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: Ipilimumab		

SYNOPSIS

Final Clinical Study Report for CA184008

TITLE OF STUDY: A Multicenter, Single Arm Phase 2 Study of MDX-010 (BMS-734016) Monotherapy in Patients with Previously Treated Unresectable Stage III or IV Melanoma

INVESTIGATORS/STUDY CENTERS: 155 subjects were treated at 50 sites in Europe and North America

PUBLICATIONS: none

STUDY PERIOD: Study Initiation Date: 6-Jun-2006 **CLINICAL PHASE:** 2

Cutoff date for the primary endpoint: 08-Nov-2007; cutoff for the final updated survival follow-up: 15-May-2009.

OBJECTIVES: The primary study objective was to evaluate the best overall response rate (BORR), as defined by modified World Health Organization (mWHO) criteria, in subjects with previously treated Stage III (unresectable) or Stage IV melanoma receiving ipilimumab 10 mg/kg. A secondary objective was to examine overall survival (OS). Other secondary objectives were to estimate progression-free survival (PFS), disease control rate, and time-to-event tumor response endpoints and to evaluate the safety profile of ipilimumab, health-related quality of life (HRQoL), and ipilimumab pharmacokinetics.

METHODOLOGY: CA184008 was an open-label, single-arm, multicenter study. The study had a 24-week induction period in which subjects received 4 doses of ipilimumab, one dose every 3 weeks through Week 10, followed by tumor assessments performed every 4 weeks starting at Week 12 and continuing through Week 24. At the end of the induction period, eligible subjects could enter a maintenance period. All subjects during maintenance underwent tumor assessments until disease progression; eligible subjects continued to receive ipilimumab every 12 weeks (Weeks 24, 36, and 48). All subjects who had a response of stable disease (SD) or better at Week 12 and who subsequently progressed were offered, at investigator's discretion, entry into CA184025 where they could receive reinduction or maintenance ipilimumab therapy, as the clinical setting dictated. Following closure of CA184008, CA184025 was amended to permit all subjects participating in CA184008 to enroll in CA184025 for at least a periodic collection of survival follow-up even if not eligible or available for the collection of more extensive data, and provided for the opportunity to collect survival information on all such subjects including those who may have died following CA184008 closure. The amendment provided for obtaining survival data from the investigator or referring physician, if permitted by local law and the institutional review board/ethics committee, in cases where a subject could not be contacted. For the purpose of the updated OS analyses presented in this report, data were collected in either CA184008 or CA184025.

NUMBER OF SUBJECTS (Planned and Analyzed): A sample size of 150 subjects was planned so that if 23 or more responses were observed (i.e., BORR ≥ 15.3%), the lower boundary of the two-sided exact 95% confidence interval (CI) for the BORR would have been at least 10%. A total of 155 subjects were treated and included in the main efficacy and safety analyses.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Subjects were males and females ≥ 16 years of age who had histologically confirmed, measurable (using mWHO criteria), Stage III or Stage IV melanoma, and had progressed during or after at least 1 prior therapeutic regimen containing 1 or more of the following: interleukin (IL)-2, dacarbazine, paclitaxel, carboplatin, fotemustine, or temozolomide. Subjects were to have a life expectancy ≥ 16 weeks and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Ipilimumab 10 mg/kg was administered as a 90-minute intravenous (IV) infusion. Batch numbers were 5J06544, 6B17599, and 6G19359. Treatment was administered at Weeks 1, 4, 7, and 10 (total of 4 doses) during the induction period, and every 12 Weeks (e.g., Weeks 24, 36, 48+) during the maintenance period, and was to continue until withdrawal of consent, progression by mWHO, toxicity requiring ipilimumab discontinuation, start of subsequent non-ipilimumab therapy, or database lock for BORR reporting.

CRITERIA FOR EVALUATION: Tumor response was evaluated by the investigator and by an independent review committee (IRC) based on mWHO criteria. The assessment of the IRC was considered primary. Exploratory endpoints were also assessed using immune-related (ir)Response criteria that were developed, using mWHO as a foundation, to systematically categorize ipilimumab clinical activity before and after progression by mWHO. Response using both mWHO and irResponse criteria was determined by the IRC.

Safety was evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), based on adverse events (AEs), physical examinations, and clinical laboratory assessments. Drug-related AEs that were consistent with immune-mediated events and considered a consequence of the intrinsic biological activity of ipilimumab (immune-related [ir]AEs) were examined for event subcategories of gastrointestinal, liver, skin, endocrine, neurological, and other. A data monitoring committee (DMC) provided independent oversight for safety, study conduct, and risk-benefit-ratio. The pharmacokinetics (PK) profile of ipilimumab was derived from serum concentration vs time data obtained at multiple scheduled assessments. Health-related quality of life (HRQoL) was measured using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, which was administered at baseline and multiple scheduled timepoints.

STATISTICAL CONSIDERATIONS: The primary efficacy analysis was based on IRC BORR (number of subjects with a BOR of complete response [CR] or partial response [PR], divided by the number of treated subjects). BORR and disease control rate (number of subjects with a BOR of CR, PR or SD, divided by the number of treated subjects) were calculated along with corresponding exact two-sided 95% CIs using the method of Clopper and Pearson. PFS was defined as the time between the first dose of study therapy and the date of progression or death, whichever occurred first, and was calculated using the Kaplan-Meier product-limit method to provide the median estimate together with a two-sided 95% CI for the median, calculated using the method of Brookmeyer and Crowley.

Overall survival was defined as the time between the first dose of study therapy and death. If a subject was still alive at the time of analysis, the subject was censored at the last known alive date. Per protocol and updated survival data were obtained. The subject's updated survival status and death or last known alive date reflected the latest date recorded in either CA184008 or CA184025. Overall survival was estimated using the Kaplan-Meier product-limit method and a 2-sided 95% CI for the median calculated using the method of Brookmeyer and Crowley. Updated survival rate at 1 year, 18 months, and 2 years was defined as the probability that a subject was alive at those timepoints following the first dose date based on the most

recent evidence obtained in both CA184008 and CA184025 and was estimated for each group using the Kaplan-Meier survival function evaluated at the relevant timepoint. Corresponding 2-sided 95% bootstrap CIs were calculated.

irResponse endpoints (irBOR, irBORR, and ir-disease control rate) were analyzed using methods similar to those used for the main response endpoints. Demographics, baseline laboratory results and HRQoL were summarized using descriptive statistics. Worst toxicity grades per subject were tabulated for AEs, irAEs, and laboratory measurements.

SUMMARY OF RESULTS

Disposition, Demographics, and Other Baseline Characteristics: A total of 155 subjects were enrolled and treated. All subjects in the induction and maintenance periods of CA184008 came off ipilimumab treatment at the time of database lock for reporting the primary endpoint (BORR). Subjects who were eligible could receive additional ipilimumab maintenance therapy in CA184025. Approximately half the subjects (51.6%) were male, 99.4% were white, and the median age was 59 years (range, 26 to 85 years). Based on the investigator's baseline assessment, all subjects had unresectable Stage III or IV malignant melanoma at study entry, 147 (94.8%) had Stage IV disease, and 86 (55.5%) subjects had M1c-stage disease. Most subjects (130, 83.9%) had ≥ 2 lesion sites. All but 1 subject had at least 1, and 82 (52.9%) had at least 4 index lesions at baseline. Most (153, 98.7%) subjects had received at least 1 prior systemic therapy in the metastatic setting, and 126 (81.3%) subjects had not responded to these therapies. Nearly all (153, 98.7%) subjects had prior surgery related to cancer, 40 (25.8%) received prior radiotherapy, and 89 (57.4%) received prior immunotherapy.

Exposure: Most (136, 87.7%) subjects were treated only in the induction period; 19 (12.3%) subjects were treated during the maintenance period; 96 (61.9%) subjects received at least 4 ipilimumab doses over both study periods.

Efficacy

BORR (Primary Endpoint)

The BORR was 5.8% (95% CI: 2.7, 10.7) as assessed by the IRC and 11.0% (95% CI: 6.5, 17.0) as assessed by the investigator (Table 1). The lower boundary of the 95% CI for the IRC-assessed BORR did not exceed the 10% target specified in the protocol. All 9 responders demonstrated PR (≥ 50% reduction in tumor burden from baseline). Five of these 9 subjects had ongoing responses time of database lock for BORR reporting. The duration of response for these subjects was 2.6+, 2.8+ (2 subjects), 3.7+, and 4.2+ months. Response was characterized in some subjects by a reduction in tumor burden from baseline after initial progression by mWHO. Six of 43 subjects who were followed post PD by mWHO had an IRC assessment of PR at time points after PD (not shown in Table 1). All 6 subjects had ≥ 50% reduction in tumor burden compared to baseline at the end of the observation period. PR was confirmed for 3 of these 6 subjects.

Table 1: BORR (Primary Endpoint) - All Treated Subjects

	10 mg/kg Ipilimumab N = 155	
	IRC Assessment	**Investigator Assessment**
Best overall response rate (BORR), n/N (%)[a]	9/155 (5.8)	17/155 (11.0)
95% CI [b]	(2.7, 10.7)	(6.5, 17.0)
Best overall response, n (%)		
Complete response, CR	0	2 (1.3)
Partial response, PR	9 (5.8)	15 (9.7)
Stable disease, SD	33 (21.3)	36 (23.2)
Progressive disease, PD	87 (56.1)	79 (51.0)
Unknown[c]	26 (16.8)	23 (14.8)

[a] Number of subjects with CR or PR / Number of treated subjects;

[b] 2-sided, exact confidence interval (Clopper and Pearson);

[c] Unknown = subjects with only baseline measurements (n = 24), no Week 12 assessment (n = 1); early censoring therapy (n = 1)

Overall Survival

Two OS analyses were performed. The initial OS analysis was performed, as specified in the protocol, on data collected at the time of database lock for BORR reporting (08-Nov-2007 cutoff, i.e., when the last treated subject had been followed for 24 weeks). The median duration of follow-up in the initial analysis was 5.5 months; 80 subjects were censored prior to the median in the initial analysis. Additional survival follow-up was collected on all subjects who had not withdrawn consent, were not lost to follow-up, and were alive at the time of the initial survival assessment based on the most recent available data from either CA184008 or CA184025. Updated survival information was current for 145/155 (93.6%) subjects, i.e., subjects who were known to have died or subjects who were known to be alive on or after the target last contact date for survival follow-up of 09-Mar-2009 (i.e., 15-May-2009 cutoff); this cutoff incorporated data from a previous survival update). The median duration of follow-up in the updated analysis was 10.1 months. Four subjects were censored prior to the median.

In the updated analysis, 109 (70.3%) subjects had died (Figure 1). The median OS was 10.2 months (95% CI: 7.6, 16.3). The 1-year survival rate was 47.2% (95% CI: 39.5, 55.1) and the 2-year survival rate was 32.8% (95% CI: 25.4, 40.5) (Table 2).

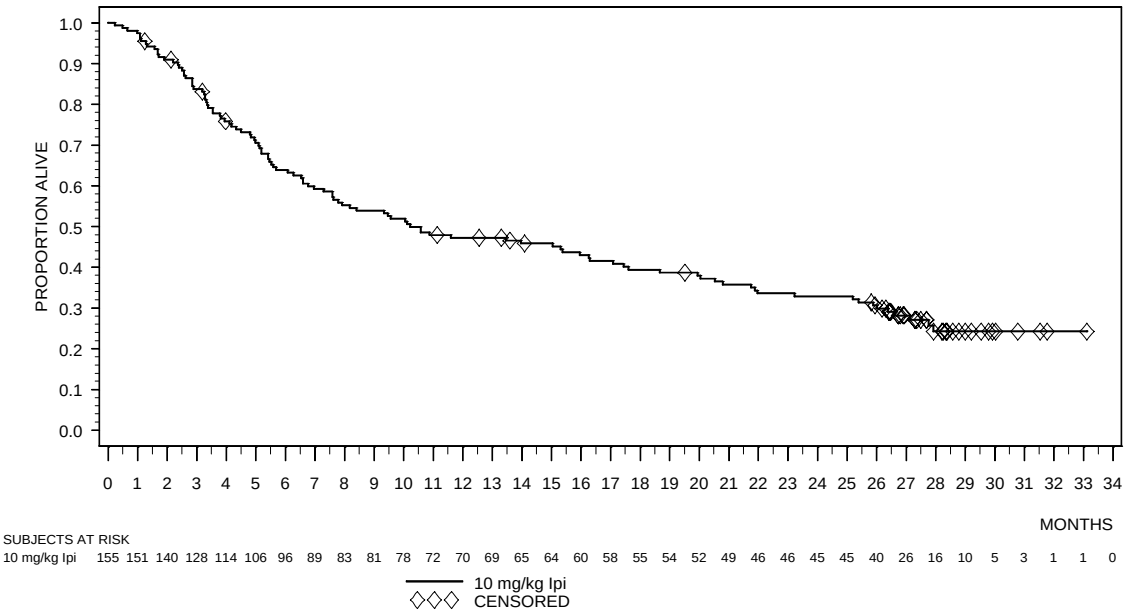
Table 2: Overall Survival (15-May-2009 Cutoff) - All Treated Subjects

	10 mg/kg Ipilimumab (N = 155)
Total Updated Survival Follow-up, Median (Months) Interquartile Range (25% - 75%)	10.05 (3.81 - 26.18)
Overall Survival, Median (Months) 95% CI (Months)[a]	10.22 (7.59, 16.30)
Survival Rate at 1 Year (%) 95% CI (%)[b]	47.22 (39.52, 55.11)
Survival Rate at 18 Months (%) 95% CI (%)[b]	39.38 (31.73, 47.24)
Survival Rate at 2 Years (%) 95% CI (%)[b]	32.83 (25.37, 40.49)

[a] Median and associated 2-sided 95% CIs calculated using the method of Brookmeyer and Crowley.

[b] Based on Kaplan-Meier estimation and CI computed using the bootstrap method.

Figure 1: Overall Survival (15-May-2009 Cutoff) - All Treated Subjects



GROUP	# OF DEATHS / # OF SUBJECTS	MEDIAN (95% CI)
10 mg/kg Ipi	109/155	10.2 (7.59 - 16.3)

LIBRARY: /wwbdm/data/ca/184/008/fa_all/blinded/analysis EXTRACT DATE: 15-MAY-2009
PROGRAM SOURCE: /wwbdm/clin/proj/ca/184/core/val/stats/sasprogs/analysis/kmplot.sas RUN DATE: 14-Apr-2010 3:00

Disease Control Rate, Stable Disease, and Progression-free Survival

The disease control rate (number of subjects who achieved CR or PR or SD) was 27.1% (95% CI: 20.3, 34.8) as assessed by the IRC and 34.2% (95% CI: 26.8, 42.2) as assessed by the investigator.

SD was reported for 33 (21.3%) as assessed by the IRC and for 36 (23.2%) subjects as assessed by the investigator. SD was characterized for some subjects by prolonged periods of stability, based on IRC-assessed tumor measurements tracking the percent reduction in index lesions over time. Twenty-four of 30 subjects with IRC-assessed SD based on index lesions had reductions in total index lesion burden compared to baseline at the last evaluable tumor assessment.

A total of 125 (80.6%) subjects progressed as assessed by the IRC or died; the median PFS was 2.56 months (95% CI: 2.56, 2.63).

Exploratory irResponse Endpoints

The irResponse was observed as a reduction in tumor burden compared to baseline (1) before progression and in the absence of new lesions; (2) after the radiographic appearance of new lesions; (3) after progression (late response); and (4) as a slow, steady decline in total tumor volume (index and new lesions) in subjects otherwise categorized as stable.

A total of 14 (9.0%) subjects demonstrated irPR (≥ 50% reduction in the total tumor burden of index and new lesions [when present] compared to baseline) (Table 3). Eleven (7.1%) subjects had irPR in the absence of new lesions; 3 (1.9%) subjects had irPR in the presence of new lesions (occurring before irPR). One (0.6%) subject had irPR after progression (irPD) (late response).

A total of 41 (26.5%) subjects demonstrated stable disease by irResponse criteria (irSD), and 21 (13.5%) subjects had irSD with a reduction ≥ 25% in total tumor burden compared to baseline at the last evaluable tumor assessment. The percent tumor reduction from baseline for these 21 subjects ranged from 27.0% to 67.9%. Three (1.9%) additional subjects had late irSD after irPD.

The ir-disease control rate (the proportion with irCR, irPR, or irSD) was 35.5% (95% CI [28.0, 43.6]). The 4 subjects with irPR and irSD after irPD (reported above) are not included in the estimate of ir-disease control rate.

Table 3: Exploratory Immune-related Response Endpoints - All Treated Subjects

	Ipilimumab 10 mg/kg N = 155
	Number of Subjects (%)
irPR (≥ 50% reduction in index and new lesions)[a]	14 (9.0)
Late irPR after irPD	1 (0.6)
irSD	41 (26.5)
irSD and ≥ 25% reduction in index and new lesions[b]	21 (13.5)
Late irSD after irPD	3 (1.9)

[a] ≥ 50% reduction compared to baseline in index and new lesions reported at the time of irPR

[b] ≥ 25% reduction compared to baseline in index and new lesions reported at the last evaluable tumor assessment

Safety

The safety profile of ipilimumab administered at 10 mg/kg reflected the mechanism of action of the drug. Most drug-related AEs were consistent with immune-mediated events and were considered to be a consequence of the intrinsic biological activity of ipilimumab. Immune-related (ir) , drug-related AEs were analyzed as a separate category of all drug-related AEs. Drug-related AEs, regardless of etiology, were reported for 83.9% of subjects and were Grade 3-4 for 27.7% of subjects. Immune-related AEs (any grade) were reported for 70.3% of subjects and were Grade 3-4 for 21.9% of subjects. irAEs (any grade) affecting the skin (76 [49.0%] subjects) and GI tract (48 [31.0%] subjects) were more frequent than irAEs affecting the liver (14 [9.0%] subjects) and endocrine system (9 [5.8%] subjects). Grade 3-4 GI and liver irAEs were reported for 13 (8.4%) and 11 (7.1%) of subjects, respectively. There were no reports of GI or colonic perforations or GI hemorrhage requiring colectomy while subjects were on study-based ipilimumab treatment. Most irAEs were reported during the induction period and resolved within days or weeks with the use of systemic corticosteroid alone or in combination with other immunosuppressant therapy.

There were 5 drug-related deaths. The causes of death were multi-organ failure, acute myeloid leukemia, acute glomerulonephritis, liver dysfunction, and hypovolemic shock.

Pharmacokinetic Results Individual plasma concentration-time data of ipilimumab were available for 5/155 subjects who had intensive PK sampling. Two subjects had missing data for Day 1 and Day 43, respectively. Ipilimumab had a mean T-half value of approximately 8.9 days (n=4, range: 6.8-12 days) and 17 days (n=4, range: 11-27 days) for the Day 1 and Day 43 dose, respectively. These values are consistent with the T-half values obtained in previous exploratory Phase 1 studies. The observed mean volume of distribution at steady-state of 5.0 L (n=4, range: 4.4-5.5 L) indicated that ipilimumab was confined primarily to extracellular fluid volume.

Pharmacodynamic Results

Increases or changes from baseline in markers of autoimmune activity were either small or isolated events. There was no clinically meaningful impact of immunogenicity and neutralizing antibodies on the safety and efficacy of ipilimumab. Only 4 subjects developed a positive anti-ipilimumab response, and none had any infusion-related or peri-infusional hypersensitivity or anaphylactic reactions. Calprotectin increases were concomitant with and did not pre-date or predict Grade 2-4 diarrhea.

Health-related Quality of Life

Overall, most changes from baseline in HRQoL domains were small to moderate, and a similar change was observed in the global health status. The trend in global health status was towards a return to baseline.

CONCLUSIONS:

- Treatment with ipilimumab resulted in antitumor activity in subjects with advanced melanoma, of whom at least 80% had not responded to prior systemic therapies. Clinically relevant reductions in tumor burden compared to baseline were reported, including reductions after initial progression by mWHO. A suggested improvement in overall survival may have been driven by late effects, including PR after PD and prolonged SD. In the final updated survival analysis, the median OS was 10.2 months.
- The safety profile of ipilimumab administered at 10 mg/kg reflected the mechanism of action of the drug. Most drug-related AEs were consistent with immune-mediated events and were considered to be a consequence of the intrinsic biological activity of ipilimumab. Skin irAEs (e.g., rash and pruritus) and GI irAEs (e.g., diarrhea and colitis) were the most common overall. There were no reports of GI or colonic perforation. irAEs were generally manageable and reversible. There were 5 drug-related deaths (multi-organ failure, acute myeloid leukemia, acute glomerulonephritis, liver dysfunction, and hypovolemic shock).

- The pharmacokinetics of ipilimumab were consistent with results obtained in previous exploratory studies. Results of pharmacodynamic assessments indicated no clinically meaningful impact of immunogenicity and neutralizing antibodies on the safety and efficacy of ipilimumab.
- Most changes from baseline in HRQoL domains were small to moderate. A similar small to moderate change was observed in overall global health status, where the trend was towards a return to baseline.

DATE OF REPORT: May 2010