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 CA184007

TITLE OF STUDY: Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Comparing the Safety of Ipilimumab Administered With or Without Prophylactic Oral Budesonide (Entocort™ EC) in Patients with Unresectable Stage III or IV Malignant Melanoma

INVESTIGATORS/STUDY CENTERS: A total of 135 subjects were enrolled at 11 sites in 6 countries.

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 7-Dec-2005 **CLINICAL PHASE:** 2

Cutoff for the primary endpoint: 26-Nov-2007; cutoff for the final updated survival follow-up: 15-May-2009

OBJECTIVES: The primary objective was to estimate the rate of Grade ≥ 2 diarrhea in subjects treated with intravenous (IV) ipilimumab at 10 mg/kg given with either prophylactic oral budesonide or placebo. Key secondary objectives were to examine the best overall response rate (BORR) and overall survival (OS) for the 2 treatment groups. Additional secondary objectives were to examine disease control rate, stable disease, and progression-free survival (PFS); evaluate the general safety of iplimumab with and without prophylactic budesonide; and identify potential predictors of tumor response and safety events, especially Grade ≥ 2 diarrhea and colitis.

METHODOLOGY: CA184007 was a double-blind, randomized, multicenter study. Subjects who received prior systemic anticancer therapy (pretreated subjects) and subjects who had received no prior systemic anticancer therapy (previously untreated subjects) were enrolled. Subjects were randomized in a 1:1 ratio to 16 weeks of either oral budesonide or placebo. Randomization was stratified by use of prior immunotherapy for malignant melanoma. The study had a 24-week induction period in which subjects received 4 doses of ipilimumab, 1 dose every 3 weeks through Week 10, followed by tumor assessments performed every 4 weeks starting at Week 12 and continuing through Week 24. Subjects with Grade ≥ 2 diarrhea or other immune-related adverse events (AEs) were to be discontinued from blinded oral study medication. At the end of the induction period, eligible subjects could enter a maintenance period in which they 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 CA184007, CA184025 was amended to permit all subjects participating in CA184007 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 CA184007 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 CA184007 or CA184025.

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 in CA184007.

NUMBER OF SUBJECTS (Planned and Analyzed): A total of 115 randomized subjects (budesonide: 58; placebo: 57) were treated and included in the main efficacy and safety analyses.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Subjects were males and females ≥ 18 years of age, who had 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 (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 IV infusion. Batch numbers were 5J06544, 6B17599, and 6G19359. Budesonide or placebo was administered as 3 capsules (9 mg budesonide or placebo) once daily until Week 12, then as 2 capsules (6 mg budesonide or placebo) once daily until Week 14, then as 1 capsule (3 mg budesonide or placebo) once daily until Week 16. Batch numbers were 5K05389 (budesonide) and 5K05379 (placebo).

CRITERIA FOR EVALUATION: Tumor response was evaluated by an independent review committee (IRC) and by investigators based on modified World Health Organization (mWHO) criteria. The IRC assessment was considered primary. Exploratory endpoints were also assessed using immune-related (ir)Response criteria that were developed, using mWHO as a foundation, as a systematic approach to categorizing ipilimumab antitumor activity before and after progression by mWHO. Response using both mWHO and irResponse criteria were based on IRC measurements.

Safety was evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, based on 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 for 6 event subcategories: gastrointestinal, liver, skin, endocrine, neurological, and other. A data monitoring committee (DMC) provided independent oversight for safety, study conduct, and benefit-risk. The PK profile of ipilimumab was derived from serum concentration vs time data obtained at multiple scheduled timepoints. The relationship between diarrhea and colitis toxicities and endoscopic and histologic indicators was explored.

STATISTICAL CONSIDERATIONS: The primary study endpoint analysis (the rate of Grade ≥ 2 diarrhea during induction) was performed when the last randomized subject was followed to Week 24. The rate of Grade ≥ 2 diarrhea prior to Week 24 was reported for each treatment group along with exact 2-sided 95% CIs, and a 2-sided 95% CI for the difference was computed. The primary efficacy analysis was based on IRC BORR (number of subjects with a best overall response [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 stable disease [SD], divided by the number of treated subjects) were calculated along with corresponding exact 2-sided 95% CIs using the method of Clopper and Pearson.

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. In this report, survival is presented based on 2 different cutoff dates: 26-Nov-2007 and 15-May-2009 (the 15-May-2009 cutoff incorporates data from an earlier survival updated based on a 01-Feb-2008 cutoff). The subject's updated survival status and death or last known alive date reflected the latest date recorded in either CA184007 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, 18 months, and 2 years was defined as the probability that a subject was alive at those timepoints following the randomization date based on the most recent evidence obtained in both CA184007 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. Immune-related (ir)Response endpoints (irBOR, irBORR, and ir disease control rate) were analyzed using methods similar to those used for the main response endpoints. Demographic and baseline laboratory results 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: 115 randomized subjects were randomized and treated at 11 sites in Europe, North America, and South America between December 2005 and January 2007. All subjects in the induction and maintenance periods stopped study therapy in CA184007 at the time of database lock for BORR reporting. Subjects who were eligible could receive additional ipilimumab reinduction or maintenance therapy in CA184025. The demographic and other baseline characteristics of randomized subjects were consistent between groups. Most subjects were male (70.4%) and white (95.7%). The median age was 59 years. All but 1 subject across groups had a PS of 0 or 1. Nearly half of the subjects were staged as M1c at study entry. Most randomized subjects (budesonide: 74.1%; placebo: 70.1%) had ≥ 2 lesion sites at baseline by investigator assessment. All but 1 subject (in the placebo group) had ≥ 1 measurable index lesion at baseline; nearly half the subjects (budesonide: 46.5%; placebo: 42.1%) had ≥ 4 measurable index lesions. Twenty-one (36.2%) and 32 (56.1%) subjects in the budesonide and placebo groups, respectively, had not received prior systemic anticancer therapy for metastatic melanoma (except for adjuvant interferon).

Exposure: Most subjects were treated in the induction period only (budesonide: 51 of 58 subjects, placebo: 51 of 57 subjects). More than half of subjects in the induction period received the target number of 4 ipilimumab doses (budesonide: 55%; placebo: 61%).

Efficacy:

BORR

Table 1 summarizes the BORR as assessed by the IRC.

Table 1: BORR as Assessed by IRC - Randomized Subjects

	Number of Subjects (%)	
	Ipilimumab+Budesonide N = 58	**Ipilimumab+Placebo N = 57**
Best Overall Response Rate [a]	7/58 (12.1)	9/57 (15.8)
95% CI [b]	(5.0, 23.3)	(7.5, 27.9)
CR	1 (1.7)	0
PR	6 (10.3)[c]	9 (15.8)[c]
SD	11 (19.0)	11 (19.3)
PD	34 (58.6)	29 (50.9)
Unknown	6 (10.3) [d]	8 (14.0)[e]

[a] Number with CR or PR / number of randomized subjects [b] 2-sided, exact CI (Clopper and Pearson)
[c] 2 additional subjects, one in each group, had unconfirmed PR after a BOR of PD, as assessed by IRC
[d] Unknown = no post-baseline assessments (N = 4), no Week 12 assessment (N = 2) [e] Unknown = no post-baseline assessments (N = 6), no Week 12 assessment (N = 2)

The IRC-assessed response was ongoing at database lock for 14 of the 16 responders (6 of the 7 responders in the budesonide group, and 8 of the 9 responders in the placebo group). The duration of response for subjects with ongoing response ranged from 0.99+ to 10.15+ months in the budesonide group and 0.95+ to 8.3+ months in the placebo group. For all 14 subjects with ongoing responses, observations were censored at the time of database lock for BORR reporting (i.e., after the last treated subject had been followed for 24 weeks). The BORR was 22.4% (95% CI: 12.5, 35.3) in budesonide group and 15.8% (95% CI: 7.5, 27.9) in the placebo group, as assessed by the investigator. The IRC-assessed BORR was similar for pretreated and previously untreated subjects within treatment groups. In the budesonide group, the BORR was 13.5% (95% CI: 4.5, 28.8) for pretreated subjects and 9.5% (95% CI: 1.2, 30.4) for previously untreated subjects. In the placebo group, the BORR was 16.0% (95% CI: 4.5, 36.1) and 15.6% (95% CI: 5.3, 32.8) respectively.

Of 21 subjects in the budesonide group and 18 subjects in the placebo group who had at least 1 tumor assessment after initial IRC-reported progression and before the initiation of non-ipilimumab anti-cancer treatment, 1 budesonide-treated subject and 1 placebo-treated subject had unconfirmed IRC-assessed PR at timepoints after PD (not shown in Table 1). Neither of these subjects was included in the estimation of BORR.

Overall Survival

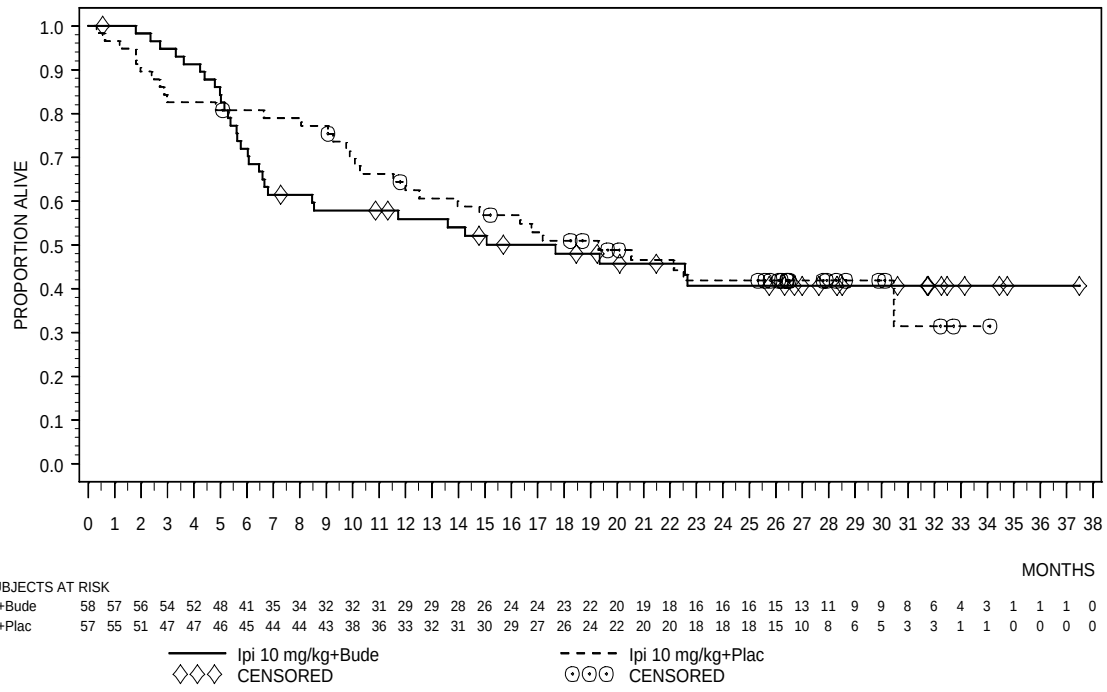
Two OS analyses were performed, the first at the time of database lock for BORR reporting (i.e., when the last randomized subject had been treated and followed for 24 weeks), based on a cutoff date of 26-Nov-2007. The median duration of follow-up was 5.7 and 6.3 months in the budesonide and placebo groups, respectively. 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 a cutoff date of 15-May-2009. OS follow-up was current for over 82% of subjects in each group. The median OS was 17.7 months in the budesonide group and 19.3 months in the placebo group (Table 2 and Figure 1). In pretreated subjects, the median OS was 7.3 months in the budesonide group and 11.5 months in the placebo group. In previously untreated subjects, the median OS could not be estimated in the budesonide group, and was 30.5 months in the placebo group (Table 2).

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

	Ipilimumab +Budesonide 10 mg/kg	**Ipilimumab +Placebo 10 mg/kg**
Per protocol population	N = 58	N = 57
Duration of follow-up (median, months)	12.7	16.3
Overall survival (median, months) (95% CI)	17.7 (6.8, 19.3)	19.3 (12.0, --)
Survival rate at 1 year (%) (95% CI)	55.9 (42.7, 68.8)	62.4 (49.4, 75.1)
Survival rate at 2 years (%) (95% CI)	40.6 (27.1, 54.4)	41.8 (28.3, 55.5)
Pretreated subjects	N = 37	N = 25
Duration of follow-up (median, months) (95% CI)	7.3	11.5
Overall survival (median, months) (95% CI)	15.1 (6.47, --)	11.5 (6.64, --)
Survival rate at 1 year (%) (95% CI)	49.9 (33.3, 66.6)	50.8 (31.5, 71.1)
Survival rate at 2 years (%) (95% CI)	31.6 (16.5, 47.6)	24.2 (8.0, 42.8)
Previously untreated subjects	N = 21	N = 32
Duration of follow-up (median, months) (95% CI)	18.5	18.5
Overall survival (median, months) (95% CI)	NR (11.7, --)	30.5 (14.0, --)
Survival rate at 1 year (%) (95% CI)	65.9 (45.0, 85.7)	71.4, (55.2, 87.2)
Survival rate at 2 years (%) (95% CI)	56.5 (30.6, 81.0)	56.6 (38.4, 74.3)

NR = median OS not reached

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



GROUP	# OF DEATHS / # OF SUBJECTS	MEDIAN (95% CI)
Ipi 10 mg/kg+Bude	32/58	17.7 (6.80 -)
Ipi 10 mg/kg+Plac	32/57	19.3 (12.0 -)

LIBRARY: /wwbdm/data/ca/184/007/fa_all/blinded/analysis EXTRACT DATE: 08-DEC-2008
PROGRAM SOURCE: /wwbdm/clin/proj/ca/184/core/val/stats/sasprogs/analysis/kmplot.sas RUN DATE: 19-Apr-2010 10:21

Disease Control

Approximately one-third of subjects achieved disease control (CR or PR or SD) as assessed by the IRC (31.0% and 35.1%, respectively) and as assessed by the investigator (41.4% and 31.6%, respectively). Stable disease was characterized by prolonged periods of stability for some subjects and by reductions in tumor burden over time. Among the 22 subjects across groups who had SD by mWHO criteria (Table 1), 19 subjects had SD based on measurements of index lesions (this assessment excluded subjects with SD based on non-index lesions) and all but 3 of these subjects had a decrease in the total volume of index lesions compared to baseline at the last evaluable IRC assessment.

A total of 44 (75.9%) subjects in the budesonide group and 42 (73.7%) subjects in the placebo group had progressed as assessed by IRC or died. The median PFS was 2.6 months in each group.

Exploratory irResponse Endpoints

The irResponse was observed as a reduction in tumor burden from 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 burden (index and new lesions) in subjects otherwise categorized as stable. Table 3 summarizes results for the irResponse endpoints. Consistent with

results showing response after progression by mWHO criteria in some subjects, response or stable disease by irResponse criteria was reported in the presence of new lesions (across treatment groups, 1 of 18 subjects with irPR, and 7 of 27 subjects with stable disease [irSD]) (data not shown). Four (6.9%) subjects in the budesonide group and 3 (5.3%) subjects in the placebo group demonstrated irSD with ≥ 25% reduction in total tumor burden of index and new lesions compared to baseline. The percent tumor reduction from baseline for these subjects ranged from 37.1% to 80.3% in the budesonide group and 59.0% to 78.7% in the placebo group.

Table 3: Exploratory Immune-related Response Endpoints - Randomized Subjects

	Number of Subjects (%)	
	Ipilimumab+Budesonide N = 58	**Ipilimumab+Placebo N = 57**
irCR (disappearance of index and new lesions)	0	1 (1.8)
irPR [a]	8 (13.8)	10 (17.5)
Late irPR (after irPD)	0	1 (1.8)
irSD	14 (24.1)	13 (22.8)
irSD and ≥ 25% reduction in tumor burden [b]	4 (6.9)	3 (5.3)
Late irSD (after irPD)	1 (1.7)	2 (3.5)

[a] ≥ 50% reduction in index and new lesions reported at the time of irPR; [b] ≥ 25% reduction in index and new lesions reported at the last evaluable tumor assessment

Safety:

Primary Endpoint - Rate of Grade ≥2 Diarrhea: The rate of Grade ≥ 2 diarrhea was similar between groups (Table 4).

Table 4: Rate of Grade ≥ 2 Diarrhea - Treated Subjects

	Number of Subjects (%)	
Subjects with Grade ≥ 2 Diarrhea [a]	**Ipilimumab+ Budesonide N = 58**	**Ipilimumab+ Placebo N = 57**
Grade ≥ 2 diarrhea rate [b]	19/58 (32.8)	20/57 (35.1)
95% CI [c]	(21.0, 46.3)	(22.9, 48.9)
Difference in rate of Grade ≥ 2 Diarrhea [d]	2.35	
95% CI [e]	(-15.2, 19.9)	

[a] Subjects reporting Grade ≥ 2 diarrhea inflammatory events regardless of causality prior to earlier of Week 24 or first maintenance treatment

[b] Subjects with Grade ≥ 2 diarrhea divided by the number of treated subjects

[c] Clopper and Pearson method

[d] Difference in rates between the budesonide group and (minus) the placebo group

[e] Estimate and 95% CI for difference in rate of Grade ≥ 2 diarrhea are computed using the Mantel-Haenszel method, stratified by prior use of immunotherapy (yes vs no) as recorded in the IVRS at randomization

General Safety: The safety profile of ipilimumab reflected the mechanism of action of the drug, and was similar between treatment groups (Table 5). Progressive disease was the most frequent cause of death; no drug-related deaths were reported. Drug-related, immune-related (ir)AEs were analyzed as a separate category of all drug-related AEs. irAEs (any grade) represented approximately 90% of all drug-related AEs; Grade 3-4 irAEs represented approximately 80% of Grade 3-4 drug-related AEs. The most common irAEs in each group were those affecting the skin (> 60%) and GI tract (> 45%). Almost all skin irAEs were Grade 1-2, while at least half of irAEs affecting the GI and liver were reported as Grade 3-4 (data not shown). There were no reports of GI or colonic perforations or GI hemorrhage requiring colectomy while subjects were on ipilimumab treatment. irAEs, including severe and serious events, were generally medically manageable with the use of systemic corticosteroid alone or in combination with other immunosuppressant therapy, and resolved within days or weeks.

Table 5: Summary of Safety -Treated Subjects

	Number of Subjects (%)	
	Ipilimumab+Budesonide N = 58	**Ipilimumab+Placebo N = 57**
Deaths	29 (50.0)	28 (49.1)
Cause of death=progressive disease	26 (44.8)	25 (43.9)
SAEs	34 (58.6)	31 (54.4)
Drug-related SAEs	26 (44.8)	21 (36.8)
AEs leading to discontinuation	15 (25.9)	18 (31.6)
Drug-related AEs		
Any grade	52 (89.7)	54 (94.7)
Grade 3-4	32 (55.2)	27 (47.4)
Immune-related adverse events (irAEs)		
Any grade	47 (81.0)	48 (84.2)
Grade 3-4	24 (41.4)	22 (38.6)

Note: Deaths are based on updated follow-up in CA184007; other safety data are based on the per protocol follow-up.

Other Observations Related to Safety

Two of 115 subjects (both in the budesonide group) developed a positive human antihuman antibody (HAHA). Neither subject had any infusion-related or peri-infusional hypersensitivity or anaphylactic reactions.

Pharmacokinetic Results Of 115 treated subjects, 15 had intensive PK sampling and were included in the PK dataset. Fourteen of these 15 subjects had sufficient data to calculate terminal half-life, and 12 subjects had sufficient data for non-compartmental PK analysis. The mean T-half value was approximately 9.6 days (N = 14, range: 6 to 17 days) and 15.2 days (N = 14, range from 8 to 29 days) from the first and third dose, respectively. The mean clearance (CL) value was 19.1 mL/h (N = 11, range from 10.8 to 35.7 mL/h) and the Vss value was 6.0 L (N = 11, range from 2.4 to 9.0 L). The small Vss indicated that ipilimumab was confined primarily to the extracellular fluid volume.

Pharmacodynamic Results

No meaningful differences in any of the pharmacodynamic results were noted between treatment groups. Overall, an increase in the mean percentage of activated and central memory T-cells and a decrease in mean percent of naive T-cells were observed at a comparable level in both arms. Of evaluable subjects, the majority had an increase and decrease in percent of activated and naive T-cells, respectively, at Weeks 4

and 12. On an individual subject level, an increase in the percentage of activated T-cells was associated with a concomitant decrease in percentage of naive T-cells. Of the evaluable subjects with changes in percent of activated or naive $CD8^+$ T cells at Week 4, the majority had further changes (increase or decrease, respectively) through Week 12.

An association between onset date of Grade 2+ GI irAEs and elevated stool calprotectin was observed; 17 of 18 subjects reporting a Grade 2-4 GI irAE with a stool calprotectin measurement in close temporal proximity to the GI irAE onset date had elevated stool calprotectin relative to baseline/Week 1. For subjects in either group with a Grade 2+ GI irAE, 5% to 52% were positive for at least one antibody to microbial antigens. Post-treatment fluctuations in the titers of these antibodies, relative to baseline, were observed. Histologic tumor necrosis and inflammation were reported for 1 subject who had post-treatment tumor resection. Histologic inflammation was reported in colon and liver biopsies during the first week on treatment and after the onset of hepatitis, respectively. An association between Grade ≥ 2 diarrhea or clinical colitis before Week 24 and early signs of inflammation in colon histologic tissue was observed. Ipilimumab-induced colitis may represent a distinct clinicopathalogic entity compared to classic inflammatory bowel disease (IBD).

Predictive Biomarker Results

No clear associations between response or worst-grade irAEs and single-nucleotide polymorphism genotypes, HLA-A2*201, or HLA allele carrier status were detected.

CONCLUSIONS

- No difference was reported in the incidence of Grade ≥ 2 diarrhea for subjects who received prophylactic budesonide with ipilimumab 10 mg/kg compared with subjects who received placebo with ipilimumab (primary endpoint).
- Treatment with ipilimumab resulted in antitumor activity in pretreated and previously untreated subjects with advanced melanoma. Clinically relevant reductions in the tumor burden compared to baseline were reported, including reductions after progression by mWHO.
- The median OS was 17.7 months in the budesonide group and 19.3 months in the placebo group as of the updated OS analysis. The projected 1-year and 2-year survival rates suggested an improvement over historical controls. Results of survival assessments may have been driven by late effects, including PR after PD and prolonged SD.
- Most drug-related AEs were consistent with immune-mediated events and reflected the mechanism of action of the drug. The most common irAEs of any grade were those affecting the skin and GI tract. Most drug-related AEs were manageable with symptomatic therapy or steroids. There were no drug-related deaths.
- Two of 115 subjects developed positive HAHAs, which were not associated with any clinically relevant AE. Ipilimumab induced an activation of T cells and dysregulation of GI mucosal immunity (i.e., fluctuation in serologic biomarkers of IBD, colonic inflammation, and clinical diarrhea and colitis). No predictive biomarkers of irAEs and objective response by mWHO were identified. The pharmacokinetic profile of ipilimumab was consistent with results obtained in previous exploratory studies.

DATE OF REPORT: May 2010