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COMPUND NUMBER: PF-3512676 (formerly CPG 7909)

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

NATIONAL CLINICAL TRIAL NO.: NCT00043368

PROTOCOL NO.: A8501015 (formerly known as Coley C016)

PROTOCOL TITLE: A Continuation Study of CPG 7909 Injection in Patients with Metastatic or Recurrent Malignancies who have Stable Disease or who have Responded to CPG 7909 Injection Therapy

Study Center(s): This study was conducted at 1 center in Germany and 17 centers in the United States.

Study Initiation Date and Completion Dates: 18 September 2002 to 14 June 2007

Phase of Development: Phase 2

Study Objective(s): The objective of this protocol was to allow subjects who had completed a clinical trial with PF-3512676 (CPG 7909) Injection to continue their current therapy if their cancer had responded or stabilized in response to treatment with PF-3512676 Injection alone or in combination with other anti-neoplastic agents. Subjects were treated according to standard of care for their specific cancers and at the discretion of their treating physician.

METHODS

Study Design: This was an open-label, continuation study of PF-3512676 Injection in subjects with various metastatic malignancies who had completed a study with PF-3512676 Injection as a single agent or in combination with another therapy immediately prior to enrolling in the present study. Subjects continued with the same dosing regimen and schedule of PF-3512676 Injection with which they were treated in the study that they had recently completed. Any proposed changes to their regimen were at the discretion of the treating physician, following consultation with the sponsor.

A subject could have remained on treatment with PF-3512676 Injection as long as their disease remained in control (responding and/or stable), the subject had discussed treatment with the investigator and the investigator felt it was in the best interest of the subject to continue PF-3512676 Injection, and there were no dose limiting toxicities. The End of

Treatment visit was performed within 28 days after treatment was discontinued. The study was complete when all subjects had their End of Treatment visit.

The study originally allowed for only 6 months of treatment; consequently, some subjects were enrolled more than once in the study.

Number of Subjects (Planned and Analyzed): There was no planned number of subjects. A total of 31 subjects were included in this continuation study.

Diagnosis and Main Criteria for Inclusion: Subjects could enroll in this continuation study immediately following completion of a Coley sponsored study of PF-3512676 Injection for the treatment of malignant disease, or following the appropriate number of treatment cycles with a combination product. Subjects were excluded if they had received any anti-neoplastic or biologic therapy (for cancer) since completing a prior study with PF-3512676 Injection, or had participated in another clinical study following participation in a study with PF-3512676 Injection. Treatment was not to have continued for women who were pregnant, lactating or unable/unwilling to use contraception.

Study Treatment: The sponsor supplied PF-3512676 Injection as a 5, 10, or 15 mg/mL solution for all subjects. Subjects were treated with PF-3512676 Injection per the dosing regimen/schedule with which they were treated in the study with PF-3512676 Injection that they had completed immediately prior to this continuation study. Administration was intravenous or subcutaneous, based on the route used for the subject in their original study. Subjects who had reached a maximum number of cycles with a combination product (such as chemotherapy) could have continued treatment with PF-3512676 Injection even if their concomitant regimen was discontinued. Any proposed changes to their regimen/schedule were at the discretion of the treating physician, following consultation with the sponsor.

Efficacy Evaluations: No efficacy evaluations were performed for this study.

Safety Evaluations: Safety monitoring was performed by the investigator according to standard of care for the cancer being treated. Adverse events (AE) were monitored at each visit. Laboratory investigations included hematology, blood chemistry, and urinalysis (monthly minimum) and immunopathology (at the end of treatment). A pregnancy test (urine) was performed in women of childbearing potential at study entry. Weight (baseline, monthly, and end of treatment visit), vital signs including temperature, heart rate, blood pressure, and respiratory rate were taken prior to and post drug administration when study drug was given during an office visit. A physical examination was performed in accordance with the normal clinical routines according to standard of care for the cancer being treated, but at a minimum was to have been done monthly.

Statistical Methods: No formal statistical analysis of this study was conducted. All clinical data collected during the course of the subject's continued participation were included in data listings as required to further the understanding of treatment with PF-3512676 Injection, modify dosing/treatment for the benefit of the subject, and to meet any reporting requirements of health authorities.

RESULTS

Subject Disposition and Demography: A total of 31 subjects were included in this continuation study: 1, 3, 3, 7, 2, 14, and 1 subjects from protocols C003, C005, C010, C014, C015, C017, and C023, respectively. Overall, 13/31 subjects (41.9%) were male and 18/31 subjects (58.1%) were female. Most subjects (27/31 subjects, 87.1%) were Caucasian; 2 subjects were black, 1 subject was Hispanic and 1 subject was of other race. Age ranged from 33 to 86 years.

Efficacy Results: No efficacy evaluations were performed in this study.

Safety Results:

Adverse Events

There were no deaths within 30 days of the last dose of study treatment. Serious adverse events (SAEs) were experienced by 3 subjects. One subject experienced an anaphylactic reaction that was considered to be life-threatening (Grade 4); this SAE started and stopped on 12 November 2004, with the subject having received PF-3512676 (10.2 mg) on 01, 08, 15, 22, and 29 October 2004. This SAE was a single episode that was considered to be definitely related to study drug; study drug was discontinued and treatment was given (diphenhydramine, epinephrine, methylprednisolone sodium succinate, and oxygen), with the subject recovering without sequelae.

All other SAEs reported (syncope reported by 1 subject [association with study drug = probable] and weight decreased and dehydration reported by 1 subject [association with study drug = possible]) were not considered to be life-threatening but required hospitalization or prolonged existing hospitalization.

Most AEs were CTC Grade 1 or 2; Grade 3/4 AEs are presented in Table S1. There were no Grade 5 AEs reported.

Table S1. Grade 3/4 Adverse Events

Source Protocol of Subject	Preferred Term	CTC Grade	Serious	Association	Outcome
C005	Angina pectoris[a]	3	No	Probable	Recovered without sequelae
	Muscle spasms	3	No	Probable	Recovered without sequelae
	Hypertension	3	No	Unlikely	Recovered without sequelae
	Angina pectoris[b]	3	No	Possible	Recovered with sequelae
	Dyspnea	3	No	Possible	Recovered with sequelae
C014	Syncope	3	Yes	Probable	Recovered without sequelae
C017	Anaphylactic reaction	4	Yes	Definite	Recovered without sequelae
	Anemia	3	No	Unlikely	Recovered without sequelae
C017	Leukopenia	3	No	Possible	Recovered without sequelae
C017	Pyrexia	3	No	Definite	Recovered with sequelae
	Erythema	3	No	Definite	Recovered without sequelae
C017	Injection site reaction	3	No	Definite	Recovered without sequelae
C017	Back pain	3	No	Unrelated	Recovered with sequelae
	Dyspnea	3	No	Unrelated	Recovered with sequelae
	Dyspnea	3	No	Unrelated	Recovered with sequelae
C017	Dehydration	3	Yes	Possible	Ongoing

[a] Verbatim term = cardiac chest pain
[b] Verbatim term = sub sternal cardiac chest pain

Injection site disorders and hematology toxicities are commonly experienced following administration of PF-3512676. One subject experienced a Grade 3 injection site reaction; this was considered to be definitely treatment-related, non-serious and the subject recovered without sequelae. Two subjects had a Grade 3/4 hematology toxicity reported as an AE: Grade 3 anemia that was considered unlikely to be treatment-related and leukopenia that was possibly related to treatment. There were no episodes of neutropenia or thrombocytopenia that were reported as Grade 3/4 AEs. There were no Grade 3/4 episodes of sepsis or flu-like symptoms. Three subjects were considered to have >Grade 1 flu-like symptoms: 1 subject with Grade 2 fatigue, 1 subject with Grade 2 headache, Grade 3 rigors, and Grade 3 musculoskeletal pain, and 1 subject with an AE of influenza.

Six subjects were withdrawn prematurely due to AEs (Table S2). All of these AEs were considered to be treatment related.

Table S2. Adverse Events Leading to Premature Withdrawal

Source Protocol of Subject	Preferred Term	CTC Grade	Serious	Association	Outcome
C005	Angina pectoris[a]	3	No	Probable	Recovered without sequelae
	Muscle spasms	3	No	Probable	Recovered without sequelae
	Visual disturbance	2	No	Possible	Recovered without sequelae
	Angina pectoris[b]	3	No	Possible	Recovered with sequelae
	Dyspnea	3	No	Possible	Recovered with sequelae
C014	Syncope	1	Yes	Probable	Recovered without sequelae
C017	Anaphylactic reaction	4	Yes	Definite	Recovered without sequelae
C017	Tremor	2	No	Probable	Recovered without sequelae
C017	Injection site reaction	3	No	Definite	Recovered without sequelae
C017	Weight decreased	2	Yes	Possible	Ongoing

[a] Verbatim term = cardiac chest pain
[b] Verbatim term = sub sternal cardiac chest pain

Clinical Laboratory Evaluations

Several subjects had observations that were reported as being clinically significant hematology results. Although not reported as being clinically significant, some subjects had hematology findings that were considered to be Grade 3 or 4:

- Subject from C014: Grade 3 absolute neutrophil count (0.75 K/µL), Week 12.
- Subject from C015: Grade 3 absolute lymphocyte count at Week 1 (15%) and End of Treatment (228/mm^3).
- Subject from C015: Grade 3 absolute lymphocyte count at End of Treatment (0.3 K/mm^3).
- Subject from C017: Grade 3 absolute neutrophil count (0.9 K/µL), Week 4.
- Subject from C017: Grade 3 platelet count at Week 1 (3 x 10^3/mm^3) and Week 2 (40 K/µL); Grade 3 WBC (1.2 x 10^3/mm^3) and Grade 4 absolute neutrophil count (0.25 x 10^3/mm^3) at Week 22.
- Subject from C017: Grade 3 platelet count (34 K/µL) at screening.

No Grade 3 or 4 non-hematologic laboratory abnormalities were reported.

Immunopathology was tested in subjects at the end of study treatment. No subjects had clinically significant findings.

Other Safety Assessments

There were no clinically important findings in the pulse, blood pressure, temperature or respiration rate data. Where recorded, ECOG performance status was 0 or 1 for all subjects. One subject had an AE of weight decreased reported that was considered to be possibly

treatment-related: the weight of the subject during Week 1 was 67.3 kg; by Week 5 this had decreased to 62.0 kg, although by Week 6 (the last recorded weight measurement) it had increased slightly to 62.7 kg. There were few physical examination abnormalities. Injection site reactions were generally Grade 1 in severity.

Poststudy survival information was recorded for 9 subjects: 8 of these subjects were alive and 1 of the subjects had died due to disease progression at the time of study closure.

CONCLUSIONS:

- A total of 31 subjects who had completed a previous study with PF-3512676 Injection, and who had responded or stabilized in response to the treatment, continued their therapy in the present study.

- Approximately half of the subjects (16/31 subjects) had early termination of the study due to disease progression.

- There were no deaths within 30 days of the last dose of study treatment.

- Most AEs were CTC Grade 1 or 2. Two subjects had a Grade 3 hematology toxicity reported as an AE: 1 subject had Grade 3 anemia and 1 subject had Grade 3 leukopenia. There were no Grade 3/4 AEs of neutropenia, thrombocytopenia, sepsis, or flu-like symptoms, although some subjects had CTC Grade 3/4 neutrophil and/or platelet counts reported in their laboratory evaluations.

- One subject experienced a CTC Grade 4 anaphylactic reaction related to injection of PF-3512676.

- Local injection site reactions were common, although only 1 subject had CTC Grade 3 injection site erythema and pain. Flu-like symptoms were less common than local injection site reactions and were CTC Grade 1 in severity in all but 3 cases.

- There were no clinically significant immunopathology findings.