BRISTOL-MYERS SQUIBB COMPANY

IPILIMUMAB

Addendum 1 to Final Clinical Study Report for CA184007

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

Indication:	Unresectable, Stage III or IV advanced melanoma
Phase:	Phase 2
Study Initiation Date:	07-Dec-2005
Study Completion Date:	Last subject last visit for assessment of the primary endpoint: 01-Aug-2007; cut off for the updated survival follow-up,09-Mar-2009
Report Date:	15-Sep-2009
Document Control Number:	930038719
Previous Version(s) of this Report:	Final CSR (27-May-2008) DCN 930026874

THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:

[redacted]

Bristol-Myers Squibb Company
Wallingford, CT 06492, USA

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

Addendum 1 to 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 in Europe, North America, and South America; 115 randomized subjects (budesonide: 58; placebo: 57) were treated

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 07-Dec-2005 **CLINICAL PHASE:** 2

Study Completion Date: Last subject last visit for assessment of the primary endpoint: 01-Aug-2007; cut off for the updated survival follow-up 09-Mar-2009

INTRODUCTION: The purpose of this addendum (#1) to the CA184007 final clinical study report (CSR) is to present the updated overall survival (OS) results with a cut-off date of 09-Mar-2009. Two previous OS analyses performed with cut-off dates of 01-Aug-2007 and 01-Dec-2007 were reported in the CA184007 final CSR. The primary objective of this study was to estimate the rate of Grade ≥ 2 diarrhea in subjects with Stage III (unresectable) or Stage IV melanoma treated with intravenous ipilimumab at 10 mg/kg when given with either prophylactic oral budesonide or placebo. Estimation of OS and survival rate at 1 year, were secondary objectives. In this addendum, further updated survival through 09-Mar-2009 is reported to support the OS and survival rate endpoints.

METHODOLOGY: Whenever possible, subjects who completed participation in CA184007 were encouraged to enroll in CA184025 for further follow-up. During and through the initial closure of the CA184007 study, subjects who had not progressed during the induction or maintenance periods at the time of database lock, or who had a response of stable disease (SD) or better at Week 12 followed by progression, were offered entry into CA184025 at the investigator's discretion, where they could continue to receive reinduction or maintenance ipilimumab therapy, as the clinical setting dictated and as specified in the protocol. CA184025 was a multi-center Phase 2 study of extended treatment with ipilimumab monotherapy or continued follow up without further treatment in subjects previously enrolled in prior ipilimumab studies. The primary objective of CA184025 was to monitor the safety of ipilimumab administered either as re-induction (10 or 3 mg/kg) or maintenance therapy (0.3, 3, or 10 mg/kg). 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 addendum, data were collected in either CA184007 or in CA184025 through the 09-Mar-2009 target date.

STATISTICAL CONSIDERATIONS: The following analyses conducted for this update were not pre-specified in the core statistical analysis plan (SAP). These were added to the core SAP via an addendum and are consistent with the pre-specified analyses presented in the core SAP. Overall survival was defined for each subject 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. 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. 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 CA184007 and CA184025 estimated for each group using the Kaplan-Meier survival function evaluated at the relevant timepoint. Corresponding two-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 response categories defined by modified World Health Organization [mWHO] criteria or immune-related response (irResponse) criteria based on measurements obtained by an independent review committee (IRC) and by baseline lactate dehydrogenase (LDH) status (≤ upper limit of normal [ULN] or ≥ ULN) in the subset of subjects with M1c disease at baseline.

SUMMARY OF RESULTS: The current updated OS analysis through 09-Mar-2009 (Table 1) provides more mature follow-up than the previous analyses reported in the final CSR with cut-off dates of 01-Aug-2007 and 01-Dec-2007. As of 09-Mar-2009, survival data in the budesonide and placebo groups were current for 48 (82.8%) and 48 (84.2%) subjects, respectively, (ie, subjects who were known to have died or subjects who were known to be alive on or after 09-Mar-2009).

Table 1: Updated Overall Survival as of 09-Mar-2009 - All Randomized Subjects

	10 mg/kg Ipilimumab + Budesonide N = 58	10 mg/kg Ipilimumab + Placebo N = 57
Median Survival Follow-up (Months)	12.67	16.33
Interquartile Range (25%-75%)	5.62 - 26.35	9.07 - 26.12
Overall Survival (Months)		
Median	17.68	19.29
95% CI (b)	(6.80, ---)	(11.99, ---)
Survival Rate at 1 Year (%)	55.87	62.41
95% CI (a)	(42.71, 68.79)	(49.37, 75.07)
Survival Rate at 18 Months (%)	47.93	50.87
95% CI (a)	(34.71, 61.19)	(37.51, 64.09)
Survival Rate at 2 Years (%)	40.57	41.78
95% CI (a)	(27.12, 54.37)	(28.30, 55.46)

(a) Based on Kaplan-Meier estimation and CI computed using the bootstrap method

(b) Median and associated 2-sided 95% CIs are calculated using the method of Brookmeyer and Crowley.

(---) the statistics are not estimable due to censored observations or median not having been observed.

In the budesonide group, as of 09-Mar-2009, survival data were current for 34 (91.9%) pretreated subjects and 14 (66.7%) previously untreated subjects (ie, subjects who were known to have died or subjects who were known to be alive on or after 09-Mar-2009) and in the placebo group, survival data were current for

23 (92.0%) pretreated and 25 (78.1%) previously untreated subject. The results of the updated OS analysis as of 09-Mar-2009 by prior anti-cancer therapy are presented in Table 2. In the budesonide group, the median OS was not reached in previously untreated subjects; only the lower bound of the 95% CI could be estimated (11.73 months). In the placebo group, the median OS in the previously untreated subjects was longer than those who had received prior anti cancer therapies (30.46 months vs 14.78 months). The survival rates were higher in the previously untreated subjects than the pretreated subjects in both treatment groups.

Table 2: Updated Overall Survival, as of 09-Mar-2009 by Prior Anti-cancer Therapy - All Randomized Subjects

	10 mg/kg Ipilimumab + Budesonide	10 mg/kg Ipilimumab + Placebo
Pretreated Subjects	N = 37	N = 25
Survival Rate at 1 Year (%)	49.85	50.82
95% CI (a)	(33.33, 66.55)	(31.50, 71.11)
Survival Rate at 18 Months (%)	37.89	38.12
95% CI (a)	(22.22, 54.28)	(20.00, 57.60)
Survival Rate at 2 Years (%)	31.58	24.20
95% CI (a)	(16.47, 47.57)	(8.00, 42.78)
Overall Survival (Months)		
Median	8.48	14.78
95% CI (b)	(6.08, 22.67)	(6.64, 20.53)
Previously Untreated Subjects	N = 21	N = 32
Survival Rate at 1 Year (%)	65.93	71.35
95% CI (a)	(45.02, 85.71)	(55.24, 87.19)
Survival Rate at 18 Months (%)	65.93	60.97
95% CI (a)	(45.02, 85.71)	(43.39, 77.68)
Survival Rate at 2 Years (%)	56.51	56.62
95% CI (a)	(30.61, 80.95)	(38.35, 74.30)
Overall Survival (Months)		
Median	---	30.46
95% CI (b)	(11.73, ---)	(13.96, ---)

(a) Based on Kaplan-Meier estimation and CI computed using the bootstrap method

(b) Median and associated 2-sided 95% CIs are calculated using the method of Brookmeyer and Crowley.

(---) the statistics are not estimable due to censored observations or median not having been observed.

Overall survival by mWHO response indicated that in both the budesonide and the placebo group, long-term survival (beyond 24 months) was not limited to responders but also included subjects with SD and a few subjects with progressive disease (PD). Subjects with an unknown response were generally individuals who had rapidly progressive disease and were discontinued prior to any follow-up assessment. In the budesonide group, at 24 months, all 7 subjects with complete response (CR)/partial response (PR), 5 of the 11 subjects with SD, and 4 of the 40 subjects with PD or unknown response were known to be still alive. In the placebo group, at 24 months, 7 of the 9 subjects with CR/PR, 6 of the 11 subjects with SD, and 5 of the 40 subjects with PD or unknown response were known to be still alive.

The median OS in M1c subjects with normal LDH and elevated LDH at baseline was 14.3 months (95% CI: 6.67, --; N = 11) and 5.93 months (95% CI: 5.93, 8.54; N = 17), respectively in the budesonide group and 22.1 months (95% CI: 2.29, --; N = 13) and 9.99 months (95% CI: 1.97, 16.3; N = 16), respectively, in the placebo group.

CONCLUSIONS: For CA184007, follow-up for OS through 2 years has been completed. The median OS was 17.68 months (95% CI: 6.80, ---) in the budesonide group and 19.29 months (95% CI: 11.99, ---) in the placebo group. The 2-year survival rate was 40.6% and 41.8%, respectively.

DATE OF REPORT: 15-Sep-2009