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COMPOUND NUMBER: PF-3512676

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

NCT NO.: NCT00254891

PROTOCOL NO.: A8501001

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

Study Centers: The study was conducted at 141 centers in 26 countries (including 5 centers that did not randomize subjects) as follows: 10 centers in Australia, 2 centers in Belgium, 4 centers in Canada, 4 centers in China, 1 center in Cyprus, 3 centers in the Czech Republic, 10 centers in France, 7 centers in Germany, 5 centers in Greece (including 1 center that did not randomize subjects), 1 center in Hong Kong, 4 centers in Hungary, 5 centers in India (including 1 center that did not randomize subjects), 1 center in Israel, 4 centers in Italy, 2 centers in the Republic of Korea, 2 centers in Mexico, 4 centers in the Netherlands, 2 centers in Poland, 4 centers in Portugal, 3 centers in South Africa, 7 centers in Spain, 2 centers in Sweden, 1 center in Switzerland, 2 centers in Taiwan, 7 centers in the United Kingdom, and 44 centers in the United States (including 3 centers that did not randomize subjects).

Study Initiation and Completion Dates: 16 November 2005 to 17 July 2008

Phase of Development: Phase 3

Study Objectives: The objectives were to assess the efficacy and safety of PF-3512676 administered in combination with paclitaxel/carboplatin 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 paclitaxel/carboplatin chemotherapy alone.

Primary Objective:

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

- To evaluate the effect of PF-3512676 on the pharmacokinetics (PK) of paclitaxel and carboplatin.

- To evaluate the PK of PF-3512676 when administered in combination with paclitaxel/carboplatin.

METHODS

Study Design: This was an international, multicenter, open-label, 2-arm, randomized Phase 3 study. 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 paclitaxel and carboplatin 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 paclitaxel and carboplatin 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 (400 per arm) over approximately 13 months. A total of 811 subjects were treated and analyzed; 384 subjects in Arm A and 427 subjects in Arm B.

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 (CT) 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 metastases 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 paclitaxel (200 mg/m^2 intravenously over 3 hours) followed by carboplatin (AUC 6 [ie, a target area under the concentration-time curve of 6 mg/mL x minute based on the Calvert formula], intravenously over 15 to 30 minutes) administered on Day 1 of a 3-week cycle. In addition, subjects received PF-3512676 administered subcutaneously at a dose of 0.2 mg/kg on Days 8 and 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 the last dose of paclitaxel/carboplatin.

Treatment Arm B: Standard platinum-based doublet chemotherapy consisting of paclitaxel (200 mg/m^2 intravenously over 3 hours) followed by carboplatin (AUC 6, intravenously over 15 to 30 minutes) administered on Day 1 of a 3-week cycle. Chemotherapy was continued for a maximum of 6 cycles. Subjects in Treatment Arm B were not permitted to cross-over 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 or partial response) 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 (RECIST). Efficacy endpoints included OS, overall confirmed objective response rate (ORR), progression-free survival (PFS), and time to tumor progression (TTP).

Pharmacokinetic Evaluations: A subset of subjects in Arm A had blood samples collected for determination of plasma PK of PF-3512676 given in combination with paclitaxel and carboplatin and for the evaluation of the effect of PF-3512676 on the PK of paclitaxel and carboplatin.

Patient Reported Outcomes: 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 [ANA], 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 versus IV), smoking history (smoked versus never smoked), and sex (male versus 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 as positive or negative or as normal or abnormal as appropriate for each test at each time point.

RESULTS

Subject Disposition and Demography: Overall, 828 subjects were randomized and were included in the All Randomized as Randomized population (Table 1); 811 of these subjects were treated and were included in the As Treated population.

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
All Randomized as Randomized			
Randomized			828
Treated	399	412	811
Completed[a]	293 (71.8)	296 (70.5)	589 (71.1)
Discontinued[a]	115 (28.2)	124 (29.5)	239 (28.9)
As Treated			
Randomized			828
Treated	384	427	811
Completed	273 (71.1)	305 (71.4)	578 (71.3)
Discontinued	111 (28.9)	122 (28.6)	233 (28.7)
Analyzed for Safety			
Adverse Events	384 (100.0)	427 (100.0)	811 (100.0)
Laboratory Data	383 (99.7)	410 (96.0)	793 (97.8)

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 (408 on Arm A, 420 on Arm B, 828 overall).

Overall, 233 treated subjects were discontinued from the study; 111 subjects who received paclitaxel/carboplatin plus PF-3512676 and 122 subjects who received paclitaxel/carboplatin. The most common reason for discontinuation was study terminated by the sponsor (ie, the subject was still alive when data collection stopped): 76 subjects who received paclitaxel/carboplatin plus PF-3512676 and 84 subjects who received paclitaxel/carboplatin were recorded as having 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=408)	Arm B (N=420)
Sex, number (%) of subjects		
Male	269 (65.9)	274 (65.2)
Female	139 (34.1)	146 (34.8)
Age, years		
Mean (standard deviation)	60.3 (9.9)	61.3 (9.9)
Median (range)	61.0 (30-85)	62.0 (30-87)
Race, number (%) of subjects		
White	327 (80.1)	327 (77.9)
Black	12 (2.9)	12 (2.9)
Asian	50 (12.3)	60 (14.3)
Other	19 (4.7)	20 (4.8)
Not reported	0	1 (0.2)
Current Disease Stage, number (%) of subjects		
Stage IIIB with effusion	45 (11.0)	52 (12.4)
Stage IV	361 (88.5)	368 (87.6)
Not given	1 (0.2)	0
Histological Classification, number (%) of subjects		
Squamous cell carcinoma	97 (23.8)	112 (26.7)
Adrenocarcinoma	234 (57.4)	244 (58.1)
Large cell	31 (7.6)	25 (6.0)
Other	55 (13.5)	46 (11.0)
ECOG Performance Status, number (%) of subjects		
0	139 (34.1)	136 (32.4)
1	252 (61.8)	265 (63.1)
2	0	2 (0.5)
3	0	1 (0.2)
Smoking Status, number (%) of subjects		
Smoked	349 (85.5)	356 (84.8)
Never smoked	58 (14.2)	64 (15.2)
Prior Weight Loss[a], number (%) of subjects		
Yes	66 (16.2)	79 (18.8)
No	342 (83.8)	341 (81.2)
Lactate Dehydrogenase, number (%) of subjects		
Normal	215 (52.7)	225 (53.6)
Abnormal	153 (37.5)	142 (33.8)

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

Efficacy Results:

Overall, 588/828 subjects (71.0%) had an event (died) and 240/828 subjects (29.0%) were censored, primarily because they were alive at the time when data collection ceased (160/240 censored subjects, 66.7%) (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 10 months for both arms, or in the percentage of subjects achieving 1-year survival, approximately 40% for both arms.

Table 3. Overall Survival - All Randomized as Randomized

Kaplan-Meier Estimate	Arm A (N=408)	Arm B (N=420)	p-value	Hazard Ratio[a]
Number (%) of Subjects with Events	293 (71.8)	295 (70.2)		
Cause of Death, number (%) of subjects[b]:				
Disease under study	254 (86.7)	261 (88.5)		
Adverse event	22 (7.5)	15 (5.1)		
Other	10 (3.4)	8 (2.7)		
Unknown	7 (2.4)	11 (3.7)		
Number (%) of Subjects Censored	115 (28.2)	125 (29.8)		
Median Survival, months (95% CI)[c]	10.02 (8.94, 11.07)	9.82 (8.80, 11.27)	0.5593[d]	0.9525 (0.8088, 1.1218)
% Subjects Achieving 1-Year Survival (95% CI)[e]	40.39% (35.48%, 45.32%)	41.62% (36.79%, 46.47%)	0.7273[f]	
Reason(s) for Censoring, number (%) of subjects				
Lost to follow-up	17 (14.78)	14 (11.20)		
Withdrawal of consent	19 (16.52)	24 (19.20)		
Other withdrawal from study	1 (0.87)	5 (4.00)		
Still alive when data collection ceased	78 (67.83)	82 (65.60)		

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.

Overall, 680/828 subjects (82.1%) had a PFS event (progression or death). The percentage of subjects with an event was similar for both arms. There was 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 35% for both arms.

Overall, 498/839 subjects (60.1%) had a TTP 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 TPP, 5.49 and 5.75 months for Arms A and B, respectively. The percentage of subjects with tumor progression at 6 months was slightly greater for Arm B (45.86%) compared to Arm A (41.60%), but this difference was not statistically significant.

A total of 115/408 subjects (28.2%; 95% CI: 23.8%, 32.6%) in Arm A and 96/420 subjects (22.9%; 95% CI: 18.8%, 26.9%) 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.

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 an improvement in emotional functioning (QLQ-C30) and 5 symptoms (insomnia [QLQ-C30], coughing, arm pain, chest pain and hemoptysis [all QLQ-LC13]). Similarly, subjects in Arm B also reported an improvement in emotional functioning (QLQ-C30), although several of the 5 symptoms that demonstrated improvement (insomnia, dyspnea, and appetite loss [QLQ-C30], and chest pain and coughing [QLQ-LC13]) were different than those in Arm A.

Subjects in Arm A reported a worsening in physical, role and social functioning (QLQ-C30), and an increase (worsening) in 6 symptom scales (fatigue and dyspnea [QLQ-C30], and sore mouth, peripheral neuropathy, alopecia and other pain [QLQ-LC13]). Individuals in Arm B noted a worsening in a number of functional scales (global health, physical, role, cognitive and social [QLQ-C30]) compared to baseline, although relatively fewer symptoms (nausea/vomiting and fatigue [QLQ-C30], and sore mouth, peripheral neuropathy and alopecia [QLQ-LC13]) were reported as worsening.

Safety Results: An overall summary of AEs is presented in Table 4. Most AEs were considered to be related to PF-3512676 and/or paclitaxel/carboplatin 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	**Paclitaxel/ Carboplatin + PF-3512676**	**Paclitaxel/ Carboplatin**	**Paclitaxel/ Carboplatin + PF-3512676[a]**	**Paclitaxel/ Carboplatin + PF-3512676**	**Paclitaxel/ Carboplatin**
Evaluable for AEs	384	427	384	384	427
Number of AEs	4478	3468	1236	3035	2136
With AEs	380 (99.0)	415 (97.2)	274 (71.4)	372 (96.9)	387 (90.6)
With SAEs	153 (39.8)	123 (28.8)	26 (6.8)	93 (24.2)	56 (13.1)
With Grade 3/4 AEs	287 (74.7)	268 (62.8)	82 (21.4)	245 (63.8)	206 (48.2)
With Grade 5 AEs	32 (8.3)	35 (8.2)	3 (0.8)	4 (1.0)	2 (0.5)
Discontinued due to AEs	96 (25.0)	89 (20.8)	28 (7.3)	57 (14.8)	50 (11.7)
Dose Reduced or Temporary Discontinuation due to AEs	206 (53.6)	146 (34.2)	66 (17.2)	184 (47.9)	125 (29.3)

AE = adverse event; SAE = serious adverse event

The most frequently reported Grade 3/4/5 AEs are summarized in Table 5. These were most frequently hematological disorders: neutropenia, thrombocytopenia and anemia, all of which were more frequently reported for subjects receiving paclitaxel/carboplatin and PF-3512676 compared to subjects receiving paclitaxel/carboplatin alone. The most frequently reported non-hematological Grade 3/4/5 AEs were dyspnea and fatigue.

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:	**Paclitaxel/ Carboplatin + PF-3512676 (N=384)**	**Paclitaxel/ Carboplatin (N=427)**	**Paclitaxel/ Carboplatin + PF-3512676 (N=384)**	**Paclitaxel/ Carboplatin + PF-3512676 (N=384)**	**Paclitaxel/ Carboplatin (N=427)**
Any adverse event	**292 (76.0)**	**281 (65.8)**	**82 (21.4)**	**247 (64.3)**	**209 (48.9)**
Neutropenia	120 (31.3)	100 (23.4)	30 (7.8)	118 (30.7)	99 (23.2)
Thrombocytopenia	43 (11.2)	15 (3.5)	7 (1.8)	42 (10.9)	14 (3.3)
Anemia	39 (10.2)	24 (5.6)	7 (1.8)	35 (9.1)	20 (4.7)
Dyspnea	33 (8.6)	35 (8.2)	1 (0.3)	4 (1.0)	3 (0.7)
Febrile neutropenia	32 (8.3)	17 (4.0)	6 (1.6)	31 (8.1)	17 (4.0)
Fatigue	27 (7.0)	25 (5.9)	8 (2.1)	19 (4.9)	18 (4.2)
Leukopenia	23 (6.0)	20 (4.7)	2 (0.5)	23 (6.0)	20 (4.7)
Pneumonia	16 (4.2)	9 (2.1)	1 (0.3)	7 (1.8)	2 (0.5)
Pulmonary embolism	15 (3.9)	16 (3.7)	2 (0.5)	2 (0.5)	0
Peripheral sensory neuropathy	14 (3.6)	11 (2.6)	1 (0.3)	14 (3.6)	11 (2.6)
Nausea	13 (3.4)	16 (3.7)	2 (0.5)	11 (2.9)	15 (3.5)
Alopecia	12 (3.1)	5 (1.2)	0	12 (3.1)	5 (1.2)
Disease progression	12 (3.1)	13 (3.0)	0	0	0
Back pain	11 (2.9)	11 (2.6)	1 (0.3)	3 (0.8)	0
Dehydration	11 (2.9)	7 (1.6)	0	8 (2.1)	6 (1.4)
Injection site reaction	11 (2.9)	0	11 (2.9)	11 (2.9)	0
Asthenia	10 (2.6)	5 (1.2)	1 (0.3)	6 (1.6)	2 (0.5)
Arthralgia	9 (2.3)	5 (1.2)	3 (0.8)	5 (1.3)	3 (0.7)
Neuropathy peripheral	9 (2.3)	17 (4.0)	1 (0.3)	8 (2.1)	16 (3.7)
Anorexia	8 (2.1)	8 (1.9)	0	5 (1.3)	7 (1.6)
Chest pain	8 (2.1)	7 (1.6)	0	0	1 (0.2)
Pain in extremity	8 (2.1)	7 (1.6)	1 (0.3)	4 (1.0)	4 (0.9)
Syncope	8 (2.1)	5 (1.2)	3 (0.8)	4 (1.0)	1 (0.2)
Vomiting	8 (2.1)	7 (1.6)	2 (0.5)	7 (1.8)	6 (1.4)

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

Local PF-3512676 injection site reactions were experienced by 276/384 subjects (71.9%) who received paclitaxel/carboplatin and PF-3512676. Most subjects who experienced a local injection site reaction had a reaction with maximum severity of mild or moderate

Flu-like symptoms were experienced by 193/384 subjects (50.3%) who received paclitaxel/carboplatin 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 by 17/384 subjects (4.4%) who received paclitaxel/carboplatin and PF-3512676 and by 3/427 subjects (0.7%) who received paclitaxel/carboplatin alone. Grade 5 (fatal) sepsis events were experienced by subjects who

received paclitaxel/carboplatin and PF-3512676 – sepsis (2 subjects), septic shock (2 subjects) and pyelonephritis (1 subject). One subject in the paclitaxel/carboplatin group died due to sepsis, but no Grade 5 episode of sepsis was reported for this subject.

The incidence of AEs in the system organ class (SOC) infections and infestations was >10 percentage points greater for subjects receiving paclitaxel/carboplatin and PF-3512676 (34.6%) compared to subjects receiving paclitaxel/carboplatin alone (22.7%).

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/48	Urticaria	79/81	3
M/66	Anaphylactic reaction	253/261	4
M/44	Influenza like illness	130/136	3
M/50	Arthralgia	23/30	1
F/58	Influenza like illness	213/315	3
	Injection site pain	213/315	3
	Injection site swelling	213/315	3
M/62	Injection site reaction	99/141	2
F/54	Cerebrovascular accident	44/96	4
M/66	Injection site reaction	141/141	2
	Erythema	141/141	2
M/65	Injection site reaction	98/181	2
F/55	Injection site reaction	149/161	2
M/62	Hypersensitivity	92/92	2
M/56	Neutropenia	103/105	2
M/59	Confusional state	29/41	3
M/74	Diarrhea	265/351	3
M/78	Renal failure acute	12/37	2
F/42	Injection site erythema	100/182	3
	Injection site swelling	100/182	4
M/78	Confusional state	87/87	1
M/60	Fatigue	68/>70	3
M/63	Hypersensitivity	44/44	2
M/57	Febrile neutropenia	77/>84	3
	Sepsis	77/84	5
	Renal failure acute	77/84	3
F/55	Hypersensitivity	71/71	2
M/63	Anaphylactic reaction	134/134	3
M/76	Thrombocytopenia	106/148	2

M = male; F = female

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

- A 72-year old female (paclitaxel/carboplatin alone) died due to an AE of cardio-respiratory arrest on Day 9, which was considered to be related to chemotherapy

- A 67-year old male (paclitaxel/carboplatin + PF-3512676) died due to an AE of pulmonary embolism, 1 day after the last dose of study drug, which was considered to be related to PF-3512676.

- A 76-year old male (paclitaxel/carboplatin alone) died due to an AE of diarrhea, 8 days after the last dose of study drug, which was considered to be related to chemotherapy.

- A 74-year old male (paclitaxel/carboplatin + PF-3512676) died due to an AE of septic shock, 8 days after the last dose of study drug, which was considered to be related to chemotherapy.

- A 57-year old male (paclitaxel/carboplatin + PF-3512676) died due to an AE of sepsis, 9 days after the last dose of study drug, which was considered to be related to PF-3512676.

- A 62-year old male (paclitaxel/carboplatin + PF-3512676) died due to an AE of septic shock, 6 days after the last dose of study drug, which was considered to be related to PF-3512676.

SAEs were experienced by 153 subjects who received paclitaxel/carboplatin and PF-3512676 and by 123 subjects who received paclitaxel/carboplatin alone (Table 4). Febrile neutropenia was the most frequent SAE, reported as an SAE on 29 occasions for subjects who received paclitaxel/carboplatin and PF-3512676 and on 17 occasions for subjects who received paclitaxel/carboplatin alone (Table 7). Neutropenia was reported as an SAE on 15 occasions for subjects who received paclitaxel/carboplatin and PF-3512676 and on 9 occasions for subjects who received paclitaxel/carboplatin alone.

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

	Number of Events	
Preferred Term	**Paclitaxel/Carboplatin + PF-3512676**	**Paclitaxel/Carboplatin**
Febrile neutropenia	29	17
Disease progression	17	16
Vomiting	17	10
Non-small cell lung cancer	15	13
Pyrexia	15	11
Neutropenia	15	9
Pneumonia	14	11
Pulmonary embolism	13	15
Anemia	13	13
Dyspnea	12	19
Nausea	12	10
Dehydration	12	8

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

An increased number of abnormal/positive immunopathology tests was common, occurring in 48.3% 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 ANA and RF. 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 10 months, with 588/828 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 680 subjects having experienced progression or death, according to investigator assessment.

- Overall, Grade 3/4/5 AEs were experienced by 292/384 subjects (76.0%) receiving paclitaxel/carboplatin + PF-3512676 and by 281/427 subjects (65.8%) receiving paclitaxel/carboplatin alone.

- Sepsis related SAEs were more common in subjects treated with chemotherapy plus PF-3512676 (17 subjects resulting in 5 deaths) than subjects treated with chemotherapy alone (3 subjects resulting in 1 death). The incidence of AEs in the SOC infections and infestations was greater for subjects receiving paclitaxel/carboplatin and PF-3512676 (34.6%) compared to subjects receiving paclitaxel/carboplatin alone (22.7%). Antibiotics were more commonly administered to subjects receiving chemotherapy plus PF-3512676 (49.7% of subjects) than subjects receiving chemotherapy alone (36.5%).

- Grade ≥3 neutropenia was more common in subjects treated with chemotherapy plus PF-3512676 (73.2%) than subjects treated with chemotherapy alone (58.8%) when laboratory and AE data were combined. Colony stimulating agents were received as concomitant treatment by 73/384 subjects (19.0%) who received paclitaxel/carboplatin plus PF-3512676 and by 53/427 subjects (12.4%) who received paclitaxel/carboplatin. Grade ≥3 thrombocytopenia was more common in subjects treated with chemotherapy plus PF-3512676 (17.2%) than subjects treated with chemotherapy alone (7.7%) when laboratory and AE data were combined. Concomitant transfusions, including transfusions of platelets or plasma, were received by 82/384 subjects (21.4%) who received paclitaxel/carboplatin plus PF-3512676 and by 55/427 subjects (12.9%) who received paclitaxel/carboplatin. No increased risk of bleeding was associated with the increased amount of Grade 3 to 5 thrombocytopenia noted in subjects treated with PF-3512676 plus chemotherapy.

- Many subjects who received PF-3512676 experienced injection site reactions (71.9% [severe or disabling for 4.7%]) or flu-like symptoms (50.3% [CTC Grade 3 or 4 for 3.1%]).

- An increased number of abnormal/positive immunopathology tests compared to baseline evaluation was common, occurring in 48.3% 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 ANA and RF. 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 paclitaxel/carboplatin plus PF-3512676 compared to paclitaxel/carboplatin alone with dose delays experienced by 37.2% and 24.8% of subjects, respectively, and dose reductions experienced by 23.4% and 16.9%, 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.