Official Title of Study:

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

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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.

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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.

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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.

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