Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient:BMS-690514		

SYNOPSIS

Final Clinical Study Report for Study CA187017

ABBREVIATED REPORT

TITLE OF STUDY: A Double-Blind, Randomized, Parallel Two-Arm Phase II of Trial BMS-690514 versus Erlotinib in Previously Chemotherapy Treated Non-Small Cell Lung Cancer Patients

INVESTIGATORS/STUDY CENTERS: Subjects were enrolled from a total of 30 sites in the U.S., Argentina, Canada, France, Korea, Poland, Spain and Taiwan.

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 03-Mar-2009 **CLINICAL PHASE:** 2

Study Completion Date: subjects are ongoing in study, (cut-off date:08-Sep-2010)

INTRODUCTION: Lung cancer is the most common cause of cancer-related mortality worldwide, claiming about 1.2 million lives annually. Non-small cell lung cancer (NSCLC) represents approximately 85% of all patients. Typically, patients develop recurrent disease and are treated with a several different second-line agents that include epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). The average progression-free survival (PFS) has remained poor at 2.2 months in the overall population of NSCLC patients. It has been postulated that the short PFS is due to either the development of resistance to EGFR TKIs or to the presence of other downstream pathways, including vascular endothelial growth factor receptor (VEGFR). In order to improve the PFS in this group of patients, BMS-690514 was developed to target EGFR/human epidermal growth factor receptors (HER) 1, 2 and 4 as well as VEGFR 1, 2 and 3 in a single oral formulation. The rationale of the study was that BMS-690514 at a dose of 200 mg daily would confer a superior PFS when compared to erlotinib at a dose of 150 mg daily in subjects who have progressive or recurrent NSCLC after treatment with one to two regimens of platinum-containing cytotoxic chemotherapy.

The results of this study are being reported in an abbreviated format with limited reporting of efficacy and full reporting of safety data, as the BMS-690514 program was terminated due to the lack of superiority over erlotinib. The analyses of pharmacokinetic (PK) and pharmacodynamic (PD) data are not reported.

OBJECTIVES: The protocol specified objectives analyzed in this abbreviated report include the following:

Primary Objective:

- To compare the PFS in subjects receiving BMS-690514 relative to erlotinib.

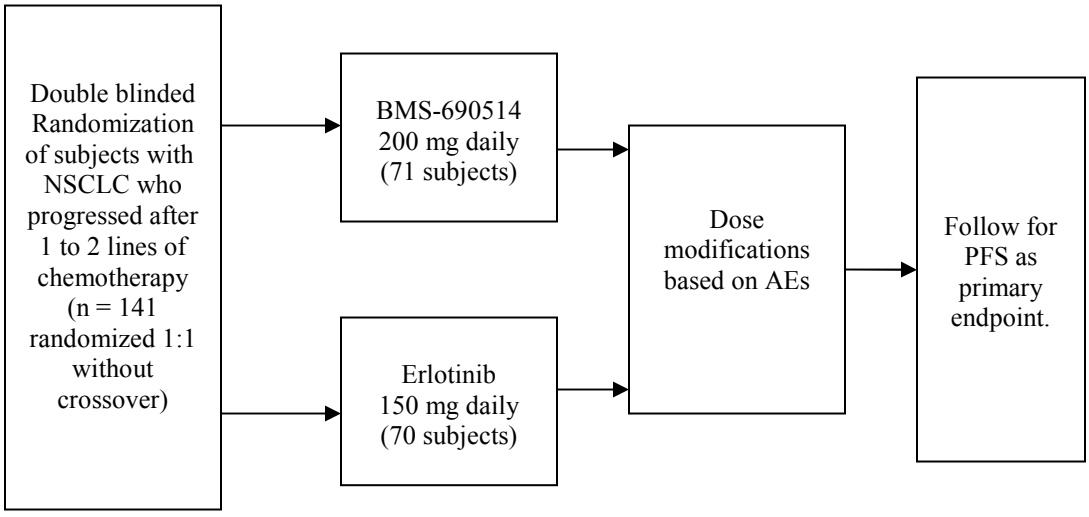
Secondary Objectives:

- To assess the safety and tolerability of both BMS-690514 and erlotinib.
- To estimate the PFS rate and tumor size change at 6 weeks (using computed tomography/magnetic resonance imaging [CT/MRI]) in subjects receiving BMS-690514 or erlotinib.

A complete list of objectives is provided in the protocol.

METHODOLOGY:

This was a double-blind, randomized, parallel two-arm study designed to directly compare BMS-690514 with erlotinib in subjects who had progressive disease after one or two previous regimens of platinum-containing cytotoxic chemotherapy (ie, erlotinib-eligible). Evaluations by CT/MRI were to be performed at baseline and every 6 weeks to evaluate tumor size change. Plasma and tumoral biomarkers were to be evaluated on a retrospective basis.



Secondary endpoints to be followed will include OS (overall survival), ORR (overall response rate), PFS rate and tumor size change at week 6 and safety. Tumor and plasma will be collected for biomarker assessments

NUMBER OF SUBJECTS (Planned and Analyzed):

A total of 140 subjects were planned to be randomized into 1:1 without crossover in this study. However, 195 subjects were enrolled and 141 subjects were randomized and treated (71 subjects to BMS-690514 200 mg and 70 subjects in erolitinib 150 mg).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Subjects included in this study were older than 18 years of age and had progression or recurrence of their NSCLC as defined in the introduction.

Additional inclusion criteria are provided in the protocol.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT:

Blinded BMS-690514 was supplied as white to off-white round 50-mg tablets. Blinded BMS-690514 was self-administered orally at the same time each day one hour before or two hours after food on a continuous daily schedule until disease progression or unacceptable toxicity.

Placebo for BMS-690514 was supplied as white to off-white round 50-mg tablets.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT:

Blinded erlotinib was supplied as gray opaque, size #00 two-piece hard gelatin 50-mg capsules, each containing two 25-mg tablets of erlotinib. Blinded erlotinib was self-administered orally at the same time each day one hour before or two hours after food on a continuous daily schedule until disease progression or unacceptable toxicity.

Placebo for erlotinib was supplied as gray opaque, size #00 two-piece hard gelatin 50-mg capsules.

CRITERIA FOR EVALUATION:

Safety:

Safety assessments were based on medical review of reported adverse events (AEs) and the results of vital sign measurements, physical examinations, and clinical laboratory tests. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0 on a continuous basis while the subject was on study and until 30 days after the last dose of study drug. Subjects were to be followed until all treatment-related AEs recovered to baseline or were deemed irreversible by the Principal Investigator. All subjects who received any study drug were considered evaluable for safety parameters.

Efficacy:

Primary efficacy was assessed by estimating PFS using baseline and periodic tumor measurements every 6 weeks by CT, MRI and other standard methods. Secondary efficacy was assessed by estimating PFS rate and tumor size change at 6 weeks.

Other:

The PK, PD and other assessments were not analyzed and reported as the BMS-690514 program was terminated due to the lack of superiority of BMS-690514 as compared with erlotinib in subjects with NSCLC in this study.

STATISTICAL CONSIDERATIONS:

The number of events and power of the study were calculated assuming an exponential PFS distribution in each arm. The final analysis of the primary endpoint would require at least 118 events (either progressions or deaths). This was the number of events required for a one-sided log-rank test at $\alpha = 0.10$ level to have 82% power to show a statistically significant difference when the true hazard ratio (HR) was 0.67 (ie, when the median PFS was 3.3 months for BMS-690514 and 2.2 months in the erlotinib arm). If the observed HR was 0.79, ie, the median in the BMS-690514 arm was ~2.8 months, a statistically significant difference was observed. At the time of the PFS analysis, it was expected that approximately 70 deaths would be observed. This was based on the assumption that the median OS was 9.7 months for BMS-690514 and 6.7 months for erlotinib. With these events, a one-sided log-rank test at $\alpha = 0.10$ level would have 60% power to show a statistically significant difference when the true HR was 0.69.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

A total of 141 subjects were randomized and treated; 54 subjects were enrolled but not randomized (39 subjects no longer met the study criteria, 8 subjects for "other" reasons, 5 subjects withdrew consent, and 2 subjects had poor/non compliance).

As of cutoff date (08-Sep-2010), of the 141 treated subjects, 12 subjects were on therapy and 129 subjects were off study therapy.

The most common reasons for discontinuation of treatment included disease progression in 100 subjects, "other" reasons in 9 subjects, and AEs unrelated to study drug in 8 subjects (Table 1).

Table 1: Subject Disposition: All Treated Subjects

	BMS-690514 200 mg	Erlotinib 150 mg	Overall
No. of Subjects Treated	71	70	141
No. of Subjects on therapy	4	8	12
No. of Subjects off study therapy	67	62	129
Reasons off study therapy			
Subject withdrew consent	2	2	4
Death	0	4	4
Study drug toxicity	3	1	4
Adverse event unrelated to study drug	6	2	8
Disease progression	51	49	100
Other	5	4	9

A total of 100 males and 41 females, with a mean age of 61.4 years (range: 26 to 83 years) were randomized to the study. The majority of subjects were White (80.9%) (Table 2).

Table 2: Baseline and Demographic Characteristics: All Treated Subjects

	BMS-690514 200 mg	Erlotinib 150 mg	Overall
N	71	70	141
Age (years)			
Mean	60.2	62.6	61.4
Min-Max	26, 81	38, 83	26, 83
Age Categorization			
<60	31 (43.7)	27 (38.6)	58 (41.1)
>=60	40 (56.3)	43 (61.4)	83 (58.9)
Gender			
Male, n (%)	48 (67.6)	52 (74.3)	100 (70.9)
Female, n (%)	23 (32.4)	18 (25.7)	41 (29.1)
Race			
White, n (%)	58 (81.7)	56 (80.0)	114 (80.9)
Black/African American, n (%)	1 (1.4)	2 (2.9)	3 (2.1)
Chinese, n (%)	0	1 (1.4)	1 (0.7)
Korean, n (%)	11 (15.5)	9 (12.9)	20 (14.2)
Taiwanese, n (%)	1 (1.4)	0	1 (0.7)
Asian other, n (%)	0	2 (2.9)	2 (1.4)

Table 2: Baseline and Demographic Characteristics: All Treated Subjects

	BMS-690514 200 mg	Erlotinib 150 mg	Overall
ECOG			
0	29 (40.8)	29 (41.4)	58 (41.1)
1	42 (59.2)	40 (57.1)	82 (58.2)
2	0	1 (1.4)	1 (0.7)

ECOG: Eastern Cooperative Oncology Group

The most common index lesion sites in BMS-690514 treatment group included lung (60 subjects; 84.5%), lymph node (20 subjects; 28.2%), and liver (13 subjects; 18.3%). The most common index lesion sites in erlotinib treatment group included lung (59 subjects; 84.3%), and lymph node (18 subjects; 25.7%).

Safety Results:

An overview of safety summary for all treated subjects is provided in Table 3.

- Overall deaths were reported in 35 (49.3%) subjects in BMS-690514 and 36 (51.4%) subjects in erlotinib treatment groups.
- Twenty-two (15.6%) subjects died within 30 days of last dose of study therapy of whom 10 (14.1%) were in BMS-690514 and 12 (17.1%) were in erlotinib treatment groups.
- Serious adverse events (SAEs) were reported for 31 (43.7%) subjects in BMS-690514 and 19 (27.1%) subjects in erlotinib treatment groups.
- Adverse events leading to discontinuation were reported for 9 (12.7%) subjects in BMS-690514 and 3 (4.3%) subjects in erlotinib treatment groups.
- All the study subjects experienced at least one AE.

Table 3: Overall Safety Summary: All Treated Subjects

	Number of subjects (%)	
	BMS-690514 200 mg	**Erlotinib 150 mg**
N	71	70
Deaths	35 (49.3)	36 (51.4)
Deaths within 30 days of last dose of study therapy.	10 (14.1)	12 (17.1)
At least one SAE		
Any Grade	31 (43.7)	19 (27.1)
Grade 3-4	21 (29.6)	7 (10)
At least one AE		
Any Grade	71 (100)	70 (100)
Grade 3-4	34 (47.9)	24 (34.3)
At least one related AE		
Any Grade	70 (98.6)	65 (92.9)

Table 3: Overall Safety Summary: All Treated Subjects

	Number of subjects (%)	
	BMS-690514 200 mg	**Erlotinib 150 mg**
Grade 3-4	34 (47.9)	24 (34.3)
AEs leading to discontinuation of study therapy		
Any Grade	9 (12.7)	3 (4.3)
Grade 3-4	3 (4.2)	1 (1.4)

Efficacy results:

No difference was seen in the primary endpoint of PFS between the BMS-690514 and erlotinib arms. The observed BMS-690514 to erlotinib HR for PFS was 1.17 and the 95% confidence interval (CI) was 0.82, 1.67. Among the EGFR-evaluable subjects (N = 93) based on retrospective tissue confirmation of EGFR mutation status, EGFR wild-type subjects were the majority represented in this study. The results showed no difference in PFS between BMS-690514 and erlotinib among EGFR-evaluable subjects with EGFR mutation-positive disease (N = 14) or EGFR wild-type disease (N = 79) (HR 1.24; 95% CI [0.78, 1.98])

Other Results:

The PK, PD and other assessments are not analyzed and reported in this report as the BMS-690514 program was terminated due to the lack of superiority of BMS-690514 as compared with erlotinib in subjects with NSCLC in this study.

CONCLUSIONS:

- BMS-690514 did not confer an improved PFS when compared to erlotinib. The safety and AE profile of BMS-690514 were consistent with the targets and were expected. Due to a lack of improved efficacy over standard of care erlotinib in both the EGFR mutated and the EGFR wild-type subjects, future development of BMS-690514 was terminated.

DATE OF REPORT: 01-Aug-2011