BRISTOL-MYERS SQUIBB COMPANY

IPILIMUMAB

Addendum 1 to Final Clinical Study Report for CA184008

A Multicenter Single Arm Phase 2 Study of MDX-010 (BMS-734016) Monotherapy in Patients with Previously Treated Unresectable Stage III or IV Melanoma

Indication:	Unresectable, Stage III or IV advanced melanoma
Phase:	Phase 2
Study Initiation Date:	06-Jun-2006
Study Completion Date:	Last subject last visit for assessment of the primary endpoint: 24-Jul-2007; cut off for the updated survival follow-up, 09-Mar-2009
Report Date:	08-Sep-2009
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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:
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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 CA184008

TITLE OF STUDY: A Multicenter Single Arm Phase 2 study of MDX-010 (BMS-734016) Monotherapy in Patients with Previously Treated Unresectable Stage III or IV Melanoma

INVESTIGATORS/STUDY CENTERS: 155 subjects were treated at 50 sites in Europe and North America

PUBLICATIONS: None

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

Study Completion Date: Date of last subject last visit for assessment of the primary endpoint: 24-Jul-2007; cutoff for the updated survival follow-up was 09-Mar-2009

INTRODUCTION: The purpose of this addendum (#1) to the CA184008 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 24-Jul-2007 and 01-Dec-2007 were reported in the CA184008 final CSR. The primary objective of CA184008 was to evaluate the best overall response rate (BORR) (as defined by modified World Health Organization [mWHO] criteria) in subjects with previously treated Stage III (unresectable) or Stage IV melanoma receiving ipilimumab. 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 CA184008 were encouraged to enroll in CA184025 for further follow-up. During and through the initial closure of the CA184008 study, subjects who had not progressed during the induction or maintenance periods at the time of database lock, or who had a response of 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 CA184008 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 first dose of study therapy 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 CA184008 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 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 the first dose of study therapy, based on the most recent evidence obtained in both CA184008 and CA184025. Survival rates were calculated using the Kaplan-Meier product-limit method. Corresponding two-sided 95% bootstrap CIs were calculated. Additional plots of OS using the Kaplan-Meier product-limit method were produced by response categories defined by mWHO criteria or immune-related response (irResponse) criteria based on measurements obtained by an independent review committee (IRC).

SUMMARY OF RESULTS: The updated OS analysis through 09-Mar-2009 (Table 1) provides more mature follow-up compared to the two previous analyses performed with cut-off dates of 24-Jul-2007 and 01-Dec-2007. With the current update, the median duration of follow-up was 10.05 months (interquartile range [25-75%] of 3.81 to 26.18 months).

The survival data were current for 145 (93.6%) subjects (ie, subjects who were known to have died or subjects who were known to be alive on or after 09-Mar-2009). One-hundred and nine (70.3%) subjects were reported to have died.

Table 1: Updated Overall Survival (09-Mar-2009) - All Treated Subjects

	10 mg/kg Ipilimumab (N = 155)
Total Updated Survival Follow-up, Median (Months) Interquartile Range (25% - 75%)	10.05 (3.81 - 26.18)
Overall Survival, Median (Months) 95% CI (Months)[a]	10.22 (7.59, 16.30)
Survival Rate at 1 Year (%) 95% CI (%)[b]	47.22 (39.52, 55.11)
Survival Rate at 18 Months (%) 95% CI (%)[b]	39.38 (31.73, 47.24)
Survival Rate at 2 Years (%) 95% CI (%)[b]	32.83 (25.37, 40.49)

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

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

Overall survival by response (mWHO) indicated similar survival among subjects with complete response (CR) or partial response (PR) and subjects with SD (Figure 2). In this study, there were 9 responders; all had a BOR of PR by IRC. At 24 months, 8 of the 9 subjects with PR, 19 of the 33 subjects with SD, and 18 of the 113 subjects with PD or unknown response were known to be still alive. Subjects with an unknown response were generally individuals who had rapidly progressive disease and were discontinued prior to any follow-up assessment.

The median OS in M1c subjects who had normal lactate dehydrogenase (LDH) (N = 33) at baseline was 13.5 months (95% CI: 5.68, 27.8 and in subjects with elevated LDH at baseline (N = 53) was 4.83 months (95% CI: 3.29, 7.79).

CONCLUSIONS: For CA184008, follow-up for OS through 2 years has been completed with a median OS of 10.22 months (95% CI: 7.59, 16.30) and a 2-year survival rate of 32.8%.

DATE OF REPORT: 08-Sep-2009