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-754807		

SYNOPSIS

Final Clinical Study Report for Study CA191004

TITLE OF STUDY: A Phase 1/2 Trial of BMS-754807 in Combination with Trastuzumab (Herceptin®) in Subjects with Advanced or Metastatic Her-2-positive Breast Cancer

INVESTIGATORS/STUDY CENTER: 8 clinical sites enrolled subjects worldwide: 3 sites in Australia, 2 sites in Canada, 1 site each in Hungary, United Kingdom and Belgium

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 04-Nov-2009 **CLINICAL PHASE:** 1/2
Study Completion Date: 15-Jan-2012

OBJECTIVES:

Primary Objective: The dose escalation phase determined the maximum tolerated dose (MTD) and a recommended Phase 2 dose (or dose range as appropriate) of BMS-754807 administered orally on a once daily schedule in combination with trastuzumab administered at standard doses intravenously on a weekly basis. The primary objective of the dose expansion phase was to assess anti-tumor response of the combination.

Secondary Objectives:

- To evaluate the safety and tolerability of the combination regimen.
- To assess the effect of the combination therapy on glucose metabolism.
- To explore whether co-medication with an oral anti-hyperglycemic agent can enable adequate tolerability of the combination therapy if BMS-754807 doses induce hyperglycemia.

Exploratory Objectives:

- To obtain BMS-754807 plasma concentration versus time data for future population pharmacokinetic (PK) analysis.
- To explore pharmacodynamic (PD) parameters of BMS-754807 including but not limited to serum levels of hormones and ligands of type 1 insulin like growth factor receptor (IGF-1R) or insulin receptor (IR) and numbers of IGF-1R positive circulating tumors cells (CTCs).
- To explore biomarkers that are potentially predictive of response to BMS-754807, including but not limited to markers of signaling pathway activity assessed by immunohistochemistry (IHC) or assessment of numbers of IGF-1R positive CTCs at baseline.
- To explore the use of CTCs for the assessment of PD effects and/or anti-tumor activity.

METHODOLOGY: This was an open-label, dose escalation study to evaluate the safety, tolerability and MTD of oral BMS-754807 in combination with trastuzumab. Trastuzumab was administered intravenously every week starting with an initial dose of 4 mg/kg on Day 1 of Week 1, followed by weekly 2 mg/kg dosings. Daily oral dosing of BMS-754807 began on Day 1 of Week 1. An oral anti-hyperglycemic agent could be administered to enhance tolerability of BMS-754807, if hyperglycemia occurred.

Dose Escalation: Subjects were enrolled to the dose escalation phase of the study in cohorts of 3. The dose of BMS-754807 in the first cohort was 50 mg, and in the subsequent cohorts were 70 mg and 100 mg. Dose escalation was guided by the incidence of dose limiting toxicities (DLTs) within the first 4 weeks and did not exceed the MTD for BMS-754807 as single agent (determined in the CA191002 study as 100 mg). If a DLT was observed in 1 of 3 subjects at a given dose level, an additional 3 subjects were to be enrolled to that dose level before further escalation. Dose escalation continued until ≥1/3 of subjects at a particular dose level had a DLT in the first 4 weeks or until the maximum dose of 100 mg was tested in 6 subjects.

Dose Expansion: Subjects received BMS-754807 at the MTD as determined in the dose escalation part of this study. Clinical safety monitoring was the same as during the dose escalation phase. If the rate of DLTs during the first 4 weeks was ≥ 1/3, these findings were to be discussed between the investigators and the Sponsor.

NUMBER OF SUBJECTS (Planned and Analyzed): Planned: 15 subjects in the dose escalation part of the study and 30 treated subjects in the dose expansion part of the study; Enrolled: 22 subjects; Treated: 15 subjects (3 were treated with 50 mg BMS-754807 + trastuzumab, 4 were treated with 70 mg BMS-754807 + trastuzumab, and 8 were treated with 100 mg BMS-754807 + trastuzumab).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Subjects with locally advanced or metastatic Her-2-positive breast cancer who failed at least one trastuzumab-containing regimen and who satisfied the inclusion and exclusion criteria were eligible to participate. All women must have had a negative pregnancy test within 24 hours prior to dosing with study medication.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: BMS-754807 drug product was available as 10 and 100 mg potency white to off-white tablets. Subjects received oral daily doses of BMS-754807. Trastuzumab was prepared as per the package insert, and administered at an initial dose of 4 mg/kg on Day 1 of Week 1, followed by weekly 2 mg/kg doses.

Table 1: Investigational Product Identification

Product	Product Identification Number	Product Batch Number	Label Batch or Lot Number
BMS-754807 10 mg tablet	754807-A010-005	8G34129, 9H39495	0C60167, 8J38397, 9M36713
BMS-754807 100 mg tablet	754807-A100-004	0H51389, 7G29907, 8G36550	0H51396, 7K28230, 0C60490, 8J38399, 9M36717

Trastuzumab product batch numbers: 0F63772 and H0646B01

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Not applicable.

CRITERIA FOR EVALUATION:

Efficacy: Tumor response was determined for all subjects by radiological imaging (e.g. computed tomography [CT] scan or magnetic resonance imaging [MRI]) as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria v1.0. Tumor assessments to evaluate response and/or progression were done every 8 weeks or more frequently, if clinically indicated.

Safety: Toxicity was evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Safety assessments were based on medical review of adverse event (AE) reports and the results of vital sign measurements, electrocardiograms (ECGs), physical examinations, and clinical laboratory tests. The incidence of AEs was tabulated and reviewed for potential significance and clinical importance.

Metabolic Parameters: Metabolic measures including the occurrence of hyperglycemia or hypoglycemia were monitored by measurement of plasma glucose and/or home glucose monitoring. These metabolic measures were also used to assess whether hyperglycemia can be controlled when subjects are co-medicated with an oral anti-hyperglycemic agent at BMS-754807 doses that induce hyperglycemia.

Pharmacokinetics : The plasma concentration versus time data from this study will be combined with data from other studies to conduct a population pharmacokinetic evaluation of BMS-754807. Results of population pharmacokinetic analyses will be reported separately.

Pharmacodynamics: The effect of receptor inhibition by BMS-754807 was evaluated by measurement of serum levels of hormones and ligands such as human growth hormone (HGH), insulin, C-peptide, IGF-1 and IGF-2.

Exploratory Measures: Tumor-material obtained at baseline were to be studied by IHC for markers such as expression or activity of IGF-1R, IR, IGF-1, IGF-2, epidermal growth factor receptor (EGFR), Her-2-receptor (HER2), protein kinase B (AKT), CTCs were obtained at pre-specified time points to explore CTCs as potential predictive or PD markers of the effect of BMS-754807 and trastuzumab.

STATISTICAL CONSIDERATIONS:

Sample Size Determination: This was a Phase 1 dose escalation study and sample size depended on observed toxicity. Three (3) to 6 subjects were to be treated at each dose level and an additional 30 subjects were to be treated at or below the MTD. If the true anti-tumor response rate was 25% or more, there would be at least a 96% chance to observe at least 4 responses among the 30 subjects in the expansion cohort. There would be less than 4% chance to observe 3 or fewer responses.

Statistical Analyses:

Safety: All recorded AEs were listed and tabulated by system organ class (SOC), preferred term (PT) and treatment. Vital signs and clinical laboratory test results were listed and summarized by treatment. Any significant physical examination findings, ECG abnormalities, and marked clinical laboratory abnormalities were listed.

Glucose homeostasis: Number of subjects who required co-medication of an anti-hyperglycemic agent were tabulated by treatment. Time to requiring co-medication was listed, and plotted by treatment. Additionally, measures for glucose homeostasis, along with changes (or percent changes) from baseline, were listed, summarized and plotted over measurement time points by treatment.

Pharmacokinetics: Data describing the plasma concentration versus time from this study were listed and summarized, including summaries and a plot of Cmin (observed plasma concentration 24 hours post dose for BMS-754807) data. These data will be combined with similar data from other related BMS-754807 studies to conduct a population pharmacokinetic evaluation of the compound. Results of population pharmacokinetic analyses will be reported separately.

Pharmacodynamic measures: Pharmacodynamics measures and corresponding percent of baseline were listed, and summarized by measurement time point and treatment. Possible associations between the PD measures of interest and BMS-754807 exposure were to be explored graphically. Any apparent dose-response relationships were to be investigated by fitting appropriate models. Exposure-responses analysis may be performed with population PK analysis and results will be reported separately.

Exploratory measures: If a sufficient number of baseline tumor biopsies were collected, logistic regression may have been used to explore the association of the expression levels of IGF-1R, IR, IGF-1, IGF-2, EGFR, HER2 and AKT and response to therapy. No exploratory analysis of predictive biomarkers was performed due to lack of objective tumor response to the therapy.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

Fifteen (15, 68.2%) of the 22 enrolled subjects received treatment with BMS-754807 and trastuzumab, and 7 subjects did not receive study drug, because they either did not meet study criteria by the time of study treatment or withdrew consent. Of the 15 treated subjects, 3 were treated with 50 mg BMS-754807 + trastuzumab, 4 were treated with 70 mg BMS-754807 + trastuzumab, and 8 were treated with 100 mg BMS-754807 + trastuzumab. Fourteen (93.3%) subjects discontinued study treatment, as per study design, due to disease progression (13, 86.7%) or due to an AE unrelated to study drug (1, 6.7%) (Table 2). One subject, in the 100 mg dose group, was continuing in the Treatment Period at the time of database lock. Twelve subjects completed the 30-day follow-up period. The study was discontinued early as when no objective responses were observed in the first 6 subjects at MTD, the sponsor decided to stop enrollment after a maximum number of 10 subjects were treated at the MTD.

Table 2: Subject Disposition - All Treated Subjects

	BMS-754807 + Trastuzumab 50 mg	**BMS-754807 + Trastuzumab 70 mg**	**BMS-754807 + Trastuzumab 100mg**	**Total**
No. of Subjects	3	4	8	15
Subjects not continuing in the treatment period (%)	3 (100.0)	4 (100.0)	7 (87.5)	14 (93.3)
Reason for not continuing in the treatment period (%)				
Disease Progression	3 (100.0)	3 (75.0)	7 (87.5)	13 (86.7)
AE unrelated to study drug	0	1 (25.0)	0	1 (6.7)
Subjects continuing in the study (%)	3 (100.0)	3 (75.0)	6 (75.0)	12 (80.0)
Subjects not continuing in the study (%)	0	1 (25.0)	1 (12.5)	2 (13.3)

One subject in the 100 mg dose group was continuing in the Treatment Period at the time of database lock

All 15 (100%) subjects in this study were female and white (Table 3). The mean age was 56 years, and 80% of the subjects were < 65 years. Physical measurements (height and weight) were similar among treatment groups in this study. The mean BMI was 25.89 kg/m^2. Eight (53.3%) subjects had baseline performance status (ECOG) of 1 and 7 (46.7%) had ECOG of 0.

Table 3 Demographic Characteristics Summary - All Treated Subjects

	BMS 50 +T N = 3	BMS 70 +T N = 4	BMS 100 +T N = 8	Total N = 15
AGE				
N	3	4	8	15
MEAN	62.3	48.5	57.5	56.1
MEDIAN	65.0	47.5	57.0	56.0
MIN , MAX	51 , 71	35 , 64	43 , 77	35 , 77
STANDARD DEVIATION	10.26	12.07	10.41	11.24
AGE CATEGORIZATION (%)				
< 65	1 (33.3)	4 (100.0)	7 (87.5)	12 (80.0)
>= 65	2 (66.7)	0	1 (12.5)	3 (20.0)
GENDER (%)				
FEMALE	3 (100.0)	4 (100.0)	8 (100.0)	15 (100.0)
RACE (%)				
WHITE	3 (100.0)	4 (100.0)	8 (100.0)	15 (100.0)

All 15 (100%) subjects had prior systemic anti-cancer therapy. Fourteen (93%) subjects had received 3 or more regimens previously, and 1 (7%) subject had 1 prior anti-cancer therapy regimen. Fourteen (93%) subjects had prior surgery and 11 (73%) subjects had prior radiotherapy.

The median duration of study therapy was similar in the 3 BMS-754807 dose groups (56 to 57 days). The median duration of trastuzumab therapy was 8.0 weeks, 6.5 weeks and 8.0 weeks for the 50 mg, 70 mg and 100 mg dose groups, respectively.

Efficacy Results:

The combination regimen of BMS-754807 and trastuzumab had no objective responses in the 8 subjects treated at the pre-specified maximum dose level of 100 mg BMS-754807 using the RECIST criteria. Three (3) subjects, all in the 100 mg BMS-754807 dose group, had a best response of stable disease. One subject remained on study for approximately 322 days (discontinued post database lock); prior to study enrollment, the subject had previously progressed after 273 days of treatment with paclitaxel and trastuzumab in the first line metastatic setting.

Safety Results:

All 15 (100%) treated subjects had AEs during the study. AEs ranged in intensity from CTCAE Grade 1 to Grade 3, except for one Grade 5 AE (in the 70 mg BMS-754807 dose group) of hepatic failure which led to death. One subject experienced an unrelated SAE Grade 3 event of progression due to breast cancer. The subject discontinued study treatment on Day 25, but the event was reported as unresolved. The subject was followed after discontinuation, as per protocol, with an outcome of death. Other than the Grade 5 AE, only subjects in the 100 mg BMS-754807 dose group had CTCAE Grade 3 AEs. The most frequently occurring AEs among all treated subjects were fatigue (10, 66.7%), nausea (9, 60.0%), diarrhea (7, 46.7%), decreased appetite (6, 40.0%), vomiting (4, 26.7%) and hyperglycemia (4, 26.7%). One subject had an SAE of Grade 3 hyperglycemia which was considered related to study drug.

Across the 3 dose groups of BMS-754807, 4 (26.7%) subjects had AEs of hyperglycemia and 3 (20.0%) subjects had AEs of hypoglycemia. One subject, in the 100 mg BMS-754807 dose group, experienced a DLT of symptomatic hyperglycemia (the subject required a dose reduction during the first 28 days). Four subjects, all in the 100 mg BMS-754807 dose group, required co-medication with an anti-hyperglycemic agent.

For subjects with available measurements, the metabolic parameters (fructosamine and HbA1c) showed an upwards trend in mean changes from baseline.

Pharmacokinetic Results:

Results of population pharmacokinetic analyses will be reported separately. A separate pharmacokinetic evaluation of plasma BMS-754807 concentrations was not planned for this study.

Pharmacodynamic Results:

Levels of insulin, C-peptide, and plasma glucose increased after the administration of BMS-754807. At the BMS-754807 100 mg dose level, the magnitude of increase in post-dose levels of insulin, C-peptide, and plasma glucose after 1 week of continuous daily dosing of BMS-754807 appeared larger than the increase after a single dose. The increases in plasma glucose were mainly non-fasting. The increase was continued up to 8 hours, suggesting more sustained inhibition of IR at the highest dose level. Increased serum levels of ligand (total IGF-1, free IGF-1) and IGF binding protein (IGFBP3) from baseline in response to BMS-754807 were observed, demonstrating inhibition of IGF-1R. Compensatory HGH increases resulting from IGF-1R inhibition were observed. However, dose-dependent changes in IGF-1 were not apparent, probably due to the small sample size and the variability of IGF-1 levels between subjects.

CONCLUSIONS:

- The MTD of the combination of daily BMS-754807 and weekly trastuzumab (2 mg/kg) was not reached in this study. BMS-754807 100 mg in combination with trastuzumab (2 mg/kg) was safe and well tolerated in locally advanced or metastatic Her-2- positive breast cancer patients.
- The combination regimen had no objective antitumor activity in this small cohort of Her-2-positive breast cancer patients who had failed prior trastuzumab-based treatment, and who were treated in this study with a range of doses of BMS-754807 in combination with trastuzumab.
- No additive or synergistic toxicities were observed.
- BMS-754807 induced dose-dependent changes in glucose, mainly non-fasting hyperglycemia, and induced increases in HbA1c and fructosamine levels.
- The effect of co-medication with anti-hyperglycemic agents on long term tolerability could not be assessed due to the limited time on treatment per subject.
- Levels of insulin, C-peptide, and plasma glucose increased after the administration of BMS-754807, demonstrating inhibition of the insulin receptor.
- Increased serum levels of ligand (total IGF-1, free IGF-1), IGFBP3 and HGH from baseline in response to BMS-754807 were observed, demonstrating inhibition of IGF-1R.

DATE OF REPORT: 31-May-2012