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

Final 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 US, Europe and India

PUBLICATIONS: None

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

Study Completion Date: 16-Jul-2010

OBJECTIVES:

Primary Objectives:

- To compare the immune-related progression-free survival (irPFS) of subjects receiving ipilimumab in combination with concurrent paclitaxel (Taxol®)/carboplatin (Paraplatin®) ("concurrent"; Arm A), and subjects receiving ipilimumab in combination with sequential paclitaxel/carboplatin ("sequential"; Arm B) to that of subjects receiving paclitaxel/carboplatin alone ("control"; Arm C) in Stage IIIb/IV non-small cell lung cancer (NSCLC) subjects using immune-related response criteria (irRC) as per the assessment of an independent review committee (IRC).

Secondary Objectives:

- To compare progression-free survival (PFS) for the NSCLC subjects in the concurrent arm versus control arm and the sequential arm versus control arm using modified World Health Organization (mWHO) criteria.
- To compare the irPFS and PFS for extensive small-cell lung cancer (SCLC) subjects in the concurrent arm versus control arm and sequential arm versus control arm using both irRC and mWHO criteria.
- To compare overall survival (OS) in the concurrent arm versus control arm and sequential arm versus control arm in subjects with NSCLC and SCLC.

- To compare immune-related best overall response rate (irBORR), immune-related disease control rate (irDCR), best overall response rate (BORR), disease control rate (DCR) of concurrent arm versus control arm and sequential arm versus control arm using irRC and mWHO criteria, respectively, for subjects with NSCLC and SCLC.
- To evaluate the safety profile in each arm for subjects with NSCLC and SCLC.
- To evaluate the association between safety and efficacy in subjects with NSCLC and SCLC.
- To evaluate candidate biomarkers of safety and/or efficacy in subjects with NSCLC and SCLC.
- To evaluate health-related quality of life (HRQoL) for subjects with NSCLC and SCLC.
- To evaluate blood samples for pharmacokinetic (PK) evaluation of ipilimumab trough concentrations and evaluation of human anti-human antibodies (HAHA) raised against ipilimumab.

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 OS.

NUMBER OF SUBJECTS (Planned and Analyzed): Two hundred ten subjects with NSCLC (70 subjects per arm) and 120-210 subjects with SCLC (40-70 subjects per arm) were planned to be randomized in the study. Two hundred four subjects with NSCLC (70, 68, and 66 subjects in the concurrent, sequential, and control arms, respectively) and 130 subjects with SCLC (43, 42, and 45 subjects in the concurrent, sequential, and control arms, respectively) were randomized in this study.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Men and women who were ≥18 years old and with histologically or cytologically confirmed lung cancer (Stage IIIb/IV NSCLC or extensive stage SCLC), with an Eastern Cooperative Oncology Group (ECOG) performance score ≤1, who met screening laboratory requirements, and who were previously untreated were included in the study. Subjects with a history of or current brain metastases, specific underlying autoimmune diseases (particularly gastrointestinal) or paraneoplastic syndromes related to SCLC were excluded from the study.

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 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.

Tumor assessments:

The primary endpoint of this study was irPFS by the IRC assessment. The key secondary endpoints include tumor response based endpoints such as PFS using mWHO criteria, BORR and irBORR. These endpoints were based on the assessment of an IRC. The IRC conducted an independent, centralized assessment of tumor response and progression. Tumor assessments (TAs) were performed for all subjects at screening, every 6 weeks during the treatment phase and every 12 weeks during the Maintenance phase until irPD. Subjects with irPD who were experiencing clinical benefit per investigator were to continue additional TAs until subsequent anti-cancer therapy or withdraw consent.

CRITERIA FOR EVALUATION:

Efficacy: The irRC was used as the primary efficacy evaluation of TAs. The irRC were developed based on the mWHO criteria to better capture the potential clinical benefit with immunotherapies such as ipilimumab. As a secondary efficacy evaluation of tumor response, the study also evaluated the mWHO criteria which represents a hybrid classification of the original WHO and response evaluation criteria in solid tumors (RECIST) tumor response classification system.

Final assessment of tumor response-related parameters such as irPFS and response were assessed by the IRC using irRC. The irRC, as per Investigator assessment, guided clinical care (i.e., duration of dosing) during the course of the study. The primary endpoint was PFS using irRC (as per the IRC assessment) in NSCLC. Secondary endpoints included irPFS in SCLC, and OS and response-related endpoints such as DCR, BORR, duration of response (DoR) using both the mWHO (as per IRC TA) and irRC as per IRC in both NSCLC and SCLC population groups. The PK of ipilimumab, pharmacodynamic markers of immunogenicity; HAHA, predictive biomarkers and HRQoL in NSCLC and SCLC subjects were also evaluated.

Safety: All subjects who received at least 1 dose of blinded ipilimumab (active or placebo) and/or paclitaxel/carboplatin were considered evaluable for safety parameters. Safety assessments included monitoring of adverse events (AEs), serious adverse events (SAEs), and clinical laboratory tests. Adverse events and laboratory values and other symptoms were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 by treatment arm for each tumor type. 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 5 subcategories of irAE: gastrointestinal (GI), liver, skin, endocrine, and other. A data monitoring committee (DMC) provided independent oversight for safety, study conduct, and risk-benefit-ratio.

Immunogenicity analysis: Development of HAHA was to be assessed at several time points. Three mL of blood for HAHA testing was to be drawn pre-infusion on Day 1, and prior to each subsequent ipilimumab or placebo dose and at the end of study (at least 70 days after the subject's final dose study medication). Blood samples for assessment were drawn on Day 1 (dose 1) pre-dose, dose 2 (week 4) pre-dose, dose 3 (week 7) pre-dose, dose 4 (week 10) pre-dose, dose 5 (week 13) pre-dose, and dose 6 (week 16) pre-dose. Maintenance phase assessments were to be scheduled every 12 weeks at pre-dose, and follow-up assessments were to be scheduled at least 70 days following final treatment.

Pharmacokinetics: The serum samples were analyzed for ipilimumab using enzyme-linked immunosorbent assay (ELISA). Samples for PK were to be collected at pre-infusion, on Day 1, weeks 4, 7, 10, 13, and 16 during treatment phase; every 12 weeks during maintenance phase; and at the end of study (at least 70 days after the subject's final dose of study medication).

Pharmacodynamics: Absolute lymphocyte count (ALC) was to be measured as part of the routine hematology panel prior to first infusion, and continuing throughout the treatment period or later. Change in ALC was investigated as a potential marker of immune activity, and as a potential predictor of efficacy.

Pharmacogenomic/Pharmacogenetics Variables: A 10 mL blood sample was to be collected on Day 1 for analysis of CTLA-4 polymorphisms (single nucleotide polymorphism [SNP] genotyping).

Outcomes research analysis: HRQoL reported by the subjects was measured through the use of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire (version 3) and EORTC QLQ-LC13 (lung cancer specific module), at all sites where appropriate translations were available and validated. The EORTC QLQ-C30 is a self administered, 30 item questionnaire, organized into 5 functional scales (physical, role, emotional, cognitive, and social), 3 symptom scales (fatigue, nausea and vomiting, and pain), a global health/QoL scale, and a number of single items assessing additional symptoms (dyspnea, sleep disturbance, constipation, and diarrhea). There are 15 questions within the functional scales, 7 within the symptom scales, 1 question for each of the 6 single item symptom scales, and 2 global health and QoL questions. For questions under the functional and symptom scales, subjects were to respond to each item on a 4-point Likert-type scale ranging from 1 (not at all) to 4 (very much).

STATISTICAL CONSIDERATIONS: Based on the assumption that irPFS of each arm follows an exponential distribution and hazard ratio of 0.6 (concurrent vs control arm, and sequential vs control arm), 100 irPFS events out of 140 NSCLC randomized subjects were needed to assure 90% power of detecting the treatment difference with one-sided alpha 0.1 between each ipilimumab-containing arms and control arm separately. No alpha adjustment was planned for multiplicity.

Based on the same assumptions as in NSCLC subjects using irRC, and the enrollment rate was 8-14 subjects per month, it was estimated that it will take approximately 16 months (10 months enrollment period and 6 months follow-up period) to randomize 80-140 SCLC subjects and observe approximately 57-100 irPFS events in concurrent and sequential arms (in sequential and controls). This provided 74%-90% power to demonstrate a statistically significant improvement in irPFS between concurrent and control (similarly between sequential and control) with one-sided alpha of 0.1

All time to event endpoints including irPFS, PFS, OS, DoR, and immune-related duration of response (irDoR) were evaluated by treatment arm for each tumor type. The survival probabilities were estimated using Kaplan-Meier (KM) product limit method, medians with corresponding 2-sided 95% confidence intervals (CIs) were reported using the method of Brookmeyer and Crowley. Kaplan-Meier curves were plotted by treatment arm for each tumor type. For each tumor type, HRs (for irPFS, PFS, and OS) and the corresponding 2-sided 95% CI were constructed for the concurrent arm vs control arm and for the sequential arm vs control arm. For each tumor type, the log-rank test with 1 sided alpha of 0.1 was performed to compare irPFS, PFS, and OS in the concurrent arm versus control arm and in the sequential arm vs control arm. No alpha adjustment for multiple comparisons was planned. Safety was summarized and listed for all treated subjects using NCI CTCAE version 3.0 by treatment arm for each tumor type.

There were multiple database locks during the course of the study. The data lock for the primary endpoint irPFS occurred on 23-Dec-2009, denoted as ia07 lock, when partial unblinding occurred for only NSCLC subjects at treatment arm level for the purpose of planned primary analysis.

The study continued with investigators, subjects and the sponsor remained blinded. The final database lock occurred on 27-Aug-2010, denoted as fa01 lock, when the remaining endpoints in this study (irPFS in the subjects with SCLC, and OS in NSCLC and SCLC study population) matured and unblinding code at subject level for both tumor types were available to sponsors.

An ad hoc database lock for OS update lock for both NSCLC and SCLC cohorts occurred on 05-Jan-2011, denoted as fa02 lock, in order to obtain updated survival status on the remaining subjects in the study. Survival update based on the this ad hoc fa02 lock are also included in this report

IrPFS and PFS in NSCLC were based on ia07 lock (23-Dec-2009) and all other efficacy and safety endpoints in this report were based on the final lock, fa01 lock (27-Aug-2010).

SUMMARY OF RESULTS IN SUBJECTS WITH NSCLC:

Disposition of Subjects:

A total of 270 subjects were enrolled at 61 sites across US, Europe, and India between February 2008 and February 2009. Two-hundred and four (204) subjects were randomized to the 3 treatments arms (70 subjects in the concurrent arm, 68 subjects in the sequential arm, and 66 subjects in the control arm). One subject who was randomized to the sequential arm was administered with ipilimumab at the first dose of chemotherapy (as in the concurrent arm) erroneously. This subject was considered under the concurrent arm for all safety analyses accounting for 71 subjects in the concurrent arm and 67 subjects in the sequential arm. However, for all efficacy analyses, the subject was considered under sequential arm accounting for 70 subjects in the concurrent arm and 68 subjects in the sequential arm. One subject who was randomized to the control arm was never treated due to unknown reasons (Table 1).

The majority of non-randomized subjects (51/66) were not randomized because they no longer met study criteria.

Table 1: Subject Disposition - NSCLC

	Concurrent Arm	Sequential Arm	Control Arm	Total
Enrolled	--	--	--	270
Randomized	70	68	66	204
Treated	71[a]	67	65	203
Still on treatment	3 (4.2)	2 (3.0)	1 (1.5)	6 (3.0)
Off treatment	68 (95.8)	65 (97.0)	64 (98.5)	197 (97.0)
Reason Off Treatment (>5%)				
Disease Progression	33 (46.5)	34 (50.7)	30 (46.2)	97 (47.8)
Death	13 (18.3)	9 (13.4)	12 (18.5)	34 (16.7)
Completed Treatment in Treatment Phase	7 (9.9)	6 (9.0)	9 (13.8)	22 (10.8)
Adverse event	7 (9.9)	4 (6.0)	3 (4.6)	14 (6.9)
Other	4 (5.6)	4 (6.0)	3 (4.6)	11 (5.4)

[a] One subject randomized to sequential arm was treated according to the concurrent arm. This subject is included in the sequential arm for efficacy (randomized) and in the concurrent arm for dosing and safety (treated).

Percentages are based on the number of subjects treated.

Baseline/Demographic Characteristics:

Of the total randomized NSCLC subject population (N=204), 151 (74%) subjects were men and 53 (26%) subjects were women. Most subjects were white (82.4%) with a median age of 61 years. Majority of subjects had an ECOG performance status of 1 (72.9%, 63.2%, and 77.3% of subjects in concurrent, sequential, and control arms, respectively) and most (84.3%, 89.7, and 74.2% of subjects in concurrent, sequential, and control arms, respectively) were at Stage IV at study entry. Most subjects (50%, 44.1%, and 57.6% of subjects in the concurrent, sequential, and control arms, respectively) had adenocarcinoma at baseline. The demography and subject characteristics were consistent across the 3 treatment arms, except for ECOG performance status and disease stage at study entry (Table 2). The baseline characteristics were consistent to what was reported in prior studies performed at similar settings.

Table 2: Demography and Subject Characteristics - Randomized NSCLC Subjects

CHARACTERISTIC	10 MG/KG IPILIMUMAB + CONCURRENT PACLITAXEL/ CARBOPLATIN N = 70	10 MG/KG IPILIMUMAB + SEQUENTIAL PACLITAXEL/ CARBOPLATIN N = 68	PLACEBO + PACLITAXEL/ CARBOPLATIN N = 66	TOTAL N = 204
	NUMBER OF SUBJECTS (%)			
Gender				
FEMALE	17 (24.3)	19 (27.9)	17 (25.8)	53 (26.0)
MALE	53 (75.7)	49 (72.1)	49 (74.2)	151 (74.0)
Race				
ASIAN	10 (14.3)	10 (14.7)	10 (15.2)	30 (14.7)
BLACK/AFRICAN AMERICAN	1 (1.4)	2 (2.9)	2 (3.0)	5 (2.5)
OTHER: HISPANIC	1 (1.4)	0	0	1 (0.5)
WHITE	58 (82.9)	56 (82.4)	54 (81.8)	168 (82.4)
Age (Years)				
N	70	68	66	204
Mean (SD)	60.3 (10.12)	60.6 (10.45)	60.6 (10.16)	60.5 (10.19)
Median	59.0	61.0	62.0	61.0
Min - Max	36.0 - 82.0	36.0 - 88.0	36.0 - 82.0	36.0 - 88.0
< 65	44 (62.9)	44 (64.7)	40 (60.6)	128 (62.7)
>= 65	26 (37.1)	24 (35.3)	26 (39.4)	76 (37.3)
Disease Stage at Study Entry				
STAGE IIIB	11 (15.7)	7 (10.3)	17 (25.8)	35 (17.2)
STAGE IV	59 (84.3)	61 (89.7)	49 (74.2)	169 (82.8)
Cell Type				
ADENOCARCINOMA	35 (50.0)	30 (44.1)	38 (57.6)	103 (50.5)
BRONCHO-ALVEOLAR CARCINOMA	1 (1.4)	1 (1.5)	0	2 (1.0)
LARGE CELL CARCINOMA	6 (8.6)	11 (16.2)	7 (10.6)	24 (11.8)
OTHER	6 (8.6)	4 (5.9)	3 (4.5)	13 (6.4)
SQUAMOUS CELL CARCINOMA	21 (30.0)	21 (30.9)	15 (22.7)	57 (27.9)
UNKNOWN	1 (1.4)	1 (1.5)	3 (4.5)	5 (2.5)
ECOG Performance Status				
0	19 (27.1)	25 (36.8)	15 (22.7)	59 (28.9)
1	51 (72.9)	43 (63.2)	51 (77.3)	145 (71.1)

Extent of Exposure in Subjects with NSCLC:

The extent of exposure to the study medication was consistent in subjects across the 3 treatment arms.

Ipilimumab: In the concurrent arm, all subjects received at least 1 dose of active ipilimumab during the study. In the sequential arm, of the 67 treated subjects, 59 subjects received at least 1 subsequent dose of active ipilimumab. In the concurrent and sequential arms, the median number of active ipilimumab doses per subject (for subjects who received at least 1 dose of active ipilimumab) was 4. In the overall study period, of the subjects who received at least 1 active ipilimumab dose, 53.4% and 46.3% of subjects in the concurrent and sequential arms, respectively, had at least 4 doses of active ipilimumab. Subjects may have received less than 4 induction doses if one or more ipilimumab or and/or placebo doses were skipped.

In the control arm, all 65 subjects received at least 1 dose of placebo with a median number of 6 doses per subject during the study. In the overall study period, 2 subjects received more than 10 doses of placebo.

Twenty-three (23) subjects in the concurrent arm and 24 subjects in the sequential arm received at least 1 dose of active ipilimumab in the maintenance phase (range=1 to 8 doses in concurrent arm and 1 to 7 doses in sequential arm). Twenty-five (25) subjects in the control arm received at least 1 dose of placebo in the maintenance phase (range=1 to 7 doses).

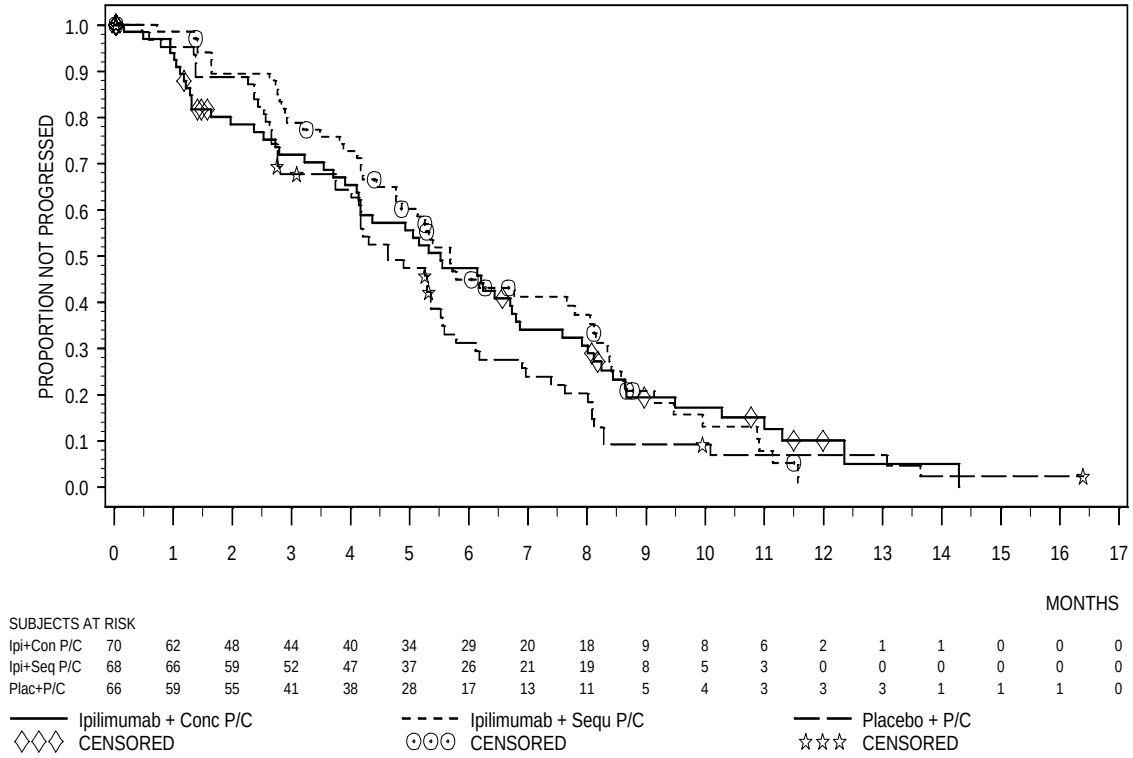
Paclitaxel and Carboplatin: All subjects (71 subjects in the concurrent arm, 67 subjects in the sequential arm, and 65 subjects in control arm) received at least 1 dose paclitaxel/carboplatin during the study; with a median dose of 4, 5, and 6 doses per subject in concurrent, sequential, and control arms, respectively. About 60.6%, 85.1%, and 70.8% of subjects in the concurrent, sequential, and control arms, respectively, received at least 4 doses of paclitaxel; and 60.6%, 83.6%, and 72.3% of subjects in the concurrent, sequential, and control arms, respectively, received at least 4 doses of carboplatin.

Efficacy Results in Subjects With NSCLC:

In subjects with NSCLC, the efficacy results were assessed by the IRC. The following were the key efficacy findings (Tables 3 and 4):

- The study met one of the co-primary objectives and improved irPFS per IRC assessment in sequential arm compared with control arm (HR=0.724, log-rank P=0.0473). The irPFS was not significantly different between concurrent arm and control arm at one-sided alpha 0.1 level, the other co-primary objective.
- Progression free survival using mWHO criteria per IRC assessment was statistically significantly longer in the sequential arm compared to the control arm (HR=0.691, log-rank P=0.0240). No significant difference was observed between the concurrent and the control arms at one-sided alpha 0.1 level.
- There was a numeric trend in OS improvement for the comparison between sequential arm and control arm based on lock dated 27-Aug-2010 though the study was not powered to detect the difference between arms. The OS analysis based on lock dated 05-Jan-2011, was consistent with the earlier analysis, with a median OS of 12.22 months in the sequential arm compared to the control arm (median OS=8.28 months) (HR=0. 866, log-rank P=0.2340).
- IrBORR and BORR, were numerically higher in sequential arm vs control arm (Table 4).

Figure 1: Kaplan-Meier Plot of IRC-Determined irPFS - Randomized NSCLC Subjects



GROUP	# OF EVENTS / # OF SUBJECTS	MEDIAN (95% CI)
Ipilimumab + Conc P/C	55/70	5.52 (4.17 - 6.74)
Ipilimumab + Sequ P/C	54/68	5.68 (4.76 - 7.79)
Placebo + P/C	56/66	4.63 (4.14 - 5.52)

LIBRARY: /wwbdm/data/ca/184/041/ia07/blinded/analysis EXTRACT DATE: 22-DEC-2009
PROGRAM SOURCE: /wwbdm/clin/proj/ca/184/core/val/stats/sasprogs/analysis/kmplot.sas RUN DATE: 29-Dec-2010 18:20

Note: Results as per 27-Aug-2010 data lock.

Table 3: Summary of Efficacy Results in NSCLC (Time to Event Endpoints) - Randomized NSCLC Subjects

Efficacy Parameter	Treatment Arm		
	Arm A Ipilimumab+ Concurrent P/C (N=70)	**Arm B Ipilimumab+ Sequential P/C (N=68) [a]**	**Arm C Placebo+ P/C (N=66)**
Primary Endpoint IRC irPFS			
No. (%) of Events	55 (78.6)	54 (79.4)	56 (84.8)
Median irPFS (months) (95% CI)	5.52 (4.17, 6.74)	5.68 (4.76, 7.79)	4.63 (4.14, 5.52)
Hazard ratio (vs control) (95% CI)	0.806 (0.553, 1.174)	0.724 (0.495, 1.059)	--
Log-rank P value (vs. control)	0.1302	0.0473	--
Secondary Endpoint			
IRC PFS per mWHO			
No. (%) of Events	58 (82.9)	56 (82.4)	61 (92.4)
Median PFS (months) (95% CI)	4.11 (2.76, 5.32)	5.13 (4.17, 5.72)	4.21 (2.76, 5.32)
Hazard ratio (vs control) (95% CI)	0.882 (0.612, 1.271)	0.691 (0.478, 0.999)	--
Log-rank P value (vs. control)	0.2502	0.0240	--
OS (Predefined final analysis dated 27-Aug-2010)			
No. (%) of Events	51 (72.9)	51 (75.0)	51 (77.3)
Median OS (months) (95% CI)	9.69 (7.59, 12.48)	12.22 (9.26, 14.39)	8.28 (6.80, 12.39)
Hazard ratio (vs. control) (95% CI)	0.988 (0.669, 1.460)	0.866 (0.587, 1.278)	--
Log-rank P value (vs. control)	0.4759	0.2340	--

[a] One subject randomized to sequential arm was treated according to the concurrent arm. This subject is included in the sequential arm for efficacy (randomized) and in the concurrent arm for dosing and safety (treated).

Abbreviations: CI=confidence interval; IRC=independent review committee; irPFS=immune-related progression-free survival; mWHO=modified World Health Organization; OS=overall survival; PFS=progression-free survival.

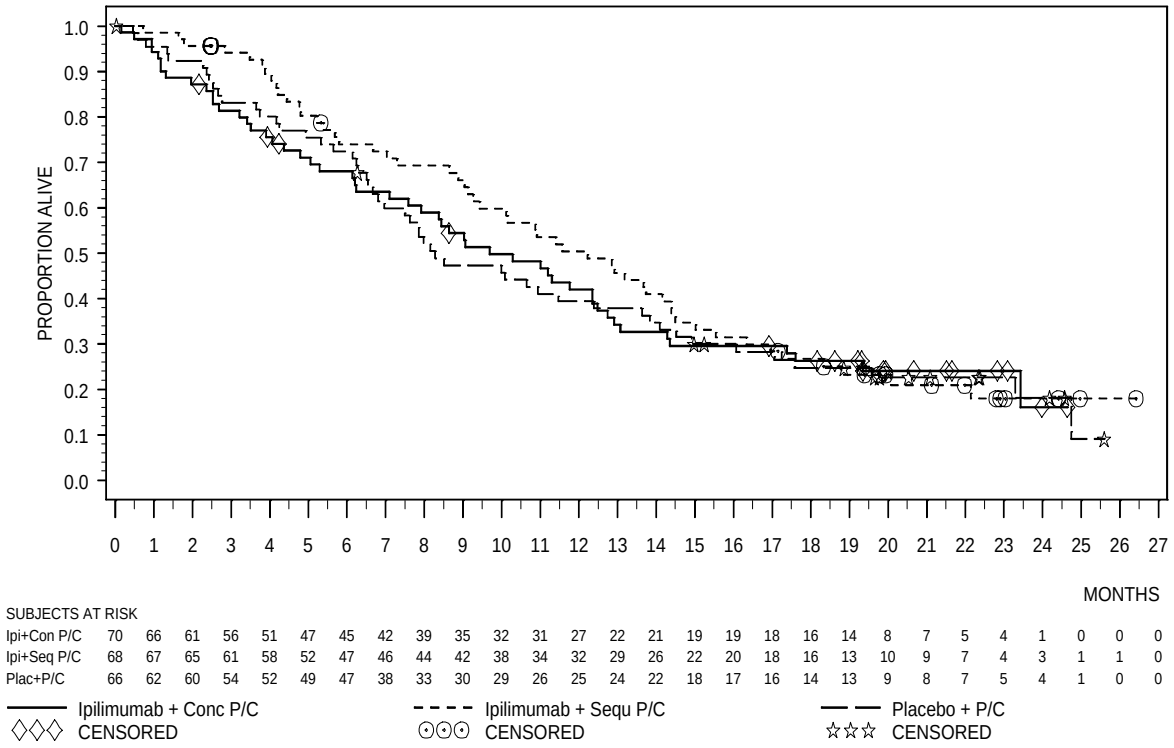
Table 4: Summary of Efficacy Results in NSCLC (Other Secondary Endpoints) - Randomized NSCLC Subjects

Efficacy Parameter	Treatment Arm		
	Arm A Ipilimumab+ Concurrent P/C (N=70)	**Arm B Ipilimumab+ Sequential P/C (N=68)[a]**	**Arm C Placebo+ P/C (N=66)**
Secondary Endpoints			
Tumor Response per irResponse Criteria			
irBORR, N (%) (95% CI)	15 (21.4) (12.5, 32.9)	22 (32.4) (21.5, 44.8)	12 (18.2) (9.8, 29.6)
irDCR, N (%) (95% CI)	49 (70.0) (57.9, 80.4)	59 (86.8) (76.4, 93.8)	54 (81.8) (70.4, 90.2)
irDoR Median in months (95% CI)	6.70 (4.21, 8.51)	5.55 (4.27, 6.74)	4.01 (4.01, 5.72)
Tumor Response per mWHO			
BORR, N (%) (95% CI)	15 (21.4) (12.5, 32.9)	22 (32.4) (21.5, 44.8)	9 (13.6) (6.4, 24.3)
DCR, N (%) (95% CI)	40 (57.1) (44.7, 68.9)	53 (77.9) (66.2, 87.1)	48 (72.7) (60.4, 83.0)
DoR Median in months (95% CI)	5.42 (4.21, 7.43)	5.55 (4.27, 6.74)	4.01 (3.94, 5.59)

[a] One subject randomized to sequential arm was treated according to the concurrent arm. This subject is included in the sequential arm for efficacy (randomized) and in the concurrent arm for dosing and safety (treated).

Abbreviations: CI=confidence interval; BORR= best overall response rate; DCR= disease control rate; DoR=duration of response; irBORR=immune-related best overall response rate; irDCR=immune-related disease control rate; irDoR=immune-related duration of response; mWHO=modified World Health Organization.

Figure 2: Kaplan-Meier Plot of Overall Survival - Randomized NSCLC Subjects



GROUP	# OF DEATHS / # OF SUBJECTS	MEDIAN (95% CI)
Ipilimumab + Conc P/C	51/70	9.69 (7.59 - 12.5)
Ipilimumab + Sequ P/C	51/68	12.2 (9.26 - 14.4)
Placebo + P/C	51/66	8.28 (6.80 - 12.4)

LIBRARY: /wwbdm/data/ca/184/041/fa01/blinded/analysis EXTRACT DATE: 17-AUG-2010
PROGRAM SOURCE: /wwbdm/clin/proj/ca/184/core/val/stats/sasprogs/analysis/kmplot.sas RUN DATE: 30-Dec-2010 11:17

Safety Results in Subjects with NSCLC:

The toxicity profile of ipilimumab combined with carboplatin/paclitaxel was consistent with safety data from single agent ipilimumab and known toxicities for carboplatin/paclitaxel, with only marginally added toxicity. The addition of carboplatin/paclitaxel did not change the spectrum, incidence, or severity of irAEs associated with ipilimumab. Furthermore, toxicities typically associated with chemotherapy (e.g., peripheral neuropathy, hematologic toxicity) were not increased in the ipilimumab-containing arms compared with the control arm. The safety profiles of both the sequential and concurrent schedules were similar (Table 5). Key safety findings included the following:

- Almost all treated subjects reported at least 1 on-study AE (100%, 95.5%, 98.5% of subjects in the concurrent, sequential, and control arms, respectively) regardless of the relationship to the study treatment; of which 56.3%, 53.7%, and 40% of subjects in the concurrent, sequential, and control arms, respectively had AEs of Grade 3-4 toxicity. AEs of Grade 5 toxicity were reported in 28.2%, 22.4%, and 27.7% of subjects in the concurrent, sequential, and control arms, respectively. Most Grade 5 AE were unrelated to study drug, and consistent with disease progression.
- Most common AEs regardless of the relationship to the study treatment (≥35% of subjects) reported across the 3 treatment arms were alopecia (38.0%, 47.8%, 47.7% of subjects in the concurrent, sequential, and control arms, respectively), fatigue (36.6%, 38.8%, 36.9% of subjects in the concurrent, sequential, and control arms, respectively).
- Drug-related AEs of any grade were reported in 78.9% of subjects in the concurrent arm, 83.6% of subjects in the sequential arm, and 83.1% of subjects in the control arm. The most commonly reported drug-related AEs of any grade across the 3 treatment arms were skin and subcutaneous tissue disorders and GI disorders.
- Drug-related AEs leading to discontinuation of any or all of the study drugs were reported in 22.5% of subjects in the concurrent arm, 10.4% subjects in the sequential arm, and 12.3% of subjects in the control arm. Most common (≥25% of subjects) drug-related AEs leading to discontinuation across the 3 treatment arms were alopecia, nausea, fatigue and diarrhea.
- SAEs of any grade regardless of the relationship to the study treatment were reported in 69.0% of subjects in the concurrent arm, 53.7% of subjects in the sequential arm and 50.8% of subjects in the control arm. Diarrhea was the most common SAE reported during the study for subjects in the concurrent (9.9% of subjects) and sequential arm (7.5% of subjects); and malignant lung neoplasm (7.7% of subjects) was the most common SAE reported in the control arm. Drug-related SAEs of any grade were reported in 28.2%, 19.4%, and 16.9% of subjects in the concurrent, sequential, and control arms, respectively.
- During the study 73.2%, 74.6%, and 78.5% of subjects in concurrent, sequential, and control arms, respectively died. Disease progression was the most common primary reason for death across all treatment arms.
    - Five deaths were considered related to treatment with study drugs (i.e., deaths either with the reason as study drug toxicity, or as Grade 5 SAE considered related to study drug). In the concurrent arm, 1 subject died due to toxic epidermal necrolysis and 1 subject due to disease progression, both events were considered to be study drug related by the investigator. In the sequential arm, 1 subject died due to erysipelas, and in the control arm, 1 subject died due to febrile neutropenia and hypotension and 1 subject died due to pulmonary hemorrhage.
    - In addition, 2 subjects experienced a drug-related SAE leading to death which the investigators reported as Grade 3 events: 1 Grade 3 erythema multiforme in the concurrent arm; and 1 Grade 3 monoplegia and Grade 4 meningitis, suspicious of Guillain-Barre Syndrome, in the sequential arm. However, the sponsor considered these deaths to be likely related to the event.
- IrAEs of any grade were reported in 64.8%, 65.7%, and 55.4% of subjects in the concurrent, sequential, and control arms, respectively. The most common irAEs were skin related, followed by GI irAE and liver irAE. Endocrine and neurological irAEs were rare, regardless of the toxicity grade. Most skin related irAEs were of lower toxicity grade.

- Skin irAEs of ≥Grade 3 were reported in 5.6%, 3% and 1.5% of subjects in the concurrent, sequential, and control arms, respectively, and were mostly alopecia and rash. GI irAEs ≥Grade 3 were observed in 7%, 6%, and 3.1% in the concurrent, sequential, and control arm, respectively, and was mostly diarrhea. Liver irAEs ≥Grade 3 were reported in 2.8%, 3%, and 0% of subjects, and were mostly increased levels of AST and ALT (Table 6).
- Typical chemotherapy-related toxicities (occurring in more than 15% of cases in the control arms were only marginally increased in the ipilimumab containing arms. (Table 7).

Table 5: Summary of Safety by Treatment Group - NSCLC Subjects

	Number of subjects (%) Worst CTC grade.....		
	Ipilimumab+ Concurrent P/C (N=71)[a]	**Ipilimumab+ Sequential P/C (N=67)**	**Placebo+P/C (N=65)**
Death	52 (73.2)	50 (74.6)	51 (78.5)
Within 30 Days of Last Dose of Study Therapy	11 (15.5)	7 (10.4)	8 (12.3)
Within 70 Days of Last Dose of Study Therapy	21 (29.6)	16 (23.9)	18 (27.7)
SAEs	49 (69.0)	36 (53.7)	33 (50.8)
Grade 3	17 (23.9)	16 (23.9)	9 (13.8)
Grade 4	10 (14.1)	4 (6.0)	5 (7.7)
Grade 5	20 (28.2)	15 (22.4)	18 (27.7)
Drug Related	20 (28.2)	13 (19.4)	11 (16.9)
Drug Related (Grade 5)	2 (2.8)	1 (1.5)	2 (3.1)
AEs Leading to Discontinuation	28 (39.4)	19 (28.4)	15 (23.1)
Drug Related (Any Grade)	16 (22.5)	7 (10.4)	8 (12.3)
Drug Related (Grade 3)	9 (12.7)	6 (9.0)	4 (6.2)
Drug Related (Grade 4)	1 (1.4)	0	0
Drug Related (Grade 5)	1 (1.4)	0	1 (1.5)
AEs	71 (100)	64 (95.5)	64 (98.5)
Grade 3-4	40 (56.3)	36 (53.7)	26 (40.0)
Drug Related (Any Grade)	56 (78.9)	56 (83.6)	54 (83.1)
Drug Related (Grade 3-4)	29 (40.8)	26 (38.8)	24 (36.9)
Drug Related (Grade 5)	2 (2.8)	1 (1.5)	2 (3.1)

[a] One subject randomized to sequential arm was treated according to the concurrent arm. This subject is included in the sequential arm for efficacy (randomized) and in the concurrent arm for dosing and safety (treated).

Abbreviations: AE=adverse event; C=carboplatin; CTC=common toxicity criteria; GI=gastrointestinal; P=paclitaxel; SAE=serious adverse event.

Table 6: Immune-Related Adverse Events in ≥5% of Subjects with NSCLC

	Number of subjects (%) Worst CTC grade								
	Concurrent Arm (N=71)			Sequential Arm (N=67)			Control Arm (N=65)		
	Total	Gr 3	Gr 4	Total	Gr 3	Gr 4	Total	Gr 3	Gr 4
Any irAE	46 (64.8)	13 (18.3)	1 (1.4)	44 (65.7)	7 (10.4)	0	36 (55.4)	4 (6.2)	0
Skin and subcutaneous tissue disorders	40 (56.3)	3 (4.2)	0	36 (53.7)	2 (3.0)	0	32 (49.2)	1 (1.5)	0
Alopecia	24 (33.8)	0	0	30 (44.8)	0	0	30 (46.2)	0	0
Rash	20 (28.2)	2 (2.8)	0	9 (13.4)	2 (3.0)	0	6 (9.2)	1 (1.5)	0
Pruritus	12 (16.9)	0	0	5 (7.5)	0	0	4 (6.2)	1 (1.5)	0
GI	21 (29.6)	5 (7.0)	0	16 (23.9)	4 (6.0)	0	12 (18.5)	2 (3.1)	0
Diarrhoea	21 (29.6)	5 (7.0)	0	15 (22.4)	3 (4.5)	0	11 (16.9)	2 (3.1)	0
Investigations	5 (7.0)	2 (2.8)	0	7 (10.4)	1 (1.5)	2 (3.0)	2 (3.1)	2 (3.1)	2 (3.1)
ALT increased	4 (5.6)	2 (2.8)	0	5 (7.5)	1 (1.5)	0	2 (3.1)	2 (3.1)	2 (3.1)
AST increased	4 (5.6)	2 (2.8)	0	4 (6.0)	0	0	2 (3.1)	2 (3.1)	2 (3.1)
Immune System Disorders	4 (5.6)	2 (2.8)	1 (1.4)	3 (4.5)	0	1 (1.5)	1 (1.5)	1 (1.5)	0

Note: An immune-related adverse event (irAE) is defined as any adverse event associated with drug exposure and consistent with an immune-mediated event.

Abbreviation: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTC=common toxicity criteria; GI=gastrointestinal; Gr=grade; irAE=immune related adverse event.

Table 7: Most Common Drug-Related Adverse Events (≥15%) - NSCLC Subjects

	Concurrent Arm (N=71)[a]			Sequential Arm (N=67)			Placebo Arm (N=65)		
	Total N (%)	**Gr 3 N (%)**	**Gr 4 N (%)**	**Total N (%)**	**Gr 3 N (%)**	**Gr 4 N (%)**	**Total N (%)**	**Gr 3 N (%)**	**Gr 4 N (%)**
Alopecia	24 (33.8)	0	0	30 (44.8)	0	0	30 (46.2)	0	0
Nausea	19 (26.8)	1 (1.4)	0	22 (32.8)	1 (1.5)	0	21 (32.3)	1 (1.5)	0
Fatigue	20 (28.2)	5 (7.0)	1 (1.4)	16 (23.9)	3 (4.5)	0	17 (26.2)	3 (4.6)	0
Diarrhea	21 (29.6)	5 (7.0)	0	15 (22.4)	3 (4.5)	0	11 (16.9)	2 (3.1)	0
Vomiting	13 (18.3)	1 (1.4)	0	12 (17.9)	1 (1.5)	0	11 (16.9)	1 (1.5)	0
Constipation	4 (5.6)	0	0	6 (9.0)	0	0	10 (15.4)	1 (1.5)	0
Arthralgia	11 (15.5)	0	0	9 (13.4)	1 (1.5)	0	7 (10.8)	0	0
Peripheral Sensory Neuropathy[b]	6 (8.5)	0	0	13 (19.4)	0	0	8 (12.3)	0	0
Peripheral Neuropathy[b]	10 (14.1)	1 (1.4)	0	7 (10.4)	0	0	16 (24.6)	1 (1.5)	0
Anemia	16 (22.5)	3 (4.2)	0	16 (23.9)	3 (4.5)	0	15 (23.1)	5 (7.7)	0
Neutropenia	10 (14.1)	2 (2.8)	7 (9.9)	10 (14.9)	1 (1.5)	0	14 (21.5)	6 (9.2)	4 (6.2)
Thrombocytopenia	10 (14.1)	3 (4.2)	3 (4.2)	11 (16.4)	4 (6.0)	0	10 (15.4)	4 (6.2)	1 (1.5)
Deaths Due to Study Drug Toxicity, N (%)		2 (2.8)			1 (1.5)			2 (3.1)	

[a] One subject randomized to sequential arm was treated according to the concurrent arm. This subject is included in the sequential arm for efficacy (randomized) and in the concurrent arm for dosing and safety (treated).

[b] As reported by the investigators (standardized MedDRA query term scope). There is no overlapping between the events of peripheral neuropathy and peripheral sensory neuropathy.

Note: The drug-related AEs selected were ≥15% in the control arm in either NSCLC, SCLC or both population groups.
Abbreviations: ipi=ipilimumab.

Immunogenicity Results in Subjects with NSCLC: The impact of immunogenicity on the safety and efficacy of ipilimumab was evaluated in subjects who developed a positive HAHA response, as it may be related to the frequency and type of infusion-related AEs, anaphylaxis, hypersensitivity, overall AEs (serious and non-serious), and discontinuations. In the subjects with NSCLC, 11 (8%) subjects in the ipilimumab-containing arms were tested positive for anti-ipilimumab antibodies at any time point. Eight (8) of these 11 subjects had positive baseline measurements which did not increase further during the study. Of the 8 subject who presented with positive titers at baseline and who did not increase further, 2 subjects experienced Grade 1 itching, exanthema or rash during treatment with ipilimumab and chemotherapy, and 2 subjects reported Grade 2 itching during treatment with ipilimumab and chemotherapy. Ipilimumab was not discontinued for any of these events. For 4 subjects, no AEs suggestive of hypersensitivity were reported. The safety profile of the 11 subjects with positive measurements at any time point was not different from subjects with negative titers. Both the proportion of subjects testing positive at any time point (8%), as well as the proportion of subject who developed a positive titer after a negative baseline assessment or had increasing titers (2.5%) was consistent with observations in previous studies.

Pharmacokinetic Results in Subjects with NSCLC:

Geometric mean ipilimumab steady-state trough concentrations appeared consistent across treatments. The population PK analysis will be presented in a separate report.

Pharmacodynamic Results with NSCLC:

The pharmacodynamic analysis results will be presented in a separate addendum report.

Other Study Results in Subjects with NSCLC:

Pharmacogenomic Analyses: The SNP and ALC analyses results will be presented in a separate addendum report.

Outcome Research Assessments: Compliance rates for the EORTC QLQ-C30 and EORTC QLQ-LC13 assessments were high at baseline (91-95% and 87-91%, respectively) and were above 50% through week 24 for all three NSCLC study arms.

The mean changes in global health status/QoL score as per the EORTC QLQ-C30 assessment, at week 24, mean changes in global health status/QoL score were -1.4, 2.9, and 3.0 for the concurrent, sequential and control arms, respectively; and reflect that HRQoL was maintained at 24 weeks.

As per the EORTC QLQ-LC13 assessments, at week 24, mean changes in dyspnea, coughing, hemoptysis, dysphagia, pain in chest, pain in arm, and pain in other parts were minimal to moderate improvement from baseline across all 3 treatment arms. Mean changes in alopecia and peripheral neuropathy worsened from baseline across all 3 study arms.

SUMMARY OF RESULTS IN SUBJECTS WITH SCLC:

Disposition of Subjects

A total of 164 subjects were enrolled at 61 sites across US, Europe, and India between February 2008 and August 2009. One-hundred and thirty (130) subjects were randomized to the 3 treatment arms (43 subjects in the concurrent arm, 42 subjects in the sequential arm, and 45 subjects in the control arm). Two (2) subjects who were randomized to concurrent and control arms were never treated for unknown reasons (Table 8).

Nearly all non-randomized subjects (33/34) were not randomized because they no longer met study criteria.

Table 8: Subject Disposition - SCLC

	Concurrent Arm	Sequential Arm	Control Arm	Total
Enrolled	--	--	--	164
Randomized	43	42	45	130
Treated	42	42	44	128
Still on treatment	2 (4.8)	0	1 (2.3)	3 (2.3)
Off treatment	40 (95.2)	42 (100.0)	43 (97.7)	125 (97.7)
Reason Off Treatment (> 5%)				
Disease Progression	14 (33.3)	27 (64.3)	23 (52.3)	64 (50.0)
Death	10 (23.8)	4 (9.5)	3 (6.8)	17 (13.3)
Completed Treatment in Treatment Phase	7 (16.7)	7 (16.7)	9 (20.5)	23 (18.0)
Adverse event	3 (7.1)	2 (4.8)	4 (9.1)	9 (7.0)

Percentages are based on the number of subjects treated

Baseline/Demographic Characteristics:

Of the total SCLC subject population (N=130), 98 subjects were men (75.4%) and 32 subjects were women (24.6%). Most subjects (97.7%) were white with a median age of 58 years. Most subjects (99.2%) at study entry had extensive stage disease (all subjects in both concurrent and sequential arms, and 97.8% of subjects in the control arm). One subject in the control arm had recurrent disease at study entry. Most

subjects (75.4%) had an ECOG performance status of 1 (79.1%, 73.8%, and 73.3% of subjects in concurrent, sequential, and control arms, respectively). Treatment arms were well balanced except for ECOG performance status and The demography and subject characteristics were similar across all the 3 treatment arms except for lesser number of elderly population (ie., subjects with >65 years of age) in the control arm (Table 9). The baseline characteristics were otherwise consistent to what was reported in prior studies performed at similar settings.

Table 9: Demography and Subject Characteristics - Randomized SCLC Subjects

CHARACTERISTIC	10 MG/KG IPILIMUMAB + CONCURRENT PACLITAXEL/ CARBOPLATIN N = 43	10 MG/KG IPILIMUMAB + SEQUENTIAL PACLITAXEL/ CARBOPLATIN N = 42	PLACEBO + PACLITAXEL/ CARBOPLATIN N = 45	TOTAL N = 130
	NUMBER OF SUBJECTS (%)			
Gender				
FEMALE	10 (23.3)	10 (23.8)	12 (26.7)	32 (24.6)
MALE	33 (76.7)	32 (76.2)	33 (73.3)	98 (75.4)
Race				
ASIAN	1 (2.3)	0	0	1 (0.8)
BLACK/AFRICAN AMERICAN	1 (2.3)	0	0	1 (0.8)
OTHER: HISPANIC	0	0	1 (2.2)	1 (0.8)
WHITE	41 (95.3)	42 (100.0)	44 (97.8)	127 (97.7)
Age (Years)				
N	43	42	45	130
Mean (SD)	58.0 (7.34)	58.9 (8.65)	58.8 (7.54)	58.5 (7.80)
Median	57.0	58.5	58.0	58.0
Min - Max	44.0 - 80.0	43.0 - 80.0	42.0 - 82.0	42.0 - 82.0
< 65	35 (81.4)	29 (69.0)	36 (80.0)	100 (76.9)
>= 65	8 (18.6)	13 (31.0)	9 (20.0)	30 (23.1)
Disease Stage at Study Entry				
EXTENSIVE	43 (100.0)	42 (100.0)	44 (97.8)	129 (99.2)
RECURRENT DISEASE	0	0	1 (2.2)	1 (0.8)
Cell Type				
OTHER	2 (4.7)	2 (4.8)	0	4 (3.1)
SMALL CELL CARCINOMA	41 (95.3)	38 (90.5)	45 (100.0)	124 (95.4)
UNKNOWN	0	1 (2.4)	0	1 (0.8)
NOT REPORTED	0	1 (2.4)	0	1 (0.8)
ECOG Performance Status				
0	8 (18.6)	11 (26.2)	12 (26.7)	31 (23.8)
1	34 (79.1)	31 (73.8)	33 (73.3)	98 (75.4)
2	1 (2.3)	0	0	1 (0.8)

Extent of Exposure in Subjects with SCLC:

The extent of exposure to the study medication was consistent in subjects across the 3 treatment arms.

Ipilimumab/placebo: In the concurrent arm all 42 subjects received at least 1 dose of active ipilimumab during the study. In the sequential arm, of the 42 treated subjects, 41 subjects received at least 1 dose of subsequent dose of active ipilimumab. In the concurrent and sequential arms, the median number of active ipilimumab doses per subject was 4. In the overall study period, of the subjects who received at least 1 active ipilimumab dose, 61.9% and 66.7% of subjects in the concurrent and sequential arms, respectively had at least 4 doses of active ipilimumab. Subjects may have received less than 4 induction doses if one or more ipilimumab or and/or placebo doses were skipped.

In the control arm, all 44 subjects received at least 1 dose of placebo with 6 doses as median per subject during the study. In the overall study period, 1 subject received more than 10 doses of placebo.

Twelve subjects in the concurrent arm and 15 subjects in the sequential arm received at least 1 dose of active ipilimumab in the maintenance phase (range=1 to 8 doses in concurrent arm and 1 to 3 doses in sequential arm). Fourteen subjects in the control arm received at least 1 dose of placebo in the maintenance phase (range=1 to 5 doses).

Paclitaxel and Carboplatin: All subjects (42 subjects in the concurrent arm, 42 subjects in the sequential arm, and 44 subjects in the control arm) received at least 1 dose paclitaxel/carboplatin during the study; with a median dose of 5 per subject in the concurrent arm and 6 doses per subject each in the sequential and control arms. About 69%, 95.2%, and 86.4% of subjects in the concurrent, sequential, and control arms, respectively, received at least 4 doses of paclitaxel and carboplatin.

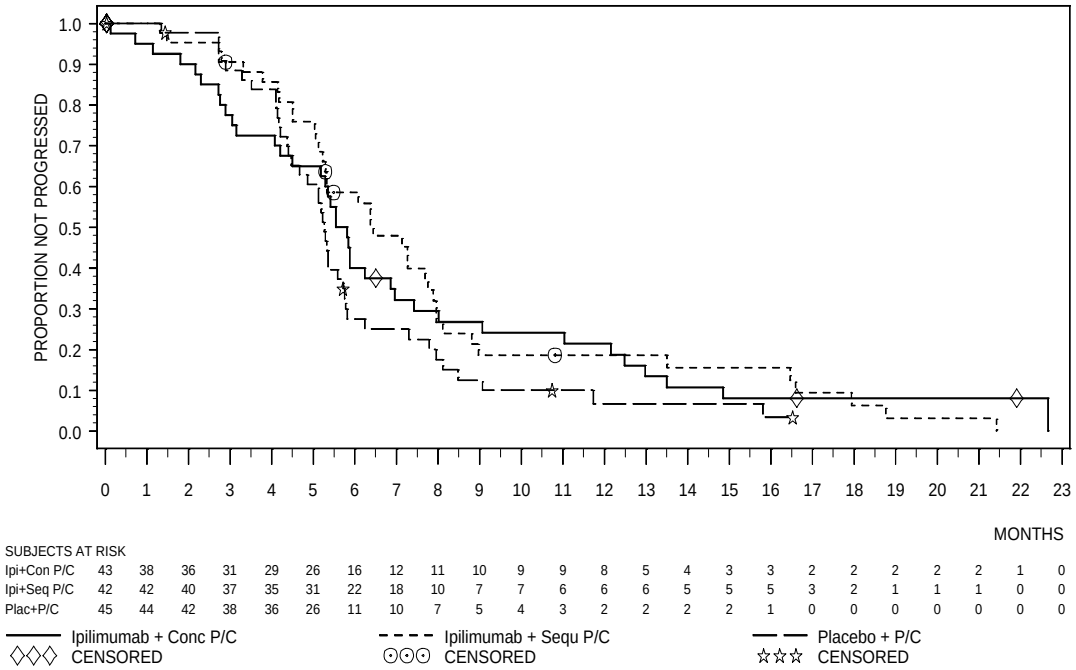
Efficacy Results in Subjects With SCLC:

In subjects with SCLC, the efficacy results were assessed by the IRC using irRC and mWHO criteria. All efficacy endpoints for the SCLC cohort were secondary. Analyses in subjects with SCLC subjects were not powered for any efficacy endpoints comparison between ipilimumab-containing arms and control arm. The following were the key efficacy findings (Table 10):

- Ipilimumab in combination with paclitaxel/carboplatin, when given in the sequential schedule significantly prolonged irPFS compared with paclitaxel/carboplatin alone (median irPFS was 6.44 vs 5.26 months, HR=0.640, log-rank P=0.0282). There was no statistically significant improvement in irPFS in the concurrent arm at one-sided alpha 0.1 level (Figure 3).
- PFS assessed using mWHO criteria criteria was not significantly different between either of the ipilimumab containing treatment arms and placebo arm at one-sided alpha 0.1 level.
- There was a trend for an improvement of OS in the sequential arm (12.94 months vs 9.92 months in the control arm; HR=0.753). (Figure 4). The median OS during the updated analysis (as of 05-Jan-2011) was consistent with the results observed at 27-Aug-2010 cutoff; with HR of 0.756 in sequential vs control arm.

The IrBORR, irDCR, BORR and DCR are summarized in the Table 11.

Figure 3: Kaplan-Meier Plot of IRC-Determined irPFS - Randomized SCLC Subjects



GROUP	# OF EVENTS / # OF SUBJECTS	MEDIAN (95% CI)
Ipilimumab + Conc P/C	37/43	5.68 (5.19 - 6.87)
Ipilimumab + Sequ P/C	38/42	6.44 (5.29 - 7.75)
Placebo + P/C	40/45	5.26 (4.67 - 5.72)

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Note: Results as per 27-Aug-2010 data lock.

Table 10: Summary of Efficacy Results in SCLC (Time to Event Secondary Endpoints) - Randomized SCLC Subjects

Efficacy Parameter	Treatment Arm		
	Concurrent Arm (N=43)	Sequential Arm (N=42)	Control Arm (N=45)
IRC irPFS per irRC			
No. (%) of Events	37 (86.0)	38 (90.5)	40 (88.9)
Median irPFS (months) (95% CI)	5.68 (5.19, 6.87)	6.44 (5.29, 7.75)	5.26 (4.67, 5.72)
Hazard ratio (95% CI) (vs. control)	0.751 (0.475, 1.188)	0.640 (0.403, 1.016)	--
Log-rank P value (vs. control)	0.1098	0.0282	--
IRC PFS per mWHO criteria			
No. (%) of Events	37 (86.0)	39 (92.9)	40 (88.9)
Median PFS (months) (95% CI)	3.89 (2.89, 5.85)	5.22 (4.14, 6.57)	5.19 (4.40, 5.59)
Hazard ratio (95% CI) (vs. control)	0.933 (0.588, 1.481)	0.927 (0.591, 1.453)	--
Log-rank P value (vs. control)	0.3846	0.3700	--
OS (Predefined final analysis dated 27-Aug-2010)			
No. (%) of Events	33 (76.7)	31 (73.8)	35 (77.8)
Median OS (months) (95% CI)	9.13 (6.67, 12.98)	12.94 (7.89, 16.46)	9.92 (8.64, 11.73)
Hazard ratio (95% CI) (vs. control)	0.947 (0.585, 1.536)	0.753 (0.461, 1.232)	--
Log-rank P value (vs. control)	0.4132	0.1287	--

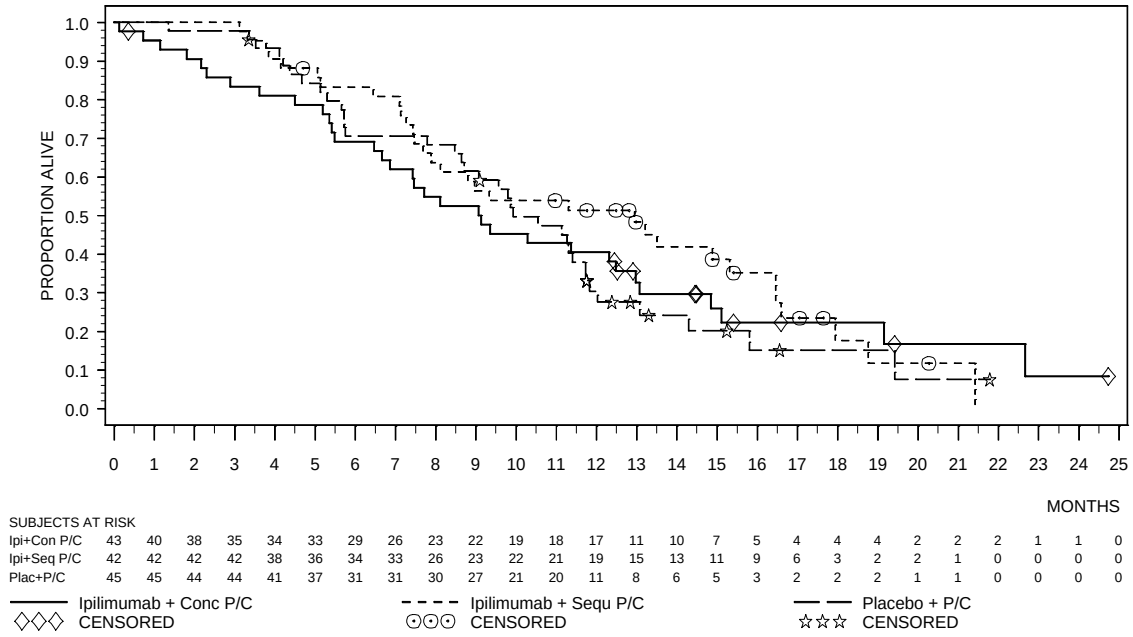
Abbreviations: CI=confidence interval; IRC=independent review committee; irPFS=immune-related progression-free survival; OS=overall survival; PFS=progression-free survival.

Table 11: Summary of Efficacy Results in SCLC (Other Secondary Endpoints) - Randomized SCLC Subjects

Efficacy Parameter	Treatment Arm		
	Concurrent Arm (N=43)	**Sequential Arm (N=42)**	**Control Arm (N=45)**
Secondary End points			
Tumor Response per irRC			
irBORR, N (%) (95% CI)	21 (48.8) (33.3, 64.5)	30 (71.4) (55.4, 84.3)	24 (53.3) (37.9, 68.3)
irDCR, N (%) (95% CI)	35 (81.4) (66.6, 91.6)	39 (92.9) (80.5, 98.5)	43 (95.6) (84.9, 99.5)
irDoR, Median in months (95% CI)	5.95 (4.53, 10.8)	5.78 (4.44, 6.67)	4.21 (3.91, 6.41)
Tumor Response per mWHO criteria			
BORR, N (%) (95% CI)	14 (32.6) (19.1, 48.5)	24 (57.1) (41.0, 72.3)	22 (48.9) (33.7, 64.2)
DCR, N (%) (95% CI)	30 (69.8) (53.9, 82.8)	34 (81.0) (65.9, 91.4)	42 (93.3) (81.7, 98.6)
DoR, Median in months (95% CI)	7.62 (4.90, 11.1)	5.78 (3.94, 6.57)	4.21 (3.91, 5.95)

Abbreviations: CI=confidence interval; BORR= best overall response rate; DCR= disease control rate; DoR=duration of response; irBORR=immune-related best overall response rate; irDCR=immune-related disease control rate; irDoR=immune-related duration of response; irRC=immune-related response criteria.

Figure 4: Kaplan-Meier Plot of Overall Survival - Randomized SCLC Subjects



GROUP	# OF DEATHS / # OF SUBJECTS	MEDIAN (95% CI)
Ipilimumab + Conc P/C	33/43	9.13 (6.67 - 13.0)
Ipilimumab + Sequ P/C	31/42	12.9 (7.89 - 16.5)
Placebo + P/C	35/45	9.92 (8.64 - 11.7)

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PROGRAM SOURCE: /wwbdm/clin/proj/ca/184/core/val/stats/sasprogs/analysis/kmplot.sas RUN DATE: 30-Dec-2010 11:17

Safety Results in Subjects with SCLC:

The toxicity profile of ipilimumab combined with paclitaxel/carboplatin in subjects with SCLC was consistent with safety data observed in subjects with SCLC. The safety profiles of both the sequential and concurrent schedules were similar (Table 12). Key safety findings included the following:

- Almost all treated subjects reported at least 1 on-study AE (97.6%, 95.2%, 97.7% of subjects in the concurrent, sequential, and control arms, respectively) regardless of the relationship to the study drug; of which 45.2%, 52.4%, and 43.2% of subjects in the concurrent, sequential, and control arms, respectively had AEs of Grade 3-4 toxicity. Adverse events of Grade 5 toxicity were reported in 28.6%, 16.7%, and 15.9% of subjects in the concurrent, sequential, and control arms, respectively. All but one Grade 5 AE were unrelated to study drug, and consistent with disease progression.
- Most common AEs regardless of the relationship to the study treatment, reported across the 3 treatment arms were alopecia (57.1%, 69%, and 63.6% of subjects in the concurrent, sequential, and control arms, respectively) and fatigue (35.7% of subjects each in concurrent and sequential arms, and 43.2% in the control arm).
- Drug-related AEs of any grade were reported in 85.7% of subjects in the concurrent arm, 95.2% of subjects in the sequential arm, and 90.9% of subjects in the control arm. The most commonly reported drug-related AEs of any grade across the 3 treatment arms were the skin and subcutaneous tissue disorders.
- Drug-related AEs leading to discontinuations were reported in 21.4% of subjects in the concurrent arm, 16.7% subjects in the sequential arm, and 15.9% of subjects in the control arm. Most common (≥25% of subjects) drug-related AEs leading to discontinuation across the 3 treatment arms were alopecia and fatigue.
- Serious adverse events of any grade regardless of the relationship to the study treatment were reported in 59.5% of subjects in the concurrent arm, 50% of subjects in the sequential arm, and 45.5% of subjects in the control arm. Malignant lung neoplasm was the most common SAE reported across the 3 treatment arms. Drug-related SAEs of any grade were reported in 23.8%, 28.6%, and 13.6% of subjects in the concurrent, sequential, and control arms, respectively.
- During the study 78.6%, 73.8%, and 79.5% of subjects in concurrent, sequential, and control arms, respectively died. Disease progression was the most common primary reason for death across all treatment arms. In the concurrent arm, one related Grade 5 SAE of hepatotoxicity was reported. No study drug related deaths were reported in the sequential or control arm.
- Immune-related adverse events of any grade were reported in 71.4%, 88.1%, and 70.5% of subjects in the concurrent, sequential, and control arms, respectively. The most common irAEs were skin related, followed by GI irAE and liver irAE. Endocrine and neurological irAEs were rare, regardless of the toxicity grade. Most skin related irAEs were of lower toxicity grade.
- Skin irAEs of ≥ Grade 3 were reported in 9.5%, 2.4% and 2.3% in the concurrent, sequential, and control arms, respectively, and were mostly alopecia, rash, and pruritus. GI irAEs ≥Grade 3 were observed in 4.8%, 11.9%, and 4.5% in the concurrent, sequential, and control arms, respectively, and was mostly diarrhea. Liver irAEs ≥Grade 3 were reported in 11.4%, 4.8%, and 0%, and were mostly increased levels of AST and ALT (Table 13).
- Typical chemotherapy-related toxicities occurring in more than 15% of cases in the control arm were only marginally increased in the ipilimumab containing arms (Table 14)

Table 12: Summary of Safety by Treatment Group - SCLC Subjects

	Number of subjects (%) Worst CTC Grade.....		
	Concurrent Arm (N=42)	**Sequential Arm (N=42)**	**Control Arm (N=44)**
Death	33 (78.6)	31 (73.8)	35 (79.5)
Within 30 Days of Last Dose of Study Therapy	6 (14.3)	2 (4.8)	1 (2.3)
Within 70 Days of Last Dose of Study Therapy	13 (31.0)	7 (16.7)	8 (18.2)
SAEs	25 (59.5)	21 (50.0)	20 (45.5)
Grade 3	7 (16.7)	6 (14.3)	4 (9.1)
Grade 4	3 (7.1)	4 (9.5)	4 (9.1)
Grade 5	12 (28.6)	7 (16.7)	7 (15.9)
Drug Related	10 (23.8)	12 (28.6)	6 (13.6)
Drug Related (Grade 5)	1 (2.4)	0	0
AEs Leading to Discontinuation	14 (33.3)	13 (31.0)	12 (27.3)
Drug Related (Any Grade)	9 (21.4)	7 (16.7)	7 (15.9)
Drug Related (Grade 3)	3 (7.1)	3 (7.1)	4 (9.1)
Drug Related (Grade 4)	2 (4.8)	2 (4.8)	0
Drug Related (Grade 5)	1 (2.4)	0	0
AEs	41 (97.6)	40 (95.2)	43(97.7)
Grade 3-4	19 (45.2)	22 (52.4)	19 (43.7)
Drug Related (Any Grade)	36 (85.7)	40 (95.2)	40 (90.9)
Drug Related (Grade 3-4)	18 (42.9)	21 (50.0)	13 (29.5)
Drug Related (Grade 5)	1 (2.4)	0	0

Abbreviations: AE=adverse event; C=carboplatin; GI=gastrointestinal; irAE=immune-related adverse events; P=paclitaxel; SAE=serious adverse event.

Table 13: Immune-Related Adverse Events in ≥5% of Subjects with SCLC

	Number of subjects (%) Worst CTC grade								
	Concurrent Arm (N=42)			Sequential Arm (N=42)			Control Arm (N=44)		
	Total	Gr 3	Gr 4	Total	Gr 3	Gr 4	Total	Gr 3	Gr 4
Any irAE	30 (71.4)	7 (16.7)	2 (4.8)	37 (88.1)	5 (11.9)	2 (4.8)	31 (70.5)	4 (9.1)	0
Skin and subcutaneous tissue disorders	29 (69.0)	4 (9.5)	0	31 (73.8)	1 (2.4)	0	28 (63.6)	1 (2.3)	0
Alopecia	24 (57.1)	0	0	28 (66.7)	0	0	26 (59.1)	0	0
Rash	15 (35.7)	2 (4.8)	0	10 (23.8)	0	0	1 (2.3)	0	0
Pruritus	10 (23.8)	0	0	8 (19.0)	1 (2.4)	0	2 (4.5)	0	0
GI	13 (31.0)	1 (2.4)	1 (2.4)	16 (38.1)	5 (11.9)	0	10 (22.7)	2 (4.5)	0
Diarrhoea	11 (26.2)	1 (2.4)	1 (2.4)	14 (33.3)	4 (9.5)	0	7 (15.9)	2 (4.5)	0
Stomatitis	4 (9.5)	0	0	1 (2.4)	0	0	3 (6.8)	0	0
Investigations	6 (14.3)	3 (7.1)	0	4 (9.5)	0	1 (2.4)	1 (2.3)	1 (2.3)	0
AST increased	4 (9.5)	2 (4.8)	0	4 (9.5)	1 (2.4)	0	0	0	0
ALT increased	4 (9.5)	2 (4.8)	0	3 (7.1)	0	1 (2.4)	0	0	0
Nervous System Disorders	1 (2.4)	0	0	3 (7.1)	0	0	2 (4.5)	0	0
Hepatobilary Disorders	3 (7.1)	0	1 (2.4)	1 (2.4)	0	1 (2.4)	0	0	0

Note: An immune-related adverse event (irAE) is defined as any adverse event associated with drug exposure and consistent with an immune-mediated event.

Abbreviation: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTC=common toxicity criteria; GI=gastrointestinal; Gr=grade; irAE=immune related AE.

Table 14: Most Common Drug-Related Adverse Events (≥15%)[a] - SCLC Subjects

	Concurrent Arm (N=42)			Sequential Arm (N=42)			Control Arm (N=44)		
	%								
	Total	**Gr 3**	**Gr 4**	**Total**	**Gr 3**	**Gr 4**	**Total**	**Gr 3**	**Gr 4**
Alopecia	24 (57.1)	0	0	28 (66.7)	0	0	26 (59.1)	0	0
Arthralgia	10 (23.8)	0	0	19 (45.2)	4 (9.5)	0	14 (31.8)	0	0
Fatigue	13 (31.0)	3 (7.1)	0	12 (28.6)	5 (11.9)	0	11 (25.0)	2 (4.5)	0
Nausea	10 (23.8)	0	0	12 (28.6)	0	0	10 (22.7)	1 (2.3)	0
Diarrhea	11 (26.2)	1 (2.4)	1 (2.4)	14 (33.3)	4 (9.5)	0	7 (15.9)	2 (4.5)	0
Vomiting	4 (9.5)	0	0	5 (11.9)	0	0	4 (9.1)	0	1 (2.3)
Constipation	4 (9.5)	0	0	3 (7.1)	0	0	4 (9.1)	0	0
Peripheral Sensory Neuropathy[b]	10 (23.8)	0	0	14 (33.3)	0	0	14 (31.8)	0	0
Peripheral Neuropathy[b]	6 (14.3)	0	0	10 (23.8)	0	0	5 (11.4)	0	0
Thrombocytopenia	5 (11.9)	2 (4.8)	0	6 (14.3)	1 (2.4)	2 (4.8)	8 (18.2)	2 (4.5)	0
Anemia	11 (26.2)	1 (2.4)	0	11 (26.2)	3 (7.1)	0	7 (15.9)	3 (6.8)	1 (2.3)
Neutropenia	11 (26.2)	5 (11.9)	1 (2.4)	9 (21.4)	5 (11.9)	2 (4.8)	6 (13.6)	1 (2.3)	2 (4.5)
Deaths Due to Study Drug Toxicity (N, %)		1 (2.4)			0			0	

[a] The drug-related AEs selected were ≥15% in the control arm in either NSCLC, SCLC or both population groups.

[b] As reported by the investigators (standardized MedDRA query term scope). There is no overlapping between the events of peripheral neuropathy and peripheral sensory neuropathy.

Abbreviations: Chemo=chemotherapy; Gr=grade; ipi=ipilimumab.

Immunogenicity Results in Subjects with SCLC: The impact of immunogenicity on the safety and efficacy of ipilimumab was evaluated in subjects who developed a positive HAHA response, especially as it may be related to the frequency and type of infusion-related AEs, anaphylaxis, hypersensitivity, overall AEs (serious and non-serious), and discontinuations. In subjects with SCLC, a total of 5 (6%) subjects in the ipilimumab-containing arms were tested positive for anti-ipilimumab antibodies at any time point. Three of these 5 subjects already had positive baseline measurements which did not further increase. Two subjects had a negative baseline assessment but tested positive after ipilimumab treatment. Of the 3 subjects who presented with positive titers at baseline, 1 subject experienced Grade 3 itching, which did not lead to discontinuation of study drugs. The other 2 subjects did not experience any symptoms suggestive of a hypersensitivity reaction. Overall, the safety profile in subjects with positive titers at any time point is similar to the subjects who tested negative at all time points. Both the proportion of subjects testing positive at any time point (6%), as well as the proportion of subjects who developed an positive titer after a negative baseline assessment (2.6%) is consistent with observations in previous studies

Pharmacokinetic Results in Subjects with SCLC:

Geometric mean ipilimumab steady-state trough concentrations appeared consistent across treatments. The population PK analysis will be presented in a separate report.

Pharmacodynamic Results in Subjects with SCLC:

The pharmacodynamic analysis results will be presented in a separate addendum report

Other Study Results in Subjects with SCLC:

Pharmacogenomic Analyses: The SNP and ALC analyses results will be presented in a separate addendum report

Outcome Research Assessments: As the sample size was too small, no analysis was conducted for subjects with SCLC.

CONCLUSIONS:

In both NSCLC and SCLC populations, ipilimumab in combination with paclitaxel/carboplatin administered in the sequential schedule demonstrated improved irPFS compared with paclitaxel/carboplatin alone. In both cohorts, tumor response assessed using irRC (irBORR) and mWHO criteria criteria (BORR) was numerically higher in both the concurrent and sequential arms compared to the control arm, with the highest levels of response in the sequential arm. Also, survival results trends were in favor of ipilimumab in the sequential schedule in subjects with NSCLC and SCLC.

The overall rates of most general safety parameters (SAEs, AEs, etc) were higher in the concurrent and sequential arms as this was an add-on study. Ipilimumab did not result in any new toxicity in combination with paclitaxel/carboplatin in either population group and did not demonstrate any considerable impact on the toxicity profile associated with paclitaxel/carboplatin. The irAEs associated with ipilimumab were similar to what has been observed with ipilimumab monotherapy.

The results show that ipilimumab can be combined with a platinum doublet in NSCLC and SCLC, with an acceptable and manageable safety profile. The results provide justification to further clinical development of ipilimumab, in a sequential schedule[1], in subjects with NSCLC and SCLC.

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[1] As predefined in the protocol and SAP, the schedule in which ipilimumab is initiated together with the 3rd cycle of chemotherapy was called "sequential schedule". Note that, in future documents, we will call this schedule "phased", to better reflect the scheduling of drugs throughout this schedule, and to differentiate this schedule from other schedules which may be truly "sequential" (i.e. ipilimumab started at the end of chemotherapy).