Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Ipilimumab		
Name of Active Ingredient: Anti CTLA4		

SYNOPSIS

Final Clinical Study Report for Study CA184022

TITLE OF STUDY: A Randomized, Double-Blind, Multi-center, Phase II Fixed Dose Study of Multiple Doses of Ipilimumab (MDX-010) Monotherapy in Patients with Previously Treated Unresectable Stage III or IV Melanoma

INVESTIGATORS/STUDY CENTERS: 214 subjects were treated at 66 sites in 13 countries

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 06-Apr-2006 **CLINICAL PHASE:** 2

Study Completion Date: Cutoff for assessment of the primary endpoint: 12-Nov-2007; cutoff for the final updated survival follow-up: 15-May-2009

OBJECTIVES:

Primary Objectives: To estimate best overall response rate (BORR) (as per modified World Health Organization [mWHO] criteria) in subjects with previously treated, therapy-refractory or intolerant, Stage III (unresectable) or Stage IV melanoma receiving ipilimumab doses of 0.3, 3, and 10 mg/kg.

Secondary Objective(s):

- To evaluate the dose-response relationship based on BORR
- To estimate the difference in BORR in subjects receiving 3 vs 0.3 mg/kg, 10 vs 0.3 mg/kg and 10 vs 3 mg/kg
- To estimate progression free survival (PFS) rate at the Week 12 assessment
- To estimate disease control rate (proportion of subjects with best response of CR + PR + SD)
- To estimate PFS
- To estimate overall survival (OS)
- To estimate survival rate at 1 year
- To estimate duration of response and define the proportion of subjects with duration of response lasting ≥ 24 weeks
- To estimate time to BOR
- To evaluate the safety profile of ipilimumab during the induction and maintenance period at each dosage level of ipilimumab

- To evaluate health-related quality of life (HRQoL)
- To obtain pharmacokinetic (PK) samples for population PK analysis

METHODOLOGY:

The study was divided into 4 periods: a screening period, an induction period (Week 1 dose visit through Week 24 tumor assessment visit), a maintenance period (Week 24 dose visit until progression or study closure), and a follow-up period. Subjects were randomized in a 1:1:1 ratio and stratified by prior treatment received: IL-2, fotemustine, dacarbazine, or temozolomide versus other treatments.

The induction period began on Day 1/Week 1 (randomization) and ended at Week 24 or upon progressive disease (PD), death, or withdrawal of consent; single dose of ipilimumab was administered intravenously (IV), every 3 weeks (Weeks 1, 4, 7, and 10), for a total of 4 doses. Four (4) tumor assessments (TAs) (radiologic and photographic) were performed at Weeks 12, 16, 20, and 24.

The maintenance period began at Week 24 and ipilimumab was administered every 12 weeks (all assessments at Week 24 were counted as induction period assessments, any dosing at Week 24 was considered as maintenance period dosing). This period included 2 categories of subjects, 1) on-treatment: subjects without PD who continued to tolerate ipilimumab, continued treatment in 12-week intervals until PD, withdrawal of consent, or study closure; 2) TAs only: subjects without PD who discontinued ipilimumab treatment due to toxicity continued with TAs in maintenance period and study procedures until PD, but received no further dosing. All subjects in the maintenance period had TAs performed every 6 weeks (Weeks 30, 36, 42, and 48). After Week 48, TAs were performed every 12 weeks.

Any subject, who did not qualify for entry into the maintenance period, was moved into the follow-up period or into a separate study CA184025. Subjects in CA184022 were eligible to enter CA184025; 1) if subjects exhibited PD at anytime during induction or maintenance in CA184022, they could be re-induced in CA184025 at 10 mg/kg of ipilimumab irrespective of their CA184022 dose or 2) if subjects enrolled into CA184025 when CA184022 closed, they could continue to receive their CA184022 blinded dose in CA184025 maintenance period or 3) if subjects who did not progress in CA184022 but discontinued treatment due to an irAE and were subsequently enrolled into CA184025 maintenance period for TAs only, they could be re-induced upon progression at 3 mg/kg of ipilimumab. The follow-up period began for all subjects with PD who did not meet the criteria for entry into CA184025 for re-induction, or chose not to enroll into CA184025.

Following closure of CA184022, CA184025 was amended to permit all subjects participating in CA184022 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 CA184022 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 CA184022 or CA184025.

NUMBER OF SUBJECTS (Planned and Analyzed): In this study, 70 patients were planned to be randomized to each of the 3 doses. With 70 patients per group, the maximum width of the exact 95% confidence interval (CI) for the BORR for the 0.3, 3, and 10-mg/kg groups were approximately 12%, 15%, and 18% if the true BORR lie in the anticipated 2-5%, 6-9%, and 10-15% ranges, respectively. The sample size was not selected to achieve a pre-specified power for a particular statistical test. The number of subjects treated and included in the efficacy and safety analyses per treatment group were 72, 71, and 71, respectively.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Subjects of either sex, at least 16 years of age (or minimum age of consent required per given regulatory authority), with advanced melanoma who received prior treatment with any regimen (non-experimental or experimental), except a CD-137 agonist or a CTLA-4 inhibitor or agonist and progressed, failed to respond (CR or PR), or did not tolerate that regimen, had life expectancy of at least 16 weeks, and Eastern Oncology Cooperative Group (ECOG) performance status score 0-1.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Ipilimumab was administered at 0.3, 3, or 10 mg/kg, depending on randomization, as a 90 minute, IV infusion, every 3 weeks at Weeks 1, 4, 7, and 10, for a total of 4 separate doses in the induction period and followed by maintenance period with ipilimumab administered IV, every 12 weeks (e.g., Weeks 24, 36, 48+). Subjects were administered with the following vendor batches of ipilimumab: 5J06544, 6B17599, and 6G19359.

CRITERIA FOR EVALUATION: Tumor response was evaluated by independent radiology review committee (IRC) based on mWHO criteria and by the investigators. The IRC assessment was considered primary. Tumor response as assessed by the IRC was based on the change from baseline in total tumor volume of index and non-index lesions. Efficacy variables included BORR, OS, and survival rate at 1 year, PFS, PFS rate at Week 12, PFS rate at Week 24, PFS rate at 1 year, duration of response, major durable response (duration $\geq$ 24 weeks) rate, time to response, disease control rate, duration of disease control, major durable disease control rate (duration $\geq$ 24 weeks), and duration of stable disease.

Exploratory endpoints were assessed using immune-related (ir)Response criteria that were developed, using mWHO as a foundation, as a preliminary approach to a systematic categorization of ipilimumab clinical activity before and after progression by mWHO. Determination of the irResponse was based solely on tumor measurements of index and new lesions recorded during the IRC review. Non-index lesions were not considered in the irResponse assessment. irResponse was defined in the core statistical analysis plan prior to database lock; it was not defined in the protocol.

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 to be a consequence of the intrinsic biological activity of ipilimumab (irAEs) were examined for 6 subcategories of irAE: gastrointestinal, liver, skin, endocrine, neurological, and other. A data monitoring committee (DMC) provided independent oversight for safety, study conduct, and risk-benefit-ratio. The HRQoL was measured using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire administered at baseline and multiple scheduled assessments.

STATISTICAL CONSIDERATIONS: The sample size was not selected to achieve a pre-specified power for a particular statistical test. The analyses based on the assessments of the IRC were considered primary. Exact, 2-sided 95% confidence intervals (CIs) for BORR (defined for each randomized group as the total number of randomized subjects in the group whose BOR is CR or PR, divided by the total number of randomized subjects in the group) within treatment group were calculated using the method of Clopper and Pearson. Two-sided 95% CIs for the odds ratio and (provided normality holds) the difference in rates, adjusting for the stratification factor prior treatment (IL-2/fotemustine/dacarbazine/temozolomide vs. other) used in randomization, was computed for the following differences in BORR: 3 vs 0.3 mg/kg, 10 vs 0.3 mg/kg and 10 vs 3 mg/kg. In addition, a 1-sided (positive), exact Cochran-Armitage trend test with a 0.05 significance level was used to evaluate the dose-response relationship.

Overall survival was defined as the time between 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 analyzed. The subject's updated survival status and death or last known alive date reflected the latest date recorded in either CA184022 or CA184025. Progression-free survival was defined as the time between the randomization date and the date of progression or death, whichever occurred first.

Overall survival and PFS were estimated 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 method of Brookmeyer and Crowley. Survival rates at 1 year, 18 months, and 2 years were defined as the probability that a subject was alive at 1 year, 18 months, and 2 years, respectively, following randomization in CA184022. Survival rates were calculated using the Kaplan-Meier product-limit method. Corresponding two-sided 95% bootstrap CIs were calculated. Comparisons of OS between the treatment groups were performed. The hazard ratio and its associated two-sided 95% CI was estimated using an unstratified Cox proportional hazards model, with treatment as the single covariate.

Time to event variables used the Kaplan-Meier product-limit method to provide the median estimate together with a 2-sided 95% CI for the median, calculated using the method of Brookmeyer and Crowley. Exploratory irResponse endpoints (irBOR, irBORR, and ir disease control rate) were analyzed using methods similar to those used for the main response endpoints.

The pharmacodynamics of stool calprotectin were examined graphically and by summary statistics. Relationships of 3 types of biomarkers - stool calprotectin, SNPs, and HLA-A2*201, to efficacy and safety were examined. The primary comparison of the EORTC HRQoL between treatment groups was a Wei-Lachin test on differences from baseline. A separate 2-sided Wei-Lachin test was conducted for each scale, comparing treatment groups. Tests were conducted at the 5% significance level.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics:

In the total population (N = 217 randomized subjects), more men than women (66.4% vs 33.6%) were randomized; the majority was white (98.6%) and the median age was 59.0 years. Except for 1 subject, all had an ECOG performance status of 0 or 1, 118 (54.4%) subjects were staged as M1c at study entry and 95% had Stage IV disease. The demography and subject characteristics were consistent across all 3 treatment groups except for the M-stage at study entry. The number of subjects with M1c-stage disease at study entry was higher in the 0.3-mg/kg group (61.6% vs 50.0% in the 3 mg/kg, and 51.4% in the 10 mg/kg), M1b- stage disease was higher in the 3-mg/kg group (29.2% vs 17.8% in the 0.3 mg/kg, and 20.8% in the 10 mg/kg), and M1a-stage disease was higher in the 10-mg/kg group (23.6% vs 13.7% in the 0.3 mg/kg, and 15.3% in the 3 mg/kg). As assessed by the IRC, approximately 83% of randomized subjects had ≥ 2 baseline disease sites (all lesions). The IRC assessed at least 1 index lesion in 201 of the 217 randomized subjects and 31.8% had ≥ 5 index lesions. About 54.5% had received prior immunotherapy, including interferon (28.1%), IL-2 (18.4%), and prior investigational immunotherapy (9.2%). All had received prior surgery related to cancer and approximately 30% of subjects received previous radiotherapy. Most subjects had normal hematology, liver function, and renal function at baseline.

Exposure:

Of the 217 randomized subjects, 214 were treated with ipilimumab. All 214 subjects were treated in the induction period, and 20 subjects were treated during the maintenance period. A total of 214 subjects received overall up to 6 doses of either 0.3, 3, or 10 mg/kg of ipilimumab during the study. In the overall study period, approximately 60% of subjects in the 0.3 and 3-mg/kg groups received 4 doses per subject. In the 10-mg/kg group, about 40% subjects received 4 doses each. Twenty-three (31.5%) subjects from the 0.3-mg/kg group, 30 (41.7%) subjects from the 3-mg/kg group, and 19 (26.4%) subjects from the 10-mg/kg group were re-induced with ipilimumab in CA184025 at 10 mg/kg.

Efficacy Results: Primary Endpoint: BORR

As assessed by the IRC, in randomized subjects, there were no responders in the 0.3-mg/kg treatment group, the BORR in the 3-mg/kg group was 4.2% (3/72 subjects), and 11.1% (8/72 subjects) in the 10-mg/kg group (Table 1). In the 3-mg/kg group, all 3 responders achieved PR. In the 10-mg/kg group, 2/8 responders achieved CR and 6/8 subjects achieved PR. At the end of the primary observation period, 6 of

the 8 responders in the 10-mg/kg group and 2 of the 3 responders in the 3-mg/kg group reported an ongoing response (durations ranging from 0.95+ to 5.5+ months).

Delayed response after PD per IRC assessment

Of 36 subjects in the 10-mg/kg group with PD assessed by the IRC (Table 1), 14 subjects were followed beyond progression. Two of these 14 subjects had IRC-reported overall response of PR after PD, 1 with a confirmed ([redacted]) and 1 remaining unconfirmed ([redacted]) because a second confirmatory scan for this subject was not available. The subject with confirmed PR was not included in the estimation of the BORR (Table 1). None of the subjects in the 3-mg/kg group or 0.3-mg/kg group who were followed (25 subjects each) post IRC progression had IRC-reported PR after PD.

Table 1: Summary of BORR and BOR - Randomized Subjects

	Ipilimumab		
	0.3 mg/kg N = 73	**3 mg/kg N = 72**	**10 mg/kg N = 72**
Best Overall Response Rate[a], n (%)	0	3 (4.2)	8 (11.1)
95% CI[b], %	(0.0, 4.9)	(0.9, 11.7)	(4.9, 20.7)
Best Overall Response, n (%)			
CR	0	0	2 (2.8)
PR	0	3 (4.2)	6 (8.3)
SD	10 (13.7)	16 (22.2)	13 (18.1)
PD	43 (58.9)	41 (56.9)	36 (50.0)
Unknown	20 (27.4)	12 (16.7)	15 (20.8)
Reason for Unknown			
Early Censoring Therapy	1 (1.4)	0	4 (5.6)
No Post-Baseline Assessments	17 (23.3)	11 (15.3)	10 (13.9)
No Week 12 Assessment	2 (2.7)	1 (1.4)	1 (1.4)

[a] n with CR or PR/N

[b] 2-sided, exact CI (Clopper and Pearson).

Secondary Endpoints

Dose-response Relationship Based on BORR

As assessed by the IRC, in randomized subjects, there was a statistically significant trend (P = 0.0015) of increased BORR with increased dose, suggesting a dose effect. Analyses performed to estimate differences in BORR between ipilimumab doses indicated that the difference in BORR between the 10 mg/kg vs the 0.3-mg/kg group was 11.2% (95% CI: 3.9, 18.5) and between the 10 mg/kg vs the 3-mg/kg group was 6.9% (95% CI:-1.7, 15.5). The difference in BORR between 3 mg/kg vs 0.3 mg/kg was 4.2% (95% CI: -0.5, 8.9). The trend test result is influenced by the large difference in BORR between the 10 mg/kg and the 0.3-mg/kg group.

Overall Survival

Two OS assessments were performed. The initial assessment was at the 12-Nov-2007 data cutoff for BORR reporting (at the last treated subject's Week 24 assessment), per protocol. An updated analysis was conducted using data available from additional follow-up, with a data cutoff date of 15-May-2009 (this cutoff incorporated data from an earlier survival update based on a 08-Feb-2008 cutoff). Updated survival was obtained for all randomized subjects who were still alive at the initial OS assessment and had not withdrawn consent for further contact, based on the most recent available data from either CA184022 or CA184025.

Per Protocol Analyses of OS (12-Nov-2007 Cutoff)

At the time of database lock for the initial assessment, 25/73 subjects in the 0.3 mg/kg, 25/72 subjects in the 3 mg/kg, and 24/72 subjects in the 10-mg/kg group had died (Figure 1). The results of the initial assessment of OS are presented in Table 2 and Figure 1.

Table 2: Overall Survival (12-Nov-2007 Cutoff) - Randomized Subjects

	Ipilimumab 0.3 mg/kg N = 73	Ipilimumab 3 mg/kg N = 72	Ipilimumab 10 mg/kg N = 72
Median follow-up (months)[a]	4.57	5.55	4.55
Interquartile range (25% to 75%), months	(2.89-5.78)	(3.42-7.21)	(2.94-7.44)
Number of subjects censored prior to median	43	42	NA[b]
Median OS (months)	7.95	9.07	---
95% CI[c]	(6.51, ---)	(8.57, 12.25)	(6.31, ----)
1-year survival rate (%)	45.11	47.80	55.28
95% CI[d]	(28.00, 67.83)	(24.96, 68.96)	(35.23, 70.16)

[a] Per-protocol follow-up period is period from randomization date to death or last known alive date per protocol follow-up.

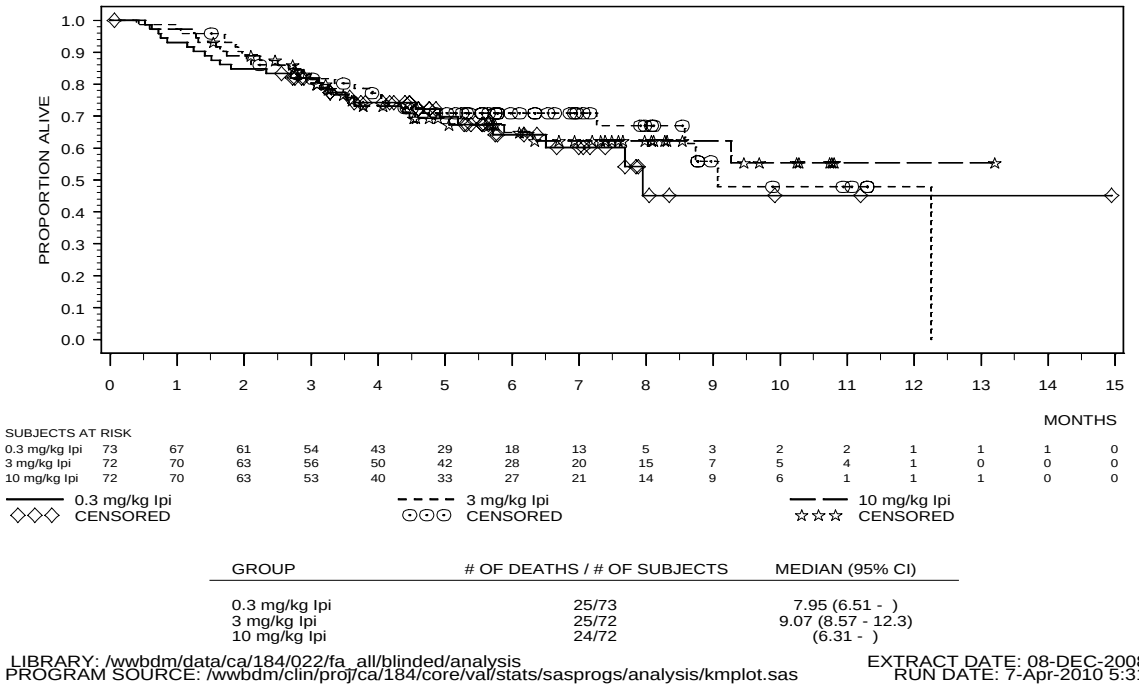
[b] Could not be assessed because median was not reached.

[c] Based on Kaplan-Meier estimation and CIs computed using the bootstrap method.

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

(---) the statistics were not estimable due to censored observations or median was not observed.

Figure 1: Overall Survival (12-Nov-2007 Cutoff) - Randomized Subjects



GROUP	# OF DEATHS / # OF SUBJECTS	MEDIAN (95% CI)
0.3 mg/kg Ipi	25/73	7.95 (6.51 -)
3 mg/kg Ipi	25/72	9.07 (8.57 - 12.3)
10 mg/kg Ipi	24/72	(6.31 -)

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

The results of the updated OS analysis are presented in and Table 3 and Figure 2. The hazard ratio (HR) for comparison of OS between the 10 mg/kg and 3-mg/kg group was 0.908 (95% CI: 0.617, 1.338), between 10 mg/kg and 0.3 mg/kg was 0.796 (95% CI: 0.544, 1.164), and between 3 mg/kg and 0.3 mg/kg was 0.888 (95% CI: 0.611, 1.292). Similar HRs were observed when comparison of OS between treatment groups was performed after adjusting for baseline covariates (ECOG performance status [0 vs 1], M-stage [M1a and M0 vs M1c and M1b vs M1c], and gender [male vs females]).

If subjects exhibited PD at anytime during induction or maintenance in CA184022, they could be re-induced in CA184025 at 10 mg/kg of ipilimumab. Twenty-three (31.5%) subjects from the 0.3 mg/kg, 30 (41.7%) subjects from the 3-mg/kg group, and 19 (26.4%) subjects from the 10-mg/kg group were re-induced in CA184025 at 10 mg/kg. The impact of re-induction at 10 mg/kg on the OS in each treatment group is not known.

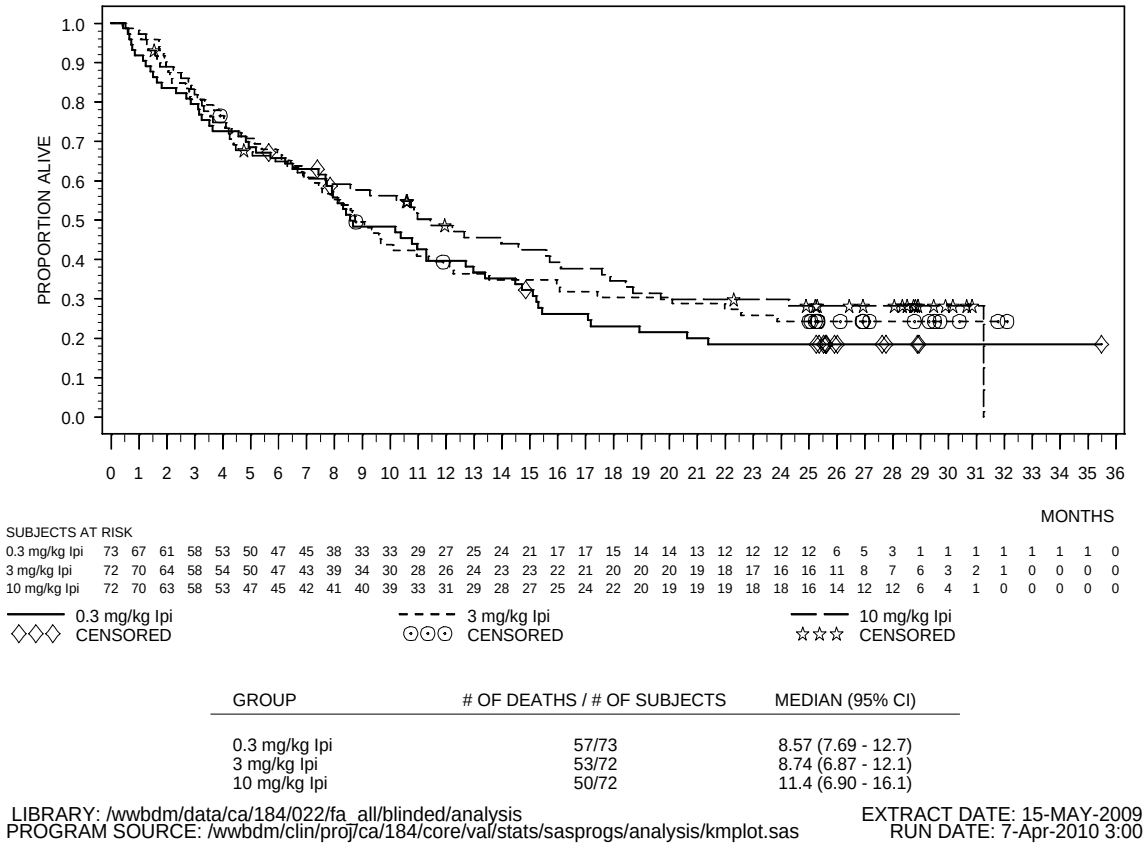
Table 3: Updated Overall Survival (15-May-2009 Cutoff) - All Randomized Subjects

	Ipilimumab		
	0.3 mg/kg N = 73	**3 mg/kg N = 72**	**10 mg/kg N = 72**
Median Survival Follow-up (Months)	8.31	8.69	10.68
Interquartile Range (25%-75%)	3.52 - 15.31	3.98 - 22.28	3.60 - 23.29
Overall Survival, Median (Months)	8.57	8.74	11.43
95% CI[c]	(7.69, 12.71)	(6.87, 12.12)	(6.90, 16.10)
Survival Rate at 1 Year (%)	39.58	39.32	48.64
95% CI[d]	(28.20, 51.19)	(27.97, 50.87)	(36.84, 60.36)
Survival Rate at 18 Months (%)	23.04	30.24	34.52
95% CI[b]	(13.39, 33.61)	(19.76, 41.43)	(23.35, 46.16)
Survival Rate at 2 Years (%)	18.43	24.20	29.81
95% CI[b]	(9.62, 28.22)	(14.42, 34.75)	(19.13, 41.14)

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

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

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



GROUP	# OF DEATHS / # OF SUBJECTS	MEDIAN (95% CI)
0.3 mg/kg Ipi	57/73	8.57 (7.69 - 12.7)
3 mg/kg Ipi	53/72	8.74 (6.87 - 12.1)
10 mg/kg Ipi	50/72	11.4 (6.90 - 16.1)

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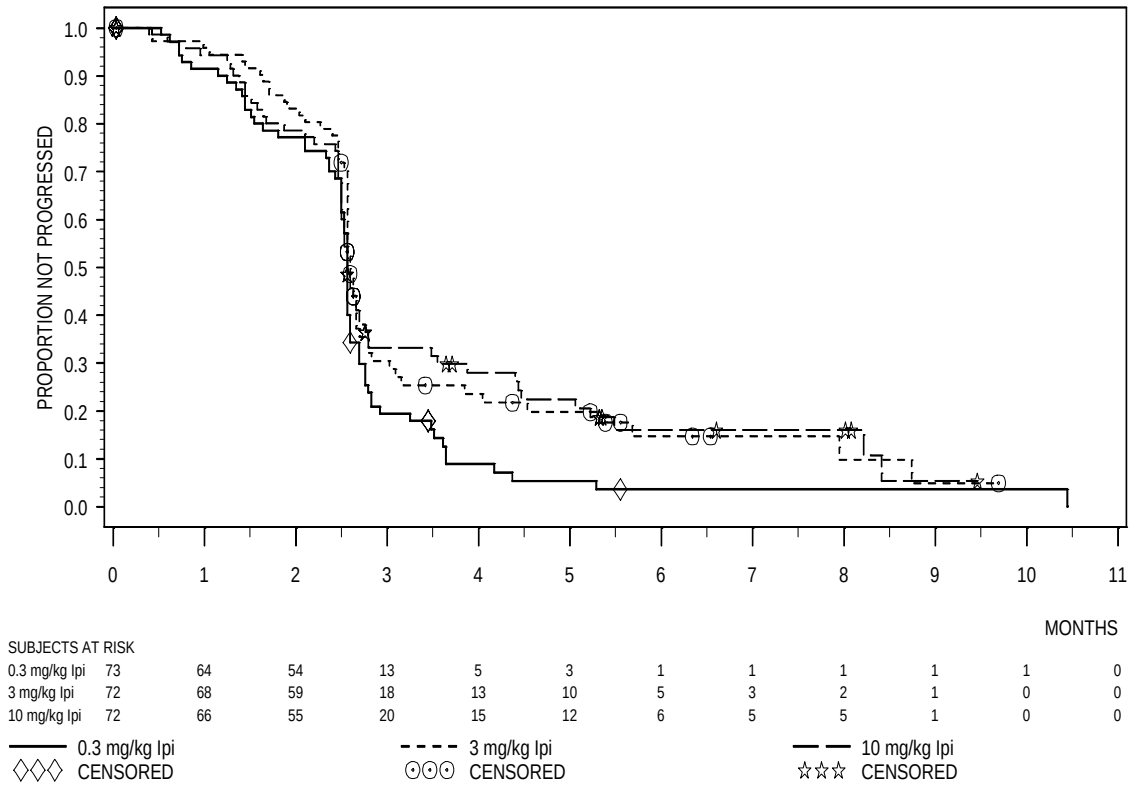
Progression Free Survival and Disease Control Rate

As assessed by the IRC, 66 (90.4%) subjects in the 0.3-mg/kg group, and 57 (79.2%) subjects each, in the 3 and 10-mg/kg groups had progressed or died at the time of database lock for BORR reporting. The median PFS for each treatment group was approximately 2.6 months (~ 10 weeks) (Figure 3). The HR for comparison of PFS between 10 mg/kg and 3-mg/kg groups was 1.032 (95% CI: 0.714, 1.492), between 10 mg/kg and 0.3-mg/kg groups was 0.709 (95% CI: 0.494, 1.019), and between 3 mg/kg and 0.3-mg/kg groups was 0.695 (95% CI: 0.485, 0.995). The PFS rate at Week 12 (assessed by IRC) was approximately 36% to 50% across the 3 treatment groups. PFS rate at Week 24 (assessed by IRC) was 2.7%, 12.9% and 18.9%, respectively.

The number of subjects with SD in the 0.3, 3 and 10-mg/kg groups was 10 (13.7%), 16 (22.2%), and 13 (18.1%), respectively (Table 1). By IRC assessment, the disease control (CR + PR + SD) rate in randomized subjects in the 10-mg/kg group was numerically greater than the 3 and 0.3-mg/kg groups; 29.2% vs 26.4% and 13.7%, respectively.

Figure 3: Kaplan-Meier Plot of IRC Progression-Free Survival - Randomized Subjects



GROUP	# OF EVENTS / # OF SUBJECTS	MEDIAN (95% CI)
0.3 mg/kg Ipi	66/73	2.56 (2.53 - 2.60)
3 mg/kg Ipi	57/72	2.60 (2.56 - 2.66)
10 mg/kg Ipi	57/72	2.56 (2.50 - 2.69)

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Exploratory Efficacy Endpoints (Immune-related Response)

Exploratory irResponse endpoints define total tumor burden as the sum of index lesion plus measurable lesion (when present) and track tumor burden over time before and after PD by mWHO. Three (4.2%) subjects in the 3 mg/kg and 7 (9.7%) subjects in the 10-mg/kg group had irPR (≥ 50% reduction in tumor burden) prior to appearance of new lesions. Of these, 2 subjects in the 3-mg/kg group and 5 subjects in the 10-mg/kg group had ongoing responses at the time of database lock. In addition, late irPR (irPR post irPD) was reported in 1 subject in the 3 mg/kg group (Table 4).

The number of subjects with irSD was 15 (20.5%), 14 (19.4%), and 17 (23.6%) in the 0.3, 3 and 10-mg/kg groups, respectively. Of these, 2 subjects in the 0.3 mg/kg group (1 with new lesion and 1 without new lesion), 2 subjects in the 3-mg/kg group (both without new lesions), and 3 subjects in the 10-mg/kg group (all 3 without new lesions) demonstrated a slow steady decline in tumor burden (≥ 25% decline in total

tumor burden). The percent tumor reduction from baseline in these 7 subjects with slow steady decline ranged from 27% to 54%. In addition, late irSD (irSD post irPD) was reported in 1 subject (1.4%) in the 0.3-mg/kg group (this subject received re-induction with ipilimumab at 10 mg/kg in CA184025), and in 3 subjects (4.2%) in the 3-mg/kg group (2 of these subjects received re-induction with ipilimumab at 10 mg/kg in CA184025).

Table 4: Exploratory Endpoints: Randomized Subjects

	Number of Subjects (%) Ipilimumab		
	0.3 mg/kg N = 73	**3 mg/kg N = 72**	**10 mg/kg N = 72**
irCR (disappearance of index and new lesions)	0	0	0
irPR (≥ 50% reduction in index and new lesions)	0	3 (4.2)	7 (9.7)
Late irPR (after irPD)	0	1 (1.4)	0
irSD (neither irCR, irPR nor irPD)	15 (20.5)	14 (19.4)	17 (23.6)
irSD (≥ 25% decline in tumor burden)[a,b]	2 (2.7)	2 (2.8)	3 (4.2)
Late irSD (after irPD)	1 (1.4)[c]	3 (4.2)[d]	0
irSD (other)	13 (17.8)	12 (16.7)	14 (19.4)

[a] Sum of products of perpendicular diameters (SPD) of all (ie, index and new measurable) lesions.

[b] By comparison of SPD at last evaluable tumor assessment with baseline SPD.

[c] irSD based on a scan from CA184025 and received re-induction with ipilimumab at 10 mg/kg in CA184025.

[d] For 2 of the 3 subjects, irSD based on scans from CA184025 and received re-induction with ipilimumab at 10 mg/kg in CA184025.

Safety Results:

Progressive disease was the most frequent reason of death across treatment groups; 1 drug-related death (Grade 3 respiratory infection) was reported in the 3-mg/kg group. The number of drug-related SAEs/AEs, and drug-related AEs leading to discontinuation increased with increasing dose of ipilimumab (Table 5). Immune-related AEs were the most frequently reported drug-related AEs.

There was a numerical increase in irAEs (any grade) with increasing dose of ipilimumab (26.4%, 64.8%, and 70.4%, respectively). The overall irAE profile was similar between the 3 and 10-mg/kg groups except for the incidence of Grade 3-4 irAEs, which was higher in the 10-mg/kg group than in the 3-mg/kg group (25.4% vs 7.0%); no Grade 3-4 irAEs were reported in the 0.3-mg/kg group. Across treatment groups, the most frequently (≥ 5%) reported irAEs were gastrointestinal disorders and skin and subcutaneous tissue disorders. The most frequently (≥ 5%) reported GI irAE was diarrhea in the 0.- mg/kg group and diarrhea and colitis in the 3 and 10-mg/kg groups. The rate of Grade 3-4 GI irAEs was 5-fold higher in the 10-mg/kg group than in the 3-mg/kg group (15.5% vs 2.8%). In the 10-mg/kg group, the most frequently (≥ 5%) reported serious GI irAE was diarrhea; 1 subject developed ulcerative colitis with GI bleed requiring colectomy. No GI perforation was reported in this study. Two subjects with serious Grade 3-4 diarrhea also reported colitis in the 10-mg/kg group, 10 subjects reported Grade 3-4 diarrhea that resolved with median time to resolution 4.43 weeks. Diarrhea and colitis were generally managed with or without steroid treatment. Across the treatment groups, majority of skin irAEs were of Grade 1-2 severity and were

infrequent. Liver irAEs were also infrequent. There were 2 (2.8%) Grade 3-4 liver irAEs occurring in the 10-mg/kg group, both cases of liver irAEs were characterized by transaminitis and both responded to steroid therapy and resolved within 4 weeks. Endocrine irAEs were infrequent and were generally effectively managed with steroids and/or hormone replacement therapy. A neurological irAE (Grade 2 meningism) was reported by 1 subject (10-mg/kg group); this event was ongoing at the time the subject left the study to enroll in CA184025. There was a numerical increase in other irAEs in the 10-mg/kg group (7.0%) compared to the 0.3 and 3-mg/kg groups (1.4% each).

Table 5: Summary of Overall Safety - Treated Subjects

	Number (%) of Subjects N = 214		
	Ipilimumab		
	0.3 mg/kg N = 72	3 mg/kg N = 71	10 mg/kg N = 71
Deaths	48 (66.7)	45 (63.4)	40 (56.3)
Within 30 days of last dose of study therapy	9 (12.5)	6 (8.5)[a]	10 (14.1)
Within 70 days of last dose of study therapy	18 (25.0)	18 (25.4)	19 (26.8)
Overall SAEs	26 (36.1)	35 (49.3)	38 (53.5)
Grade 5	15 (20.8)	14 (19.7)	15 (21.1)
Drug-related (Any Grade)	6 (8.3)	13 (18.3)	19 (26.8)
Drug-related (Grade 5)	0	0[a]	0
Drug-related AEs leading to discontinuation (Any	2 (2.8)	5 (7.0)	11 (15.5)
Drug-related (Grade 3-4)	2 (2.8)	4 (5.6)	9 (12.7)
Drug-related (Grade 5)	0	0	0
Overall AEs (Any Grade)	68 (94.4)	69 (97.2)	71 (100.0)
Drug-related AEs (Any Grade)	46 (63.9)	55 (77.5)	59 (83.1)
Drug-related AEs (Grade 3-4)	7 (9.7)	10 (14.1)[a]	19 (26.8)
Drug-related AEs (Grade 5)	0	0	0
Overall irAEs (Any Grade)	19 (26.4)	46 (64.8)	50 (70.4)
Grade 3-4	0	5 (7.0)	18 (25.4)
GI irAEs (Any Grade)	12 (16.7)	23 (32.4)	28 (39.4)
Grade 3-4	0	2 (2.8)	11 (15.5)
Liver irAEs (Any Grade)	0	0	2 (2.8)
Grade 3-4	0	0	2 (2.8)
Endocrine irAEs (Any Grade)	0	4 (5.6)	3 (4.2)
Grade 3-4	0	2 (2.8)	1 (1.4)
Skin irAEs (Any Grade)	9 (12.5)	32 (45.1)	33 (46.5)
Grade 3-4	0	1 (1.4)	3 (4.2)
Neurological irAEs (Any Grade)	0	0	1(1.4)

Table 5: Summary of Overall Safety - Treated Subjects

	Number (%) of Subjects N = 214		
	Ipilimumab		
	0.3 mg/kg N = 72	3 mg/kg N = 71	10 mg/kg N = 71
Grade 3/4	0	0	0
Other irAEs (Any Grade)	1 (1.4)	1 (1.4)	5 (7.0)

[a] [redacted] died due to treatment-related Grade 3 respiratory infection on Day 51, within 30 days of last dose date. The cause of death was specified as "other" on the Death CRF page.

Pharmacodynamic Results: Individual within-subject patterns of stool calprotectin levels over time were not consistent within treatment groups or response categories. No associations between stool calprotectin levels, SNPs or HLA genotypes and irAEs and/or clinical benefit were apparent.

Health-related Quality of Life: Most changes from baseline in HRQoL domains were small to moderate and similar change was observed in overall global health status. The trend in global health status was towards return to baseline.

CONCLUSIONS:

- Treatment with ipilimumab resulted in anti-tumor activity in subjects with advanced melanoma, of whom almost 80% had failed prior systemic therapy due to disease progression. In addition, this study demonstrated a statistically significant dose effect based on BORR, with the highest activity in the 10-mg/kg group. There were also a numerically improved median OS and 1- and 2-year survival rates at 10 mg/kg compared with 3 and 0.3 mg/kg.
- The safety profile of ipilimumab administered at doses of 0.3, 3, and 10 mg/kg was tolerable and demonstrated a manageable safety profile. Most drug-related AEs were consistent with immune-mediated events and were considered to be a consequence of the intrinsic biological activity of ipilimumab. Overall, skin irAEs (e.g., rash and pruritus) and GI irAEs (e.g., diarrhea and colitis) were the most common. There were no reports of GI or colonic perforation. irAEs were generally manageable and reversible. There was only 1 drug-related death in this study.
- The increase in BORR from 4% to 11% between the 3 and 10-mg/kg groups along with manageable safety differences between doses, suggests a more favorable benefit-risk profile for the 10-mg/kg dose. There were no responders at the 0.3-mg/kg dose; however, the low incidence of mild to moderate irAEs suggests a mild biologic effect at the 0.3-mg/kg dose.
- 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 and similar change was observed in overall global health status. The trend in global health status was towards return to baseline.

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