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: Agonistic Anti-CD137 monoclonal antibody		

SYNOPSIS

Final Clinical Study Report for Study CA186006

ABBREVIATED REPORT

TITLE OF STUDY: A Randomized, Multi-Dose, Open-Label, Phase II Study of BMS-663513 as a Second-line Monotherapy in Subjects with Previously Treated Unresectable Stage III or Stage IV Melanoma

INVESTIGATORS/STUDY CENTERS: Subjects were enrolled at 29 investigational sites: 2 in Canada, 2 in Denmark, 5 in France, 6 in Germany, 5 in Italy, and 9 in the USA.

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 17-Mar-2008 **CLINICAL PHASE:** Phase II

Study Completion Date: 12-Oct-2009

INTRODUCTION: Prior clinical experience with monotherapy BMS-663513 was based on a single open-label, ascending, multi-dose, Phase I/II study in subjects with locally advanced or metastatic solid tumors (CA186001). No maximum tolerated dose (MTD) for BMS-663513 was achieved up to the maximum protocol-specified dose (15 mg/kg every 3 weeks), and the results from CA186001 demonstrated BMS-663513 was tolerable across a wide dose range. Confirmed partial responses were observed in 4 subjects at 1.0 mg/kg (2 subjects), 3 mg/kg (1 subject), and 10 mg/kg (1 subject). An additional 10 subjects had stable disease. Only subjects with melanoma attained responses.

The data from CA186001 confirmed that following intravenous administration over 60 minutes, once every 3 weeks, BMS-663513 has linear pharmacokinetics (PK) in humans; maximum observed concentration (Cmax) and area under the concentration-time curve (AUC) increased in proportion to dose from 0.3 mg/kg to 15 mg/kg. Both apparent total body clearance after intravenous administration (CL) and volume of distribution at steady-state after intravenous administration (Vss) showed no apparent dose dependency over the 0.3-15 mg/kg dose range. Steady-state levels of BMS-663513 in serum are reached within 2-4 cycles following intravenous administration over 60 minutes, once every three weeks.

This Phase 2 study (CA186006) in subjects with Stage III (unresectable) or Stage IV melanoma was designed to determine a level of antitumor activity that would support definitive efficacy determination in Phase 3 studies and to assess a variety of doses and schedules of BMS-663513 in order to provide for optimal dose/schedule selection for utilization in future Phase 3 studies.

As of 05-Jan-2009 (protocol amendment 06) all dosing was discontinued and no retreatment was allowed due to the reporting of 2 fatal cases of drug-related hepatotoxicity in the program. This abbreviated report is focused on reporting all safety along with key efficacy and PK results of the study; other planned

objectives/assessments (PK and PD associations, immune system markers, and potential predictive markers of biological response) are not presented in this report.

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

1) 6-month progression-free survival (PFS) rate following treatment with BMS-663513 in each arm (primary objective of the study).
2) median PFS time, tumor response rate, 1-year survival rate and median survival in each arm
3) safety profile for each arm
4) pharmacokinetics of BMS-663513 for each arm

A complete list of objectives is provided in the protocol.

METHODOLOGY: This was a randomized, multi-dose, open-label, parallel 4-arm study in subjects with Stage III (unresectable) or Stage IV melanoma. The study was divided into three phases: the screening/baseline phase, the treatment phase and the follow-up phase. BMS-663513 was administered at 0.1, 1 or 5 mg/kg every 3 weeks or 1 mg/kg every 6 weeks. Tumor assessments were performed at Week 12 post randomization and every 6 weeks thereafter followed by every 12 weeks after Week 48. Subjects with documented disease progression by modified World Health Organization (mWHO) criteria were allowed to continue receiving BMS-663513 at the Investigator's discretion after consultation with the medical monitor for up to 1 year from the date of progression. Subjects entering the follow up phase required 30 day and 60 day clinic visits after the last dose of BMS-663513. All subjects were followed for overall survival (OS). Following the 60 day clinic visit subjects entered the long-term follow-up to evaluate OS and telephone contact was made every 12 weeks for up to one year after the last subject was randomized into the study.

NUMBER OF SUBJECTS (Planned and Analyzed): Up to 160 subjects were planned, 159 were enrolled and randomized, and 158 were treated and evaluated.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Male and female subjects at least 18 years of age with histologically or cytologically confirmed Stage III (unresectable) or Stage IV melanoma were eligible for this study. Subjects received one line of prior systemic treatment with any regimen (non-experimental or experimental) and relapsed, failed to respond (CR or PR) or did not tolerate that regimen. Subjects who received adjuvant, neoadjuvant, local perfusion, or local or palliative radiation therapy only were not eligible unless they also received one additional line of systemic therapy for metastatic disease.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT: BMS-663513 for injection was supplied by BMS in individual 10 mL vials each containing 100 mg of the drug substance, as a clear, colorless to pale yellow 10 mg/mL solution. The drug substance was diluted to between 0.1 mg/mL and 3.0 mg/mL with 0.9% Sodium Chloride Injection USP prior to IV administration. Following Amendment 05, the drug substance was diluted to between 0.05 mg/mL and 3.0 mg/mL.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT: No reference therapy was administered in this study.

CRITERIA FOR EVALUATION:

Safety: Safety was evaluated for all treated subjects using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v3.0 (CTCAE, v3.0; publish date: August 9, 2006). Adverse events (AEs) were mapped to preferred term and body system using the Medical Dictionary for Regulatory Activities (MedDRA). Safety assessments were based on medical review of adverse event reports, vital sign measurements, physical examinations and clinical laboratory tests. The incidence of AEs were tabulated and reviewed for potential significance and clinical importance. The reporting period for safety data was from the date of first on-study dose up to 60 days after the last dose was received.

Efficacy: At baseline, each investigator picked index lesions (lesions that were to be measured throughout the study) and non-index lesions to be followed at each tumor evaluation. Best response on-study and date of progression were obtained by comparing per time point responses to baseline tumor burden using

mWHO criteria. The primary objective of the study was to determine the 6-month PFS rate following treatment with BMS-663513 in each arm. However, due to premature discontinuation of the study therapy, hypothesis testing was not conducted. Instead, estimates and associated one-sided 90% confidence interval for 6-month PFS rate, PFS, 1-year OS rate and OS are provided. No p-values are reported. Duration of response is not presented. As treatment with BMS-663513 was suspended, some subjects discontinued treatment before the first anti-tumor assessment. Not all subjects had data for at least one anti tumor assessment available at the time of database lock; thus, the results are presented as intention to treat.

Pharmacokinetics (PK): Blood samples were collected to assess the serum PK of BMS-663513. Data of the concentration of BMS-663513 in serum will be used in conjunction with samples from other studies as part of a population PK assessment when appropriate.

Other Results: The planned assessment of a population PK analysis of BMS-663513 for each arm, evaluation of the exploratory PD and predictive biomarkers in serum, peripheral blood mononuclear cells (PBMCs), whole blood, or tumor tissue (if applicable), and assessment of the immunogenicity of BMS-663513 on inducing serum Human Anti Human Antibodies (HAHA) were not performed.

STATISTICAL CONSIDERATIONS: Baseline and efficacy analyses were conducted on all randomized subjects, grouped according to arm assigned at randomization. Safety analyses were based on all treated subjects, grouped by treatment received.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: All subjects were off treatment; a majority of subjects (113; 71%) discontinued due to disease progression and 22 (13.8%) discontinued for administrative reasons by Sponsor (ie, no retreatment allowed due to the reporting of 2 fatal cases of drug-related hepatotoxicity in the program). Other reasons for discontinuation of study therapy are shown in Table 1. The study population consisted of males (59.1%) and females (40.9%). A majority of the randomized subjects were White (99.4%). Subjects ranged in age from 25 to 85 years (median age = 59.0 years; Table 2). All except 3 (1.9%) of the subjects had an Eastern Cooperative Oncology Group (ECOG) status of 0 (77.4%) or 1 (20.1%) at their initial assessment.

Table 1: Subject Disposition

	0.1 mg/kg Q3W	1.0 mg/kg Q3W	1.0 mg/kg Q6W	5.0 mg/kg Q3W	Overall
No. of Subjects Randomized	41	39	40	39	159
No. of Subjects Treated	41	38	40	39	158
No. of Subjects Discontinued	41	39	40	39	159
Reason for Discontinuation					
Administrative reason by Sponsor	5	9	6	2	22
AE unrelated to study drug	3	0	1	3	7
Disease progression	32	20	32	29	113
Other (never treated)	0	1	0	0	1
Study drug toxicity	1	8	0	5	14
Subject withdrew consent	0	1	1	0	2

Table 2: Baseline and Demographic Characteristics

	0.1 mg/kg Q3W	1.0 mg/kg Q3W	1.0 mg/kg Q6W	5.0 mg/kg Q3W	Overall
Age (years); median	55.0	60.0	61.0	59.0	59.0
Gender					
Male (n, %)	22 (53.7)	23 (59.0)	26 (65.0)	23 (59.0)	94 (59.1)
Female (n, %)	19 (46.3)	16 (41.0)	14 (35.0)	16 (41.0)	65 (40.9)
Race					
White (n, %)	41 (100.0)	39 (100.0)	39 (97.5)	39 (100.0)	158 (99.4)
Other (n, %)	0	0	1 (2.5)	0	1 (0.6)

Safety Results: The median duration of study therapy was 11.9 weeks in 1 mg/kg q3w treatment group and 12.0 weeks in the other three treatment groups (0.1 mg/kg q3w, 1 mg/kg q6w, and 5 mg/kg q3w). The duration of study therapy across all four groups ranged from 2.4 weeks to 38.6 weeks.

There were 24 deaths within 60 days of study therapy (Table 3). Seventeen of the 24 subjects died as a result of disease progression, and seven others died due to either study drug toxicity (2 subjects), unknown (1 subject) or other reasons (4 subjects). On-study, drug-related Significant Adverse Events (SAEs) were reported in 24 of 158 subjects treated with BMS 663513. The majority of SAEs were reported in the Investigations (alkaline phosphatase [ALT] in 9 subjects, 5.7%; aspartate aminotransferase AST in 8 subjects, 5.1%) and Blood and Lymphatic System Disorders (neutropenia in 4 subjects, 2.5%; febrile neutropenia in 3 subjects, 1.9%; and thrombocytopenia in 2 subjects, 1.3%). No other SAE was reported in more than one subject. AEs led to discontinuation of study treatment in 34 subjects (21.5%) treated with BMS-663513 The majority of AEs leading to discontinuations were reported in the Investigations Systems: AST increased in 9 subjects (5.7%), ALT increased in 8 subjects (5.1%), and abnormal liver function test in 2 subjects (1.3%). In addition cerebral hemorrhage led to discontinuation in 3 subjects (1.9%) and febrile neutropenia led to discontinuation in 2 subjects (1.3%). No other adverse events (AEs) led to discontinuation in more than one subject.

Of the 158 subjects treated with BMS-663513 in this study, 153 subjects (96.8%) were reported to have had at least 1 AE regardless of relationship to study medication. In all four treatment groups, 31.7% (0.1 mg/kg q3w) to 50.0% (1.0 mg/kg q3w) of subjects had reported Grade 3/4 AEs. At least 1 AE considered related to study medication was reported in 123 subjects (77.8%). In all four treatment groups, 9.8% (0.1 mg/kg q3w) to 41.0% (5.0 mg/kg q3w) of subjects had reported drug related Grade 3/4 AEs.

Grade 3-4 hematology abnormalities reported were neutropenia (17 subjects; 11%), leukopenia (15 subjects; 9.6%), thrombocytopenia (5 subjects; 3.2%) and anemia (8 subjects; 5.1%). Grade 3-4 liver function abnormalities reported were elevated ALT (24 subjects; 15.0%), elevated AST (22 subjects; 14.0%), elevated total bilirubin (4 subjects; 2.6%), elevated ALP (8 subjects; 5.4%), and albumin (3 subjects; 2.0%).

Drug-related concurrent elevations in ALT or AST (≥ Grade 2) and total bilirubin (≥ Grade 2) are considered to be indicators of severe drug-induced liver injury (DILI). Drugs that result in this kind of liver injury have a higher risk of causing fulminant hepatic failure and/or death. In this study, a total of 6/158 (3.8%) subjects developed severe DILI with 3/158 (1.9%) identified as drug-related. All cases occurred in subjects treated with a BMS-663513 dose ≥ 1 mg/kg.

Table 3: Overview of Safety - All Treated Subjects

	0.1 mg/kg Q3W (N=41)	1.0 mg/kg Q3W (N=38)	1.0 mg/kg Q6W (N=40)	5.0 mg/kg Q3W (N=39)	Overall (N=158)
Number of Deaths (n, %)	29 (70.7)	26 (66.7)	30 (75.0)	26 (66.7)	111 (69.8)
Number of Deaths within 60 Days of Last Dose (n, %)	4 (9.8)	8 (21.1)	3 (7.5)	9 (23.1)	24 (15.2)
- Disease Progression (n, %)	3 (7.3)	6 (15.8)	2 (5.0)	6 (15.4)	17 (10.8)
- Study drug toxicity (n, %)	0	1 (2.6)	0	1 (2.6)	2 (1.3)
- Unknown (n, %)	0	1 (2.6)	0	0	1 (0.6)
- Other (n, %)	1 (2.4)	0	1 (2.5)	2 (5.1)	4 (2.5)
Number of Subjects With At Least 1 SAE (n, %)	20 (48.8)	22 (57.9)	12 (30.0)	20 (51.3)	74 (46.8)
Number of Subjects With At Least 1 Tx-related SAE (n, %)	2 (4.9)	10 (26.3)	1 (2.5)	11 (28.2)	24 (15.2)
Number of Subjects Discontinuing Due to AEs (n, %)	6 (14.6)	11 (28.9)	5 (12.5)	12 (30.8)	34 (21.5)
Number of Subjects With At Least 1 AE (n, %)	39 (95.1)	37 (97.4)	38 (95.0)	39 (100.0)	153 (96.8)
Number of Subjects With At Least 1 Tx-related AE (n, %)	28 (68.3)	30 (78.9)	32 (80.0)	33 (84.6)	123 (77.8)

Efficacy: The 6-month PFS rate, the median PFS best response, the 1-year survival rate, and the median survival for the four treatment groups are shown in Table 4. Two subjects met the criteria for PR and one subject met the criteria for CR. Eight (8) unconfirmed responses were also noted but were categorized as stable disease due to lack of confirmation. Stable disease was recorded as the best clinical response for a total of 25 of 159 subjects (Table 4) for a rate of 15.7%. Doses as low as 0.1 mg/kg had anti-tumor activity.

Table 4: Summary of Efficacy Findings

	0.1 mg/kg Q3W	1.0 mg/kg Q3W	1.0 mg/kg Q6W	5.0 mg/kg Q3W
Progression-Free Survival (PFS)				
6-month PFS Rate	6.50%	14.25%	5.56%	4.62%
Median PFS (months)	2.69	2.73	2.69	2.79
Overall Survival (OS)				
1-Year Survival Rate	33.37%	39.63%	27.05%	33.97%
Median Survival (months)	7.59	9.17	7.95	6.7
Response				
Complete Response (n, %)	1 (2)	0	0	0
Partial Response (n, %)	0	1 (3)	1 (3)	0
Stable Disease (n, %)	6 (15)	8 (21)	6 (15)	5 (13)
Objective Response Rate (n, %)	1 (2.44)	1 (2.56)	1 (2.50)	0

Pharmacokinetics (PK): The geometric mean steady-state trough levels of BMS-663513 following administration of intravenous infusions of BMS-663513 increased with increasing dose (Table 5).

Table 5: Summary Statistics of Cmin Values for BMS-663513 on Selected Study Days

TREATMENT GROUP	STATISTIC	CMIN (μg/mL) DAY 22	DAY 43	DAY 85	DAY 127
0.1 mg/kg 3 weeks	N	40	35	16	6
	GEO.MEAN	0.16	0.18	0.22	0.15
	%CV	159	124	295	56
	MEDIAN	0.13	0.13	0.13	0.13
1.0 mg/kg 3 weeks	N	34	33	15	6
	GEO.MEAN	2.01	2.99	4.49	5.11
	%CV	152	57	53	54
	MEDIAN	2.04	3.85	5.83	7.11
1.0 mg/kg 6 weeks	N	NA	37	21	11
	GEO.MEAN	NA	0.36	0.52	0.71
	%CV	NA	104	87	72
	MEDIAN	NA	0.34	0.58	0.61
5.0 mg/kg 3 weeks	N	29	28	14	5
	GEO.MEAN	17.85	31.32	35.84	27.68
	%CV	33	52	49	40
	MEDIAN	18.72	30.39	37.40	34.55

NOTE: VALUES BELOW LLQ(0.25 μg/mL) WERE SET TO 0.125 μg/mL FOR COMPUTATION OF SUMMARY STATISTICS
NA = not available

CONCLUSIONS:

- The dose and schedule of BMS-663513 were the most important factors identified as contributing to the development of hepatotoxicity; the frequency and severity of hepatotoxicity reached a plateau at doses ≥ 1 mg/kg on an every-3-week schedule.
- The MTD of BMS-663513 administered on an every-3-week schedule is < 1 mg/kg.
- BMS-663513 in the dose range of 0.1 to 5 mg/kg elicits anti-tumor activity.

DATE OF REPORT: 01-Dec-2010