2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: ABT–869	**Volume:**	
Name of Active Ingredient: linifanib	**Page:**	
Title of Study: A Phase 2 Randomized, Placebo-Controlled, Double-Blind Study of Carboplatin/Paclitaxel in Combination with ABT-869 Versus Carboplatin/Paclitaxel Alone in Subjects with Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) as First-Line Treatment		
Coordinating Investigator: Suresh S. Ramalingam, MD Department of Hematology and Medical Oncology Winship Cancer Institute of Emory University 1365 Clifton Rd NE, C-3090 Atlanta, GA 30322		
Study Sites: 37 sites in the United States, Australia, Brazil, Czech Republic, Singapore, and Russia participated in the study.		
Publications: 3		
Studied Period (Years): First Subject First Visit: 26 June 2008 Last Subject Last Visit: 04 April 2012	**Phase of Development:** 2	
Objectives: The primary objective of the study was to assess if the addition of oral linifanib to carboplatin and paclitaxel could prolong progression-free survival (PFS) compared with carboplatin and paclitaxel alone in subjects with NSCLC. The secondary objectives of the study were to evaluate overall survival and other efficacy endpoints, as well as the safety and tolerability of each of the treatment arms. The tertiary objectives were to evaluate Quality of Life, performance status, and body weight.		
Methodology: This was a Phase 2, randomized, placebo-controlled, double-blind, multicenter study of the efficacy and tolerability of carboplatin and paclitaxel (at standard dose and schedule) plus 7.5 mg or 12.5 mg of linifanib versus carboplatin and paclitaxel alone in subjects with documented advanced or metastatic NSCLC as first-line chemotherapy. An open-label, lead-in cohort of 7 subjects was monitored for 2 cycles (1 cycle was defined as 3 weeks) to assess the PK interactions and the safety of the combination of 0.20 mg/kg once daily linifanib with carboplatin and paclitaxel. An alternative dose of linifanib could have been explored based on the tolerability of the combination.		

Methodology (Continued):

Dosing of carboplatin/paclitaxel began on Cycle 1 Day 1, and linifanib dosing began on Cycle 1 Day 3 (to determine single agent PK for both carboplatin/paclitaxel and linifanib). Subjects continued to dose linifanib daily (Days 1 through 21 of every 21-day cycle). Subjects continued to receive carboplatin/paclitaxel on Day 1 of each 21-day cycle for a maximum of 6 cycles. For subjects in the lead-in cohort, study visits were conducted weekly for the first 2 cycles and then Day 1 of every subsequent 21-day cycle.

Randomization into the blinded portion of the study began after the open-label cohort had completed 2 cycles of open-label therapy. Subjects were randomized in a 2:2:1:1 ratio, with one-third of the subjects being randomized to the 7.5 mg linifanib group (carboplatin/paclitaxel + 7.5 mg linifanib), one-third of the subjects being randomized to the 12.5 mg linifanib group (carboplatin/paclitaxel + 12.5 mg linifanib), one-sixth of the subjects being randomized to carboplatin/paclitaxel + placebo for 7.5 mg linifanib group, and one-sixth of the subjects being randomized to carboplatin/paclitaxel + placebo for 12.5 mg linifanib group. For the purpose of statistical analysis, the placebo groups were combined to form the carboplatin/paclitaxel + placebo treatment group. Dosing of oral linifanib/placebo occurred with the start of the carboplatin/paclitaxel infusion on Cycle 1 Day 1. Approximately 120 subjects were to be enrolled at approximately 45 sites.

For subjects in the randomized portion, study visits occurred weekly for the first cycle and then Day 1 of every subsequent 21-day cycle. All subjects received standard carboplatin (area under the plasma concentration-time curve [AUC] 6 mg/mL/min) and paclitaxel (200 mg/m^2) on Day 1 of each 21-day cycle, via intravenous (IV) infusion for a maximum of 6 cycles.

Subjects who experienced toxicities due to study treatment (carboplatin/paclitaxel or linifanib/placebo) could have had a delay in the dosing schedule or a dose modification of the study drug. Subsequent cycles of therapy were to be administered if there was no evidence of disease progression and observed toxicities had recovered adequately.

Redacted information – 03Sep2015

Linifanib/placebo was continued as a single agent following the completion of carboplatin/paclitaxel therapy until disease progression or the subject met the criteria outlined in Section [redacted] of the protocol. After discontinuation from the study, subjects were to have survival assessments at an interval of every 3 months for 2 years, then at an interval of 6 months for the next 3 years, and then annually (or as needed to allow for more frequent survival analyses). These assessments were to continue until either the subject died, became lost to follow-up, or until study termination by Abbott.

Number of Subjects (Planned and Analyzed):

Overall, 135 subjects were planned. Seven subjects enrolled in the lead-in cohort received linifanib and were included in the pharmacokinetic (PK) and safety analyses. For the randomized portion, 138 subjects were randomized and included in the efficacy analyses; 136 subjects received study drug and were included in the safety analyses.

Diagnosis and Main Criteria for Inclusion:

Male and female subjects ≥ 18 years of age diagnosed with recurrent, advanced, or metastatic non-squamous NSCLC with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and adequate bone marrow, renal function, hepatic function, and partial thromboplastin time.

Test and Reference Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Not applicable to an abbreviated clinical study report.

Duration of Treatment:

Therapy was to continue as a single agent following the completion of carboplatin and paclitaxel therapy until disease progression or toxicities prohibited further continuation.

Criteria for Evaluation

Efficacy: Progression free survival (PFS) and overall survival (OS).

Pharmacokinetic: Plasma concentrations and PK parameters of linifanib and its inactive metabolite (A-849529), carboplatin, and paclitaxel.

Safety: Adverse events, laboratory assessments, vital signs, multigated acquisition, echocardiogram, and physical examinations.

Statistical Methods

Efficacy:

The primary efficacy analysis was a comparison of PFS (radiographic progression, clinical progression, or death) distributions between the placebo group and each of the linifanib groups using Kaplan-Meier methodology and stratified log-rank test. Cox proportional hazard models stratified by ECOG performance status and gender were used to test for treatment effect.

The secondary efficacy analysis of OS compared the distribution of time to death for the placebo group with each of the linifanib groups using Kaplan-Meier methodology and the stratified log-rank test. Stratification was by ECOG performance status and gender.

Pharmacokinetic:

The effects of coadministration of paclitaxel on the PK of linifanib were addressed by analyzing linifanib PK variables on Cycle 2 Day 1 (linifanib with carboplatin/paclitaxel) and Cycle 1, Day 21 (linifanib alone), including time to maximum observed plasma concentration (T_{max}), maximum observed plasma concentration (C_{max}), and area under the plasma concentration-time curve (AUC). A PK variable was transformed if the transformed variable provided a more nearly symmetric probability distribution. A linear mixed model was performed by including day as a classification factor and treating subject as a random effect (in effect, equivalent to a paired t-test.). Within the framework of linear mixed model for C_{max} and AUC, a 90% confidence interval (CI), as well as the point estimate, were provided for the ratio of the central value on the day of carboplatin/paclitaxel dosing (Cycle 2, Day 1) to the central value for linifanib administered alone (Cycle 1, Day 21). Likewise, the effects of coadministration of linifanib on the PK of carboplatin/paclitaxel were addressed by analyzing the Cycle 1, Day 1 and Cycle 2, Day 1 carboplatin/paclitaxel PK variables.

Statistical Methods (Continued)

Safety:

Safety summaries were presented for each drug regimen and included all subjects who received at least 1 dose of study drug.

The number and percentage of subjects having treatment-emergent adverse events were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. The tabulations were also provided with further breakdowns by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0 toxicity grade and relationship to study drug. Serious adverse events, events leading to discontinuation of study drug, events leading to interruption of treatment or reduction of dosage, adverse events of special interest, and events leading to death were summarized by study drug regimen.

Subjects experiencing potentially clinically significant changes in laboratory data and vital sign values according to the Abbott–defined criteria (very low and very high values) were listed and summarized by study drug regimen.

Summary/Conclusions

Efficacy Results:

In comparison with the placebo group (median PFS = 164 days), PFS was statistically significantly longer for the 7.5 mg linifanib group (median = 196 days) and 12.5 mg linifanib group (median = 203 days), with stratified hazard ratios of 0.545 (95% CI 0.334 – 0.890) and 0.580 (95% CI 0.355 – 0.946), respectively. In comparison with the PFS of the placebo group with a cutoff date of 75 events of disease progression or death within 42 days of last disease progression (median 164 days), PFS was statistically significantly longer for the 7.5 mg linifanib group (median 252 days) but not the 12.5 mg linifanib group (median 221 days), with stratified hazard ratios of 0.509 (95% CI 0.283 – 0.917) and 0.640 (95% CI 0.366 - 1.119), respectively. Overall survival was not statistically significantly different between the placebo group and either linifanib group.

Pharmacokinetic Results:

Paclitaxel and carboplatin appeared to have a negligible effect on the dose-normalized linifanib C_{max} and AUC_{24}. The ratios of the central values and 90% CI of the dose-normalized linifanib C_{max} and AUC_{24} in the presence of paclitaxel and carboplatin were 0.94 (90% CI 0.73 – 1.20) and 1.17 (90% CI 0.82 – 1.65), respectively. Linifanib appeared to have a negligible effect on paclitaxel C_{max} and AUC_{48}. The ratios of the central values and 90% CI of paclitaxel C_{max} and AUC_{48} in the presence of linifanib were 0.72 (90% CI 0.44 – 1.17) and 0.80 (90% CI 0.53 – 1.21), respectively. Linifanib appeared to have a negligible effect on carboplatin C_{max} and AUC_{24}. The ratios of the central values and 90% CI of carboplatin C_{max} and AUC_{24} in the presence of linifanib were 1.14 (90% CI 0.92 – 1.42) and 0.95 (90% CI 0.79 – 1.14), respectively.

Summary/Conclusions (Continued)

Safety Results:

Overall, when combined with carboplatin/paclitaxel, subjects receiving linifanib had more adverse events that were grade ≥ 3, serious, led to study drug reduction/interruption, or led to discontinuation of study drug, than those receiving placebo combined with carboplatin/paclitaxel.

Compared with the placebo group, a statistically significantly greater proportion of subjects experienced adverse events of dysphonia, pneumothorax, oral candidiasis, anemia, and hypothyroidism in the 7.5 mg linifanib group and thrombocytopenia, diarrhea, palmar-plantar erythrodysesthesia syndrome, weight decreased, and hypertension in the 12.5 mg linifanib group. Generally, these events are known effects of VEGF inhibition or treatment-disease interactions (pneumothorax). The higher rates of anemia and oral candidiasis have not been observed in other studies of linifanib and are of unclear significance.

Compared with the placebo group, a statistically significantly greater proportion of subjects reported grade ≥ 3 adverse events in the 7.5 mg linifanib group. A statistically significantly greater proportion of subjects experienced grade ≥ 3 adverse events of thrombocytopenia in the 7.5 mg linifanib group and 12.5 mg linifanib group compared with the placebo group. Compared with the placebo group, a statistically significantly greater proportion of subjects in the 7.5 mg linifanib group experienced a serious adverse event. A statistically significantly greater proportion of subjects experienced a treatment emergent adverse event that led to discontinuation of study drug in the 7.5 mg group compared with the placebo group.

Clinically meaningful changes in laboratory values were reflective of agents in the anti-vascular endothelial growth factor class (increased UPCR; proteinuria). Although a greater proportion of subjects in the 7.5 mg linifanib group experienced an adverse event of anemia, the decreases in hemoglobin and hematocrit were similar to the placebo and 12.5 mg linifanib groups. Small mean decreases in weight were observed in both linifanib groups. The mean decreases in weight were statistically significantly greater for the 12.5 mg linifanib group compared with the placebo group. More subjects receiving linifanib had LVEF decreases ≥ 10% during treatment. However, LVEF decreases were generally not associated with ejection fractions of < 50% or adverse events.

Conclusions:

In comparison with the placebo group (median = 164 days), PFS was statistically significantly longer for the 7.5 mg linifanib group (median = 196 days) and 12.5 mg linifanib group (median = 203 days), with stratified hazard ratios of 0.545 (95% CI 0.334 – 0.890) and 0.580 (95% CI 0.355 – 0.946), respectively.

Overall survival was not statistically significantly different between the placebo group and either linifanib group.

The PK of linifanib did not appear to change after coadministration with carboplatin/paclitaxel.

Paclitaxel and carboplatin PK appeared to be similar after administration as a single agent and in combination with linifanib.

Subjects receiving linifanib combined with carboplatin/paclitaxel had more adverse events that were grade ≥ 3, serious, or led to reduction, interruption, or discontinuation of study drug, than those receiving placebo combined with carboplatin/paclitaxel.

Conclusions (Continued):

The rate of thrombocytopenia, including grade 3 or 4 events, was higher in subjects treated with linifanib versus placebo. These events were generally manageable, and only 1 subject discontinued linifanib due to an adverse event of thrombocytopenia. Platelet counts below 50×10^9/L were reported in 4.3%, 21.4%, and 27.7% of subjects treated with carboplatin/paclitaxel combined with placebo, 7.5 mg linifanib, and 12.5 mg linifanib, respectively.

Compared with the placebo group, a statistically significantly greater proportion of subjects experienced adverse events of dysphonia, pneumothorax, oral candidiasis, anemia, and hypothyroidism in the 7.5 mg linifanib group and thrombocytopenia, diarrhea, palmar-plantar erythrodysesthesia syndrome, weight decreased, and hypertension in the 12.5 mg linifanib group. Generally, these events are known effects of VEGF inhibition or treatment-disease interactions (pneumothorax). The higher rates of anemia and oral candidiasis have not been observed in other studies of linifanib and are of unclear significance.

Compared with the placebo group, known VEGF inhibition-related adverse events in the hypertension SMQ and hypothyroidism SMQ were more common in the linifanib groups.