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-CTLA-4		

SYNOPSIS

Addendum Clinical Study Report for Study CA184041

TITLE OF STUDY: A Randomized, Double-Blind, Parallel, Three Arm, Multicenter, Phase II Trial Evaluating the Efficacy and Safety of Ipilimumab (BMS-734016) in Combination with Taxol®/Paraplatin® (Paclitaxel/Carboplatin) Compared to Taxol®/Paraplatin® Alone in Previously Untreated Subjects with Lung Cancer

INVESTIGATORS/STUDY CENTERS: 61 study centers in United States (US), Europe and India

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 08-Feb-2008 CLINICAL PHASE: 2B

Study Completion Date: 16-Jul-2010

OBJECTIVES:

This is a clinical study report (CSR) addendum for CA184041, a Phase 2 study to evaluate ipilimumab activity in subjects with untreated non small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The purpose of this CSR addendum is to report results for candidate biomarkers of safety or efficacy (secondary objective) in subjects with NSCLC and in subjects with SCLC receiving ipilimumab in combination with concurrent paclitaxel (Taxol®)/carboplatin (Paraplatin®), ipilimumab in combination with sequential paclitaxel/carboplatin, or–paclitaxel/carboplatin alone. The primary efficacy and other secondary efficacy and safety objectives of this study were reported in the final CSR. Of note, although immune-related progression-free survival (irPFS) was analyzed in this study, the biomarker analysis focused on overall survival (OS) to be consistent with earlier studies devoid of irPFS.

METHODOLOGY:

Study CA184041 was a double-blind, randomized, parallel, 3 arm multi-center Phase 2 study. Subjects were randomized in a 1:1:1 ratio into 1 of the 3 arms, which are stratified by tumor type and study site:

- concurrent arm/Arm A (4 doses of ipilimumab with paclitaxel/carboplatin followed by 2 doses of placebo with paclitaxel/carboplatin)
- sequential arm/Arm B (2 doses of placebo with paclitaxel/carboplatin followed by 4 doses of ipilimumab with paclitaxel/carboplatin),
- control arm/Arm C (6 doses of placebo with paclitaxel/carboplatin);

Subjects experiencing clinical benefit were to continue on the blinded study drug (ipilimumab/placebo) maintenance therapy every 12 weeks until immune-related progressive disease (irPD) assessed by the investigator or until intolerable toxicity. All subjects were followed up for toxicity/progression and overall survival (OS).

NUMBER OF SUBJECTS:

All of the 203 and 128 NSCLC and SCLC treated subjects, respectively, were included in the pharmacodynamic absolute lymphocyte count (ALC) dataset, and between 34.5% and 93.6% of NSCLC subjects, and between 40.6% and 96.1% of SCLC treated subjects were included in the analysis populations for summaries and statistical analysis of derived ALC measures and their association with clinical activity (CA) or OS.

Human leukocyte antigen-A (HLA-A) and HLA-B allele frequencies and frequencies of subjects carrying each allele were summarized for all treated subjects. A genotype score for at least 1 of the 2 loci was available for 139 NSCLC and 110 SCLC subjects.

Allele and genotype frequencies for 3 single nucleotide polymorphisms (SNPs) in the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) gene were summarized for all treated subjects, as treated, with SNP data. Genotype scores for all 3 SNPs were available for 113 NSCLC and 79 SCLC subjects.

CRITERIA FOR INCLUSION:

For ALC analyses, all treated subjects who had an unambiguous date of first ipilimumab dose and at least 1 ALC evaluation during the induction-dosing period were included in the Pharmacodynamic dataset.

For HLA and CTLA-4 SNP genotyping, all samples with a valid measurement in treated patients were included in the analysis.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

Ipilimumab 10 mg/kg was administered (in the concurrent and sequential arms) as a single dose intravenously (IV) over 90 minutes every 3 weeks as part of induction. Subjects could also receive additional maintenance ipilimumab at a dose of 10 mg/kg administered IV over 90 minutes every 12 weeks starting 24 weeks after the first ipilimumab dose.

Treatment with blinded ipilimumab (active or placebo) was administered until immune-related tumor progression as defined by the immune-related response criteria (irRC) was observed or intolerable toxicity occurred.

Subjects were administered with the following vendor batches of ipilimumab:

BMS-734016 50mg vials - 6G19359, 6M14406, 6M14407, 7C35207, 7D26952, 7D24553, 7D26954, and 7H22093.

BMS-734016 200 mg - 9J49139, 9K48044, 9J49141, 6M14887, 7H23841, 7J27973, 7J27975, 8L42822, 8L42821, 9B54737, 9H39439, 9H48717, 9K48044, 9J49139, and 9B54737.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

Paclitaxel: One hundred seventy-five (175) mg/m^2 was administered as a single dose IV over 3 hours every 3 weeks (up to 6 doses). Subjects were administered with the following vendor batches of paclitaxel: 7E25167, 8D31598, 8M29143, and 8M29257.

Carboplatin: Area under the curve (AUC)=6 was administered as a single dose IV over 30 minutes every 3 weeks (up to 6 doses). Subjects were administered with the following vendor batches of carboplatin: 8D31634, 8G37593, and 8L35305.

Placebo: Matched placebo for ipilimumab was administered (in the control arm) as a single dose IV over 90 minutes every 3 weeks (up to 6 doses) as part of induction. Subjects could also receive additional maintenance placebo administered IV over 90 minutes every 12 weeks starting 24 weeks after the first placebo dose.

Treatment with paclitaxel and carboplatin was administered until immune-related tumor progression as defined by the irRC was observed or unacceptable toxicity occurred for a maximum of 6 treatment doses.

CRITERIA FOR EVALUATION:

Sample collection and consent to biomarker analyses was mandatory in this study.

Absolute lymphocyte counts (ALC) were obtained throughout the study as part of the hematology panel. Results collected from 28 days prior to the first treatment with any study medication through the end of the Induction-Dosing Period were included in the analyses of ALC.

Low resolution HLA genotyping was performed for HLA-A and HLA-B.

A 10 mL blood sample was to be collected on Day 1 for analysis of CTLA-4 polymorphisms (SNP genotyping). The following polymorphisms were analyzed: rs1863800, rs231775 and rs3087243.

For predictive biomarker analyses, a binary response measure based on immune-related best overall response (irBOR) was used. A benefit CA group included subjects with confirmed immune-related complete response (irCR), confirmed immune-related partial response (irPR), or with immune-related stable disease (irSD) ending not earlier than 24 weeks from date of first dose. A non-benefit no CA included subjects that are irPD or irSD ending earlier than 24 weeks from date of first dose.

STATISTICAL CONSIDERATIONS:

The mean change in ALC over time for each treatment group and corresponding two-sided 95% confidence intervals (CIs) were estimated using an extended (i.e., mixed) linear model that included ALC as response variable, fixed effects of treatment group, linear splines of time since first dose with knots at the dates of the induction doses, and the treatment-by-time interactions, and a spatial-exponential within-subject correlation structure. Conditional F-tests were used to assess mean ALC changes over time and the difference between treatment groups in the pattern of change in ALC over time. Fitted mean ALC versus weeks since first dose was plotted by treatment group.

The relationship between CA and rate of change in ALC over time was assessed by 4 separate analyses; using all ALC measurements from baseline through study Week 7 (pre-dose 3) for all 3 treatment arms (Slope3): using all ALC measurements from baseline through study Week 13 (pre-dose 5) for concurrent and control arms (Slope5), using all ALC measurements from study Week 7 (pre-dose 3) through study Week 13 (pre-dose 5) for sequential and control arms (Slope3-5), and using all ALC measurements from study Week 7 (pre-dose 3) through the end of study Week 18 for sequential and control arms (Slope3-7).

Distributions of baseline ACL (ALC1), Slope3, Slope5, Slope3-5 and Slope3-7 were summarized by treatment group, and frequencies and joint frequencies of selected dichotomized ALC measures were tabulated by treatment. Scatter plots of selected pairs of ALC measures were generated, by treatment.

Distributions of ALC measures were summarized by treatment and CA group. Joint frequencies of selected dichotomized ALC measures and CA group were tabulated by treatment. Linear logistic regression was used to estimate and test dependence of CA probability on each ALC measure (as a continuous-valued predictor), treatment group, and treatment-by-measure interaction. Reported odds ratios (ORs) were scaled to give the fold-change in odds of CA when increasing ALC1 by 1 unit, or Slope3, Slope5, Slope3-5 or

Slope3-7 by 0.1 units. Slope3, Slope5, Slope3-5 and Slope3-7 versus ALC1, respectively, were plotted by treatment and CA group.

Cox proportional hazards (PH) models were used to assess the dependence of OS on ALC measures. The models included the following linear predictors: ALC measure (ALC1, Slope3, Slope5, Slope3-5 or Slope3-7), treatment group, and interaction between ALC measure and treatment group. These models assumed a constant fold-change in hazard for every 1 unit change in ALC measure. Wald tests were used to test hypotheses that individual hazard ratios (HRs), or ratios of HRs, were 1. Two-sided 95% CIs were based on the Wald test statistics. Likelihood-ratio tests were used to test overall ALC-measure and interaction effects.

Low resolution HLA genotyping is expected to produce, for each patient, a pair of haplotype scores ("alleles") for HLA locus A and a pair for HLA locus B. We can refer to each pair of alleles as a genotype. Many different alleles at each locus are known to be distinguishable by the assay being used. These data were analyzed at the individual allele level, for each locus separately.

Single nucleotide polymorphism allele and genotype frequencies were tabulated. The relationships between the binary response variable (benefit versus non-benefit CA probability) and SNP genotype as well as treatment arm and treatment-arm-by-genotype interactions were investigated using logistic regression methods. Associations were summarized by point estimates and 95% CI of ORs.

SUMMARY OF RESULTS:

Of the 203 and 128 NSCLC and SCLC treated subjects, respectively, 203 and 128 (100.0%), respectively, were included in the Pharmacodynamic ALC dataset. For analyses of associations between CA, OS and ALC measures, between 34.5% and 93.6% of NSCLC subjects, and between 40.6% and 96.1% of SCLC treated subjects were available. All NSCLC treated subjects had at least 1 and up to 20 ALC evaluations during the induction-dosing period, with a median of 8. All SCLC treated subjects had at least 1 and up to 18 ALC evaluations during the induction-dosing period, with a median of 9. The distribution of number of ALC evaluations per subject was similar among treatment groups.

An extended linear model for longitudinal data was used to estimate mean ALC as a function of both time and treatment group. This model allowed the pattern of change in mean ALC over time possibly to differ among the treatment groups. The model-estimated mean ALC values at date of first ipilimumab/placebo dose were similar among the treatment groups. The mean ALC statistically increased over time in all treatment groups ($p < 0.0001$ for NSCLC subjects, $p = 0.0001$for SCLC subjects). Furthermore, the pattern of ALC change during the induction-dosing period differed significantly between the treatment groups ($p = 0.046$ for concurrent vs. placebo, $p = 0.0001$ for sequential vs. placebo for NSCLC subjects; and $p = 0.347$ for concurrent vs. placebo, $p = 0.063$ for sequential vs. placebo for SCLC subjects). Estimated mean ALC decreased considerably prior to first dose of ipilimumab or placebo in all treatment groups, and then increased over time during the induction-dosing period in the ipilimumab groups but not the placebo group.

No association was apparent between ALC1 and CA. In the concurrent group, mean (and median) ALC1, Slope3 and Slope5 and in the sequential group mean (and median) ALC1, Slope3-5 and Slope3-7 values were similar between the CA and no-CA subgroups for both NSCLC and SCLC.

Based on a Cox PH model, no significant effect of baseline ALC, treated as a continuous-valued predictor, on OS was observed in either NSCLC ($p = 0.270$) or SCLC subjects ($p = 0.418$). A similar lack of association was observed when ALC1 was dichotomized as >= 1 versus < 1.

Primarily relevant for the concurrent group, there were no statistically significant effects of Slope3 on OS ($p = 0.252$) nor for the sequential group of Slope3-5 on OS ($p = 0.198$) in NSCLC subjects, and similarly for SCLC subjects ($p = 0.145$ for Slope3 and $p = 0.243$ for Slope3-5).

Human leukocyte antigen-A (HLA-A) and HLA-B allele frequencies and frequencies of subjects carrying each allele were summarized for all treated subjects. A genotype score for at least 1 of the 2 loci was available for 139 NSCLC and 110 SCLC subjects. Sixteen (16) and 13 unique HLA-A alleles were observed in the NSCLC and SCLC subjects, respectively. Twenty-five (25) and 21 unique HLA-B alleles were observed in the NSCLC and SCLC subjects, respectively. Twenty-three (23) NSCLC and 17 SCLC subjects were homozygous for HLA-A, and 10 NSCLC and 9 SCLC for HLA-B. No clear associations between HLA allele carrier status and response were apparent.

Allele and genotype frequencies for 3 SNPs in the CTLA-4 gene - rs1863800 (assay ID AH39SFT), rs231775 (assay ID C___2415786_20), and rs3087243 (assay ID C___3296043_10) were summarized for all treated subjects, as treated, with SNP data. Genotype scores for all 3 SNPs were available for 113 NSCLC and 79 SCLC subjects. None of the SNPs was monomorphic in these samples of subjects, and minor allele frequencies ranged from 33.2% to 48.7%. An exact test of Hardy-Weinberg equilibrium (HWE) was performed for each SNP. No statistically significant departures from HWE were observed for either NSCLC or SCLC subjects.

For both NSCLC and SCLC subjects, and for both treatment comparisons, no statistically significant associations between CA and SNP genotype were observed. There was limited power to detect such associations, given the relatively small number of subjects with SNP data (ranging from 40 to 57 subjects per analysis).

CONCLUSIONS:

- Results of biomarker analyses are consistent between NSCLC and SCLC subjects.
- Mean ALC increased over time after initiation of treatment in the concurrent and sequential ipilimumab groups but not in the placebo group. The timing of the ALC increase was consistent with the schedule, i.e. at the first dose of ipilimumab.
- There was an attenuated ALC effect with no compelling evidence of association between clinical activity and rate of change in ALC for any of the treatment groups; however the ability to make statistical interpretations was limited by the small sample sizes.
- Higher ALC at baseline and the rate of change in ALC over time was not significantly associated with OS.
- No clear associations between CA and HLA-A or HLA-B allele carrier status were detected.
- No clear associations between CA or OS and the three tested CTLA-4 polymorphisms (rs1863800, rs231775 and rs3087243) were detected.

DATE OF REPORT: 16-Sep-2011