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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.: 00321308

PROTOCOL NO.: A8501004

PROTOCOL TITLE: A Randomized Phase II Trial of Pemetrexed with or without PF-3512676 for the Treatment of Patients with Locally Advanced or Metastatic Non Small Cell Lung Cancer after Failure of One Prior Chemotherapy Regimen for Advanced Disease

Study Centers: 10 in total (7 in the US, 2 in Germany, 1 in Italy)

Study Initiation and Completion Dates: 20 September 2006 to 31 January 2008

Phase of Development: Phase 2

Study Objectives: The study objectives were to assess the efficacy and safety of PF-3512676 administered in combination with pemetrexed for the treatment of subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) who had failed 1 prior chemotherapy regimen.

Primary Objective:

- To assess Progression Free Survival (PFS) in subjects randomized to pemetrexed plus PF-3512676 (Investigational Treatment Arm; Arm A) and in subjects randomized to pemetrexed alone (Control Treatment Arm; Arm B).

Secondary Objectives:

- To assess secondary measures of efficacy for PF-3512676 administered in combination with pemetrexed.
- To assess the safety and tolerability of PF-3512676 administered in combination with pemetrexed.
- To assess the health-related quality of life and disease/treatment related symptoms of subjects treated with PF-3512676 in combination with pemetrexed.

METHODS

Study Design: This was a multicenter, open-label, randomized, 2-arm, Phase 2 trial. It was planned to enroll a total of at least 130 eligible subjects with locally advanced or metastatic NSCLC after failure of 1 prior chemotherapy regimen for advanced disease. Subjects were randomized (1:1) to either the investigational treatment arm (Arm A, pemetrexed and PF-3512676) or to the control treatment arm (Arm B, pemetrexed alone). Randomization was stratified by best response to prior chemotherapy and time since the end of prior chemotherapy. These factors had been found to impact response to pemetrexed in a previous study.

The study treatment period was defined by treatment cycles; each treatment cycle was 3 weeks in duration. Treatment was administered until disease progression, unacceptable treatment-related toxicity, or subject refusal to continue study treatment. Subjects in Arm A who discontinued pemetrexed for reasons other than disease progression were to enter the Maintenance Phase and continue to receive PF-3512676 weekly. Subjects discontinuing all treatments in the absence of disease progression continued to be monitored for efficacy and safety in the Observation Phase until disease progression or initiation of subsequent anticancer therapy. Following radiological documentation of disease progression or initiation of subsequent anticancer therapy, subjects were followed monthly for survival status.

Number of Subjects (Planned and Analyzed): It was planned to enroll a total of at least 130 eligible subjects. While the study was active, the sponsor made the decision that all trials in NSCLC in which PF-3512676 was combined with cytotoxic chemotherapy, including this study, should be stopped, following review of data from other studies by an independent Data Safety Monitoring Committee. At the time administration of PF-3512676 was discontinued, 35 of the planned 130 subjects had received treatment.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were 18 years of age or older with a histologically or cytologically confirmed diagnosis of NSCLC. Subjects were to have shown evidence of progressive disease following prior platinum-based chemotherapy for NSCLC. Subjects with any histological/cytological evidence of small cell or carcinoid lung cancer, uncontrolled pleural effusion, known central nervous system metastases, active infection or pre-existing autoimmune disease were not eligible. Eligible subjects were to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate organ function.

Study Treatment:

Treatment Arm A: On Day 1 of each 3-week cycle, subjects received pemetrexed 500 mg/m^2 as a 10-minute intravenous infusion. In addition, subjects received PF-3512676 administered subcutaneously at a dose of 0.2 mg/kg on Days 8 and 15 of each cycle. 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 pemetrexed.

Treatment Arm B: On Day 1 of each 3-week cycle, subjects received pemetrexed 500 mg/m^2 as a 10-minute intravenous infusion. Subjects in Treatment Arm B were not permitted to cross-over to receive PF-3512676.

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

Efficacy Evaluations: Determination of objective tumor response was performed according to Response Evaluation Criteria in Solid Tumors. Radiologic imaging was performed every 2 cycles during chemotherapy; following discontinuation of therapy, imaging was repeated every 6 weeks until radiological documentation of disease progression or initiation of subsequent anticancer therapy.

Patient Reported Outcomes (PRO): Changes in health-related quality of life and disease/treatment-related symptoms were assessed in each subject using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (QLQ-C30) and supplementary module for lung cancer (QLQ-LC13).

Safety Evaluations: Subjects were evaluated for adverse events (AEs) and concomitant medication use, changes in clinical laboratory assessments and ECOG performance status. AEs were graded using NCI (National Cancer Institute) Common Terminology Criteria for Adverse Events (CTCAE), v3.0.

Statistical Methods: The primary endpoint of the trial was PFS. Safety data were evaluated using descriptive statistics.

RESULTS

Subject Disposition and Demography: A total of 36 subjects were assigned to treatment; 35 subjects were treated and 1 subject was not treated as the physician decided to start a course of radiotherapy immediately, instead of chemotherapy. A total of 22 subjects completed the study (meaning the subject died in the context of this study) and 13 subjects discontinued.

Table S1. Subject Evaluation Groups

Number of Subjects	Overall	Arm A (Pemetrexed plus PF-3512676)	Arm B (Pemetrexed Alone)
Assigned to Study Treatment[a]	36	18	18
Treated[b]		15	20
Completed Study[b]		7	15
Discontinued Study[b]		8	5
Analyzed for Safety[b]			
Adverse Events[b]		15	20
Laboratory Data[b]		15	18

[a] As Randomized
[b] As Treated (subjects randomized to Arm A who did not receive PF-3512676 are classed as pemetrexed alone).

Chemotherapy was discontinued for 32 subjects, with the most common reason being progressive disease (17 subjects); only 3 subjects (1 in Arm A and 2 in Arm B) discontinued chemotherapy due to AEs. All 12 subjects in Arm A discontinued PF-3512676, most commonly due to termination of the study by the sponsor (7 subjects); 2 subjects discontinued PF-3512676 due to AEs.

Demographic data were similar for both treatment arms.

Table S2. Summary of Selected Demographic and Baseline Characteristics

Number (%) of Subjects	Arm A (Pemetrexed plus PF-3512676) (N=18)	Arm B (Pemetrexed Alone) (N=18)
Sex		
Male	13 (72.2)	12 (66.7)
Female	5 (27.8)	6 (33.3)
Age Category		
<65 Years	14 (77.8)	11 (61.1)
≥65 to ≤70 years	2 (11.1)	6 (33.3)
>70 years	2 (11.1)	1 (5.6)
Race		
White	18 (100.0)	17 (94.4)
Black	0 (0)	1 (5.6)
Best Prior Response to Chemotherapy[a]		
Complete/Partial Response	7 (38.9)	5 (27.8)
Stable/Progressive Disease/Unknown	11 (61.1)	12 (66.7)
Not Specified	0	1 (5.6)
Time Since End of Prior Chemotherapy[ab]		
<3 months	10 (55.6)	10 (55.6)
≥3 months	8 (44.4)	7 (38.9)
Not Specified	0	1 (5.6)
Histological Classification		
Large Cell	1 (5.6)	2 (11.1)
Adenocarcinoma	12 (66.7)	10 (55.6)
Squamous Cell Carcinoma	3 (16.7)	4 (22.2)
Other	2 (11.1)	1 (5.6)
Not Specified	0	1 (5.6)

[a] According to strata based on CRF.
[b] The last date of prior medication in regimens was used to compute this duration from the CRF data without regard to whether the drug was a chemotherapy agent or target agent.

Efficacy Results:

Since the study was stopped early, the sample size was lower than planned which limits the interpretability of the PFS, overall survival and objective response endpoints. No additional efficacy evaluations were performed.

Safety Results: An overall summary of AEs is presented in Table S3. The number of AEs reported was similar for both groups, with 15 subjects (100%) in Arm A and 19 subjects (95%) in Arm B reporting AEs.

Table S3. Summary of Treatment Emergent AEs (All Causalities)

	Arm A (N=15)	Arm B (N=20)
Number of AEs	158	159
Subjects with AEs	15	19
Subjects with SAEs	5	11
Subjects with Grade 3 or 4 AEs	13	13
Subjects with Grade 5 AEs	1	3
Subjects Discontinued Due to AEs	2	8
Subjects with Dose Reduced or Temporary Discontinuation Due to AEs	4	1

AE = adverse event; SAE = serious adverse event
Includes data up to 28 days after the last dose of study drug.
Arm A = chemotherapy plus PF-3512676; Arm B = chemotherapy alone

Non-hematological AEs of CTC Grades 3, 4 or 5 that occurred in 1 or more subjects in either treatment arm are summarized in Table S4. Fatigue was the most common non-hematologic CTC Grade 3 or higher AE, reported by 6 subjects (40%) in Arm A and 2 subjects (10%) in Arm B. There were no CTCAE Grade 5 AEs that were considered to be related to either PF-3512676 and/or background treatment.

Table S4. Incidence and Frequency of Treatment Emergent Non-Hematological AEs, CTCAE Grades 3 to 5 (All Causalities)

Number (%) of Subjects	Arm A (N=15)	Arm B (N=20)
Fatigue	6 (40.0)	2 (10.0)
Injection site reaction	4 (26.7)	0
Dyspnoea	3 (20.0)	2 (10.0)
Dyspnoea exertional	0	2 (10.0)
Flu-like illness	2 (13.3)	0
Cough	1 (6.7)	2 (10.0)
Pneumonia	2 (13.3)	2 (10.0)
Pulmonary embolism	0	2 (10.0)

Table shows non-hematological AEs of Grade 3, 4 or 5 reported by at least 1 subject in Arm A and/or Arm B.
Arm A = pemetrexed plus PF-3512676; Arm B = pemetrexed alone

Bleeding events were reported by some subjects. Epistaxis was reported by 3 subjects (20.0%) in Arm A and by 2 subjects (10.0%) in Arm B (all Grade 1), haemoptysis was reported by 2 subjects (10.0%) in Arm B (Grade 1) and intra-abdominal hemorrhage was reported by 1 subject (Grade 2) in Arm A.

Injection site reactions were frequently reported following administration of PF-3512676 in Arm A, being reported in 73.3% of subjects. Four subjects (26.7%) reported reactions classed as severe but none were reported as disabling. One subject (6.7%) had their dose permanently discontinued due to injection site reactions.

Flu-like symptoms attributed to PF-3512676 were also frequently reported following administration of PF-3512676 in Arm A, being reported in 46.7% of subjects. Two subjects

(13.3%) reported Grade 3 symptoms but no subjects reported Grade 4 symptoms. No subjects had their doses permanently discontinued due to flu-like symptoms.

Hematologic toxicities such as neutropenia and thrombocytopenia were frequently reported as AEs with CTC Grades 3 and 4 (no Grade 5 hematologic AEs were reported). Table S5 summarizes the frequency of these toxicities when laboratory and AE data are combined. The frequencies of these abnormalities were similar for the 2 treatment arms.

Table S5. Summary of Selected Hematology Toxicities, CTC Grades 3 and 4 (Laboratory and AE Data Combined)

Hematology Parameter	Maximum CTC Grade	Arm A (Pemetrexed plus PF-3512676) (N=15)	Arm B (Pemetrexed Alone) (N=20)
Hemoglobin	3	1 (6.7)	4 (20.0)
	4	1 (6.7)	0
Lymphocytes	3	3 (20.0)	5 (25.0)
	4	3 (20.0)	4 (20.0)
Neutrophils	3	2 (13.3)	3 (15.0)
	4	1 (6.7)	3 (15.0)
Platelets	3	1 (6.7)	1 (5.0)
	4	1 (6.7)	2 (10.0)
White Blood Cells	3	2 (13.3)	2 (10.0)
	4	0	1 (5.0)

CTC = Common Terminology Criteria. No Grade 5 abnormalities were reported.

Five subjects (2 from Arm A, 3 from Arm B) were reported to have died during the reporting period, as detailed in Table S6.

Table S6. Deaths During the Reporting Period

Arm	Sex/ Age	Related to Pemetrexed	Related to PF-3512676	MedDRA Preferred Term for AEs Considered to Have Caused Death of Subject
A	M/74	Yes[a]	No	Infection, neutropenia, respiratory failure, thrombocytopenia
	M/54	No	No	Pneumonia
B	M/52	No	NA	Respiratory failure, disease progression
	M/61	No	NA	Apnoea, hypotension
	M/67	No	NA	Disease progression, non-small cell lung cancer

[a] With the exception of respiratory failure (not considered treatment related).
NA = not applicable

Other serious adverse events (SAEs) were reported by 13 subjects, as detailed in Table S7.

Table S7. Non-Fatal SAEs During the Reporting Period

Arm	Sex/ Age[a]	MedDRA Preferred Term for SAE	Related to Pemetrexed	Related to PF-3512676	Outcome
A	F/58	Pneumonia	No	No	Recovered
	F/59	Abscess	Yes[b]	Yes	Recovered
	M/54	Fatigue[c]	Yes	No	Recovering
		Rash[c]	Yes	No	Recovered
	M/61	Back pain	No	No	Recovered
B	M/52	Pneumonia	Yes	NA	Death due to other cause
		Disease progression	No	NA	Death due to other cause
	F/62	Gastroenteritis	Yes	NA	Recovered
		Dyspnoea	Yes	NA	Recovered
		Thrombocytopenia	Yes	NA	Recovered
		Anemia	Yes	NA	Recovered
	F/58	Anemia	Yes	NA	Recovered
		Bronchitis	No	NA	Recovered
		Pancytopenia	Yes	NA	Recovered
	M/56	Anemia	Yes	NA	Recovered
	M/64	Neutropenia	Yes	NA	Recovered
		Thrombocytopenia	Yes	NA	Recovered
		Dyspnoea exertional	No	NA	Recovered
	M/59	Pain	No	NA	Unknown
		Pulmonary embolism	No	NA	Recovered
		Tachyarrhythmia	No	NA	Not recovered
	F/67	Pneumonia	No	NA	Recovered
	M/52	Pulmonary embolism	No	NA	Recovered
		Deep vein thrombosis	No	NA	Recovered
	M/60	Hypercalcemia	No	NA	Recovered
		Dehydration	No	NA	Recovered
	M/48	Drug toxicity	No	NA	Recovered

[a] Age at time of event.
[b] Investigator causality (sponsor did not consider SAE to be related to chemotherapy).
[c] Onset of SAE prior to Day 1.
NA = not applicable

Six of these 27 SAEs, where the outcome of the AE was not death, were infections. Two of these infections (pneumonia and abscess) occurred in 1 Arm A subject. Four Arm B subjects each reported one infection as an SAE. Arm B infections included pneumonia (2), gastroenteritis and bronchitis.

CONCLUSIONS:

- The median duration of PF-3512676 treatment for Arm A was 6 weeks. Sponsor decision to terminate the study was the most common reason PF-3512676 was discontinued for Arm A subjects.

- Hematologic toxicities such as neutropenia and thrombocytopenia were frequently reported as AEs with CTC Grades 3 and 4. The frequencies of these abnormalities were similar for the 2 treatment arms.

- Many subjects who received PF-3512676 experienced injection site reactions (73.3% [severe for 26.7%]) or flu-like symptoms (46.7% [severe for 13.3%]). No subjects reported disabling injection site reactions or flu-like symptoms. Additionally, a higher incidence of CTC Grade 3 or greater fatigue was reported in subjects who received PF-3512676 compared to subjects who received pemetrexed alone (40% versus 10%).

- No unexpected SAEs related to PF-3512676 were reported.

- In this prematurely terminated study with a smaller sample size than planned, it was not possible to meaningfully asses the effect of the addition of PF-3512676 to pemetrexed on progression-free survival or overall survival.