BRISTOL-MYERS SQUIBB COMPANY

IPILIMUMAB

Addendum 1 to Final Clinical Study Report for CA184004

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

Indication:	Unresectable, Stage III or IV advanced melanoma
Phase:	Phase 2
Study Initiation Date:	16-Nov-2005
Study Completion Date:	Last subject last visit for assessment of the primary endpoint: 30-Oct-2007; cut off for the updated survival follow-up,09-Mar-2009
Report Date:	28-Oct-2009
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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:
[redacted]
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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 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 at 14 sites in 7 countries; 82 were randomized and treated with ipilimumab (3 mg/kg: 40 subjects, 10 mg/kg: 42 subjects)

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 16-Nov-2005 **CLINICAL PHASE:** 2

Study Completion Date: Last subject last visit for assessment of the primary endpoint: 30-Oct-2007; cut off for the updated survival follow-up 09-Mar-2009

INTRODUCTION: The purpose of this addendum (#1) to the CA184004 final clinical study report (CSR) is to present the updated overall survival (OS) results with a cut-off date of 09-Mar-2009.

METHODOLOGY: Whenever possible, subjects who completed participation in CA184004 were encouraged to enroll in CA184025 for further follow-up. 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. During and through the initial closure of the CA184004 study, subjects who had been non-progressors at the Week 12 tumor assessments 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. 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 CA184004 or in CA184025 through the 09-Mar-2009 cut-off 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 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. 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 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 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 follow-up for OS through 22 months has been completed for this study. The current updated OS analysis through 09-Mar-2009 (Table 1) provides more mature follow-up than the previous analysis reported in the final CSR with cut-off date of 30-Oct-2007.

As of 09-Mar-2009, in both treatment groups, except for 1 subject each, survival data were current (i.e., subjects who were known to have died or subjects who were known to be alive on or after 09-Mar-2009) for all subjects (39 [97.5%] and 41 [97.6%], respectively). For the 2 subjects without current follow-up, the last contact was ≥ 181 days.

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

	3 mg/kg Ipilimumab N = 40	10 mg/kg Ipilimumab N = 42
Median Survival Follow-up (Months)	12.17	11.20
Interquartile Range (25%-75%)	(4.96 - 23.24)	(4.67 - 22.83)
Survival Rate at 1 Year (%)	52.00	45.24
95% CI (a)	(36.59, 67.32)	(30.95, 59.52)
Survival Rate at 18 Months (%)	33.80	35.19
95% CI (a)	(19.78, 49.08)	(21.16, 49.89)
Overall Survival (Months)		
Median	12.81	11.20
95% CI (b)	(9.49, 17.64)	(6.08, 16.92)

(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 median OS was similar in the previously untreated and pretreated subjects in both treatment groups (Table 3.2). In the 3 mg/kg group, the survival rates at 1 year and 18 months were also similar in the previously untreated subjects and the pretreated subjects. In the 10 mg/kg group, the survival rate at 18 months was higher in the previously untreated subjects than the pretreated subjects (42.9% and 31.0%, respectively). However, the small number of subjects at risk, and wide CIs, precluded meaningful interpretation of such an observed difference in this small-sample Phase 2 study.

Table 3.2: Overall Survival as of 09-Mar-2009 by Prior Anti-cancer Therapy - Randomized Subjects

	3 mg/kg Ipilimumab	10 mg/kg Ipilimumab
Pretreated Subjects	N = 26	N = 28
Survival Rate at 1 Year (%)	49.23	46.43
95% CI (a)	(29.91, 68.83)	(28.57, 64.29)
Survival Rate at 18 Months (%)	32.82	30.95
95% CI (a)	(15.38, 51.92)	(14.29, 49.33)
Overall Survival (Months)		
Median	11.53	11.43
95% CI (b)	(5.98, 23.95)	(6.74, 16.92)
Previously Untreated Subjects	N = 14	N = 14
Survival Rate at 1 Year (%)	57.14	42.86
95% CI (a)	(28.57, 85.71)	(21.43, 71.43)
Survival Rate at 18 Months (%)	35.71	42.86
95% CI (a)	(14.29, 64.29)	(21.43, 71.43)
Overall Survival (Months)		
Median	13.67	10.66
95% CI (b)	(3.48, ---)	(3.38, 24.94)

(a) Based on Kaplan-Meier estimation and CIs 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.

The median OS in M1c subjects with normal LDH and elevated LDH at baseline was 17.6 months (95% CI: 9.49, --, N = 9) and 10.7 months (95% CI: 3.48, 13.9, N = 12), respectively, in the 3 mg/kg group and 19.3 months (95% CI: 11.4, --, N = 15) and 4.60 months (95% CI: 2.83, 8.18, N = 12), respectively, in the 10 mg/kg group.

CONCLUSIONS: For CA184004, 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.

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