.1)	2 (0.5)	10 (2.5)	9 (2.1)
Pneumonia	14 (3.6)	14 (3.3)	1 (0.3)	2 (0.5)	4 (0.9)
Diarrhea	10 (2.5)	5 (1.2)	2 (0.5)	7 (1.8)	3 (0.7)
Back pain	9 (2.3)	7 (1.6)	1 (0.3)	1 (0.3)	0
Neutrophil count decreased	9 (2.3)	5 (1.2)	1 (0.3)	9 (2.3)	5 (1.2)
Dehydration	8 (2.0)	2 (0.5)	1 (0.3)	5 (1.3)	1 (0.2)
Hypokalemia	8 (2.0)	3 (0.7)	1 (0.3)	7 (1.8)	1 (0.2)
Pain in extremity	8 (2.0)	4 (0.9)	2 (0.5)	3 (0.8)	0

N= number of subjects
Grade 3/4/5 AEs reported for >2% of subjects in either group are presented, ranked by frequency for the gemcitabine/cisplatin + PF-3512676 group (all causalities).

Local PF-3512676 injection site reactions were experienced by 267/393 subjects (67.9%) who received gemcitabine/cisplatin and PF-3512676. Most subjects who experienced an injection site reaction had a reaction with maximum severity of mild or moderate.

Flu-like symptoms were experienced by 165/393 subjects (42.0%) who received gemcitabine/cisplatin and PF-3512676. Most subjects who experienced flu-like symptoms had symptoms with maximum severity of Grade 1 or 2.

Sepsis, including associated preferred terms, was experienced with Grade 3/4/5 severity by 5/393 subjects (1.3%) who received gemcitabine/cisplatin and PF-3512676. One subject experienced Grade 5 (fatal) sepsis.

Subjects who discontinued PF-3512676 due to AEs that were considered to be due to study drug (ie, PF-3512676) are summarized in Table 6.

Table 6. Permanent Discontinuations from PF-3512676 due to Adverse Events that were Considered to be PF-3512676 Related

Sex/Age	Preferred Term	Start Day/Stop Day	Grade
M/54	Bronchospasm	196/196	3
F/45	Thrombocytopenia	114/115	4
F/56	Thrombocytopenia	114/118	4
M/71	Thrombocytopenia	78/81	4
M/54	Edema peripheral	57/61	2
M/64	Subdural hemorrhage	44/44	3
F/64	Injection site induration	134/190	2
F/63	Blindness transient	79/81	4
M/55	Pneumonitis	125/136	3
M/65	Injection site erythema	127/141	1
	Edema peripheral	127/141	1
	Cellulitis	127/141	1
	Pain in extremity	127/141	1
M/75	Dizziness	149/176	2
	Syncope	149/149	3
M/56	Myalgia	34/41	1
M/57	Thrombocytopenia	84/98	4
M/62	Injection site reaction	126/152	4
F/52	Thrombocytopenia	107/108	4
	Pain in extremity	100/112	3
M/68	Pyrexia	197/201	2
F/74	Thrombocytopenia	118/135	2
F/47	Injection site inflammation	64/>64	3
	Injection site injury	44/71	3
	Pyrexia	57/59	3
F/45	Pyrexia	89/92	3
F/64	Injection site erythema	57/84	3
F/51	Asthenia	111/119	3
M/71	Polyarthritis	106/134	3
F/58	Injection site reaction	15/112	3
M/65	Influenza like illness	121/127	2
M/60	Chills	106/107	1
F/64	Pleuritic pain	85/85	1
M/49	Back pain	70/98	2

There were 6 deaths that were considered to be related to either PF-3512676 or chemotherapy:

- A 54-year old male (gemcitabine/cisplatin alone) died due to an AE of multi-organ failure, on Day 9, which was considered to be related to chemotherapy.
- A 71-year old male (gemcitabine/cisplatin alone) died due to an AE of renal failure, on Day 17, which was considered to be related to chemotherapy
- A 72-year old male (gemcitabine/cisplatin alone) died due to an AE of respiratory failure, 12 days after the last dose of study drug, which was considered to be related to chemotherapy.

- A 68-year old male (gemcitabine/cisplatin alone) died due to an AE of therapeutic agent toxicity, 2 days after the last dose of study drug, which was considered to be related to chemotherapy.

- A 68-year old male (gemcitabine/cisplatin + PF-3512676) died due to an AE of pulmonary embolism, on Day 45, which was considered to be related to chemotherapy.

- A 55-year old male (gemcitabine/cisplatin + PF-3512676) died due to AEs of anemia, neutropenia, thrombocytopenia, diarrhea, and dehydration, 14 days after the last dose of study drug, all of which were considered to be related to PF-3512676. Fatal AEs of death (unknown cause) and hypotension were also recorded for this subject, neither of which was considered to be due to study drug.

Thrombocytopenia was the most frequent serious adverse event (SAE; Table 7).

Table 7. Summary of Most Frequent Serious Adverse Events - As Treated

	Number of Events	
Preferred Term	**Gemcitabine/Cisplatin + PF-3512676**	**Gemcitabine/Cisplatin**
Thrombocytopenia	55	17
Neutropenia	25	10
Anemia	20	20
Vomiting	19	11
Pneumonia	18	22
Disease progression	17	19
Pyrexia	17	7
Dehydration	16	3
Dyspnea	15	8
Non-small cell lung cancer	14	17
Febrile neutropenia	10	5
Nausea	10	4
Diarrhea	9	10

Serious adverse events reported on ≥10 occasions for subjects in either group are presented, ranked by frequency for the gemcitabine/cisplatin + PF-3512676 group.

An increased number of abnormal/positive immunopathology tests was common, occurring in 44.5% of subjects who had immunopathology assessments at both baseline and end of treatment. The most common abnormal tests noted after exposure to PF-3512676 were anti-ssDNA followed by RF and ANCA. Formation of anti-dsDNA antibodies was rare.

CONCLUSIONS:

- Addition of PF-3512676 to chemotherapy had no significant improvement in OS or PFS. Median OS was approximately 11 months, with 573/839 subjects experiencing death. No significant improvement in OS due to the addition of PF-3512676 to chemotherapy was noted for any subset of subjects analyzed. Median PFS was approximately 5 months for

both treatments, with 700 subjects having experienced progression or death, according to investigator assessment.

- Overall, Grade 3/4/5 AEs were experienced by 343/393 subjects (87.3%) receiving gemcitabine/cisplatin + PF-3512676 and by 312/426 subjects (73.2%) receiving gemcitabine/cisplatin alone.

- Grade ≥3 thrombocytopenia was more common in subjects treated with chemotherapy plus PF-3512676 (67.9%) than subjects treated with chemotherapy alone (38.7%) when laboratory and AE data were combined. Concomitant transfusions, including transfusions of platelets or plasma, were received by 176/393 subjects (44.8%) who received gemcitabine/cisplatin plus PF-3512676 and by 98/426 subjects (23.0%) who received gemcitabine/cisplatin. Bleeding AEs were experienced by 73/393 subjects (18.6%) who received gemcitabine/cisplatin and PF-3512676 and by 57/426 subjects (13.4%) who received gemcitabine/cisplatin alone.

- Grade ≥3 neutropenia was more common in subjects treated with chemotherapy plus PF-3512676 (74.0%) than subjects treated with chemotherapy alone (50.9%) when laboratory and AE data were combined. Colony stimulating agents were received as concomitant treatment by 64/393 subjects (16.3%) who received gemcitabine/cisplatin plus PF-3512676 and by 33/426 subjects (7.7%) who received gemcitabine/cisplatin. Grade ≥3 anemia was more common in subjects treated with chemotherapy plus PF-3512676 (38.2%) than subjects treated with chemotherapy alone (23.2%) when laboratory and AE data were combined.

- Sepsis, including associated preferred terms, was experienced with Grade 3/4/5 severity by 5/393 subjects (1.3%) who received gemcitabine/cisplatin and PF-3512676. One subject experienced Grade 5 (fatal) sepsis. The incidence of AEs in the SOC infections and infestations was greater for subjects receiving gemcitabine/cisplatin and PF-3512676 (32.3%) compared to subjects receiving gemcitabine/cisplatin alone (22.5%). Antibiotics were more commonly administered to subjects receiving chemotherapy plus PF-3512676 (49.1% of subjects) than subjects receiving chemotherapy alone (35.4%).

- Many subjects who received PF-3512676 experienced injection site reactions (67.9% [severe or disabling for 10.4%]) or flu-like symptoms (42.0% [CTC Grade 3 or 4 for 4.6%]).

- An increased number of abnormal/positive immunopathology tests was common, occurring in 44.5% of subjects who had immunopathology assessments at both baseline and end of PF-3512676 treatment. The most common abnormal tests noted after exposure to PF-3512676 were anti-ssDNA followed by RF and ANCA. Formation of anti-dsDNA antibodies was rare. Since these tests were not performed in subjects receiving chemotherapy only, it is currently unknown whether this increase in the number of abnormal/positive immunopathology tests is a result of exposure to PF-3512676 or due to the natural history of NSCLC.

- The proportion of subjects with dose delays or dose reductions for chemotherapy was greater for subjects who received gemcitabine/cisplatin plus PF-3512676 compared to gemcitabine/cisplatin alone with dose delays experienced by 52.9% and 32.4% of subjects, respectively, and dose reductions experienced by 43.3% and 26.8%, respectively.

- With little exception, the improvements and deteriorations observed in aspects of HQoL (eg, emotional, physical, social, and role functioning), and lung cancer specific symptoms (eg, dyspnea, coughing, pain, fatigue), were consistent between the 2 treatment arms.