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 Study CA184004

TITLE OF STUDY: An Exploratory Study to Determine Potential Predictive Markers of Response and/or Toxicity in Patients with Unresectable Stage III or IV Malignant Melanoma Randomized and Treated with Ipilimumab (MDX-010/BMS-734016) at Two Dose Levels

INVESTIGATORS/STUDY CENTERS: A total of 101 subjects were enrolled and 82 were randomized at 14 sites in 7 countries.

PUBLICATIONS: none

STUDY PERIOD: Study Initiation Date: 16-Nov-2005

Study Completion Date: Cutoff for the primary endpoint: 03-Mar-2008; cutoff for survival follow-up: 15-May-2009

CLINICAL PHASE: 2

OBJECTIVES:

Primary Objective: To analyze pre-treatment characteristics of the patient and/or tumor with clinical tumor response in patients with unresectable Stage III and IV melanoma, in order to identify candidate markers predictive of response and/or serious toxicity to ipilimumab dosed at 3 or 10 mg/kg q 3 weeks.

Secondary Objectives:

- To evaluate Best Overall Response Rate (BORR), (as per modified World Health Organization [mWHO] criteria) in this patient population receiving ipilimumab doses of 3 mg/kg and 10 mg/kg
- To estimate the following in this patient population:

  i) Disease control rate (proportion of patients with best response of complete response (CR) or partial response (PR) or stable disease (SD)

  ii) Progression free survival (PFS) rate at Week 12

  iii) PFS

  iv) Overall survival (OS)

  v) Survival rate at 1 year

  vi) Duration of response and the proportion of patients whose duration of response is ≥ 24 weeks

  vii) Time to response

- To evaluate the safety of ipilimumab at the 3-mg/kg and 10-mg/kg doses in this patient population
- To estimate the sensitivity and specificity of any candidate marker or combination of markers for prediction of clinical response and/or serious toxicity to ipilimumab
- To compare the messenger ribonucleic acid (mRNA), protein and microscopic profiles pre- and post-treatment tumor specimens in patients treated with ipilimumab at 3 or 10 mg/kg q 3 weeks
- To compare delayed-type hypersensitivity (DTH) response, antibody response, peripheral blood mRNA expression, and PBMC functional attributes pre- and post-treatment in patients treated with ipilimumab at 3 or 10 mg/kg q 3 weeks
- To obtain pharmacokinetic blood samples for population pharmacokinetic analysis
- To assess the effects of ipilimumab on electrocardiogram (ECG) parameters

METHODOLOGY: CA184004 was a Phase 2, randomized, double-blind, multicenter, biomarker study. Enrolled subjects included those with and without prior systemic anticancer therapy. Subjects were randomized in a 1:1 ratio to 3 mg/kg or 10 mg/kg ipilimumab, stratified by use of prior immunotherapy for malignant melanoma. Subjects underwent pre- and post-treatment biomarker assessments including baseline blood for single-nucleotide polymorphisms, and pre- and post-treatment immune monitoring and tumor biopsy. All subjects also had pre- and post-treatment serial, triplicate ECG assessment.

The study had a 24-week induction period in which subjects received 4 doses of ipilimumab (1 dose every 3 weeks) through Week 10. Eligible subjects with SD or better through the Week 24 tumor assessment (TA) were started on maintenance ipilimumab (3 mg/kg or 10 mg/kg every 3 months). At the time of progression, subjects with SD or better at the Week 12 TA were offered entry into CA184025 at the investigator's discretion, where subjects could receive 3 mg/kg or 10 mg/kg ipilimumab depending on eligibility. Subjects with documented progressive disease (PD) during the induction or maintenance periods who did not meet the criteria for reinduction or chose not to enroll in CA184025 were to continue in a follow-up period.

Tumor assessments were performed every 4 weeks from Weeks 12 through 24 and every 12 weeks thereafter. In accordance with decisions made prior to database lock and consistent with the Statistical Analysis Plan (SAP) but not specified in the protocol, subjects were censored for response if and when they underwent excision or resection of 1 or more index lesions, as these might have influenced the tumor assessment.

Whenever possible, subjects who completed participation in CA184004 were encouraged to enroll in CA184025 for further follow-up. CA184025 was a multicenter Phase 2 study of extended treatment with ipilimumab monotherapy, or continued follow-up without further treatment, in subjects previously enrolled in prior ipilimumab studies. During and through the initial closure of CA184004, subjects who had been non-progressors at the Week 12 TAs were eligible to receive re-induction with 10 mg/kg in CA184025 (both subjects and investigators remained blinded to the CA184004 dosing assignment). Following initial closure of CA184004, CA184025 was amended to permit all subjects participating in CA184004 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 CA184004 closure. In cases where a subject could not be contacted, 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. Data supporting the OS analyses were collected in either CA184004 or in CA184025 through 09-Mar-2009.

NUMBER OF SUBJECTS: Assuming that 30% of subjects in each group have CR, PR, or SD at 24 weeks, a 2-sided, $\alpha = 0.05$ test based on a logistic regression of response against biomarker level will have 90% power to detect between response rates: 30% when the biomarker is at its mean value, and 49% or 16% when the biomarker is 1 standard deviation above or below its mean, respectively, ie, an odds ratio of

2.24 or 0.44. The test based on a logistic model including terms for dose effect and dose-biomarker interaction will have a reduced power of 86%. The maximum widths of the exact 95% confidence intervals (CIs) for BORR in the 3-mg/kg and 10-mg/kg groups will be approximately 21% and 24% when the true rates are in the expected 6% to 9% and 10% to 15% ranges, respectively.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Subjects were males and females ≥ 18 years of age with histologically- or cytologically-confirmed, measurable, Stage III or IV malignant melanoma. Subjects were to have a life expectancy ≥ 4 months and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Ipilimumab was administered as a 90-minute intravenous infusion. Batch numbers were 5J06544 and 6G19359. Treatment was administered at Weeks 1, 4, 7, and 10 (4 doses total) during the induction period and every 12 weeks during the maintenance period, and was to continue until progression, study drug-related toxicity leading to ipilimumab discontinuation, start of alternative non-ipilimumab therapy, withdrawal of consent, or study closure.

CRITERIA FOR EVALUATION: Tumor response was evaluated by investigators based on mWHO criteria; an independent radiology review committee was not employed to review the assessments. As determined prior to database lock, and consistent with the SAP but not pre-specified in the protocol, subjects were censored for response if and when they underwent excision or resection of 1 or more index lesions, as these might have influenced the tumor assessment. Safety was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events, based on adverse events (AEs), physical examinations, and clinical laboratory assessments. Drug-related AEs that were consistent with immune-mediated events and with the intrinsic biological activity of ipilimumab (immune-related [ir]AEs) were examined in 6 subcategories: gastrointestinal (GI), liver, skin, endocrine, neurological, and other. An independent data monitoring committee reviewed safety data.

STATISTICAL CONSIDERATIONS: The relationships of 6 types of biomarkers to efficacy and safety were analyzed. These biomarker types were SNP genotypes, presence of HLA allele 2A*201, medium-resolution HLA-A genotypes, immunohistochemistry and hematoxylin and eosin (H&E) measures of fresh tumor biopsies, humoral response to tumor antigens, and stool calprotectin. Associations between biomarkers and efficacy measures were analyzed in all response-evaluable subjects. Associations between biomarkers and safety measures were analyzed in all treated subjects.

For the purposes of these biomarker analyses, an efficacy measure (response category) based on investigator-determined best overall response (BOR) was used. A Benefit group was defined to include subjects with an investigator BOR of CR, PR, or prolonged SD lasting until at least 24 weeks from date of first dose. Subjects who underwent excision or resection of 1 or more index lesions were not included in the Benefit group, even if they achieved an investigator BOR of CR, PR or prolonged SD.

A Non-Benefit group was defined to include subjects with an investigator BOR of PD, or subjects with SD ending prior to 24 weeks from date of first dose. An Unknown group was defined to include those subjects with a BOR of Unknown, or of SD with duration censored before 24 weeks from date of first dose and a death date either missing or at least 24 weeks from date of first dose.

Four safety variables were defined and analyzed separately. For each subject, the 4 variables indicated the worst grade of irAE by class: (1) gastrointestinal (diarrhea or colitis); (2) liver; (3) skin; and (4) other. Each variable took on values in 3 ordered categories, defined by worst grade: Grade 0 (absence of an event), Grade 1, and Grade 2-5.

Summary statistics were tabulated by day and treatment for the following pharmacodynamic outcomes and their corresponding changes from baseline: stool calprotectin, response to delayed type hypersensitivity (DTH) skin tests, humoral response to viral and bacterial vaccines, humoral response to tumor antigens, flow cytometry outcomes, messenger RNA (mRNA) expression in peripheral blood, mRNA expression in

fresh tumor biopsies, and immunohistochemistry and H&E measures of fresh tumor biopsies. The time course of pharmacodynamic (PD) outcomes was investigated graphically. If there was an indication of a meaningful pattern across time, further analysis was performed to characterize the relationship. These analyses were performed for each PD outcome as appropriate.

Imaging-based efficacy endpoints were based on investigator-assessed BORR (number of subjects with a BOR of CR or PR, divided by the number of treated subjects). BORR and disease control rate (DCR) (number of subjects with a BOR of CR, PR or SD, divided by the number of treated subjects) were calculated along with corresponding exact 2-sided 95% CIs using the Clopper and Pearson method. PFS was defined as the time between the first dose of study therapy and the date of progression or death, whichever occurred first. PFS was calculated using the Kaplan-Meier product-limit method to provide the median estimate together with a 2-sided 95% CI for the median, calculated using the Brookmeyer and Crowley method. Demographic and baseline laboratory results were summarized using descriptive statistics. Worst toxicity grades per subject were tabulated for AEs, irAEs, and laboratory measurements.

Overall survival was defined as the time between the randomization date 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 CA184004 or CA184025. Overall survival was estimated using the Kaplan-Meier product-limit method and a 2-sided 95% confidence interval (CI) for the median calculated using the method of Brookmeyer and Crowley. Updated survival rate at 1 year was defined as the probability that a subject was alive at 1 year following the randomization date based on the most recent evidence obtained in both CA184004 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. Overall survival and survival rate analyses were also performed by prior systemic anti-cancer therapy within treatment group. Additional Kaplan-Meier plots of OS were produced by baseline lactate dehydrogenase (LDH) status (≤ upper limit of normal [ULN] or ≥ ULN) in the subset of subjects with M1c disease at baseline.

The core statistical analysis plan for the ipilimumab clinical program required censoring for response-based endpoints for all surgeries, including those that occurred prior to the first TA. Since this would have potentially censored all subjects, even in cases where the biopsy was inconsequential for the tumor assessment, prior to database lock a decision was made to consider only an excisional or resectional biopsy of an index lesion after the baseline TA as a censoring surgical resection. These biopsy types were considered more intrusive than other biopsy types conducted during the study, and could have influenced the tumor assessment.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Baseline Characteristics: Eighty-two subjects (3 mg/kg: 40 subjects; 10 mg/kg: 42 subjects) were randomized at 14 sites in Europe, North America, and South America between January 2006 and May 2007. All treated subjects were off study-drug treatment at database lock. Demographic and other baseline characteristics were generally consistent between groups. Most subjects had an ECOG performance status of 0 and approximately one-third of subjects in each group (3 mg/kg: 35.0%, 10 mg/kg: 33.3%) had not received prior systemic anticancer therapy for metastatic melanoma.

Fewer subjects with metastatic distribution classified as M1c were assigned to the 3-mg/kg group (55.0%) than to the 10-mg/kg group (66.7%). In addition, fewer subjects in the 3-mg/kg group had ≥ 4 index lesions (47.5% vs 61.9%), and pretreatment events (40.0% vs 61.9%).

Exposure: The observation period extended through the end of the induction period (i.e., Week 24) for the last subject enrolled. Most subjects were treated in the induction period only (3 mg/kg: 35 of 40 subjects, 10 mg/kg: 36 of 42 subjects). The majority of these subjects received all 4 induction doses.

Primary Objective - Predictive Biomarkers: Several biomarkers appeared to be associated with benefit (defined as BOR of CR, PR, or SD lasting at least 24 weeks from first dose) (Table 1), including increases in circulating absolute lymphocyte count (ALC) by Week 12. Other biomarkers that appeared to be associated with benefit included increases in tumor infiltrating lymphocytes by Week 4, and baseline expression of FoxP3 or the immunoregulatory enzyme indoleamine 2,3-dioxygenase (IDO) (both markers of T-cell suppression) in tumor biopsies. Of these, only the change in ALC appeared to be related to dose. No associations between efficacy or safety measures and SNP genotypes, presence of allele A2*201 at locus HLA-A, or medium-resolution HLA-A genotypes were observed.

Table 1: Predictive Biomarker Key Results

	Observed Effect				
	Benefit Group	**Non-Benefit Group**	**Dose Response**	**Predictive for Response**	**Predictive for Toxicity**
Circulating Absolute Lymphocyte Count (mean rates, by Week 12) (P=0.00042*)	• 3 mg/kg: 30 cells/mL/ week increase • 10 mg/kg: 153 cells/mL/ week increase	• 3 mg/kg: 19 cells/mL/ week decrease • 10 mg/kg: 30 cells/mL/ week increase	Yes	Yes	Not analyzed
Tumor infiltrating lymphocytes by Week 4 (by H & E) (P=0.005*)	• 4/7 increase • 0/7 decrease • 3/7 no change	• 2/20 increase • 3/20 decrease • 15/20 no change	No	Yes	Not analyzed
FoxP3 expression at baseline by IHC of tumor biopsies (P=0.014*)	• 6/8 evaluable subjects positive	• 9/25 evaluable subjects positive	Not applicable	Yes	Not analyzed
IDO expression at baseline by IHC of tumor biopsies (P=0.012*)	• 3/8 evaluable subjects positive	• 3/27 evaluable subjects positive	Not applicable	Yes	Not analyzed

* P-values uncorrected for multiple testing.

Secondary Objective - Pharmacodynamic Biomarkers:

The mean frequencies of circulating activated (HLA-DR^{+}) CD4 and CD8 effector T cells increased after ipilimumab treatment, without an apparent dose effect. No meaningful mean changes from baseline were observed in frequencies of the FoxP3^{+} CD25^{bright} CD4 T regulatory cell populations at either dose.

For HLA-DR^{+} CD4 effector T cells, the mean change from baseline in frequency of activated cells was as follows:

- 3-mg/kg: 17.7% at baseline, mean changes from baseline of 10.3% by Week 4, 5.0% by Week 12
- 10-mg/kg: 14.6% at baseline, mean changes from baseline of 9.1% by Week 4, 6.6% by Week 12

For HLA-DR^{+} CD8 effector T cells, the mean change from baseline in frequency of activated cells was as follows:

- 3-mg/kg: 26.7% at baseline, mean changes from baseline of 7.7% by Week 4, 5.9% by Week 12
- 10-mg/kg: 18.2% at baseline, mean changes from baseline of 2.4% by Week 4, 2.3% by Week 12

For subjects who underwent pre- and post-dose measurement of DTH skin reactions, increases in strength of response were observed in the 3- and 10-mg/kg groups, respectively, as follows: tetanus (5/7 and 3/6 subjects), tuberculin (7/15 and 4/15 subjects), candida (4/6 and 2/7 subjects), and trichophyton (3/4 and 2/5 subjects). No apparent dose effect was seen.

Humoral responses to common antigens such as pneumococcus and tetanus were observed in most subjects by Week 7 including some subjects who did not receive pneumococcal vaccines or tetanus boosters prior to or during the course of the study. Conversely, only subjects who received the influenza vaccine had an increase in humoral responses to any of the influenza antigens by Week 7.

The frequency of positive humoral response to tumor antigens at baseline across treatment groups was: DHFR (0.0%), MAGE4 (3.9%), MELAN A (10.4%), NY-ESO-1 (19.5%), p53 (3.9%) and SSX2 (3.9%). Of the subjects with at least 1 post-baseline measurement, an increase of at least 5-fold titer was observed across treatment groups in 4.3% of anti-DHFR, 10.1% of anti-MAGE4, 23.2% of anti-MELAN A, 18.8% of anti-NY-ESO-1, 4.3% of anti-p53 and 20.3% of anti-SSX2.

Stool calprotectin was hypothesized to be a sensitive and early biomarker of GI irAEs and possibly liver irAEs. However, no apparent association between elevated levels of stool calprotectin and onset of GI or liver AEs was observed. No meaningful differences between dose groups in stool calprotectin outcomes and corresponding changes from baseline were noted.

Expression in tumor biopsies of 466 mRNA probe sets had a significant change from baseline. Those with significant increased expression included various immune-response genes. Genes with significant decreased expression included known melanoma antigens. No probe sets had significant differences in expression between the 2 treatment groups.

Secondary Objective - Efficacy:

BORR

In this study, 4 (10.0%) randomized subjects in the 3-mg/kg group and 5 (11.9%) randomized subjects in the 10-mg/kg group were censored from all response-based analyses (BORR, PFS, DCR, time to response, and duration of response) because of an excisional or resectional biopsy of 1 or more index lesions. Therefore, data relating to objective response rate should be interpreted with caution.

There was no clear dose effect in response-related endpoints (Table 2). The objective response rate (CRs plus PRs) was numerically lower in the 3-mg/kg group (7.5%) than in the 10-mg/kg group (11.9%), and the only CR was noted in the 10-mg/kg group. However, the rate of SD was numerically higher in the 3-mg/kg group (25.0%) than in the 10-mg/kg group (7.0%), and the rates of PD were comparable (47.5% and 57.1%, respectively).

The BORR in subjects with no prior systemic anticancer therapy for metastatic melanoma (ie, first line) was 1 of 14 subjects (7.1%) and 0 of 14 subjects (0%) in the 3-mg/kg and 10-mg/kg groups, respectively. The BORR for subjects with prior systemic therapy was 2 of 26 subjects (7.7%) and 5 of 28 subjects (17.9%), respectively.

Table 2: Best Overall Response Rate - Randomized Subjects

	Number of Subjects (%)	
	3 mg/kg Ipilimumab N = 40	**10 mg/kg Ipilimumab N = 42**
Best Overall Response Rate [a]	3 (7.5)	5 (11.9)
95% CI [b], %	(1.6, 20.4)	(4.0, 25.6)
CR	0	1 (2.4)
PR	3 (7.5)	4 (9.5)
SD	10 (25.0)	3 (7.1)
PD	19 (47.5)	24 (57.1)
Unknown	8 (20.0)[c]	10 (23.8)[d]

[a] N with CR or PR / N [b] 2-sided, exact CI (Clopper and Pearson)

[c] Unknown = censored due to excisional or resectional biopsy of index lesions (N = 4), no post-baseline assessments (N = 4)

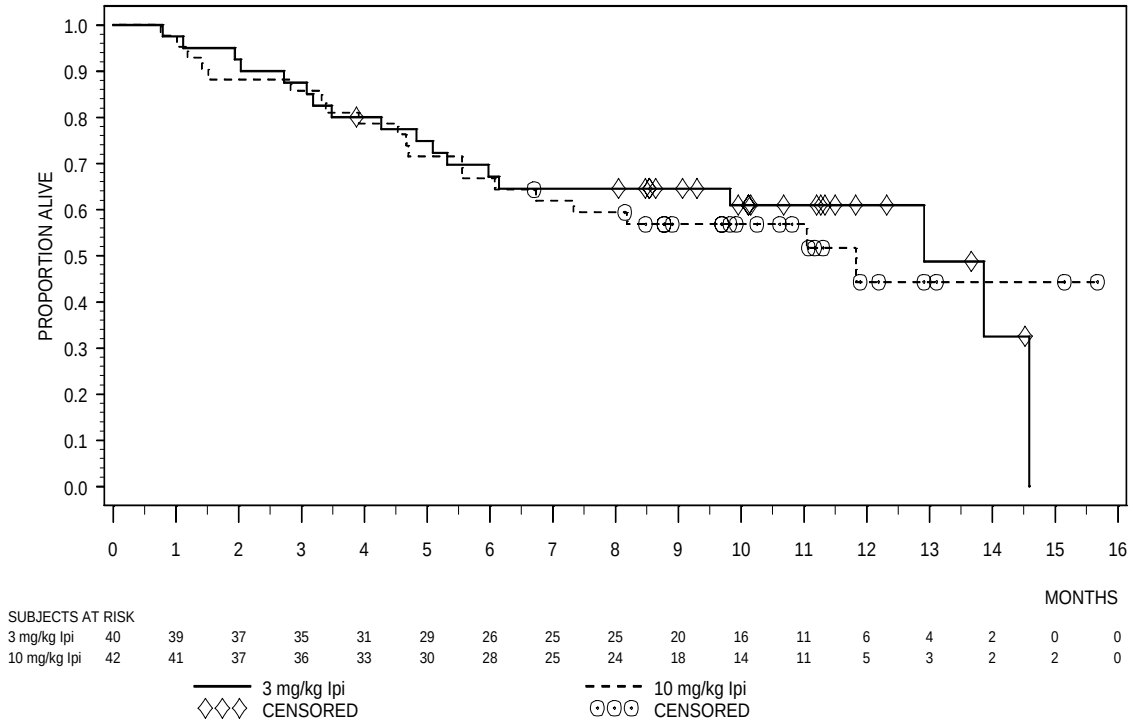
[d] Unknown = censored due to excisional or resectional biopsy of index lesions (N = 5), no post-baseline assessments (N = 5)

Overall Survival

Per Protocol Analyses of OS (03-Mar-2008 Cutoff)

A total of 18 (45.0%) subjects in the 3-mg/kg group and 20 (47.6%) subjects in the 10-mg/kg group died. With a median follow-up of 8.9 and 8.6 months, respectively, and follow-up data that were current for over 97% of subjects, the 1-year survival rate estimate was 60.9% (95% CI: 41.7%, 74.9%) and 44.2% (95% CI: 24.1%, 64.1%), respectively. The median OS was 12.9 months (95% CI 6.1, 14.6) and 11.8 months (95% CI 6.1, --), respectively (Figure 1).

Figure 1: Overall Survival (03-Mar-2008 Cutoff) - Randomized Subjects



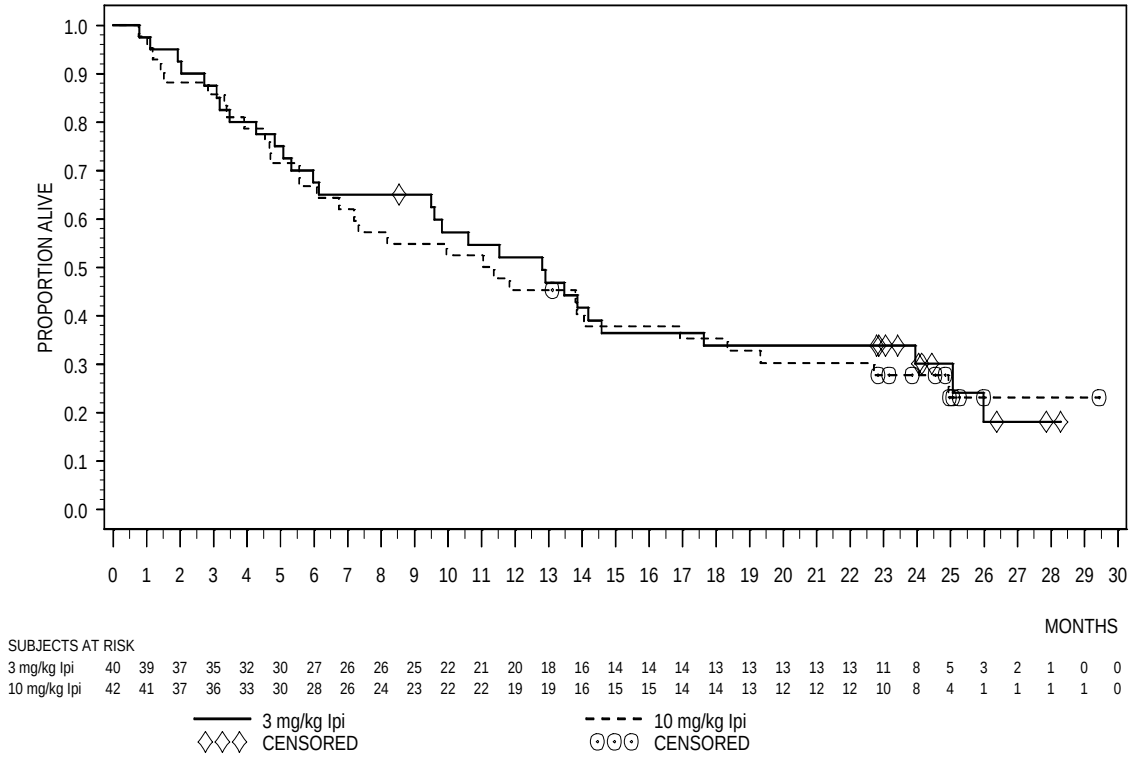
GROUP	# OF DEATHS / # OF SUBJECTS	MEDIAN (95% CI)
3 mg/kg Ipi	18/40	12.9 (6.14 - 14.6)
10 mg/kg Ipi	20/42	11.8 (6.08 -)

LIBRARY: /wwbdm/data/ca/184/004/fa_all/blinded/analysis EXTRACT DATE: 04-MAY-2009
PROGRAM SOURCE: /wwbdm/clin/proj/ca/184/core/val/stats/sasprogs/analysis/kmplot.sas RUN DATE: 4-Apr-2010 17:34

Updated Analyses of OS (15-May-2009 Cutoff)

Updated analyses of OS, based on a target last subject last contact date of 09-Mar-2009, were conducted to reflect a longer follow-up than was captured in the original per-protocol analyses. In the updated analysis, a total of 29 (72.5%) subjects in the 3-mg/kg group and 31 (73.8%) subjects in the 10-mg/kg group had died. With a median follow-up of 12.2 and 11.2 months, respectively, and follow-up data that were current for over 97% of subjects, the 1-year survival rate estimate was 52.0% (95% CI: 36.6, 67.3) and 45.2% (95% CI: 31.0, 59.5), respectively. The 18-month survival rate estimate was 33.8% (95% CI: 19.8, 49.1) and 35.2% (95% CI: 21.2, 49.9), respectively. The median OS was 12.8 months (95% CI: 9.5, 17.6) and 11.2 months (95% CI: 6.1, 16.9), respectively (Figure 2).

Figure 2: Overall Survival (15-May-2009 Cutoff) - Randomized Subjects



GROUP	# OF DEATHS / # OF SUBJECTS	MEDIAN (95% CI)
3 mg/kg Ipi	29/40	12.8 (9.49 - 17.6)
10 mg/kg Ipi	31/42	11.2 (6.08 - 16.9)

LIBRARY: /wwbdm/data/ca/184/004/fa_all/blinded/analysis/ EXTRACT DATE: 04-MAY-2009
PROGRAM SOURCE: /wwbdm/clin/proj/ca/184/core/val/stats/sasprogs/analysis/kmplot.sas RUN DATE: 8-Apr-2010 15:30

Progression-free Survival and Disease Control Rate

The median PFS was 2.63 months in the 3-mg/kg group and 2.56 months in the 10-mg/kg group. A total of 28 (70.0%) subjects in the 3-mg/kg group and 32 (76.2%) subjects in the 10-mg/kg group had progressed or died. The DCR was 32.5% and 19.0%, respectively.

Safety: The safety profile of ipilimumab was acceptable and reflected the mechanism of action of the drug (Table 5). Progressive disease was the most frequent reason for death in each group. Two drug-related deaths were reported (1 in each group, both large intestine perforations). Most drug-related AEs were consistent with immune-mediated events and were considered to be a consequence of the intrinsic biological activity of ipilimumab. 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.

Table 5: Summary of Safety - Treated Subjects

	Number of Subjects (%)	
	Ipilimumab 3 mg/kg N = 40	**Ipilimumab 10 mg/kg N = 42**
Deaths - total	18 (45.0)	20 (47.6)[a]
Within 70 days of last dose	8 (20.0)[b]	8 (19.0)
Within 30 days of last dose	3 (7.5)	4 (9.5)
Drug-related SAEs	7 (17.5)	8 (19.0)
AEs leading to discontinuation	5 (12.5)	11 (26.2)
Grade 3-4 drug-related AEs	6 (15.0)	13 (31.0)
irAEs - total	22 (55.0)	28 (66.7)
Gastrointestinal	11 (27.5)	19 (45.2)
Liver	0	2 (4.8)
Endocrine	2 (5.0)	2 (4.8)
Skin	16 (40.0)	21 (50.0)
Neurological	0	0
Other	1 (2.5)	3 (7.1)

[a] One subject reported a Grade 4 large intestine perforation leading to death, considered certainly related to ipilimumab by the investigator, beyond 70 days after last dose

[b] One subject reported a Grade 5 large intestine perforation considered probably related to ipilimumab by the investigator

ECGs:

No clinically meaningful changes from baseline in heart rate, QRS, or PR intervals were observed on treatment. There were no AEs, discontinuations, or deaths related to ECG abnormalities. One subject in the 3-mg/kg group reported a Grade 3 QTcB prolongation on treatment. At baseline, this subject reported Grade 2 QTcB prolongation and QRS prolongation (> 120 msec) consistent with a medical history of left bundle branch block. Across groups, 22 subjects reported on-study QTcB prolongations.

CONCLUSIONS:

- Predictive biomarkers: dose-related increase in ALC after the initiation of treatment was associated with benefit (defined as objective response or SD lasting until at least 24 weeks from first dose) (P = 0.00042). Baseline expression of tumor FoxP3 and IDO, and increase from baseline of tumor-infiltrating lymphocytes, were also associated with benefit (P = 0.014, 0.012, and 0.005, respectively).
- Pharmacodynamic biomarkers: activation of circulating effector T-cells and enhancement of humoral response to specific common antigens were observed. T-cell activation was not dose dependent.
- Biomarkers that were not predictive of benefit or safety: SNP genotypes, HLA allele 2A*201, and medium-resolution HLA-A genotypes were not predictive of benefit or safety. Stool calprotectin levels were not predictive of GI inflammatory events of any grade.
- Objective response and durable (≥ 24 weeks) SD in subjects with advanced melanoma were observed. There was no consistent dose effect. However, the small study size, censoring of subjects who underwent excision or resection of 1 or more index lesions, and imbalance in prognostic variables between groups, limits the interpretation of these data.
- Follow-up for OS through 22 months has been completed. The median OS was 12.81 months (95% CI: 9.49, 17.64) in the 3-mg/kg group and 11.20 months (95% CI: 6.08, 16.92) in the 10-mg/kg group. The 18-month survival rate was 33.8% and 35.2%, respectively.
- Drug-related toxicity was most commonly related to the GI tract and skin. The overall safety profile was consistent with the immune-stimulating mechanism of action. The drug-related events were generally manageable, nearly all reversible with oral or systemic steroids, and rarely life-threatening.
- There were no clinically significant ECG changes from baseline.

DATE OF REPORT: 31-May-2010