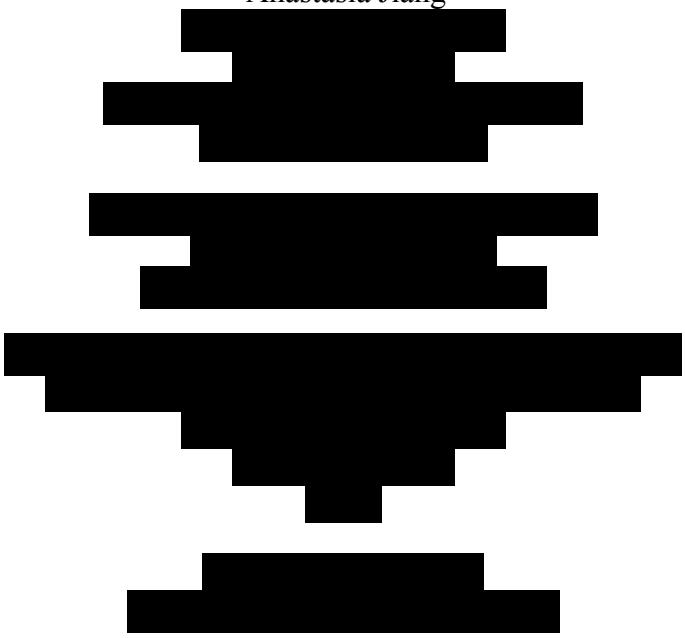
Protocol Number: CA184153
IND Number: N/A
Ex-US Non-IND
EUDRACT Number 2014-002604-25
Date: 18-Jan-2012
Revised Date 11-Dec-2014

Clinical Protocol CA184153

A Randomized, Multicenter, Double-Blind, Multinational, Phase 3 Trial Comparing the Efficacy of Ipilimumab in Addition to Paclitaxel and Carboplatin versus Placebo in Addition to Paclitaxel and Carboplatin in Subjects with Stage IV/Recurrent Non-Small Cell Lung Cancer (NSCLC) with Squamous Histology

Revised Protocol Number: 02
Incorporates Administrative Letter 01 and Amendment 02

Study Director/Central Medical Monitor
Anastasia Jiang



Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 02	11-Dec-2014	Incorporates Amendment 02 and Administrative Letter 01
Amendment 02	11-Dec-2014	[redacted] In addition changes have been made to address minor inconsistencies and to provide additional clarity.
Administrative Letter 01	01-Jul-2014	The purpose of this administrative letter is to correct the protocol title and assign a EUDRACT number to the study.
Revised Protocol 01	19-May-2014	Incorporates Amendment(s) 01
Amendment 01	19-May-2014	The purpose of this amendment is to align the CA184153 protocol with the CA184104 protocol (update the study Primary Endpoint, modify Secondary Endpoints, implement a dosing limit of ipilimumab in the study to 3 years, and incorporate other minor changes for consistency and clarity). Immune-related response endpoints will be removed due to inherent challenges in data collection to support these analyses, and lack of validation of immune-related endpoints in Phase 2. Section numbering and section titles have been updated in some instances, due to section deletions and/or modification of endpoints. Additional changes have been made to address minor inconsistencies and to provide additional clarity. Additional standard BMS wording per the most recent version of the BMS Clinical Protocol Template has been added.
Original Protocol	18-Jan-2012	Not applicable

SYNOPSIS

Clinical Protocol CA184153

Protocol Title: A Randomized, Multicenter, Double-Blind, Phase 3 Trial Comparing the Efficacy of Ipilimumab in Addition to Paclitaxel and Carboplatin versus Placebo in Addition to Paclitaxel and Carboplatin in Subjects with Stage IV/Recurrent Non-Small Cell Lung Cancer (NSCLC) with Squamous Histology.

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

Ipilimumab 10 mg/kg IV or placebo, Induction: q 3 weeks for up to 4 doses starting at Cycle 3, Maintenance: q 12 weeks for eligible subjects, for a maximum treatment period of 3 years from the first dose of blinded study therapy.

Paclitaxel 175 mg/m^2 IV q 3 weeks for up to 6 doses starting at Day 1.

Carboplatin AUC = 6 IV q 3 weeks for up to 6 doses starting at Day 1.

Noninvestigational Product(s), Dose and Mode of Administration, Duration of Treatment with Noninvestigational Product(s):

Not applicable.

Study Phase: 3

Research Hypothesis: Among subjects with Stage IV (per the 7th IASLAC- International Association for the Study of Lung Cancer - classification) or recurrent non-small cell lung cancer (NSCLC) of squamous histology, who are treated with paclitaxel, carboplatin and blinded study therapy, overall survival in subjects assigned to treatment with phased ipilimumab will be superior to overall survival in subjects assigned to treatment with phased placebo.

Objectives:

Primary Objective: To compare Overall Survival (OS) of subjects with Stage IV/recurrent NSCLC of squamous histology who have been randomized to ipilimumab in addition to paclitaxel and carboplatin versus placebo in addition to paclitaxel and carboplatin, and have received at least one dose of blinded study therapy.

Secondary Objectives:

- Compare OS among all randomized subjects between the 2 treatment arms,
- Compare Progression-Free Survival (PFS) per mWHO among all randomized subjects who received at least one dose of blinded study therapy,
- Compare selected efficacy endpoints only for randomized Chinese subjects (ie, Chinese subset among all randomized subjects),
  - OS among all randomized Chinese subjects,
  - OS among all randomized Chinese subjects who received at least one dose of blinded study therapy,
  - PFS per mWHO among all randomized Chinese subjects who received at least one dose of blinded study therapy,

  between the 2 treatment arms.

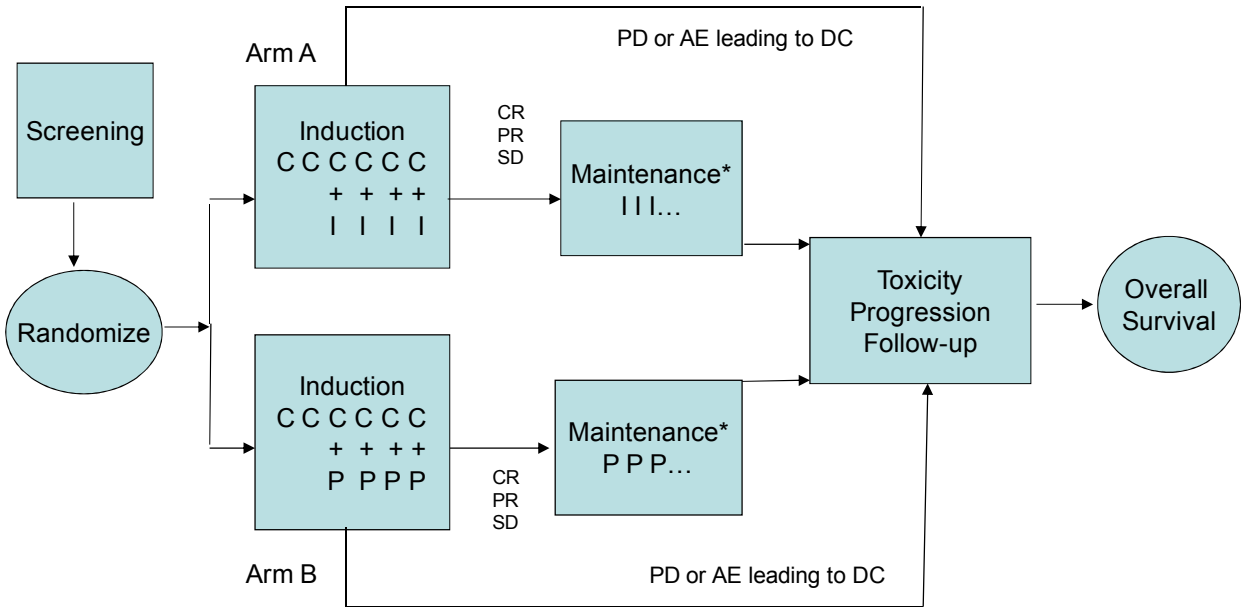
Study Design: This is a randomized, multicenter, double-blind Phase 3 study in chemotherapy naive subjects with Stage IV or recurrent NSCLC of squamous histology. The target study population in this trial will include primarily Asian subjects from China with additional subjects from other Asian and/or non-Asian countries. The study will randomize approximately 867 eligible NSCLC squamous histology subjects, from China, other Asian and/or non-Asian countries, at a 1:1 ratio to 1 of 2 treatment arms, stratified by ECOG performance status, smoking status and gender.

Subjects will receive 1 of 2 treatment regimens:

- Arm A: Paclitaxel 175 mg/m^2 IV q 3 weeks for up to 6 doses starting at randomization. Carboplatin AUC = 6 IV q 3 weeks for up to 6 doses starting at randomization. ipilimumab 10 mg/kg IV, Induction: q 3 weeks for up to 4 doses starting at Cycle 3, ipilimumab Maintenance: q 12 weeks for eligible subjects beginning 9 weeks after last ipilimumab induction dose.
- Arm B: Paclitaxel 175 mg/m^2 IV q 3 weeks for up to 6 doses starting at randomization. Carboplatin AUC = 6 IV q 3 weeks for up to 6 doses starting at randomization. Placebo, Induction: q 3 weeks for up to 4 doses starting at Cycle 3, and Placebo Maintenance: q 12 weeks for eligible subjects beginning 9 weeks after last placebo induction dose.

This study is divided into 4 phases: Screening, Induction, Maintenance and Follow-up (Toxicity/Progression Follow-up and Overall Survival Follow-up).

Figure 1: Study Schematic



I = ipilimumab P = placebo C = chemotherapy

*For a maximum duration of 3 years from the first dose of blinded study therapy

Study Population: Men and women who are ≥ 18 years old with histologically or cytologically confirmed Stage IV or recurrent NSCLC of predominantly squamous histology with ECOG performance ≤ 1, who have met screening requirements, and who are previously untreated with chemotherapy for the treatment of for locally advanced or metastatic lung cancer. Subjects with specific underlying autoimmune diseases (particularly gastrointestinal), history of motor neuropathy or toxic endothelial necrolysis (TEN), and brain metastases will be excluded.

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for CA184153		
Medication[a]	**Potency**	**IP/Non-IP**
Ipilimumab Injection, 200 mg/vial	5 mg/mL	40 mL vial, 1-panel, open label
Taxol® (for IV infusion)	100 mg	Vial 1-Panel, open label
Taxol® (for IV infusion) - for local sourcing in China	30 mg	Vial 1-Panel, open label
Paraplatin®	450 mg	Vial 1-Panel, open label

[a] TAXOL and PARAPLATIN may be locally sourced if necessary. Packaging and storage would be dependent on local procurement.

Study Assessments:

Safety Assessments: All subjects who receive at least 1 dose of study treatment (ipilimumab, placebo, paclitaxel or carboplatin) will be evaluated for safety parameters.

Efficacy Assessments: All randomized subjects who received at least one dose of blinded study therapy will be evaluated for efficacy analyses unless otherwise specified. In addition, a selected set of efficacy analyses will be performed on all randomized subjects. Overall survival will be defined as the time from the date of randomization until the date of death. For those subjects who have not died, OS will be censored on the last date the subject was known to be alive.

Progression Free Survival (PFS) defined by mWHO among all the randomized subjects who received at least one dose of blinded study therapy will be analyzed as a secondary endpoint.

Radiologic Assessments: CT/MRI imaging of the chest and abdomen is required at screening and every 6 weeks in the induction phase and every 12 weeks in the maintenance phase until no longer meeting criteria. Brain scan at screening is required to rule out the presence of brain metastases. A bone scan is required at screening except where prohibited by local regulations (until appropriate approvals are obtained).

Statistical Considerations:

Sample Size Consideration for the Primary Objective (all Randomized Subjects):

This study will randomize approximately 867 subjects in a 1:1 ratio to ipilimumab + carboplatin/paclitaxel arm and placebo + carboplatin/paclitaxel arm. Assuming a 24% dropout rate during the first two cycles of chemotherapy alone period (ie, the proportion of subjects who never receive blinded therapy due to any reason), it is estimated that approximately 660 subjects will receive blinded study therapy.

In the primary endpoint of overall survival among the randomized subject who received at least one dose of blinded study therapy, an exponential distribution and a true hazard ratio [ipilimumab + carboplatin/paclitaxel vs placebo + carboplatin/paclitaxel] of 0.75 post chemotherapy alone period is assumed. It is also assumed that the median OS for chemotherapy alone arm after two cycle of chemotherapy is 10 months. A total of 467 events out of 660 randomized

subjects who received blinded study therapy will provide 86% power to detect a statistically significant difference in OS among all randomized subjects who received blinded study therapy between treatment arms with a Type I error rate of 5% based on a 2-sided log-rank test. In this study, it is estimated that 85% of the randomized subjects (ie, 736 subjects) will come from China. Out of the 736 randomized Chinese subjects it is estimated that 558 subjects will receive blinded study medication. A total of 397 events in this population will still provide 80% of power to detect a statistically significant difference in the primary endpoint.

With the current design, the overall hazard ratio for OS among all randomized subjects is approximately 0.81 based on the simulation results with an estimated dropout rate of 24% during the first two cycles of chemotherapy. This assumes a piecewise exponential distribution with a hazard ratio of 1 during the first 2 cycles of chemotherapy alone and a true hazard ratio of 0.75 after that. A total of 644 events out of 867 randomized subjects will provide 75% power to detect a statistically significant difference in OS among all randomized subjects between treatment arms with a Type I error rate of 5% based on a 2-sided log-rank test.

Assuming that the enrollment follows a piecewise constant accrual rate (5 subjects per month during Months 1 - 3, 10 subjects per month during Months 4 - 6, and 28 subjects per month for the rest of the accrual period), it is estimated that total accrual will take approximately 33 months and the study will take 45 months to complete.

Sample size calculation described above was based on 10,000 simulation results in which OS follows a piecewise exponential distribution. The statistical software R version 2.11.1 was used for this exercise.

The analysis will not be conducted until the following 2 conditions have both been met: 1) 468 OS events have been observed in randomized subjects treated with at least one dose of blinded study therapy and 2) 644 OS events have been observed in all randomized subjects. The primary analysis will include all events available at the time of the database lock.

Summary of Statistical Analyses

All hypothesis testing will be two-sided. All hypothesis testing will be based on a significance level of 0.05.

Methods for Primary Endpoint

The distribution of OS among randomized subjects who received at least one dose of blinded study therapy will be compared between treatment arms using a two-sided unstratified log-rank test. The stratified log-rank test p value, hazard ratio and its associated two-sided 95% confidence interval (CI) will be estimated via an unstratified Cox model with treatment arm as the only covariate, unless otherwise indicated.

The event-free OS probabilities for each treatment arm will be estimated and plotted using the Kaplan-Meier (KM) product-limit method. The estimates of medians and two-sided 95% CIs will be calculated via complementary log-log transformation. KM estimates of OS rates for randomized subjects who received at least one dose of blinded study therapy at the following, but not limited to, time points: 6 months, 1 year, 18 months and 2 years and associated two-sided log-log transformed 95% confidence interval will be calculated.

[redacted]

[redacted]

Safety

Descriptive statistics of safety will be presented for all treated subjects who received at least one dose of blinded study therapy using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 by treatment arm. All on-study AEs, drug-related AEs, immune-related AEs, SAEs, and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v3.0 criteria by system organ class and by preferred term. The listings by subject will be produced for all deaths, all SAEs, and all AEs leading to discontinuation of study drug. On-study laboratory parameters, including hematology, serum chemistry, liver function, and renal function will be summarized using worst grade per NCI CTCAE v3.0 criteria. The reporting period for these subjects will be from the first dose of blinded study therapy to 90 days after the last dose is received.

A selected set of the safety analyses described above will be repeated for all treated subjects including those who never received blinded study therapy due to reason such as, but not limited to, death, disease progression or intolerable adverse events occurred during the first two cycles of chemotherapy. The reporting period for safety data will be from first dose of study medication to 90 days (> 5 half lives) after last dose is received.

In addition, selected safety analyses will be performed for all treated Chinese subjects who received at least one dose of blinded study therapy and/or on all treated Chinese subjects regardless of whether or not they received blinded study therapy. Details will be provided in SAP.

Immune-related Adverse Events (irAEs)

Immune-related adverse events (irAEs) are AEs of unknown etiology, which are consistent with an immune phenomenon and identified by the investigator as study treatment related. The irAEs will be defined using a predefined list of MedDRA high_level group terms, high-level terms and preferred terms; changes may be made to this list with each new version of MedDRA. Six (6) subcategories of irAEs will be reported: GI, liver, skin, endocrine, neurological, and other. Immune-related AE summaries will also be produced on diarrhea as a separate grouped term.

Analysis of irAEs will be based on all treated subjects who received at least one dose of blinded study therapy, and the reporting period will be from the first dose of blinded study therapy to 90 days after the last dose is received.

Immune-mediated Adverse Reactions (imARs)

This study will also describe immune-mediated adverse reactions (imARs) using the same adjudication algorithm and predefined list of AEs of special interest (enterocolitis, hepatitis, dermatitis, endocrinopathies, neuropathies, and other) used for the USPI. Specifically, adjudication as an imAR will take into account results from further work-up (eg, biopsies), the use of concomitant immunosuppression and its effect on the AE, as well as possible alternative etiologies, but not the causality as reported by the investigator. Of note, some of the criteria for adjudication will be modified to reflect the fact that ipilimumab will be combined with chemotherapy in this study. Alternative etiologies (eg, infection), how the AE was evaluated (eg, evidence of inflammation on biopsy) and intervention used to treat the imAR (eg, immunosuppression, blood transfusion) will be captured on CRF pages.

The sponsor will adjudicate the adverse events for potentially being immune-mediated in both experimental and control arm in a blinded manner.

Analysis of imARs will be based on all treated subjects who received at least one dose of blinded study therapy and the reporting period will be from the first dose of blinded study therapy to 90 days after the last dose is received.

Pharmacokinetics

All available pharmacokinetic (PK) data will be listed. PK data obtained from this study may be pooled with data from other studies to perform an integrated population PK analysis (including assessment of covariate effects on PK), as well as exposure-response analysis for selected safety and efficacy endpoints. These analyses will be described in a separate report(s).

Pharmacodynamics

Two (2) types of Absolute Lymphocyte Count (ALC) analyses will be done: pharmacodynamic and predictive. Both analyses will include all treated subjects with known date of first dose of ipilimumab or placebo. Pharmacodynamic analyses will examine the patterns of change in ALC over time and how these patterns might differ between treatment arms. Predictive analyses will examine the relationship between ALC and measures of response such as OS. Further details will be described in the SAP.

Pharmacogenomics

Not applicable.

Outcomes Research

Among subjects who received at least one dose of blinded study therapy, the distribution of time to symptom progression (defined as an increase of at least 15 mm from baseline prior to receiving any study drug in any of the three symptoms (cough, pain and dyspnea)) will be estimated using KM method. Subjects who do not show deterioration in symptoms will be censored on the last assessment date that all three symptoms (dyspnea, cough, and pain) were assessed. The estimates of medians and two-sided 95%CIs will be calculated.

TABLE OF CONTENTS

1.2 Research Hypothesis

Among randomized subjects with Stage IV (per the 7th IASLAC- International Association for the Study of Lung Cancer - classification) or recurrent non-small cell lung cancer (NSCLC) of squamous histology, who are treated with paclitaxel and carboplatin and phased blinded study therapy, overall survival in subjects assigned to treatment with phased ipilimumab will be superior to overall survival in subjects assigned to treatment with phased placebo.

1.3 Objectives

1.3.1 Primary Objective

To compare Overall Survival (OS) of subjects with Stage IV/recurrent NSCLC of squamous histology who have been randomized to ipilimumab in addition to paclitaxel and carboplatin versus placebo in addition to paclitaxel and carboplatin, and have received at least one dose of blinded study therapy.

1.3.2 Secondary Objectives

- Compare OS among all randomized subjects between the 2 treatment arms
- Compare Progression-Free Survival (PFS) per mWHO among all randomized subjects who received at least one dose of blinded study therapy between the 2 treatment arms
- Compare selected efficacy endpoints only for randomized Chinese subjects (ie, Chinese subset among all randomized subjects)
  - OS among all randomized Chinese subjects,
  - OS among all randomized Chinese subjects who received at least one dose of blinded study therapy,
  - PFS per mWHO among all randomized Chinese subjects who received at least one dose of blinded study therapy

between the 2 treatment arms.

[redacted]

1.5 Overall Risk/Benefit Assessment

Subjects to be enrolled in this study will present with Stage IV or recurrent NSCLC of squamous histology. Paclitaxel in combination with carboplatin at the dose and schedule used in this study is considered as a key standard of care in this patient population.[24]

Study CA184041 established the clinical activity of ipilimumab in combination with carboplatin and paclitaxel in terms of irPFS and PFS when ipilimumab is administered using a phased schedule to patients with NSCLC, regardless of their histology (squamous or non squamous histology). There was also an observed numerical improvement of OS. There is no data that have definitively established that an improvement in irPFS is correlated with improvement in OS in NSCLC since CA184041 is the first study that used irRC in this setting. However, it is usually considered that PFS is a surrogate marker for survival in NSCLC.[25] In the 041 study, a significant improvement of irPFS per irRC was observed in the two ipilimumab containing treatment groups when compared to the control arm and PFS per mWHO improved in the phased schedule. These data suggest that it is reasonable to consider that the addition of ipilimumab using a phased schedule to carboplatin and paclitaxel will provide an improvement of OS in subjects treated with that regimen.

In addition, a post-hoc analysis of the efficacy endpoints by histology (squamous vs non squamous histology) indicated that the clinical benefit (irPFS, mWHO PFS and OS) is numerically greater in subjects with a squamous histology compared to that of subjects with non-squamous histology for the phased schedule of ipilimumab.

In CA184041, 138 subjects with NSCLC received ipilimumab in combination with carboplatin and paclitaxel (with concurrent or phased schedule) in order to establish the safety profile of the combination. There was no increase in severity of AEs that are classically observed in subjects treated with carboplatin and paclitaxel. The spectrum of irAEs that were reported in CA184041 is similar to that observed during the metastatic melanoma program when the drug was administered at a dose of 10 mg/kg. These irAEs were, in the vast majority of the cases, manageable or reversible when the irAE management algorithms were followed. Two drug-related treatment deaths were reported (toxic epidermal necrolysis and polyradiculoneuritis (Guillian Barre Syndrome)), that led to amending the algorithm for skin irAEs and to the design of an algorithm specific for neurological irAEs.

Overall, the safety profile of ipilimumab in combination with carboplatin and paclitaxel appears to be similar to that reported in studies where it was administered as a single agent. Also, the addition of ipilimumab to carboplatin and paclitaxel did not result in an increase in the incidence or severity of adverse events that are generally attributed to this doublet.

These data indicate that the safety of ipilimumab when combined with carboplatin and paclitaxel is generally manageable, and that its administration in combination with carboplatin and paclitaxel has an acceptable risk/benefit ratio supporting the evaluation of this triplet in Phase 3. The safety profile of the combination of ipilimumab with carboplatin and paclitaxel when administered to patients with squamous histology is consistent with that of the ITT population of CA184041 that included all NSCLC histologies.

The proposed study will carefully monitor the occurrence of adverse events, with particular attention paid to immune-related adverse events. In addition, a Data Monitoring Committee (DMC) will oversee subjects' safety at pre-specified time points during the course of this study.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

2.3.1 Withdrawal of Consent

To facilitate the collection of survival data, several levels of consent withdrawal have been instituted for this study.

- Withdrawal from study treatment and/or procedures in the Induction or Maintenance Phase but allowance of Follow-Up procedures
- Withdrawal from Follow-Up procedures but allowance of contact every 12 weeks for survival
- Withdrawal from all study related procedures and contacts but will allow reporting of survival status.

The importance of Survival Follow-up must be clearly communicated to study subjects. Unless the subject clearly states otherwise, they must be contacted every 12 weeks for survival follow-up. In addition, collection of information about subsequent therapy for treatment of lung cancer is an essential component of subject follow-up.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a randomized, multicenter, double-blind Phase 3 study in chemotherapy naive subjects with Stage IV or recurrent NSCLC of squamous histology. The primary objective is to compare Overall Survival (OS) of subjects with Stage IV/recurrent NSCLC of squamous histology who have been randomized to ipilimumab in addition to paclitaxel and carboplatin versus placebo in addition to paclitaxel and carboplatin and have received at least one dose of blinded study therapy.

The target study population in this trial will include primarily Asian subjects from China with additional subjects from other Asian and/or non-Asian countries. (Section 1.1.5).

The study will randomize up to approximately 867 eligible NSCLC squamous histology subjects from China, other Asian and/or non-Asian countries, at a 1:1 ratio to 1 of 2 treatment arms, stratified by ECOG performance status, smoking status (heavy smokers, defined as smoked ≥ 10 pack years, vs light/non-smoker, defined as all subjects who do not meet the criteria for heavy smoker) and gender.

A pack-year is defined as the number of packs of cigarettes a person has smoked every day multiplied by the number of years he or she has smoked. Since 1 pack is 20 cigarettes, a person who has smoked 20 cigarettes a day for a year is considered to have smoked 1 pack year. Someone who has smoked 30 cigarettes a day (1½ packs) for 3 years has smoked 4,5 pack years (1½x3), and so on.

ECOG performance status, smoking status, and gender were chosen as stratification factors because of their potential influence on survival.[26,27,28]

Following the planned analysis of the primary endpoint, Survival follow-up data may be collected for up to 5 years from the end of study enrollment.

3.1.1 Treatment Arms

Subjects will receive 1 of 2 treatment regimens:

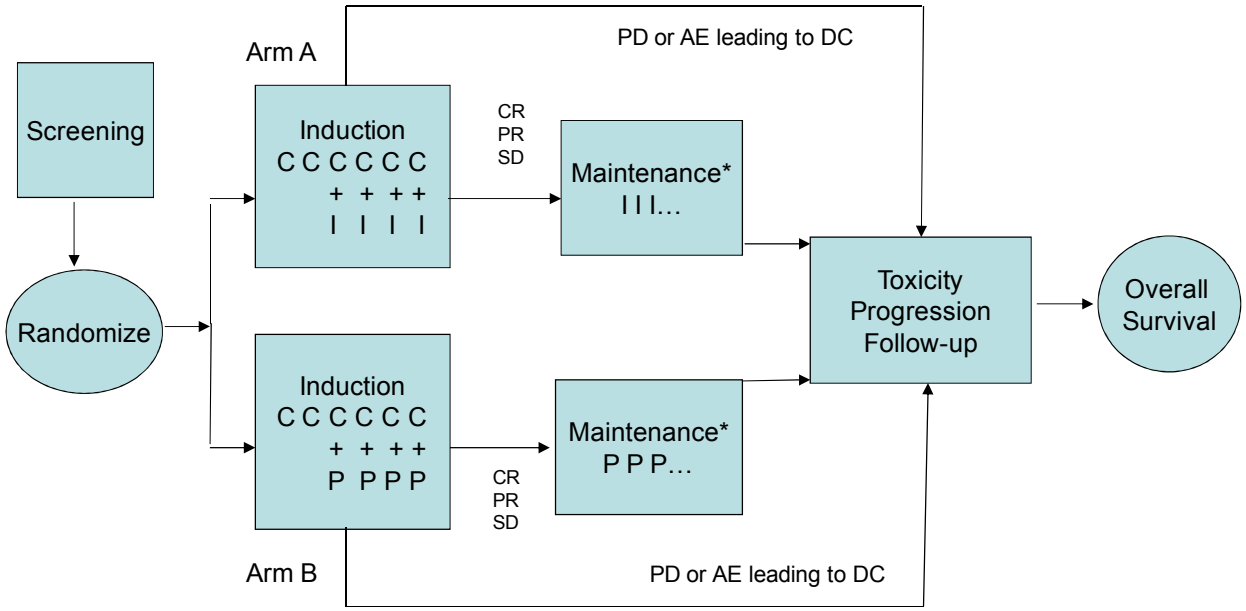
- Arm A: Paclitaxel 175 mg/m^2 IV q 3 weeks for up to 6 doses starting at randomization. Carboplatin AUC = 6 IV q 3 weeks for up to 6 doses starting at randomization. ipilimumab 10 mg/kg IV, Induction: q 3 weeks for up to 4 doses starting at Cycle 3, ipilimumab Maintenance: q 12 weeks for eligible subjects beginning 9 weeks after last ipilimumab induction dose, for a maximum treatment period of 3 years from the first dose of ipilimumab.
- Arm B: Paclitaxel 175 mg/m^2 IV q 3 weeks for up to 6 doses starting at randomization. Carboplatin AUC = 6 IV q 3 weeks for up to 6 doses starting at randomization. Placebo, Induction: q 3 weeks for up to 4 doses starting at Cycle 3, and Placebo Maintenance: q 12 weeks for eligible subjects beginning 9 weeks after last placebo induction dose, for a maximum treatment period of 3 years from the first dose of placebo.

No subject crossover between treatment arms is allowed in this study.

3.1.2 Treatment Flow

This study is divided into 4 phases: Screening, Induction, Maintenance and Follow-up (Toxicity/Progression Follow-up and Overall Survival Follow-up).

Figure 3.1.2-1: Study Schema



I = ipilimumab P = placebo C = chemotherapy

*For a maximum duration of 3 years from the first dose of blinded study therapy

3.1.2.1 Screening Phase

- Begins after subject signs the informed consent form (ICF);
- Establishes subject eligibility;
- Ends upon randomization.

3.1.2.2 Induction Phase

- Begins with randomization, in most cases this will occur on the same date as the first dose of chemotherapy administration;
- Administration of paclitaxel and carboplatin every 3 weeks for up to 6 doses starting at randomization. Administration of blinded study drug (ipilimumab or placebo) every 3 weeks starting at Cycle 3 for up to 4 doses;
- Tumor assessments (TAs) must be performed at Weeks 7, 13, 19, and 25 regardless of dosing;

- Subjects must remain in the Induction Phase and complete all required evaluations unless PD is established or subject discontinues all study treatment (blinded study drug, paclitaxel, and carboplatin). Refer to Section 4.5.3.
- Ends at:
  - subject entrance to the Maintenance Phase; or
  - PD (subject enters the Follow-Up phase);
  - Discontinuation of all study treatment administration (subject completes the End of Treatment Visit and enters the Toxicity/Progression Follow-up Phase; subject may start second line therapy).

3.1.2.3 Maintenance Phase

- Begins 9 weeks after last induction dose of blinded study drug (ipilimumab or placebo);
- Eligible subjects will receive blinded study drug (ipilimumab or placebo) every 12 weeks starting 9 weeks after last ipilimumab induction dose, for a maximum treatment period of 3 years from the first dose of blinded study therapy. Tumor Assessments will be performed every 12 weeks starting with Week 25 until mWHO PD, or until the end of treatment for subjects who continue to be treated beyond mWHO PD per Section 4.5.3.1;
- Maintenance Ends upon:
  - PD (subject may start second line therapy);
  - An AE requiring discontinuation of blinded study drug (End of Treatment Visit must be completed and the subject must enter the Toxicity/Progression Follow-up Phase, subject may start second line therapy); or
  - Reaching the 3 year dosing limit.

3.1.2.4 End of Treatment Visit

- Completed when subjects discontinue all study treatment (blinded study drug, paclitaxel, and carboplatin). See Section 4.5.3.
- End of Treatment visit may coincide with the visit where the decision to discontinue all study treatment was made or may be scheduled up to 6 weeks after all study treatment has been discontinued.

3.1.2.5 Toxicity/Progression Follow-up Phase

- Begins after the completion of the End of Treatment visit
- For subjects who have NOT experienced mWHO PD, tumor assessments (TA) will be performed as follows:
  - For subjects who **did not** complete the Induction Phase, TAs will be performed as described in the Induction Phase (at Weeks 7, 13, 19, and 25) and then every 12 weeks until mWHO PD or the start of subsequent therapy for lung cancer.

  - For subjects who completed the Induction Phase, TAs will be performed every 12 weeks until mWHO PD or the start of subsequent therapy for lung cancer, beginning at Week 25.
- Adverse Event assessments will continue until all AEs have resolved, returned to baseline, or are deemed irreversible. All subjects will be followed for AEs for a minimum of 90 days following the last dose of any study treatment, even if second line therapy has been initiated.
- All subsequent therapy for the treatment of lung cancer will be collected
- Ends when both PD occurs and AEs have been followed for up to 90 days following the last dose of any study treatment and subsequent systemic anti-cancer therapy is initiated.

3.1.2.6 Overall Survival Follow-up Phase

- Begins upon discontinuation from the Toxicity/Progression Follow-up Phase
- For all subjects, contact will be made (in person or by telephone) every 12 weeks upon entry into this phase to evaluate Overall Survival and collect data on the initiation of subsequent therapy for the treatment of lung cancer.

Induction Phase visits have a visit window of ± 3 days. Maintenance Phase and Follow up visits have a visit window of ± 14 days. Blinded study drug (ipilimumab or placebo) dosing visits should be scheduled according to the previous dose date and the windows calculated according to this date. Blinded study drug (ipilimumab or placebo) dosing must be no less than 18 days apart. If there is an unacceptable toxicity, blinded study drug dosing may be delayed up to 21 days (if > 21 days, please consult the medical monitor before resuming dosing).

3.2 Post Study Access to Study

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug for a maximum treatment period of 3 years from the first dose of blinded study therapy. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of the sponsor and in accordance with local regulatory practices. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Willing and able to provide informed consent

2) Target Population

a) Subjects with NSCLC of predominantly squamous histology documented by histology or cytology from brushing, washing or needle aspiration of a defined lesion but not from sputum cytology alone

b) Subjects must present with Stage IV or Recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer (IASLC) classification)

c) At least 1 measurable tumor lesion, as defined by mWHO criteria, that is not located in a previously irradiated area

d) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 at study entry

e) Accessible for treatment and follow-up. Subjects enrolled in this trial must be treated at the participating centers

f) Re-enrollment: permitted for a subject who has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). If re-enrolled, the subject must be reconsented.

3) Age and Reproductive Status

a) Males and Females, ages 18 years inclusive or more.

b) Not applicable per Amendment 02

c) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

d) Women must not be breastfeeding.

e) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with blinded study drug (s) plus 5 half-lives of blinded study drug (75 days) plus 30 days (duration of ovulatory cycle) for a total of 105 days post-treatment completion.

f) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with blinded study drug (s) plus 5 half-lives of the blinded study drug (75 days) plus 90 days (duration of sperm turnover) for a total of 165 days post-treatment completion.

g) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide[29,30]
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy.
- Complete Abstinence*

  *Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom*.

  * A male and female condom must not be used together

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) History of or current brain metastases

b) Malignant pleural effusion that is recurrent despite appropriate supportive care

2. Medical History and Concurrent Diseases

a) Documented history of severe autoimmune or immune mediated symptomatic disease that required prolonged (more than 2 months) systemic immunosuppressive (ie, steroids) treatment such as:

i) Ulcerative colitis and Crohn's disease

ii) Rheumatoid arthritis, systemic progressive sclerosis (scleroderma)

iii) Systemic Lupus Erythematosus

iv) Autoimmune vasculitis (eg, Wegener's Granulomatosis)

b) Subjects with history of motor neuropathy considered of autoimmune origin (eg, Guillain-Barré Syndrome)

c) Subjects with a history of toxic epidermal necrolysis (TEN)

d) Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent or completing questionnaires

e) Serious uncontrolled medical disorder that, in the opinion of the investigator, would impair the ability of the subject to receive protocol therapy

f) Prior malignancy, active within 5 years, except for locally curable cancers that have been apparently cured and need no subsequent therapy, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast

g) HIV positive or HBsAg positive or active Hepatitis C infection based on testing done during the screening period

h) Prior systemic therapy for locally advanced or metastatic lung cancer including vaccines and other targeted therapies

i) Prior radiation therapy or loco-regional surgeries are allowed

ii) Adjuvant/neo-adjuvant systemic therapy for lung cancer is allowed if completed at least 1 year prior to enrollment into this study

i) Subjects with ≥ Grade 2 peripheral neuropathy

j) History of allergy or hypersensitivity to any component of the treatment

3. Physical and Laboratory Test Findings

a) Inadequate hematologic function defined by:

i) Absolute neutrophil count (ANC) < 1,500/mm^3, or

ii) Platelet count < 100,000/mm^3; or

iii) Hemoglobin level < 9 g/dL

b) Inadequate hepatic function as defined by either:

i) Total bilirubin level ≥ 2.5 times the upper limit of normal (ULN);

ii) AST and ALT levels ≥ 2.5 times the ULN or ≥ 5 times the ULN if liver metastases are present

c) Inadequate renal function defined as calculated creatinine clearance < 50 ml/min based on the standard Cockroft and Gault formula

4. Allergies and Adverse Drug Reactions

a) Not Applicable per Protocol Amendment 02

5. Other Exclusion Criteria

a) Chronic use of immuno-suppressive drugs (ie, corticosteroids used in the management of cancer or non-cancer related illnesses). Use of corticosteroids are allowed if used as premedication for chemotherapy administration or on study management of an AE

b) Any immunotherapy for the treatment of cancer

c) Prior treatment with any inhibitor or agonist of T-cell co-stimulation

d) Prisoners or subjects who are involuntarily incarcerated

e) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal.

Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are

practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

Refer to Exclusion Criteria 4 (Section 3.3.2) for prohibited and/or restricted treatments related to subject eligibility for this study.

No other anti-cancer therapy (ie, chemotherapy, immunotherapy, radiotherapy, hormonal therapy, molecular targeted therapy, surgery, or traditional Chinese medicines (eg, Zi long Jin pian; Kang lai te or any TCM with indication of anti-cancer)) or experimental medications will be permitted while subjects are on the study treatment.

Systemic corticosteroids are authorized only for the prevention of anaphylaxis and fluid retention associated with the administration of paclitaxel.

Steroids should not be administered at other time points while receiving all study treatments with the exception of treating AEs of interest or adrenal insufficiency. In particular, steroids must not be used for the treatment of emesis. Topical use or ocular use of corticosteroids is permitted. Steroids administered as a spray for the management of asthma are also allowed.

GM-CSF/G-CSF (granulocyte-colony stimulating factor) will be permitted. However, the use of growth factors is allowed as per their respective label indications to treat chemotherapy induced neutropenia (eg, febrile neutropenia). They must not be used for the treatment of cancer or for any primary prophylaxis while on study.

3.4.2 Other Restrictions and Precautions

Radiotherapy: Subjects are allowed to receive palliative radiotherapy for painful bone lesions. Targeted external beam irradiation should not be used in the primary lung field where assessment for tumor is indicated.

The metabolism of TAXOL is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when TAXOL is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4.

Caution should also be exercised when TAXOL is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8.

Potential interactions between TAXOL, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Subject meets Treatment Stopping Criteria as specified in Section 4.5.3.
- The total length of treatment is limited to 3 years. Subjects that have reached this limit must be discontinued from treatment and enter the Toxicity/Progression Follow-Up phase.

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Study Follow up

In this study, OS of subjects with Stage IV/recurrent NSCLC of squamous histology is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously

authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, backbone therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

Table 4-1: Study Drugs for CA184153

Product Description / Class and Dosage Form[a]	Potency	Type IP/Non-IMP	Blinded or Open Label	Packaging	Storage Conditions (per label)
Ipilimumab Injection, 200 mg/vial	5 mg/mL	40 mL vial, 1-panel, open label	5 vials per box, 1-panel, open label	Clear, colorless liquid. Light (few) particles may be present	Store refrigerated, 2° - 8°C (36° - 46°F). Protect From Light. Protect From Freezing.
Taxol® (for IV infusion)	100 mg	Vial 1-Panel, open label	NA	Clear colorless to slightly yellow viscous solution	(20° - 25°C); Protect from Light. Retain in original container.
Taxol® (for IV infusion) - locally sourced in CHINA only	30 mg	Vial 1-Panel, open label	NA	Clear colorless to slightly yellow viscous solution	(20° - 25°C); Protect from Light. Retain in original container.
Paraplatin®	450 mg	Vial 1-Panel, open label	NA	A slightly yellow solution	Store unopened vials at 25°C; Protect from Light

[a] TAXOL and PARAPLATIN may be locally sourced, if necessary. Packaging and storage would be dependent on local procurement. Locally sourced Taxol and Carboplatin will be stored according to labeling and package insert.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) is/are: ipilimumab 5 mg/mL solution or placebo (0.9% sodium chloride injection, USP, or 5% dextrose injection) Taxol® (paclitaxel) 100 mg and Paraplatin® (carboplatin) 450 mg.

[redacted]

4.2 Noninvestigational Product

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered noninvestigational products.

4.3 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Please refer to the current version of the Investigator Brochure for complete storage, handling, dispensing, and infusion information for ipilimumab.[33]

4.3.1 Packaging and Labeling

Study medication will be provided as open-label containers. The labels will contain the protocol prefix, batch number, content, storage conditions, and dispensing instructions along with the IND caution statement.

Ipilimumab will be supplied at a concentration of 5 mg/mL in vials containing 40 mL.

The TAXOL® and PARAPLATIN® vials will be labeled with a one-panel label containing the protocol prefix, batch number, content, storage conditions and dispensing instructions.

Locally sourced TAXOL and PARAPLATIN will contain minimal or no additional labeling, as required by local regulations.

4.4 Method of Assigning Subject Identification

4.4.1 Enrolment

After informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. The following information is required for subject registration:

- Date of birth;
- Date of informed consent;
- Gender.

This study permits the re-enrollment of a subject who has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). If re-enrolled, the subject must be reconsented.

4.4.2 Randomization

After completion of all Screening Phase evaluations, site personnel will make another call to the IVRS to obtain a treatment assignment.

The IVRS will randomly assign subjects to 1 of 2 treatment groups (A or B) in a 1:1 ratio using a stratified permuted block randomization method with respect to the following stratification factors:

- ECOG Performance Status (0 vs 1);
- Smoking status (heavy vs light/non-smoker);
- Gender (male vs female).

Randomization will be performed based on a randomization schedule generated and maintained by the Randomization Group within Bristol-Myers Squibb.

The procedures for using the IVRS will be detailed in a separate document.

4.5 Selection and Timing of Dose for Each Subject

If all 3 drugs are given on the same day, subjects must receive the blinded study drug (ipilimumab or placebo) infusion first, followed by paclitaxel then carboplatin. Carboplatin must follow the paclitaxel in order to minimize frequency and/or intensity of myelosuppression.

In the Induction Phase, all subjects will receive blinded ipilimumab at 10 mg/kg (or placebo given as 2 mL/kg) intravenously over 90 minutes (not to be infused in less than 70 minutes) every 3 weeks (starting at Cycle 3) for up to 4 doses.

Paclitaxel (175 mg/m^2 according to the BSA obtained through the Dubois-Dubois formula - up to 5% range is allowable per institutional standards) will be administered intravenously over 3 hours (or as per local standard of care) every 3 weeks for up to 6 doses starting at randomization and carboplatin (AUC = 6, rounded to nearest 50mg as per institutional standards), will be administered intravenously over 30 minutes ((or as per local standard of care - longer infusions are acceptable as per institutional standards) every 3 weeks for up to 6 doses starting at randomization.

Premedication for paclitaxel will be administered per standard of care and label instructions.

Creatinine clearance must be calculated prior to every dose of carboplatin based on the formula below:

Cockroft-Gault formula for estimating creatinine clearance in mL/min based on serum creatinine:

Men: $\frac{[(140 - \text{age (y)}) * \text{weight (kg)}]}{[72 * \text{serum creatinine (mg/dL)}]}$

Women: $\frac{[(140 - \text{age (y)}) * \text{weight (kg)}]}{[72 * \text{serum creatinine (mg/dL)}]} * 0.85$

Note: Due to differences in serum creatinine units, sites may use the standard Cockroft-Gault formula used at their institution. In order to ensure consistent dosing across the study, AUC should be calculated using the Calvert formula.

Chemotherapy (Carboplatin and Paclitaxel - not ipilimumab) doses may be capped per institutional standards.

Subjects who stay in the Induction Phase must not have more than 6 doses of paclitaxel/carboplatin.

In the Maintenance Phase, eligible subjects will receive blinded ipilimumab (active or placebo) intravenously over 90 minutes every 12 weeks, for a maximum treatment period of 3 years from the first dose of blinded study therapy. Treatment Arm A will receive active ipilimumab and Arm B will receive placebo.

In the Toxicity/Progression and Overall Survival Follow-up Phases, there is no dosing of any investigational products (includes blinded study drug (ipilimumab or placebo)).

4.5.1 Recommended Dose Modifications of Blinded Ipilimumab (Active or Placebo)

Blinded study drug related toxicities must be resolved to baseline or ≤ Grade 1 prior to administering the next dose. Dose delay, up to 21 days, is allowed so toxicities return to ≤ Grade 1 or baseline. If blinded study drug is delayed then chemotherapy dosing must be delayed, and vice versa. If delaying chemotherapy is not felt to be in the best interest of the subject, discussion with the medical monitor is strongly encouraged. No dose reductions for blinded study drug (ipilimumab or placebo) are allowed. Treatment modifications will be made based on safety criteria specified below.

4.5.1.1 Liver Function Tests (LFTs) Required Prior to Blinded Study Drug Administration

Liver function tests (AST, ALT, total bilirubin) will be evaluated for every subject prior to administration of blinded study drug (ipilimumab or placebo). Blood samples must be collected and analyzed within 3 days prior to dosing from the local lab.

LFT results must be reviewed by the principal investigator or designee prior to blinded study drug administration and meet dosing criteria specifications (< 2.5 x ULN for AST and ALT or < 5 x ULN if liver metastases are present and T. bilirubin < 2.5 x ULN) prior to dosing. If

abnormal LFT values are detected, the subject must be managed using the hepatotoxicity algorithm in the Investigator's Brochure and dosing modifications described in Sections 4.5.1 to 4.5.2.

4.5.1.2 Delay of One Dose of Blinded Study Drug

It may be necessary to delay (maximum of 21 days) study drug dosing for the following AE(s)

- Any Grade 2 non-skin related adverse event, except for laboratory abnormalities;
- Any Grade 3 laboratory abnormality

It is necessary to delay (maximum of 21 days) study drug dosing for the following AE(s):

- Any Grade 3 skin-related AE, regardless of causality;
- Elevated Liver Function Tests, as defined in Section 4.5.1.1
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

4.5.1.3 Criteria to Resume Treatment with Blinded Study Drug

Treatment may resume when the AE(s) resolve(s) to Grade 1 or baseline value. If treatment must be delayed for > 3 weeks (> 42 days from previous dose), please contact the medical monitor before resuming dosing.

If a subject discontinues the blinded study drug, the subject may continue to receive 1 or both chemotherapy drugs.

4.5.1.4 Treatment of Blinded Study Drug Related Infusion Reactions

Infusion reactions should be graded according to Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 Allergic reaction/hypersensitivity criteria. Severe infusion reactions require the immediate interruption of blinded study drug therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms. In each case of an infusion reaction, the investigator should institute treatment measures according to the best available medical practice. The following treatment guidelines are suggested:

CTCAE Grade 1 Allergic reaction/hypersensitivity (transient flushing or rash, drug fever < 38°C).

- Treatment: Decrease the blinded study drug infusion rate by 50% and monitor closely for any worsening.

CTCAE Grade 1 or Grade 2 Allergic reaction/hypersensitivity manifesting only as delayed drug fever (starting after the completion of the blinded study drug infusion).

- Treatment: Maintain blinded study drug dose and infusion rate for future infusions. Consideration could be given to administration of acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) prior to the subsequent blinded study drug infusion, if not otherwise contraindicated in subjects. Dose and schedule of these agents is entirely at the investigator's discretion.

CTCAE Grade 2 Allergic reaction/hypersensitivity (Rash, flushing urticaria, dyspnea, drug fever > 38°C).

- Treatment: Interrupt blinded study drug infusion. Administer bronchodilators, oxygen, etc as medically indicated. Resume infusion at 50% of previous rate once infusion reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening.

CTCAE Grade 3 or Grade 4 Allergic Reaction/Hypersensitivity: A CTCAE Grade 3 hypersensitivity reaction (symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/ angioedema; hypotension) or a Grade 4 hypersensitivity reaction (anaphylaxis).

- Treatment: Stop the blinded study drug infusion immediately and disconnect infusion tubing from the subject. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc, as medically indicated. Contact the Medical Monitor and document as a serious adverse event (Section 6.1). No further blinded study drug treatment to be administered.

4.5.1.5 Re-treatment with Blinded Study Drug Following Infusion Reactions

Once the blinded study drug infusion rate has been decreased due to an infusion reaction, it will remain decreased for all subsequent infusions. If the subject has a second allergic/infusion reaction with the slower infusion rate, the infusion should be stopped and the subject should be discontinued from blinded study drug. If a subject experiences a Grade 3 or 4 allergic/infusion reaction at any time, the subject should be discontinued from blinded study drug. If there is any question as to whether an observed reaction is an allergic/infusion reaction of Grades 1 - 4, the Medical Monitor should be contacted immediately to discuss and grade the reaction.

4.5.1.6 Treatment of Blinded Study Drug Related Isolated Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the study drug or to an infectious etiology. If a subject experiences isolated drug fever, for the next dose, pre-treat with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion), repeat antipyretic dose at 6 and 12 hours after blinded study drug infusion. The infusion rate will remain unchanged for future doses. If a subject experiences recurrent isolated drug fever following pre-medication and post dosing with an appropriate

antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate. If fever recurs following infusion rate change, the investigator should assess the subject's level of discomfort with the event and use clinical judgment to determine if the subject should receive further blinded study drug.

4.5.2 Dose Modifications of Chemotherapy

Study drug related toxicities must be resolved to baseline or ≤ Grade 1 prior to administering the next dose (except alopecia or Grade 2 fatigue). A maximum of 2 dose reductions per chemotherapy agent are permitted; if additional reductions are required, that particular agent must be discontinued. Once the dose has been decreased, it should remain reduced for all subsequent administrations or further reduced if necessary. There will be no dose escalations in this study. Chemotherapy treatment may be delayed up to 21 days if the reason for the delay is toxicity/adverse event. All subsequent chemotherapy doses must be rescheduled according to the last chemotherapy dose administration date.

The dose levels for paclitaxel and carboplatin are listed below in Table 4.5.2-1:

Table 4.5.2-1: Dose Levels for Paclitaxel and Carboplatin

	Paclitaxel Dose	Carboplatin Dose
Starting dose	175 mg/m^2	AUC 6
Dose level -1	150 mg/m^2	AUC 5
Dose level -2	100 mg/m^2	AUC 4.5

4.5.2.1 Recommended Dose Modifications for Hematologic Toxicity

Dose adjustments are based on nadir blood counts since the preceding chemotherapy administration. Dose level adjustments are relative to that of the preceding administration (see Table 4.5.2.1-1).

Table 4.5.2.1-1: Recommended Paclitaxel and Carboplatin Dose Modifications for Hematologic Toxicity[a]

Drug related toxicity	Paclitaxel	Carboplatin
Neutrophils (ANC) < 500/mm^3 lasting ≥ 5 days	Decrease 1 dose level	Decrease 1 dose level
Febrile neutropenia (body temperature ≥ 38.5°C and ANC < 1,000/mm^3)	Decrease 1 dose level	Decrease 1 dose level
Platelets < 25,000/mm^3	Decrease 1 dose level	Decrease 1 dose level
Platelets < 50,000/mm^3 with significant bleeding or requiring blood transfusion	Decrease 1 dose level	Decrease 1 dose level
Grade 4 hemoglobin (< 6.5 g/100 mL)	Decrease 1 dose level	Decrease 1 dose level

[a] If considered in the best interest of the patient and consistent with local practice, investigators may decide to use supportive measures / treatment and/or secondary prophylaxis instead of dose reductions for the next cycle. Also, if toxicity can clearly be attributed to one of the drugs, the investigator may choose to only dose reduce one of the cytotoxics.

4.5.2.2 Recommended Dose Modifications for Non-hematologic Toxicities

Paclitaxel and carboplatin dose adjustments for non-hematologic toxicity during treatment are described in Table 4.5.2.2-1. All dose modifications should be made based on the worst grade toxicity. For all toxicity ≤ Grade 2 the dose level for all drugs should be maintained, except for neuropathy.

Table 4.5.2.2-1: Recommended Paclitaxel and Carboplatin Dose Modifications for Non-hematologic Toxicity[a]

Drug Related Toxicity	Paclitaxel	Carboplatin
Nausea/vomiting ≥ Grade 3 despite optimal medical treatment	Decrease 1 dose level	Decrease 1 dose level
Stomatitis ≥ Grade 3	Decrease 1 dose level	Decrease 1 dose level
Diarrhea ≥ Grade 3 despite optimal medical treatment	Decrease 1 dose level	Decrease 1 dose level
Neuropathy (sensory or motor), Grade 2 lasting > 7 days OR Grade 3 lasting < 7 days	Decrease 1 dose level	No modification

Table 4.5.2.2-1: Recommended Paclitaxel and Carboplatin Dose Modifications for Non-hematologic Toxicity[a]

Drug Related Toxicity	Paclitaxel	Carboplatin
Neuropathy (sensory or motor) Grade 3 lasting ≥ 7 days OR Neuropathy Grade 4 (sensory or motor)	Discontinue paclitaxel	No modification
Other Grade ≥ 3 toxicities (except fatigue and transient arthralgia and myalgia)	Adjusted as medically indicated after discussion with Sponsor	Adjusted as medically indicated after discussion with Sponsor

[a] If considered in the best interest of the patient and consistent with local practice, investigators may decide to use supportive measures / treatment and/or secondary prophylaxis instead of dose reductions for the next cycle. Also, if toxicity can clearly be attributed to one of the drugs, the investigator may choose to only dose reduce one of the cytotoxics.

4.5.3 Discontinuation of Study Treatment (Treatment Stopping Criteria)

4.5.3.1 Discontinuation of All Study Treatment

All study treatment must be discontinued if PD by mWHO is observed unless all four of the following criteria are met:

- Subject has received at least 1 dose of blinded study drug, and blinded study drug has not been previously discontinued
- AND disease progression is declared on the basis of one small lesion not considered clinically significant
- AND there is no change of symptoms or in performance score
- AND the investigator considers there is no need to administer immediately a second line treatment.

If all the criteria mentioned above are met, the investigator may continue to administer the blinded study drug with or without chemotherapy. If the subject does not continue to meet the above criteria, all study drugs (chemotherapy and blinded study drug) should be discontinued. If delaying chemotherapy is not felt to be in the best interest of the subject, discussion with the medical monitor is strongly encouraged.

4.5.3.2 Permanent Discontinuation of Blinded Study Drug (Ipilimumab)

The blinded study drug (ipilimumab or placebo) will be discontinued if the subject experiences:

- Grade 3 or 4 motor neuropathy, regardless of causality.

The blinded study drug (ipilimumab or placebo) will be discontinued if the subject experiences unacceptable toxicity defined as:

- Any AE attributable to the blinded study drug that requires permanent discontinuation of study drug; or
- Any AE which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued blinded study drug dosing.

The blinded study drug administration will be discontinued if at least 1 of the following related adverse event(s) occurs:

- Any ≥ Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy OR requires systemic treatment;
- Any ≥ Grade 3 bronchospasm or other hypersensitivity reaction;
- Any other ≥ Grade 3 non-skin related adverse event with the exception of laboratory abnormalities, Grade 3 nausea and vomiting, Grade 4 neutropenia, Grade 3 and 4 thrombopenia;
- Any Grade 4 laboratory abnormalities, except AST, ALT, or T. bilirubin:
  - AST or ALT > 8 x ULN,
  - T. bilirubin > 5 x ULN,
- Any other Grade 4 AE;
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued blinded study drug dosing;
- Subject experiences an allergic/infusion reaction while receiving study drug at a slower infusion rate due to a prior allergic/infusion reaction.

If a subject discontinues the blinded study drug, the subject may continue to receive 1 or both chemotherapy drugs.

4.5.3.3 Permanent Discontinuation of Paclitaxel

If unacceptable toxicities related to paclitaxel occur, as determined by investigator judgment, paclitaxel will be discontinued but the other drugs may be continued.

4.5.3.4 Permanent Discontinuation of Carboplatin

If unacceptable toxicities related to carboplatin occur, as determined by investigator judgment, carboplatin will be discontinued but the other drugs will be continued.

4.6 Blinding/Unblinding

The Sponsor, subjects, investigator, and site staff will be blinded to the study drug administered (ipilimumab or placebo). Each investigative site must assign an unblinded pharmacist/designee, and an unblinded site monitor will be assigned to provide oversight of drug supply and other unblinded study documentation.

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject, **in which knowledge of the investigational product is critical to the subject's management**, the blind for that subject may be broken by the treating investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should have determined that the information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product-related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

Designated staff of Bristol-Myers Squibb Research & Development may be unblinded prior to database lock to facilitate the bioanalytical analysis of pharmacokinetic samples. A bioanalytical scientist in the Bioanalytical Sciences department of Bristol-Myers Squibb Research & Development (or a designee in local bioanalytical laboratory) will be unblinded to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples from control group subjects.

In cases of accidental unblinding, contact the medical monitor and ensure every attempt is made to preserve the blind.

4.7 Treatment Compliance

Treatment compliance will be assessed by investigator report on the case report forms and Source Data Verification by Site Monitors.

4.8 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

All study drug returned to BMS must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container. Returned supplies should be in the original containers (eg, subject kits that have clinical labels attached). Empty containers should not be returned to BMS.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused study drug, those that were supplied by the sponsor, should be arranged by the responsible Study Monitor.

All unused and/or partially used study drug may be destroyed on site providing the site has an applicable standard operating procedure on file.

Arrangements for the return of study drug will be made by the responsible Study Monitor.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: CA184153 Screening Procedural Outline

Procedure	Screening Visit (within 28 Days prior to Induction Phase)	Notes
Eligibility Assessments		
Informed Consent	X	Section 2.3
Screening (IVRS)	X	Section 4.5.1
Inclusion/Exclusion Criteria	X	Section 3.3
Medical History	X	Section 5.3.1
ECOG Performance Status	X	Section 5.3.5
HIV, Hepatitis B, Hepatitis C	X	Section 5.3.6.4
Pregnancy Test WOCBP only	X	Negative pregnancy test required at Screening Section 5.3.4
Safety Assessments		
Physical Examination	X	Section 5.3.1
Pre-Treatment Events	X	Section 5.3.1
Laboratory Tests		
Chemistry	X	Section 5.3.6.1
Hematology	X	Section 5.3.6.2
Efficacy Assessments		
MRI/CT of Chest and Abdomen	X	Section 5.4.2.1
MRI/CT of Brain	X	Section 5.4.2.1

Table 5.1-1: CA184153 Screening Procedural Outline

Procedure	Screening Visit (within 28 Days prior to Induction Phase)	Notes
Bone Scan	X	Must be done within 42 days of randomization. Repeat if clinically indicated. Method used as per institutional guidelines Section 5.4.2.1

Table 5.1-2: CA184153 Induction Procedural Outline

Procedure	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6		Notes
	W1 D1	W4	W7	W10	W13	W16	W19	
	± 3 DAYS							
Eligibility Assessments								
ECOG Performance Status	X	X	X	X	X	X	X	Section 5.3.5
Pregnancy Test WOCBP only	X	X	X	X	X	X		Subject must have a negative pregnancy test within 24 hours prior to start of study drug Section 5.3.4
Safety Assessments								
Vital Signs	X	X	X	X	X	X		Prior to and every 30 minutes during blinded study drug administration Section 5.3.2
Weight & Body Surface Area	X	X	X	X	X	X		Weight taken and BSA calculated within 3 days prior to each dose Section 5.3.1
Height	X							Section 5.3.1
Adverse Events Assessment		X	X	X	X	X	X	Targeted physical exam done if clinically indicated Section 6
Concomitant Medications	X	X	X	X	X	X	X	Section 3.4
ECG (12 Lead)			X					Section 5.3.3
Lung Cancer Symptom Scale (LCSS)	X	X	X	X	X	X		LCSS to be administered prior to subject seeing the physician, undergoing any tests and/or receiving tests or study drug administration Section 5.7

Table 5.1-2: CA184153 Induction Procedural Outline

Procedure	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6		Notes
	W1 D1	W4	W7	W10	W13	W16	W19	
	± 3 DAYS							
Healthcare Resource Utilization				X	X	X		Section 5.8.1
Laboratory Tests								
Chemistry	X	X	X	X	X	X		AST, ALT, T.Bilirubin must be collected, analyzed and reviewed within 3 days prior to study drug administration C-reactive protein done at Day 1 and Cycle 3 only Section 5.3.6.1
Hematology	X	X	X	X	X	X		CBC with differential must be collected and analyzed within 3 days prior to study drug administration Section 5.3.6.2
Urinalysis	X	X	X	X	X	X		Section 5.3.6.3
Endocrine Panel	X		X	X	X	X		TSH must be collected prior to blinded study drug dosing. Section 5.3.6.5
Pharmacokinetic Assessments								
Pharmacokinetics & ADA			X	X	X	X		Samples must be collected prior to study drug administration. For sample timing see Table 5.5.1-1

Table 5.1-2: CA184153 Induction Procedural Outline

Procedure	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6		Notes
	W1 D1	W4	W7	W10	W13	W16	W19	
	± 3 DAYS							
Efficacy Assessments								
MRI/CT Chest & Abdomen			X		X		X	May be performed up to 7 days prior to the visit. Section 5.4.2.1
Study Drug								
Complete Screening (IVRS)	X							Section 4.4.2
Paclitaxel	X	X	X	X	X	X		Section 4
Carboplatin	X	X	X	X	X	X		Section 4
Randomize (IVRS)	X							Section 4.4.2
Blinded Study Drug ipilimumab or Placebo			X	X	X	X		Section 4. The total length of treatment is limited to 3 years from the first dose of blinded study therapy. Subjects that have reached this limit must be discontinued from treatment and enter the Toxicity/Progression Follow-up phase.

Table 5.1-3: CA184153 Maintenance Phase Procedural Outline

Procedure	Week 25 Every 12 Weeks ± 14 Days	Notes
Eligibility Assessments		
ECOG Performance Status	X	Section 5.3.5
Pregnancy Test WOCBP only	X	Negative pregnancy test required within 24 hours prior to each dose of study drug. Section 5.3.4
Safety Assessments		
Vital Signs	X	Once prior to dosing Section 5.3.2
Weight	X	Weight taken within 3 days prior to each dose Section 5.3.1
Adverse Event Assessment	X	Section 6
Concomitant Medications	X	Section 3.4
Lung Cancer Symptom Scale	X	LCSS collected at a maximum of 4 Maintenance visits. Section 5.7
Healthcare Resource Utilization	X	Section 5.8.1
Laboratory Tests		
Chemistry	X	AST, ALT, T.Bilirubin must be collected, analyzed and reviewed within 3 days prior to study drug administration Section 5.3.6.1
Hematology	X	CBC with differential must be collected and analyzed within 3 days prior to study drug administration Section 5.3.6.2
Urinalysis	X	Section 5.3.6.3

Table 5.1-3: CA184153 Maintenance Phase Procedural Outline

Procedure	Week 25 Every 12 Weeks ± 14 Days	Notes
Endocrine Panel	X	TSH must be collected prior to blinded study drug dosing Section 5.3.6.5
Pharmacokinetic (PK) Assessments		
Pharmacokinetics & ADA	X	Collected at the First Maintenance Visit, then yearly. Table 5.5.1-1
Efficacy Assessments		
MRI/CT Chest & Abdomen	X	Week 25 scans must be performed and evaluated prior to entry into the Maintenance Phase Section 5.4.2.1
Study Drug		
Blinded Study Drug ipilimumab or Placebo	X	Section 4. The total length of treatment is limited to 3 years from the first dose of blinded study therapy. Subjects that have reached this limit must be discontinued from treatment and enter the Follow-Up phase

Table 5.1-4: CA184153 End of Treatment and Follow-Up Phase Procedural Outline

Procedure	**End Of Treatment** Within 6 weeks of decision to discontinue study treatment	**Toxicity/Progression Follow-Up Phase** Every 12 Weeks ± 14 Days	**Overall Survival Follow-Up Phase** Every 12 Weeks ± 14 Days	Notes
Eligibility Assessments				
ECOG Performance Status	X	X		Section 5.3.5
Safety Assessments				
Adverse Event Assessment	X	X		Section 6
Concomitant Medications	X	X		Section 3.4
Targeted Physical Examination	X			Section 5.3.1
Lung Cancer Symptom Scale	X	X		Section 5.7
ECG (12 Lead)	X			Section 5.3.3
Laboratory Assessments				
Chemistry	X	X		Section 5.3.6.1
Hematology	X	X		Section 5.3.6.2
Urinalysis	X	X		Section 5.3.6.3
Pharmacokinetic (PK) Assessments				
Pharmacokinetics & ADA	X			Section 5.5.1
Efficacy Assessments				
MRI/CT Chest & Abdomen		X		Done until mWHO PD, or until the start of subsequent therapy for lung cancer. Section 5.4.2.2

Table 5.1-4: CA184153 End of Treatment and Follow-Up Phase Procedural Outline

Procedure	**End Of Treatment** Within 6 weeks of decision to discontinue study treatment	**Toxicity/Progression Follow-Up Phase** Every 12 Weeks ± 14 Days	**Overall Survival Follow-Up Phase** Every 12 Weeks ± 14 Days	Notes
Survival Follow-up				
Subject Contact			X	Section 3.1.2.6
Evaluation of subsequent therapy			X	Section 3.1.2.6

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments during the Screening will be permitted (this does not include parameters that require a confirmatory result).

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

5.2 Study Materials

Placebo (0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection) and in-line infusion filters will be provided by the site pharmacy. In cases where local regulations do not allow sites to provide placebo, the sponsor/designee may provide it.

The sponsor (or designee) will also supply:

- Study document file binder
- IVRS Manual
- CRFs (electronic and paper)
- National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0
- Lung Cancer Symptom Scale (LCSS).

5.3 Safety Assessments

All subjects who receive at least 1 dose of study treatment (ipilimumab, placebo, paclitaxel, or carboplatin) will be evaluated for safety parameters. Additionally, any occurrence of an SAE from the time of consent forward will be documented.

Safety will be evaluated for all treated subjects using the NCI CTCAE version 3.0. Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests. The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance.

5.3.1 Medical History, Physical Exam, Physical Measurements

Medical history will be obtained at the Screening Visit. Medical history must include date of diagnosis of lung cancer, including histological or cytological documentation of malignancy.

A complete physical examination including height, weight, body surface area (BSA) will be performed within 3 days prior to Day 1. Weight must be taken and BSA calculated (for chemotherapy dosing if applicable) using the Dubois-Dubois formula, **within 3 days prior to each dose,** for purposes of dose calculation.

Subsequent targeted physical examinations will be performed if clinically indicated and at the End of Treatment Visit. Any physical examination finding that qualifies as an AE or SAE must be documented on the appropriate CRF pages.

Pre-Treatment events present within 2 weeks of starting study therapy, whether or not related to current disease, will be captured prior to study start. Any worsening (≥ Grade 1 from Baseline) will be documented as an AE in the CRF.

5.3.2 Vital Signs

Vital signs to include: blood pressure (BP), heart rate, respiration rate, and temperature.

During blinded study drug infusions (ipilimumab or placebo) in the Induction Phase, vital sign measurements must be collected prior to dosing and every 30 minutes for the duration of the blinded study drug (ipilimumab or placebo) infusion. During Maintenance Phase infusions vital signs must be collected once prior to dosing. Vital signs are to be captured in the patient record and any abnormal values must be reported as an Adverse Event.

5.3.3 Electrocardiogram (ECG)

All subjects will be required to have a 12-lead ECG prior to dosing at Cycle 3 and again at the End of Treatment visit. Additional ECGs must be obtained if clinically indicated.

5.3.4 Pregnancy Testing

WOCBP are required to have pregnancy tests performed. A negative pregnancy test must be documented at the Screening visit. Additionally, WOCBP must exhibit a *negative serum or urine pregnancy* (minimum sensitivity 25 IU/L or equivalent units of HCG) *within 24 hours prior to the start of study drug*.

The Screening pregnancy test may need to be repeated prior to the start of study drug dosing.

In addition, a urine pregnancy test (serum or urine with a minimum sensitivity 25 IU/L or equivalent units of HCG) must be performed within 24 hours prior to dosing at every study drug administration visit.

5.3.5 ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status will be evaluated and documented at Screening and at each dosing visit as outlined in Section 5.1. See Appendix 1 for description of ECOG status.

5.3.6 Laboratory Testing

All protocol-specified laboratory tests must be analyzed and reported by the local lab.

Laboratory tests are obtained as part of screening and to determine eligibility. Results of safety laboratory collections (ie, CBC, LFT and creatinine) must be obtained and reviewed in advance of blinded study drug dosing. Screening results may be used for C1D1 assessments if within the required window. Any W1D1 requirement not done during screening still needs to be completed.

- LFTs during Induction and Maintenance Phase labs must be collected within a window of up to 3 days prior to dosing blinded study drug.

5.3.6.1 Chemistry

Serum chemistry will be obtained as outlined in Section 5.1 and will include:

- albumin,
- amylase (**lipase should be monitored when amylase is abnormal with clinical significance**),
- urea or BUN,
- creatinine,
- ALT,
- AST,
- LDH,
- serum alkaline phosphatase,
- direct bilirubin,
- total bilirubin,
- glucose,
- total protein,
- sodium,
- potassium,
- chloride,
- HCO3 or equivalent,
- calcium,
- phosphorous,
- uric acid,
- C-reative protein (CRP).

Additional draws must be incorporated when monitoring recovery from any non-hematologic AE (eg, elevations in ALT, AST).

C-reactive protein (CRP) to be measured at baseline and prior to first blinded study drug (ipilimumab or placebo) dose.

Note: LFTs (ALT, AST, and T. bilirubin) and TSH must be performed within 3 days prior to each blinded ipilimumab dosing visit. The results of the LFT tests must be reviewed by the principal investigator (or designee) prior to dosing.

5.3.6.2 Hematology

A CBC with differential will be obtained as outlined in Section 5.1 and will include:

- hemoglobin,
- hematocrit,
- red blood cell count,
- white blood cell count,
- platelets (direct platelet count),
- differential counts. The CBC differential includes enumeration of:
  - neutrophils,
  - lymphocytes,
  - eosinophils,
  - monocytes,
  - basophils,
  - any atypical blood cells.

Additional draws must be incorporated when monitoring recovery from any hematologic AE.

Note: CBC with differential must be collected and analyzed within 3 days prior to each chemotherapy dosing visit. Results of these tests must be reviewed by the principal investigator (or designee) prior to dosing.

5.3.6.3 Urinalysis

A urinalysis will be obtained as outlined in Section 5.1 and will include a gross examination including:

- specific gravity,
- protein,
- glucose,
- blood.

A microscopic evaluation will also be performed, as needed, to include

- WBC/HPF,
- RBC/HPF,
- any additional findings.

5.3.6.4 HIV and Hepatitis Panel

At screening, testing must be performed for:

- HIV,
- hepatitis C antibody,
- HBsAg.

These tests will be repeated during the course of the study if clinically indicated.

5.3.6.5 Specialty Labs

The endocrine panel consists of:

- TSH
- free T3
- free T4

all performed at Day 1.

- TSH should be also repeated at Cycles 3 through 6.
- Free T3 should be repeated as clinically indicated.

5.3.7 Imaging Assessment for the Study

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

5.4 Efficacy Assessments

5.4.1 Primary Efficacy Assessment

Every effort will be made to collect survival data on all randomized subjects who received at least one dose of blinded study drug, including subjects withdrawn from treatment for any reason, who are eligible to participate in the study (eg, not incarcerated) and who have not withdrawn consent for survival data collection. If the death of a subject is not reported, every

date collected in this study representing a date of subject contact will be used in determining the subject's last known alive date.

5.4.2 Secondary Efficacy Assessments

In this study, mWHO criteria will be used to assess subjects' tumor response to study treatment and guide clinical care. The investigator will determine the mWHO response at each tumor assessment (Section 5.4.2.4). The Best Overall Response for the subject will be calculated by the Sponsor based on the overall timepoint tumor response recorded in the tumor assessment eCRF.

5.4.2.1 Radiological Assessment of Tumor Lesions

CT/MRI imaging of the chest and abdomen is required at Screening and at each tumor assessment (TA), regardless of the location of known metastases. In addition, CT/MRI scans must be obtained of anatomic regions not covered by the chest and abdomen scans in subjects where there is clinical suspicion of deep soft tissue metastases (eg, lesions in the thigh). Such additional CT/MRIs will be required at Screening when deep soft tissue disease is known/suspected and must be consistently repeated at all TAs if a deep soft tissue lesion is identified during Screening. The same imaging modality must be used for all TAs.

Brain scans (CT or MRI) are required at Screening to rule out CNS metastases. Brain scans to be repeated as clinically indicated.

A bone scan (per institutional standards) is required at screening except where prohibited by local regulations. If local regulations require additional approvals of a bone scan, enrollment may begin without the bone scan until appropriate approvals are obtained. The bone scan must be repeated if there is clinical suspicion of bone metastases during the study.

Similar methods of TA and similar techniques must be used to characterize each identified and reported lesion at Screening and all subsequent tumor assessments. Imaging-based evaluation is preferred to clinical examination. Helical (spiral) CT scans of the chest and abdomen are preferred. If not available, conventional (non helical, non-spiral CT) should be used; however, a measurable lesion must not have the longest diameter smaller than 20 mm. IV contrast should be used for all CT scans; if IV contrast is contraindicated, oral contrast maybe used, or MRI should be used at the Screening exam and at all TA time points. Subjects who develop contrast allergy after study enrollment must be followed by MRI for subsequent tumor measurements.

Sections should be contiguous, similarly sized and consistent from visit-to-visit. Section thickness must be based on institutional standards (eg, from 5 to 8 mm, 10 mm cuts are not recommended). Chest x-rays and ultrasound are not acceptable methods to measure disease. Response and progression of disease must be documented by CT or MRI similar to the methods used at Screening.

If an abnormal bone scan is observed at any time point throughout the study, a repeat bone scan must be performed prior to the confirmation of a complete response (eg, the remaining metastatic lesions must have resolved). In case of new lesions such as pleural effusion, cytology must be

performed to identify and confirm malignancy. Skin and soft tissue lesions will be captured as non-measurable lesions through physical examination only.

Any subject who develops an objective tumor response (CR or PR) is required to undergo confirmatory scans no less than 4 weeks since the prior scan in order to verify the reliability of the radiologic finding

Tumor assessments are required until mWHO PD, or until the end of treatment for subjects who continue to be treated beyond mWHO PD per Section 4.5.3.1, or until the start of subsequent therapy for lung cancer for subjects who have discontinued study therapy.

5.4.2.2 Definition of Measurable/Non-measurable Lesions

- Measurable lesions are lesions that can be accurately measured in 2 perpendicular diameters, with at least one diameter ≥ 20 mm and the other dimension ≥ 10 mm (10 mm x 10 mm for spiral CT with cuts of 5 mm). The area will be defined as the product of the largest diameter with its perpendicular.
- Non-measurable (evaluable) lesions are all other lesions, including unidimensional measurable disease and small lesions (lesions without at least 1 diameter ≥ 20 mm) on conventional CT or MRI or ≥ 10mm or spiral CT), and any of the following: lesions occurring in a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques and cystic lesions.

All measurable and non-measurable lesions should be assessed at Screening and at the defined TA time points (see Section 5.1). Extra assessments may be performed, as clinically indicated, if there is a suspicion of progression.

5.4.2.3 Definition of Index/Non-index Lesions

At Screening, measurable lesions, up to a maximum of **5 lesions per organ and 10 lesions in total,** must be identified as *index* lesions to be measured and recorded on the CRF. The *index* lesions should be representative of all involved organs. In addition, *index* lesions must be selected based on their size (eg, lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the subject's tumor burden. At Screening, a Sum of the Products of Diameters (SPD) for all *index* lesions will be calculated. The baseline SPD will be determined from the screening scans. The baseline SPD will be used as the reference point to determine the objective tumor response of the *index* lesions at each TA post randomization.

Measurable lesions, other than *index* lesions, and all sites of non-measurable disease, will be identified as *non-index* lesions. *Non-index* lesions will be recorded on the CRF and will be

evaluated at the same assessment time points as the *index* lesions. In subsequent assessments, *non-index* lesions will be recorded as complete response, stable or progression.

Calculation of Sum of Product of Diameters (SPD)

SPD is an estimation of tumor burden based on the index lesions observed at baseline. The 2 greatest perpendicular diameters are used to estimate the size of each tumor lesion. The SPD is calculated as the sum of the product of the diameters for index tumor lesions. Several variations of the SPD are identified for the purpose of classification of tumor responses.

SPD at Screening: The sum of the product of the diameters for all index lesions identified at screening assessment prior to randomization.

SPD at TA: For every post randomization TA collected, per protocol Section 5.1 or as clinically indicated, the SPD at TA will be calculated using tumor imaging scans. Only index lesions are included in the calculation.

SPD Nadir: For tumors that are assessed more than one time after baseline, the lowest value of the SPD (SPD Baseline or SPD at TA) is used to classify subsequent TAs for each subject.

5.4.2.4 Definition of Tumor Response using mWHO

The mWHO criteria were developed as a hybrid tumor response classification system using elements of both the WHO and RECIST criteria in an attempt to more accurately measure tumor lesions and estimate tumor responses. In this study, the response per mWHO as determined by the investigator will serve as the basis of key secondary endpoints and to guide clinical care.

To determine timepoint overall response per mWHO post randomization, all timepoint assessments are considered. The assessment taken at screening will be considered baseline.

To determine timepoint overall response per mWHO post randomization, all timepoint assessments are considered. The assessment taken at screening will be considered baseline.

At each timepoint, timepoint overall response per mWHO will be calculated based on index lesion response, non-index lesion response, and new lesion response, as follows:

Definition of Index Lesion Timepoint Response Using mWHO

- Complete Response: Complete disappearance of all index lesions.
- Partial Response: Decrease, relative to baseline, of 50% or greater the SPD.
- Stable Disease: Does not meet criteria for complete or partial response, in the absence of progressive disease or inability to determine.
- Progressive Disease: At least 25% increase in the SPD from the nadir.
- Unknown: Response cannot be determined (eg, due to image quality).

Definition of Non-Index Lesion Timepoint Response Using mWHO (based on non-index lesions present at baseline)

- Complete Response: Complete disappearance of all non-index lesions.
- Stable Disease: A decrease or tumor stabilization of one or more non-index lesions in the absence of complete disappearance, progressive disease, or inability to determine.
- Progressive Disease: Unequivocal progression of non-index lesion(s)
- Unknown: Response cannot be determined (eg, due to image quality).

Definition of New Lesion Timepoint Response Using mWHO

- Absent: No unequivocal new lesion is present
- Present: At least 1 unequivocal new lesion is present
- Unknown: Response cannot be determined (eg, due to image quality).

Definition of Timepoint Overall Response (OR) Using mWHO

All subjects will have the OVERALL RESPONSE at each timepoint classified based on timepoint index lesion response, non-index lesion response, and new lesion response, as outlined below:

- Complete Response (CR): Disappearance of all known disease. Complete response for index lesions, complete response for non-index lesions, and the absence of unequivocal new lesions.
- Partial Response (PR): An index lesion response of CR or PR, a non-index response of CR or SD, and the absence unequivocal new lesions, provided the criteria for CR are not met.
- Stable Disease (SD): An index lesion response of SD, a non-index lesion response of SD, and the absence of unequivocal new lesions.
- Progressive disease (PD): Any of the following:
  - An index lesion response of PD
  - A non-index lesion response of PD
  - The presence of an unequivocal new lesion.
- Unknown (UN) Not classifiable above. Tumor assessments which cannot be evaluated (eg, due to image quality, inability to assess all relevant lesions, etc) will be reported as UN.

Table 5.4.2.4-1 summarizes how overall response is determined based on evaluation of index, non-index and new lesions:

Table 5.4.2.4-1: Overall Response per Tumor Assessment Timepoint

Index Lesions	Non-index Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	SD	No	PR
PR	CR or SD	No	PR
SD	CR or SD	No	SD
PD	Any Result	Any Result	PD
Any Result	PD	Any Result	PD
Any Result	Any Result	Yes	PD

5.5 Pharmacokinetic Assessments

Trough serum samples for pharmacokinetic (PK) assessments will be analyzed for ipilimumab by a validated assay. PK samples will be collected according to the schedule listed in Table 5.5.1-1 in all treated subjects.

Blood for PK and Anti Drug Antibody (ADA) testing will be drawn pre-dose starting at Cycle 3 and prior to each subsequent blinded study drug dose (ipilimumab or placebo), at the first maintenance dose, then yearly, and at the end of treatment (a serum PK trough sample and ADA will be collected at the discontinuation of study medication at the End Of Treatment visit).

Separate, detailed instructions for the collection, processing, handling, labeling, storage, and shipment of PK and ADA samples will be provided in the central lab manual.

5.5.1 PK and Human Anti-human Antibody (ADA) Assessments

ADA will be evaluated using validated assay at specified time points as noted in Table 5.5.1-1. Samples that confirm positive for ADA will be further tested for drug neutralizing activity using a validated, cell-based functional neutralizing antibody (NAb) assay.

Table 5.5.1-1: PK and ADA Sampling Schedule

Sample Collection Time			Time (Relative To Dosing) hours:min	PK Collection	ADA Collection
Cycle No.	**Study Day**	**Time (Event)**			
3	**Week 7**	0 H (pre-dose)	00:00 (pre-dose)	X	X
4	**Week 10**	0 H	00:00 (pre-dose)	X	X
5	**Week 13**	0 H	00:00 (pre-dose)	X	X
6	**Week 16**	0 H	00:00 (pre-dose)	X	X
Maintenance (First Dose)	**Week 25**	0 H	00:00 (pre-dose)	X	X

Table 5.5.1-1: PK and ADA Sampling Schedule

Sample Collection Time			Time (Relative To Dosing) hours:min	PK Collection	ADA Collection
Cycle No.	Study Day	Time (Event)			
Maintenance (Yearly)[a]		0 H	00:00 (pre-dose)	X	X
End of Treatment		0 H	00:00 (pre-dose)	X	X

[a] Yearly maintenance PK and ADA sample should be drawn approximately 1 year from the first Maintenance Dose sample collection.

5.6 Biomarker Assessments

Not Applicable

5.7 Outcomes Research Assessments

Quality of life (QoL) will be assessed using the Lung Cancer Symptom Scale (LCSS). The LCSS is designed as a lung cancer-specific measure of QoL, specifically for use in clinical trials. It evaluates 6 major symptoms associated with lung malignancies and their effect on overall symptomatic distress, functional activities, and global QoL. It captures in detail those dimensions most likely to be influenced by therapeutic interventions and evaluates other dimensions globally. The LCSS will be administered as outlined in Table 5.1-2, Table 5.1-3, and Table 5.1-4 during the Induction, Maintenance, End of Treatment and Toxicity/Progression Follow-up Phases, respectively.

The LCSS consists of 9 visual analogue scales that are administered in a fixed order and completed by the subject. Subject training involves a face-to-face interview initially for demonstration of visual analogue scale (VAS) with a simple example question related to the weather with telephone interview acceptable once the subject is familiar with VAS. For telephone interview, a time is set with the subject that the observer will call and the subject is either given the LCSS at the last contact or mailed the cards prior to the "telephone appointment". Administration time is approximately 5 minutes.

It is recommended that the LCSS be administered before the subject sees or talks with the physician, undergoes any tests or treatments, and/or receives results of any tests (x-rays, blood tests, etc). The subject should perform the assessment alone. Family members or significant others should be asked to leave, but if they decline, proceed with administering the instrument. Reinforce that the response desired is the subject's response. If a subject cannot recall, refuses to complete, or cannot complete the scale, record the reason for non-compliance on the card (ie, "too ill" or "could not understand concept."). Detailed administration instructions for the LCSS are provided in Appendix 2.

In addition to the patient scale, there is an optional observer scale in the LCSS. The observer scale will not be used in this study.

5.8 Other Assessments

5.8.1 Healthcare Resource Utilization

Healthcare resource utilization data (eg, hospitalizations, non-protocol specified medical visits, etc) will be collected for all randomized patients. The resource utilization captured is specific to hospital admission utilization data and non protocol specified visits related to study therapy. Resource utilization questions will be asked during the study at all treatment visits beginning with Week 10.

5.9 Results of Central Assessments

Not Applicable

5.10 Pharmacodynamics Assessments

Absolute Lymphocyte Count (ALC) will be measured as part of the routine hematology panel at frequent time points, starting before first treatment and continuing throughout the treatment period or later. ALC will be investigated as a potential marker of immune activity, and as a potential predictor of efficacy.

5.11 Pharmacogenomic/Pharmacogenetic Assessments

Not applicable.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

> Related: There is a reasonable causal relationship between study drug administration and the AE.
> Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A ***serious AE (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose (except for single incidence of non-serious dosing error), potential drug-induced liver injury and cancer are not always serious by regulatory definition, these events must be handled as SAEs (see Section 6.1.1 for reporting pregnancies).

In any studies where endpoints are excluded from regular reporting as SAEs, any component of a study endpoint that is considered related to study therapy must be handled as SAE.

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or life threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)

- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting.

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 90 days of discontinuation of dosing or within 30 days of the last visit for screen failures. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should collect any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: See Contact Information list.

SAE Facsimile Number: See Contact Information list.

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for pregnancy reporting): See Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS/designee using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.1.1.1 Clinical Safety Program

The Clinical Safety Program (CSP) is a process to collect and analyze additional clinical information on adverse events of interest (EOIs) in an effort to enhance understanding of product safety. During the course of the study, AEs and SAEs recorded in the database are monitored for specific EOIs. Once an EOI is identified, additional eCRF pages, which are designed to collect relevant supplemental information pertaining to the EOI, are made available to the site.

The ipilimumab program will be collecting CSP data on potential contributing factors for serious dermatologic adverse events of interest in this study. Serious dermatological AEs observed to date include Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), and were reported in < 1% (4/658) of subjects treated at 10 mg/kg. Investigators are strongly encouraged to discuss any serious AE with the Medical Monitor.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.2.2 Adverse Events of Interest

Adverse events of interest are AEs consistent with an immune-mediated mechanism and include enterocolitis, dermatitis, hepatitis, endocrinopathies and neuropathies, although other less common immune-mediated AEs have been reported as well. The severity of these immune-mediated AEs may range from mild to severe and life threatening.

These AEs of interest will be evaluated as follows:

1) Immune-related adverse events (irAEs): These are AEs that are 1) AEs of interest (per description above) and 2) drug related by the investigator.
2) Immune-mediated adverse reactions (imARs): AEs of special interest will also be adjudicated by the investigator as an imAR (yes) or not an imAR (no) or unknown. The rationale for imAR adjudication is in Section 1.1.4.3. The imAR CRF module must be completed for all AEs of special interest including 1) investigator adjudication of AE as imAR (yes or no) and 2) reason, and objective evidence as applicable, to support the basis for that decision.

The characterization of an AE as an imAR or not is based on retrospective review of the AE that takes into account the context (eg, concomitant therapies, medical history, etc), evaluation, treatment and outcome. Therefore, for purposes of managing an AE, the investigator should refer to the guidance in the protocol and Investigator Brochure for evaluation and treatment and not use the case definitions. Data relative to these evaluations and interventions must be included in the source documentation and recorded on the appropriate eCRF. The complete case definitions for classifying AEs as an imAR are provided as an Appendix in the IB, however in general:

1) AEs of interest should first be evaluated for exclusion as an imAR:
   a) Typical reasons an event is not considered an imAR
      i) Likely due to concomitant drug/chemotherapy/radiation and thus unlikely an imAR
      ii) Documented evidence of tumor, tumor progression, or tumor related as the most likely cause of the event
      iii) Same grade event at baseline/medical history/pre-treatment event
      iv) Event likely caused by infection, or other disease process (eg, infection) or etiology
      v) Resolves in less than 1 week without immunosuppression (a definition based on review of resolution for immune-mediated AEs of interest from ipilimumab program) suggests that the AE is not an imAR
      vi) Other reasons may also be valid (see Case Definitions)
2) If the investigator is unable to exclude, then the AE of interest should be evaluated as an imAR:
   a) Typical reasons an event is considered an imAR:
      i) Inflammation per pathology or endoscopy
      ii) Radiologic, imaging, laboratory, or other diagnostic procedure the provides or suggest evidence of an inflammatory process
      iii) Improves/resolves after immunosuppression (eg, favorable evolution when treated by immunosuppressive drugs supports the AE to be an imAR.)
      iv) Similar to previous imAR in same organ (based on clinical data from ipilimumab program that imARs may recur in same organ
      v) Other reasons may also be valid such as AE persists greater than 1 week or worsens (see Case Definitions).

Occasionally, AEs of interest will not have enough information to classify as imAR or not, in which case, the AE should be classified as unknown

6.3 Laboratory Test Abnormalities

Laboratory test values captured as part of the study should be recorded on the appropriate laboratory test results pages of the CRF. The following laboratory abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject or a female partner of a male study participant is pregnant or may have been pregnant at the time study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued for the female study participant in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional ingestion or infusion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

To provide independent oversight of safety, study conduct and efficacy, a Data Monitoring Committee (DMC) will be instituted.

The DMC will meet every 6 months (± 2 months) to ensure that subject safety is carefully monitored. The DMC might also be consulted on an ad-hoc basis should a safety signal emerge, and may also convene an ad-hoc meeting on its own initiative. Following the review, the DMC will recommend continuation, modification, or discontinuation of the study based on observed toxicities.

A separate DMC charter will describe the activities of this committee, details regarding the interim analysis and the stopping rules.

The DMC will have access to reports of unblinded study data including analyses addressing population characteristics, dosing, safety, and efficacy updated as available prior to each of its meetings. To ensure preservation of the study blind, all unblinded study reports will be produced by an independent statistician. The independent statistician will receive unblinding codes directly from the IVRS vendor and will provide unblinded reports directly and solely to the DMC. The content of the unblinded reports will be described in the DMC charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

This study will randomize approximately 867 subjects in a 1:1 ratio to ipilimumab + carboplatin/paclitaxel arm and placebo + carboplatin/paclitaxel arm. Assuming a 24% dropout rate during the first two cycles of chemotherapy alone period (ie, the proportion of subjects who never receive blinded therapy due to any reason), it is estimated that approximately 660 subjects will receive blinded study therapy

In the primary endpoint of overall survival among the randomized subject who received at least one dose of blinded study therapy, an exponential distribution and a true hazard ratio [ipilimumab + carboplatin/paclitaxel vs placebo + carboplatin/paclitaxel] of 0.75 post chemotherapy alone period is assumed. It is also assumed that the median OS for chemotherapy alone arm after two cycle of chemotherapy is 10 months. A total of 467 events out of 660 randomized subjects who received blinded study therapy will provide 86% power to detect a statistically significant difference in OS among all randomized subjects who received blinded study therapy between treatment arms with a Type I error rate of 5% based on a 2-sided log-rank test. In this study, it is estimated that 85% of the randomized subjects (ie, 736 subjects) will come from China. Out of the 736 randomized Chinese subjects it is estimated that 558 subjects will receive blinded study medication. A total of 397 events in this population will still provide 80% of power to detect a statistically significant difference in the primary endpoint.

With the current design, the overall hazard ratio for OS among all randomized subjects is approximately 0.81 based on the simulation results with an estimated dropout rate of 24% during the first two cycles of chemotherapy. This assumes a piecewise exponential distribution with a hazard ratio of 1 during the first 2 cycles of chemotherapy alone and a true hazard ratio of 0.75 after that. A total of 644 events out of 867 randomized subjects will provide 75% power to detect a statistically significant difference in OS among all randomized subjects between treatment arms with a Type I error rate of 5% based on a 2-sided log-rank test.

Assuming that the enrollment follows a piecewise constant accrual rate (5 subjects per month during Months 1 - 3, 10 subjects per month during Months 4 - 6, and 28 subjects per month for the rest of the accrual period), it is estimated that total accrual will take approximately 33 months and the study will take 45 months to complete.

Sample size calculation described above was based on 10,000 simulation results in which OS follows a piecewise exponential distribution. The statistical software R version 2.11.1 was used for this exercise.

The analysis will not be conducted until the following 2 conditions have both been met: 1) 468 OS events have been observed in randomized subjects treated with at least one dose of blinded study therapy and 2) 644 OS events have been observed in all randomized subjects. The primary analysis will include all events available at the time of the database lock.

8.2 Populations for Analyses

- **All Enrolled Subjects**: All subjects who signed an informed consent form and were registered into the IVRS.
- **Randomized Subjects who received at Least One Dose of Blinded Study Therapy**: All enrolled subjects who were randomized and received at least 1 dose of blinded study therapy (ipilimumab/placebo). Unless otherwise indicated, demography, baseline characteristics and efficacy endpoints (including the primary endpoint of OS) will be analyzed in this population **grouped as randomized**.
- **Randomized Chinese Subjects who received at Least One Dose of Blinded Study Therapy**: All enrolled Chinese subjects who were randomized and received at least 1 dose of

blinded study therapy (ipilimumab/placebo). Unless otherwise indicated, demography, baseline characteristics and efficacy endpoints (including the primary endpoint of OS) will be analyzed in this population **grouped as randomized**.

- **All Randomized Subjects**: All enrolled subjects who were randomized to a treatment arm. Analyses of demography and baseline characteristics, proportion of subjects who discontinued study medication before receiving blinded study therapy, as well as selected efficacy endpoints, will be performed on this population, **grouped as randomized**, as sensitivity analyses.
- **All Randomized Chinese Subjects**: All enrolled subjects who were randomized to a treatment arm. Analyses of demography and baseline characteristics, proportion of subjects who discontinued study medication before receiving blinded study therapy, as well as selected efficacy endpoints, will be performed on this population, **grouped as randomized**, as sensitivity analyses.
- **Treated Subjects who received at least One Dose of Blinded Study Therapy**: All subjects who received at least 1 dose of blinded study therapy (ipilimumab/placebo). Unless otherwise indicated, safety analyses will be performed in this population **grouped as treated**, from the first dose of blinded study therapy to 90 days after the last dose.
- **Treated Chinese Subjects who received at least One Dose of Blinded Study Therapy**: All Chineses subjects who received at least 1 dose of blinded study therapy (ipilimumab/placebo). Unless otherwise indicated, safety analyses will be performed in this population **grouped as treated**, from the first dose of blinded study therapy to 90 days after the last dose.
- **All Treated Subjects**: All subjects who received at least 1 dose of study treatment. Selected safety analyses will be repeated on this population **grouped as treated**. Details will be provided in the Statistical Analysis Plan.
- **All Treated Chinese Subjects**: All Chinese subjects who received at least 1 dose of study treatment. Selected safety analyses will be repeated on this population **grouped as treated**. Details will be provided in the Statistical Analysis Plan.
- **PK data set**: All available serum time-concentration data from randomized subjects dosed with ipilimumab.
- **Pharmacodynamic data set**: ALC data for all randomized and treated subjects with known date of first dose of ipilimumab or placebo.
- **Outcomes Research Subjects**: Unless otherwise specified, analyses of change from baseline for each outcomes research indicator will be based on all randomized subjects who received at least one dose of blinded study medication and who had at least 1 baseline and 1 post-randomization LCSS assessment, **grouped as randomized**.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

Overall survival (OS) in the population of all randomized subjects who received at least one dose of blinded study therapy will be defined as the time from the date of randomization until the date

of death. For those subjects who have not died, OS will be censored on the last date the subject was known to be alive.

Every effort will be made to collect survival data on all subjects, including subjects withdrawn from treatment for any reason, who are eligible to participate in the study (eg, not incarcerated) and who have not withdrawn consent for survival data collection. If the death of a subject is not reported, every date collected in this study representing a date of subject contact will be used in determining the subject's last known alive date.

8.3.2 Secondary Endpoint(s)

The secondary efficacy endpoints include OS in the population of all randomized subjects, and Progression-free Survival (PFS) among all randomized subjects who received at least one dose of blinded study therapy using mWHO criteria. In addition, selected efficacy endpoints (ie, OS among all randomized subjects who received blinded study therapy, OS, and PFS per mWHO all randomized subjects who received blinded study therapy) will be repeated only for all randomized Chinese subjects (ie, Chinese subset among all randomized subjects).

8.3.2.1 OS among All Randomized Subjects

Among all randomized subjects, OS will be defined as the time from the date of randomization until the date of death. For those subjects who have not died, OS will be censored on the last date the subject was known to be alive.

8.3.2.2 Progression-free Survival Per mWHO among Subjects who Received Blinded Study Therapy

Progression-free survival (PFS) among all randomized subjects who received at least one dose of blinded study therapy per mWHO criteria will be defined as the time between the date of randomization and the date of progression per mWHO criteria or death, whichever occurs first. A subject who dies without reported progression per mWHO criteria will be considered to have progressed on the date of death. For those subjects who remain alive and have not progressed, PFS will be censored on the date of last evaluable tumor assessment. For those subjects who remain alive and have no recorded post-baseline tumor assessment, PFS will be censored on the day of randomization.

[redacted]

8.3.3.2 Safety Endpoints

The safety endpoints include serious and non-serious adverse events, laboratory evaluations, dose exposure and modifications. In addition, abnormal vital signs and physical examination findings are also included. Analyses will be described in Section 8.4.3.

8.4 Analyses

The following general considerations apply to statistical analyses if not otherwise specified:

- Baseline characteristics analyses will be performed for all randomized subjects who received at least one dose of blinded study therapy. Most recent baseline evaluation (counting backward from randomization date) collected will be used for baseline analyses. Selected baseline characteristics analyses will be repeated on all randomized subjects regardless of whether or not they will receive blinded study therapy.
- Efficacy analyses (including primary and secondary efficacy endpoints, except for OS on all randomized subjects) will be performed for all randomized subjects who received at least one dose of blinded study therapy and for all randomized Chinese subjects who received at least one dose of blinded study therapy, as randomized, unless otherwise indicated. Analysis on OS secondary endpoint will be performed for all randomized subjects and on all randomize Chinese subjects separately, regardless of whether or not they received blinded study therapy.
- Drug exposure and safety analyses will be performed for all treated subjects who received at least one dose of blinded study drug, and for all treated Chinese subjects who received at least one dose of blinded study drug separately, grouped as treated, unless otherwise mentioned. A selected set of safety analyses will be performed for all treated subjects. A detailed list of these analyses will be included in the Statistical Analysis Plan.
- Details on statistical analyses will be described in the Statistical Analysis Plan (SAP).

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline laboratory results will be summarized by treatment arm using descriptive statistics for all randomized subjects who received at least one dose of blinded study therapy and all randomized Chinese subjects separately.

Selected baseline characteristics analyses will be repeated on all randomized subjects and on all randomized Chinese, separately, regardless of whether or not they will receive blinded study therapy. Detailed list will be included in the SAP.

8.4.2 Efficacy Analyses

All hypothesis testing will be two-sided. All hypothesis testing will be based on a significance level of 0.05

Analyses of the primary endpoint (OS) and majority of secondary and exploratory efficacy endpoints will all be based on all randomized subjects who received at least one dose of blinded study therapy with the exception of the secondary endpoint of overall survival in all randomized and in all randomized Chinese subjects. Analyses of selected efficacy endpoints will be performed for all randomized Chinese subjects who received at least one dose of blinded study therapy, in all randomized subjects regardless of whether they received or not blinded study therapy, and/or on all randomized Chinese subjects regardless of whether or not they received blinded study therapy. Additional details are documented in the SAP.

8.4.2.1 Methods for Primary Endpoint

The distribution of OS among randomized subjects who received at least one dose of blinded study therapy will be compared between treatment arms using a two-sided log-rank test unstratified. The stratified-rank test p-value, hazard ratio and its associated two-sided 95% CI will be estimated via an unstratified Cox model with treatment arm as the only covariate, unless otherwise indicated.

The event-free OS probabilities for each treatment arm will be estimated and plotted using the Kaplan-Meier (KM) product-limit method. The estimates of medians and two-sided 95% CIs will be calculated via complementary log-log transformation. KM estimates of OS rates for randomized subjects who received at least one dose of blinded study therapy at the following, but not limited to, time points: 6 months, 1 year, 18 months and 2 years and associated two-sided log-log transformed 95% confidence interval will be calculated.

[redacted]

[redacted]

8.4.2.3 Efficacy Subset Analysis

Baseline Subsets

OS among randomized subjects who received at least one dose of blinded study therapy will also be summarized within subsets at baseline (Section 8.4.1) (with two-sided 95% CI for the medians calculated via complementary log-log transformation). The hazard ratios and associated two-sided 95% CIs, of phased ipilimumab vs phased placebo will be computed using unstratified Cox model with treatment as the single covariate.

- Age (< 65, ≥ 65)
- Gender (male, female)
- ECOG performance status (0, 1)
- Smoking (heavy smoker, light/non-smoker)
- M-stage (M1a, M1b or recurrent disease).

8.4.2.4 Sensitivity Analysis

If the primary analysis of OS among randomized subjects who received at least one dose of blinded study therapy is statistically significant, additional sensitivity analyses such as stratified log-rank test by the stratification factors of Eastern Cooperative Oncology Group (ECOG) performance status (PS), smoking status and gender, to compare OS between the 2 treatment arms will be conducted be conducted (more details will be provided in the Statistical Analysis Plan):

In addition, although it is expected that the balance from randomization will be preserved among treatment arms in the population of randomized subjects who received at least one dose of blinded study therapy, an imbalance may occur by chance. At the time of final analysis, key prognostic factors, such as stratified factors and baseline disease characteristics will be summarized between the 2 treatment arms in this population. Should imbalance occur, sensitivity analyses will be conducted to evaluate the robustness of the treatment effect.

8.4.2.5 Efficacy Analysis for All Randomized Chinese Subjects

The following selected efficacy analyses are planned for all randomized Chinese population and additional details will be provided in the SAP:

- The event-free OS probabilities among subjects who received at least one dose of blinded study therapy for each treatment arm will be estimated and plotted using the KM product-limit method for each region. The estimates of medians and two sided 95% CIs will be calculated using a log-log transformation.
- In the population of randomized subjects who received at least one dose of blinded study therapy, the OS among hazard ratio and its associated two sided 95% CI will be presented.
- The event-free OS probabilities among all randomized subjects regardless of whether or not they received blinded study therapy will be estimated and plotted using the KM product-limit method for each region. The estimates of medians and two sided 95% CIs will be calculated using a log-log transformation.
- In the population of among all randomized subjects regardless of whether or not they received blinded study therapy, the OS among hazard ratio and its associated two sided 95% CI will be presented.
- In the population of randomized subjects who received at least one dose of blinded study therapy, the event-free PFS probabilities for each treatment arm will be estimated and plotted using the KM product-limit method for each region. The estimates of medians and two sided 95% CIs will be calculated by the Brookmeyer and Crowley method.
- In the population of randomized subjects who received at least one dose of blinded study therapy, the PFS hazard ratio and its associated two sided 95% CI will be presented.
- In the population of randomized subjects who received at least one dose of blinded study therapy, BORR per mWHO for each treatment arm will be estimated together with exact two-sided 95% CI.

8.4.3 Safety Analyses

Descriptive statistics of safety will be presented for all treated subjects who received blinded study therapy using the NCI CTCAE version 3.0 by treatment arm. All on-study AEs, drug-related AEs, immune-related AEs, SAEs, and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v3.0 criteria by system organ class and by preferred term. The listings by subject will be produced for all deaths, all SAEs, and all AEs leading to discontinuation of study drug. On-study laboratory parameters, including hematology, serum chemistry, liver function, and renal function will be summarized using worst grade per NCI CTCAE v3.0 criteria. The

reporting period for these subjects will be from the first dose of blinded study therapy to 90 days (5 half lives) after the last dose is received.

A selected set of the safety analyses described above will be repeated for all treated subjects including those who never received blinded study therapy due to reason such as, but not limited to, death, disease progression or intolerable adverse events occurred during the first two cycles of chemotherapy. The reporting period for safety data will be from first dose of study medication to 90 days (>5 half lives) after last dose is received.

In addition, selected safety analyses will be performed for all treated Chinese subjects who received at least one dose of blinded study therapy and/or on all treated Chinese subjects regardless of whether or not they received blinded study therapy. Details will be provided in SAP.

8.4.3.1 Immune-related Adverse Events (irAEs)

Immune-related adverse events (irAEs) are AEs of unknown etiology, which are consistent with an immune phenomenon and identified by the investigator as study treatment related. The irAEs will be defined using a predefined list of MedDRA high-level group terms, high-level terms and preferred terms; changes may be made to this list with each new version of MedDRA. Six subcategories of irAE will be reported: GI, liver, skin, endocrine, neurological, and other. Immune-related AE summaries will also be produced on diarrhea as a separate grouped term.

Analysis of irAEs will be based on all treated subjects who received at least one dose of blinded study therapy, and the reporting period will be from the first dose of blinded study therapy to 90 days after the last dose is received.

8.4.3.2 Immune-mediated Adverse Reactions

This study will also describe immune-mediated adverse reactions (imARs) using the same adjudication algorithm and predefined list of AEs of special interest (enterocolitis, hepatitis, dermatitis, endocrinopathies, neuropathies, and other) used for the USPI. Specifically, the determination of imAR will take into account available clinical evidence through ruling out non-inflammatory etiologies such as infection or tumor progression, and consideration of evidence of inflammation such as tumor biopsies or responsiveness to steroids, but not the causality assessment of the investigator. imARs are likely to be inflammatory events associated with ipilimumab treatment. Documentation of surveillance, intervention and outcomes are to be documented in the CRFs for inclusion of the imAR assessment. Analysis of imARs will be based on all treated subjects who received at least one dose of blinded study therapy and the reporting period will be from the first dose of blinded study therapy to 90 days after the last dose is received. The Sponsor will adjudicate the adverse events for potentially being immune-mediated in both experimental and control arm in a blinded manner. Analysis of imARs will be based on all treated subjects who received at least one dose of blinded study therapy and the reporting period will be from the first dose of blinded study therapy to 90 days after the last dose is received.

8.4.4 Pharmacokinetic Analyses

All available pharmacokinetic data will be listed. PK data obtained from this study may be pooled with data from other studies to perform an integrated population PK analysis (including assessment of covariate effects on PK), as well as exposure-response analysis for selected safety and efficacy endpoints. These analyses will be described in a separate report(s).

8.4.5 Pharmacodynamic Analyses

Two types of ALC analyses will be done: pharmacodynamic and predictive. Both analyses will include all treated subjects with known date of first dose of ipilimumab or placebo. Pharmacodynamic analyses will examine the patterns of change in ALC over time and how these patterns might differ between treatment arms. Predictive analyses will examine the relationship between ALC and measures of response such as OS. Further details will be described in the SAP.

8.4.6 Pharmacogenomic Analyses

Not applicable.

8.4.7 Outcomes Research Analyses

Among subjects who received at least one dose of blinded study therapy, the distribution of time to symptom progression (defined as an increase of at least 15 mm from baseline prior to receiving any study drug in any of the three symptoms (cough, pain and dyspnea)) will be estimated using KM method. Subjects who do not show deterioration in symptoms will be censored on the last assessment date that all three symptoms (dyspnea, cough, and pain) were assessed. The estimates of medians and two-sided 95%CIs will be calculated.

8.4.8 Other Analyses

Not applicable.

8.5 Interim Analyses

Not applicable.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented in the CRF.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS/designee.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents: (eg, Quality of Life Questionnaires).

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS/designee.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a

copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

Bristol-Myers Squibb or designee will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

For sites using an electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which may be reported on the SAE form and Pregnancy Surveillance form, respectively. The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or subinvestigator and who is delegated this task on the Delegation of Authority Form. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report. For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

For this single site protocol, the Principal Investigator for the site will sign the clinical study report.

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth

in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

11 LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse Event
ALT	Serum Glutamate Pyruvate Transaminase (SGPT)
ALC	Absolute Lymphocyte Count
ANA	Antinuclear Antibody
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase (SGOT)
AUC	Area Under the Curve
BMS	Bristol-Myers Squibb
BOR	Best Overall Response
BORR	Best Overall Response Rate
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CRR	Complete Response Rate
CSP	Clinical Safety Program
CTLA-4	Cytotoxic T Lymphocyte Antigen 4
DCR	Disease Control Rate
DMC	Data Monitoring Committee
DOR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
EOI	Events of Interest
ESR	Expedited Safety Report
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GM-CSF	Granulocyte-Colony Stimulating Factor
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio

Term	Definition
HRQoL	Health Related Quality of Life
HRT	Hormone Replacement Therapy
IAG	Image Acquisition Guidelines
IASLC	International Association for the Study of Lung Cancer
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
imAR	Immune-mediated Adverse Reactions
irAE	Immune-related Adverse Events
irBOR	Immune-related Best Overall Response
irBORR	Immune-related Best Overall Response Rate
irCR	Immune-related Complete Response
ir DCR	Immune-related Disease Control Rate
irDOR	Immune-related Duration of Response
irPD	Immune-related Progressive Disease
irPFS	Immune-related Progression Free Survival
irPR	Immune-related Partial Response
irRC	Immune-related Response Criteria
irSD	Immune-related Stable Disease
IRB	Independent Review Board
IRC	Independent Review Committee
IVRS	Interactive Voice Response System
KM	Kaplan-Meier
LCSS	Lung Cancer Symptom Scale
LFT	Liver Function Tests
LR	Late Response
mAb	Monoclonal Antibody
MDX	Medarex, Inc.
mWHO	Modified WHO
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse events
NCCN	National Comprehensive Cancer Network

Term	Definition
NK	Natural Killer
NOS	Not Otherwise Specified
NSCLC	Non Small Cell Lung Cancer
OR	Overall Response
OS	Overall Survival
PD	Pharmacodynamic
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response
PS	Performance Status
QoL	Quality of Life
REMC	Restricted Maximum Likelihood
RF	Rheumatoid Factor
ROC	Receiver Operating Characteristic
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SCLC	Small Cell Lung Cancer
SDR	Stable Disease Rate
SJS	Stevens Johnson Syndrome
SPD	Sum of the Product of the Diameters
TA	Tumor Assessments
TEN	Toxic Epidermal Necrolysis
TNF	Tumor Necrosis Factor
VEGF	Vascular Endothelial Growth Factor
WOCBP	Women of Child Bearing Potential
ULN	Upper Limit of Normal

APPENDIX 2 LUNG CANCER SYMPTOM SCALE (LCSS)

Standard Procedures:

1) It is recommended that the patient scale be administered **before** the patient sees or talks with the physician, undergoes any tests or treatments, and/or receives results of any tests (x-rays, blood tests, etc).
2) The patient should be **assessed alone**. Family members or significant others should be asked to leave, but if they decline, proceed with administering the instrument. Reinforce that the response desired is the **patient's response**. Make an effort to have no other hospital personnel in the room.
3) Test administrators should **remain with the patient** to given instructions, answer questions, and facilitate completion on time.
4) The **order of the cards is important**. Cards should be presented in an order progressing from the least threatening items to the most threatening ones as they were tested. Thus, the cards are in the following fixed order through use of spiral binding:

   First: *** Example question about the weather**

   Then: 1) Appetite loss
   2) Fatigue
   3) Cough
   4) Shortness of breath
   5) Blood in sputum
   6) Pain
   7) Symptoms from lung cancer
   8) Normal activities
   9) Quality of life
5) Convey the following introduction to the patient (not necessarily verbatim):

   "In addition to measuring changes in your tumor, we also want to find out exactly how you feel, and we need your help. This scale asks about your lung cancer symptoms. It takes approximately 5 - 8 minutes to complete the first time and, generally, 3 - 5 minutes once you are familiar with the scale. You may be asked to complete the scale multiple times throughout the course of your treatment and follow-up period."
6) Give simple, clear instructions for completing the scale: "Please put a mark along each line where it would best describe **the symptoms of your lung cancer DURING THE PAST DAY** (within the last 24 hours). Focus on your lung cancer symptoms, not symptoms related to some other health problem you may have."
7) If the patient has difficulty with the time frame, remind the patient that **"today" means the past day (or within the last 24 hours)**. Tell the patient this short time frame is needed because symptoms fluctuate rapidly and it is difficult to remember accurately beyond that time frame.
8) Emphasize that it is the **patient's personal feelings** that count, and there are **no right or wrong answers** to any of the questions. Reflect the questions back to the patient to obtain the patient's subjective response. If the patient asks what does "as much as it could be" mean,

reply that it means "as bad as you believe it can be" (not necessarily verbatim). If a patient asks what you mean by "normal activities," again reply "whatever normal activities mean to you."

Any further explanation by the administrator of the instrument may influence the patient's answer.

9) Reinforce that the patient should read the questions and pay particular **attention to the words at the extremes of the line** because they change on different cards.
10) Present the **example question first** (How good is the weather today?). **Demonstrate making a vertical mark** on the example question line. **Do not proceed until the patient understands.** The patient will be less likely to make an "X" or "√" on the line if properly "trained."
11) Be sure that the patient understands that marks can be made on the end markers (either 0 or 100) by **extending the end mark**. Many patients have a tendency to mark beside the line to mean a **true zero or true 100**, which then is actually measured as 1 - 2 mm. instead of zero. Again, it is best to **demonstrate extending the end marker** for a true "none" or true "as much as it can be."
12) Allow the patient to read and complete **one card at a time** before continuing to the next card. Most patients should **not need the cards read** to them.
13) As each question is presented, **check to see if the patient understands key words** such as "fatigue" and "sputum."
14) If the patient asks for more explanation for **item #7** related to **total symptomatic distress**, respond that it means: "All together, how bad are your symptoms from lung cancer?"
15) If the patient speaks another language, provide an interpreter fluent in that language to administer the scale. The LCSS patient form is now available in many languages.
16) **Check** to be sure the patient has **not skipped a card**. If one was skipped, ask the patient about that card. If the patient refuses to complete a card, ask, "Why?" as it may be simple to reassure the patient.

Administration by Telephone

The LCSS has been easily administered by telephone to patients who have previously completed the measure in an **initial face-to-face interview** (in which the use of a visual analogue scale has been demonstrated and the patient shows understanding). A time is set with the patient that the observer will call and the patient is either given the LCSS at the last contact or mailed the cards prior to the **"telephone appointment"**.

1) When the patient answers the telephone, **ask the patient to get the LCSS patient form while you remain on the telephone**. Remind the patient that the LCSS should be completed without help from others (such as family members or helpers).
2) Review the instructions for the LCSS **as if administering the scale in person** and **wait on the telephone while the patient completes** the 9 items (usually 3 - 5 minutes).
3) Remind the patient that a "true zero" ("none") or "true 100" ("as much as it can be") is represented by extending the short lines at the end of the long line, not by making a mark beside one of them.

4) After completion of the telephone interview, ask the patient to seal the self-addressed envelope and write the date on the back of the envelope. The patient should then be asked to either mail the envelope the next day or bring it to the next appointment.

Copying the Instrument

Photocopying will lengthen the lines of the LCSS patient scale. To recreate the patient scale, printing is recommended.