Bristol-Myers Squibb Company

Final Clinical Study Report for Study CA165020

Abbreviated Report

A Randomized, Two-Cohort Phase II Study of Two Doses of BMS-275183 Given On A Weekly Schedule in Patients with Pre-Treated Non-Small Cell Lung Cancer

Indication:	Non-small cell lung cancer
Phase:	2
Study Initiation Date:	08-Oct-2004
Study Completion Date:	29-Mar-2006
Report Date:	20-Mar-2007
Document Control Number:	930017903
Previous Version(s) of this Report:	None

THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:
[redacted]
Bristol-Myers Squibb
Wallingford, CT USA 06492 USA

SYNOPSIS

Final Clinical Study Report for CA165020

TITLE OF STUDY: A Randomized, Two-cohort Phase II Study of Two Doses of BMS-275183 Given on a Weekly Schedule in Patients with Pre-treated Non-small Cell Lung Cancer

INVESTIGATORS/STUDY CENTERS: 10 study centers: 7 in Europe and 3 in the United States

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 08-Oct-2004 **CLINICAL PHASE:** 2

Study Completion Date: 29-Mar-2006

REASON FOR AN ABBREVIATED REPORT: The current study closed early when the objective of assessing the clinical activity of the 2 doses being evaluated could no longer be met. This was the result of the discontinuation of the 200 mg/m^2 weekly dose as a result of treatment-related serious adverse events (SAEs) at the 200 mg/m^2 dose and the subsequently closure of the study when similar SAEs were reported at the 120 mg/m^2 weekly dose. Therefore, an abbreviated report format is being used that presents complete safety data. In addition, summary statistics for pharmacokinetic parameters and the sponsor's assessment of best tumor response are presented.

OBJECTIVES: Protocol-specified objectives analyzed in this abbreviated report include the following:

- to evaluate the safety of each of 2 doses of BMS-275183
- to assess the pharmacokinetics of BMS-275183 following weekly, oral administration

A complete list of objectives is provided in the protocol.

METHODOLOGY: This open-label, dose-ranging, Phase 2 study in subjects with pretreated non small-cell lung cancer (NSCLC) was designed to assess the efficacy and safety of 2 doses (120 mg/m^2 and 200 mg/m^2 given on a continuous weekly schedule) of the oral taxane BMS-275183. Subjects had received prior treatment with either one prior cisplatin- or carboplatin-based regimen (Cohort 1) or a platinum- and docetaxel or pemetrexed containing regimen, followed by gefitinib or erlotinib and were considered resistant to treatment with prior platinum, docetaxel or pemetrexed and gefitinib or erlotinib (Cohort 2). Subjects in each cohort were to be randomized to receive BMS-275183 administered orally at either 120 or 200 mg/m^2 as a single dose once a week on a continuous weekly schedule. A 2-stage, modified Gehan design was used in each of the 4 cohort/treatment combinations to test whether BMS-275183 yielded a tumor response rate that was of clinical interest.

Dose modifications for hematologic and non-hematologic toxicity were allowed for each individual subject based on tolerability. Toxicity was assessed continuously during the study; tumor assessments were performed every 6 weeks. Subjects were followed for a minimum of 4 weeks after the last dose of study therapy or until all study related toxicities had resolved to baseline, stabilized, or were deemed irreversible, whichever was longer.

At 7 designated study sites, blood samples for pharmacokinetic evaluation were collected before and up to 48 hours after the first dose of BMS-275183 in Cycle 1.

NUMBER OF SUBJECTS PLANNED AND ANALYZED: Planned: up to 180 planned in order to get at least 160 response-evaluable subjects. **Enrolled and treated:** 31 enrolled and treated, 17 in the 120 mg/m^2 arm and 14 in the 200 mg/ m^2 arm.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Adult subjects (18 years or older) with histologically or cytologically confirmed NSCLC and uni- or bidimensionally measurable disease by modified WHO criteria, with an ECOG performance status (PS) of 0 – 2, and a life expectancy of at least 12 weeks were eligible to participate in this study. Subjects in Cohort 1 were to have progressive disease (PD) during or following therapy with one prior cisplatin- or carboplatin based regimen given for Stage III or IV NSCLC or for recurrent metastatic disease. Subjects in Cohort 2 were to have received prior treatment with a platinum and docetaxel or pemetrexed-containing regimen given either in combination or sequentially, followed by gefitinib or erlotinib, given for Stage III or IV NSCLC or for recurrent metastatic disease and be considered resistant to treatment with platinum, docetaxel or pemetrexed and gefitinib or erlotinib.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: BMS-275183 was supplied as 5 or 25 mg capsules and administered orally as either 120 or 200 mg/m^2 doses once a week on a continuous weekly schedule. Subjects were to be fasting at least 8 hours prior to drug administration and at least 2 hours post-dose. A treatment cycle was defined as 3 weeks (21 days). Treatment duration was to consist of at least 2 cycles. Duration of the treatment was to be based on tumor reassessments every 6 weeks. Subjects with PD were taken off treatment; treatment was also to be discontinued if unacceptable toxicity occurred. Additional reasons of discontinuation included informed consent withdrawal, sponsor decision, imprisonment, or compulsory detention.

Subjects with stable disease (SD) or a partial response (PR) were to receive treatment until PD or for as long as it was in the subject's best interest to continue treatment, up to a maximum of 18 cycles. Subjects with SD or PR could receive additional treatment beyond the 18th cycle if it was in their best interest, and was agreed to by both the investigator and the sponsor. Subjects who achieved a complete response (CR) were to receive treatment for up to 4 cycles post confirmation of CR.

BMS-275183 was from the following batch numbers: 5 mg: 3G74421 and 4G81480 and 25 mg: 3A67970, 3F69085, 3G69734, 3G69745, and 4G81690.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: There was no reference therapy in this study.

CRITERIA FOR EVALUATION:

Efficacy: Subjects were considered evaluable for response if they had a histologically or cytologically confirmed NSCLC and had received a minimum of 2 cycles of study drug.

Safety: Safety data were to be analyzed on all subjects who had received at least 1 dose of BMS-275183. Safety was evaluated according to the National Cancer Institute Common Toxicity Criteria (CTC) for Adverse Events, Version 3.0, based on recorded adverse events (AEs), SAEs, electrocardiogram (ECG) parameters, and abnormal laboratory parameters.

Pharmacokinetics: Single-dose pharmacokinetics parameters, Cmax, Tmax, AUC(0-T), AUC(INF), and T-HALF, were derived from BMS-275183 plasma concentration vs time data.

STATISTICAL CONSIDERATIONS: As stated above, the study was closed since it could no longer meet the objective of assessing the clinical activity of the 2 doses being evaluated. Thus, all statistical analyses described in the protocol were not conducted. Most of the 31 subjects treated were in Cohort 1. Due to the small number of subjects in Cohort 2, analyses were performed by treatment arm rather than by treatment arm/cohort combination.

Demographic, baseline characteristics, extent of exposure, and safety data in each treatment arm were summarized using descriptive statistics. Tumor response, as defined by sponsor assessment, was analyzed for all response-evaluable subjects**.**

All available pharmacokinetic data from subjects who received BMS-275183 were included in the pharmacokinetic data set. Tabulations and summary statistics by dose were provided for pharmacokinetic parameters (Cmax, AUC(INF), AUC(0-T), Tmax and T-Half) of BMS-275183. Geometric means and coefficients of variation (CV%) were reported for Cmax, AUC(INF) and AUC(0-T). Median, maxima and

minima were presented for Tmax and means and standard deviations were for all other parameters. Scatter plots of Cmax, AUC(INF) and AUC(0-T) versus dose were examined for relationship to dose.

RESULTS

Disposition, Demographics, and Other Pertinent Baseline Characteristics: Thirty-one subjects were enrolled and treated, 27 into Cohort 1 (15 in the 120 mg/m2 arm and 12 in the 200 mg/m2 arm) and 4 into Cohort 2 (2 in each arm) (Appendix 1.9). After drug-related SAEs (2 of which were fatal) were reported with the 200 mg/m2 weekly dose, the 200 mg/m2 dose was discontinued and all 8 subjects in the 200 mg/m2 arm who were still on-treatment continued on the 120 mg/m2 weekly dose.

All 31 treated subjects went off treatment, the primary reasons being disease progression (48%), study drug toxicity (19%), and death (16%). The treatment arms were well balanced with respect to demographics except for age in that more subjects in the 200 mg/m^2 arm were ≥ 65 and fewer subjects were < 65 compared to the 120 mg/m^2 arm. The population was primarily male (61%) and white (94%), ranged in age from 38 to 80 years (median of 55 years), and had an ECOG performance status of 0 or 1 (87%).

A majority of subjects had either poorly differentiated/undifferentiated (42%) or unknown histological grade (23%) at initial diagnosis. More than 90% of subjects were at Stage IV of disease at study entry. The predominant disease sites were lung (87%) and lymph node (42%). The median number of courses for both treatment arms was 2 (range: 1 to 12, 120 mg/m^2, and 1 to 19, 200 mg/m^2).

Efficacy Results: Subjects in both treatment arms received a median of 6 weeks of therapy, as well as a median of 2 courses of therapy and a median of 6 doses per subject. Of the 30 response-evaluable subjects, 1 subject had an overall response of CR (200 mg/m^2) and 2 subjects had PR (1 in each treatment arm). Five subjects in the 120 mg/m^2 arm and 2 in the 200 mg/m^2 arm had a sponsor's assessed best overall response of SD.

Safety Results:

Summary of Safety Information

	BMS-275183 Treatment Arm		
	120 mg/m^2 N = 17	**200 mg/m^2 N = 14**	**All N = 31 N (%)**
Subjects who died	9 (53%)	9 (64%)	18 (58%)
Subjects who died within 30 days of last dose	3 (18%)	3 (21%)	6 (19%)
Subjects with died due to study drug toxicity	0	3 (21%)[a]	3 (10%)
Subjects with an SAE	9 (53%)	7 (50%)	16 (52%)
Subjects with an AE leading to study discontinuation	6 (35%)	6 (43%)	12 (39%)
Subjects with treatment-related AEs	16 (94%)	14 (100%)	30 (97%)
Subjects with treatment-related Grade 3/4 AEs	5 (29%)	5 (36%)	10 (32%)
Selected Grade 3/4 laboratory abnormalities			
- Leukopenia	4 (24%)	5 (36%)	9 (29%)
- Neutropenia	2 (12%)	6 (43%)	8 (26%)
- Thrombocytopenia	1 (6%)	2 (14%)	3 (10%)

[a] 1 each of septic shock, infectious bilateral pneumopathy, and chest infection.

Of the 18 deaths during the study, 15 (48%) were due to disease progression and 3 (10%) were due to study drug toxicity (septic shock, infectious bilateral pneumopathy, and chest infection, all in the 200 mg/m^2 arm). The death due to chest infection was reported for a subject after the 200 mg/m^2 weekly dose had been reduced to 120 mg/m^2 weekly. Three of the 6 deaths occurring within 30 days of last dose were due to disease progression.

SAEs were considered related to BMS-275183 in 4 subjects (24%) in the 120 mg/m^2 arm (Grade 3 diarrhea in 1 subject; Grade 2 neutropenia in 1 subject; Grade 3 motor neuropathy, Grade 3 sensory neuropathy, Grade 4 leukopenia, Grade 4 thrombocytopenia, and Grade 3 anemia in 1 subject; and Grade 3 elevated AST in 1 subject) and 5 subjects (36%) in the 200 mg/m^2 arm (Grade 2 nausea and vomiting in 1 subject; Grade 3 fatigue, Grade 4 mucositis, Grade 2 motor neuropathy, Grade 3 febrile neutropenia, Grade 4 diarrhea, and Grade 5 septic shock in 1 subject; Grade 4 febrile neutropenia and Grade 5 infectious bilateral pneumopathy in 1 subject; Grade 3 increased dyspnea and Grade 2 endobronchial infection in 1 subject; and Grade 4 neutropenia and Grade 5 chest infection in 1 subject).

Treatment-related AEs leading to discontinuation of study therapy were reported in 3 subjects (18%) in the 120 mg/m^2 arm (paraesthesia, motor and sensory neuropathy, and infectious pneumopathy) and 5 subjects (36%) in the 200 mg/m^2 arm (endobronchial infection, paraesthesia, sensory neuropathy, febrile neutropenia, fatigue, mucositis, nausea, vomiting, poor diabetes control, and increased dyspnea).

All subjects experienced at least 1 AE. Diarrhea, fatigue and neutropenia were the 3 main treatment-related AEs. Neuropathy was reported in nearly half of the subjects (Grade 2, 23%, and Grade 3, 9.7%). No subjects reported Grade 4 neuropathy. Grade 3/4 leukopenia and Grade 3/4 neutropenia were the predominant hematologic abnormalities.

Pharmacokinetic Results: Overall BMS-275183 exposures, as measured by AUC(INF) and AUC(0-T), were higher for the 200 mg/m^2 dose group than the 120 mg/m^2 dose group. The increases in geometric means were 45% and 55%, respectively, which is less than the 67% increase in dose. However, these results should be interpreted with caution because of the small sample size and large inter-subject variance (CV > 100%).

Summary Statistics for BMS-275183 Pharmacokinetic Parameters

	BMS-275183 Pharmacokinetic Parameters				
Dose Level (mg/m^2)	Cmax (ng/mL) Geom. Mean (CV %)	AUC(INF) (ng·h/mL) Geom. Mean (CV %)	AUC(0-T) (ng·h/mL) Geom. Mean (CV %)	Tmax (h) Median (Min, Max)	T-Half (h) Mean (SD)
120 (n = 14)	386 (85)	1740 (117)	1376 (115)	1.00 (0.50, 3.00)	24.88 (7.42)
200 (n = 9)	400 (95)	2519 (102)	2135 (103)	1.50 (1.00, 3.00)	18.76 (3.86)

Pharmacokinetic samples were collected for 2 of the 3 subjects who died due to SAEs; BMS-275183 exposures associated with the 2 subjects as measured by AUC(INF) and AUC(0-T) were among the 3 highest observed.**Pharmacodynamic Results:** There were no protocol-defined pharmacodynamic objectives in this study.

Other Results: The study was closed since it could no longer meet the objective of assessing the clinical activity of the 2 doses being evaluated. As a result, the impact of BMS-275183 on lung cancer symptoms as measured by the FACT-L questionnaire was not evaluated.

CONCLUSIONS: Although recommended from Phase 1 study results, the dose of 200 mg/m^2 administered orally on a continuous weekly schedule proved to be above the maximum tolerated dose in NSCLC subjects who had received prior chemotherapy. This led to the discontinuation of the 200 mg/m^2 dose for safety reasons. The study was closed when the objective of assessing the clinical activity of the 2 doses being evaluated could not be met. Evidence of efficacy, including a complete response, was noted, warranting further investigations with a different dose and schedule.

DATE OF REPORT: 20-Mar-2007