2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-869		
Name of Active Ingredient: linifanib		

Title of Study:

An Open-Label, Randomized, Phase 2 Study of Efficacy and Tolerability of ABT-869 in Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC)

Coordinating Investigator:

Dr. Eng Huat Tan
National Cancer Centre Singapore
11 Hospital Drive
Singapore 16910

Study Site(s): Twenty-seven investigative sites (18 in the United States, 3 in Canada, 2 in France, 2 in Singapore, and 2 in Taiwan) enrolled subjects into the study.

Publications: There are 6 published abstracts and 1 manuscript based on this study.

Tan EH, Goss GD, Salgia R, et al. Phase 2 trial of linifanib (ABT-869) in patients with advanced non-small cell lung cancer. J Thorac Oncol. 2011;6(8):1418-25.

Soo RA, Goss GD, Salgia R, et al. Linifanib treatment in patients with non-small cell lung cancer (NSCLC): Phase II results [abstract 7590]. J Clin Oncol. 2010;28 Suppl:560s.

Tan E, Salgia R, Besse B, et al. ABT-869 in non-small cell lung cancer (NSCLC): Interim results [abstract 8074]. J Clin Oncol. 2009;27 Suppl:425s.

Tan E, Goss GD, Salgia R, et al. A phase 2 trial of linifanib treatment in non-small cell lung cancer (NSCLC) patients [abstract 416]. Ann Oncol. 2010;21 Suppl 8:viii139.

Tan E, Goss GD, Salgia RR, et al. Phase II results of ABT-869 treatment in patients with non-small cell lung cancer (NSCLC) [abstract 9013]. Eur J Cancer Suppl. 2009;7(2):509.

McKeegan EM, Ansell PJ, Davis G, et al. Baseline plasma biomarker signature is associated with improved survival in advanced NSCLC patients on linifanib. [abstract 505]. Ann Oncol. 2012;23 Suppl 9.

McKeegan EM, Chakravartty A, Ansel PJ, et al. Association of baseline plasma biomarker signature with survival in advanced NSCLC patients on linifanib. [abstract e13583]. J Clin Onco1. 2012;30 Suppl. 15.

Studied Period (Years):	**Phase of Development:** 2
First Subject First Visit: 03 August 2007 Last Subject Last Visit: 17 August 2010 for the main portion of the study; 14 June 2012 for the extension portion of the study.	

Objective:

The primary objectives of this study were to determine the efficacy of 0.10 mg/kg and 0.25 mg/kg linifanib using Response Evaluation Criteria in Solid Tumors (RECIST 1.0) and to establish the safety/tolerability profile of linifanib in subjects with advanced or metastatic NSCLC. The secondary objectives of this study were to identify potential biomarkers that correlate and/or predict efficacy and toxicity in subjects with advanced or metastatic NSCLC and to explore if there are any ethnic differences in tumor response to linifanib between Asian and non-Asian NSCLC populations. The tertiary objectives of this study were to assess additional efficacy endpoints such as quality of life, changes in weight, and performance status.

Methodology:

This was a Phase 2, randomized, open-label, international, multicenter study of the efficacy and tolerability of low-dose (0.10 mg/kg) and high-dose (0.25 mg/kg) linifanib in male and female subjects with advanced or metastatic NSCLC who had received at least 1 but not more than 2 systemic regimens (excluding an adjuvant or neo-adjuvant regimen). Approximately 120 subjects (approximately 60 non-Asian and 60 Asian subjects) with documented advanced or metastatic NSCLC were to be enrolled.

Linifanib was administered as an oral solution or tablet at either 0.10 mg/kg or 0.25 mg/kg. Within each ethnicity group, subjects were randomized in a 1:1 ratio, with half of the subjects being randomized to the 0.10 mg/kg linifanib dose group and the other half to the 0.25 mg/kg linifanib dose group. There were no scheduled dosing breaks; however, dose reductions or drug holidays due to study drug-related toxicities could occur, based on the discretion of the principal investigator. Subjects randomized to receive 0.10 mg/kg of linifanib whose disease progressed were offered the opportunity to cross over to the 0.25 mg/kg dose of linifanib at the investigator's discretion after evaluating the clinical benefit of continued exposure to linifanib.

The screening procedures, including baseline radiographic tumor assessments, were performed within 21 days prior to Study Day 1. If the Screening Visit was performed more than 7 days prior to Day 1, the physical examination, laboratory tests, and a pregnancy test (for female subjects of childbearing age) were to be repeated on Day 1. Vital signs, performance status, and quality-of-life assessments were performed on Day 1 for all subjects.

Study visits were conducted at Study Day 1, weekly for the first 4 weeks, and Day 1 of every subsequent 4-week period. Investigators evaluated the subject for evidence of clinical disease progression at each visit. Radiographic tumor assessments were conducted at the end of every 8 weeks and were assessed using RECIST 1.0. Toxicities were graded at each study visit according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). Subjects continued dosing with linifanib until they experienced clinical or radiographic disease progression; unacceptable toxicities deemed possibly or probably related to linifanib that had not resolved to at least grade 1 or to the subject's baseline status within 14 days of onset; toxicities requiring more than a 2-week dose interruption; requirement for radiotherapy, surgery or alternate antineoplastic agents; inability to comply with the protocol; or withdrawal of consent. When an investigator determined that a subject should discontinue the study, a Final Visit was conducted, marking the end of the main study. Subjects who were doing well on linifanib were allowed to continue treatment with study drug in an extension portion of the study; these subjects were monitored for safety.

Methodology (Continued):

All subjects were to have 1 Follow-up Visit approximately 30 days after the last dose of linifanib. If the subject discontinued the study due to toxicities attributable to linifanib, additional Follow-up Visits were to be conducted at least every 30 days until the toxicity diminished to an acceptable level or was determined to be stable or irreversible. Subjects were to have survival assessments every 4 to 6 months following discontinuation from the study or as needed to allow for more frequent survival analyses, for a period of up to 2 years.

Number of Subjects (Planned and Analyzed):

Approximately 120 subjects (approximately 60 non-Asian and 60 Asian subjects) with documented advanced or metastatic NSCLC were to enroll in this study. Within each ethnicity, group, half of the subjects were to receive 0.1 mg/kg linifanib, and half were to receive 0.25 mg/kg linifanib.

Diagnosis and Main Criteria for Inclusion:

Male and female subjects (≥ 18 years of age) with advanced or metastatic NSCLC who had received at least 1 but not more than 2 systemic regimens (excluding an adjuvant or neo-adjuvant regimen), had at least 1 lesion measurable by computed tomography (CT) scan as defined by RECIST 1.0 that had not received radiation therapy, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.

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

Linifanib was supplied by Abbott as an oral solution at a concentration of 50 mg/mL or as a solid tablet formulation at concentrations of 2.5 mg and 10 mg, as summarized below. Lot number 11-000114 was added for the extension portion of the study.

Study Drug	Formulation	Lot Number
Linifanib	50 mg/mL oral solution	07-012309, 07-013481, 08-015187, 08-016985
	2.5 mg tablet	07-013792, 08-015430, 08-015741, 08-017022, 08-017023, 09-022075, 11-000114
	10 mg tablet	07-013793, 08-015431, 08-015742, 08-018910, 09-022095

Duration of Treatment:

Subjects were to continue dosing with linifanib until criteria for discontinuation, including disease progression or unacceptable drug-related toxicity, were met.

Criteria for Evaluation

Efficacy: tumor assessments, target lesion measurement, performance status, and quality of life.

Safety: adverse events, laboratory assessments, vital signs, and physical examination.

Statistical Methods

Efficacy:

The primary efficacy endpoint was the progression-free rate (PFR) at Week 16, based on clinical assessment by the investigator and radiographic assessment by the central imaging center using RECIST 1.0. The secondary efficacy endpoints were objective response rate (ORR), best response rate, time to disease progression (TTP), progression-free survival (PFS), and overall survival (OS); all radiographic tumor assessment data for secondary efficacy endpoints were based on review by the central imaging center. The tertiary endpoints were quality of life (QoL), assessed by the European Organization for Research and Treatment of Cancer quality-of-life questionnaire (EORTC QLQ C30), performance status, assessed by ECOG, and weight.

Safety:

The safety of linifanib was assessed by evaluating study drug exposure, adverse events, serious adverse events, oncology-related events, all deaths, and changes in laboratory parameters and vital sign parameters.

Treatment-emergent adverse events (i.e., events that had onset on or after the day of the first dose of study drug through 30 days after the last dose of study drug) were summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) version 13.1. The number and percent of subjects experiencing an adverse event at a given NCI CTCAE toxicity grade, causal relationship to study drug, adverse events that resulted in study drug discontinuation, study drug dose reduction, and study drug dose interruption, and serious adverse events were provided for each dose group and overall. The percentages of subjects experiencing an adverse event were compared between the 2 dose groups using Fisher's exact test.

Deaths were listed and summarized for each dose group and overall. The number of deaths was summarized for (1) deaths occurring within 30 days of the last dose of study drug, (2) deaths occurring more than 30 days after the last dose of study drug and (3) all deaths in the study, regardless of the number of days after the last dose of study drug.

Changes from Baseline were summarized for each scheduled postbaseline visit and for the Final Visit for blood chemistry, hematology, urinalysis, and vital sign variables. For all laboratory and vital sign summaries, baseline was defined as the last non-missing measurement collected on or prior to the first dose of study drug. The Final Visit was defined as the last non-missing measurement collected within 30 days following the last dose of study drug. Changes from Baseline were compared between dose groups using an analysis of covariance (ANCOVA) with dose group as the factor and baseline measurement as the covariate.

Blood chemistry and hematology values were categorized according to NCI CTCAE grades, and shifts from baseline grades to maximum and final postbaseline grades were assessed. The maximum grade was based on values occurring within 30 days of the last dose of study drug. The number and percentage of subjects with shifts from baseline grade 0-2 to grades 3-4 were compared between dose groups using Fisher's exact test.

Subjects experiencing potentially clinically significant changes in laboratory data and vital sign values according to the Abbott-defined criteria for potentially clinically significant (very low and very high) values were listed.

Summary/Conclusions

Efficacy Results:

This study compared linifanib 0.10 mg/kg and linifanib 0.25 mg/kg in male and female subjects with advanced or metastatic NSCLC who had received at least 1 but not more than 2 systemic regimens (excluding an adjuvant or neo-adjuvant regimen). The primary endpoint of this study was PFR at Week 16. The secondary endpoints were ORR, best response rate, TTP, PFS, and overall survival.

For the primary endpoint, progression was based on radiographic progression assessed by the central imaging center and clinical progression assessed by the investigator. No statistically significant difference was observed between the 2 dose groups in the progression-free rate at Week 16 in intent-to-treat (ITT) analysis set subjects. The progression free rate at Week 16 was 32.3% [95% CI: 21.2% – 45.1%] in the 0.10 mg/kg dose group and 33.8% [95% CI: 23.2% – 45.7%] in the 0.25 mg/kg dose group. Similar results were obtained for PFR at Week 16 based on radiographic and clinical progression assessed by the investigator. There was no statistically significant dose group difference in PFR at Week 16 within subgroups of non-Asian and Asian subjects. Additionally, there were no statistically significant differences between ethnicity groups overall or within each of the dose groups in the PFR at Week 16.

No statistically significant difference was observed between the 2 dose groups in the objective response rate by RECIST 1.0 when assessed by the central imaging center in the ITT analysis set. The ORR was 3.1% [95% CI: 0.4% – 10.7%] in the 0.10 mg/kg dose group and 6.8% [95% CI: 2.2% – 15.1%] in the 0.25 mg/kg dose group. Results were similar for the ORR by RECIST 1.0 when assessed by the investigator. There was no statistically significant dose group difference in the objective response rate by RECIST 1.0 within subgroups of non-Asian and Asian subjects in the ITT analysis set. Additionally, there were no statistically significant differences between ethnicity groups overall or within dose groups.

The best response was stable disease in approximately half of subjects in both dose groups when assessed by the central imaging center (55.4% for 0.10 mg/kg and 56.8% for 0.25 mg/kg) and by the investigator (49.2% for 0.10 mg/kg and 47.3% for 0.25 mg/kg). When assessed by the central imaging center, partial response was observed in 7.7% and 14.9% of subjects in the 0.10 mg/kg and 0.25 mg/kg dose groups, respectively. A larger percentage of Asian subjects who received linifanib 0.25 mg/kg had a partial response (30.8% versus ≤ 13.0% in the other groups). A similar pattern was observed for best response when assessed by the investigator.

No statistically significant difference was observed between the 2 dose groups in progression-free survival in ITT analysis set subjects when radiographic progression was based on the central imaging center and clinical progression was assessed by the investigator. The median time of progression-free survival was 106 days [95% CI: 60 – 130 days] (3.5 months) in the 0.10 mg/kg dose group and 108 days [95% CI: 93 – 136 days] (3.6 months) in the 0.25 mg/kg dose group.

No statistically significant difference was observed between the 2 dose groups in time to disease progression in ITT analysis set subjects when radiographic progression was based on the central imaging center and clinical progression was assessed by the investigator. Similar results were obtained when time to disease progression was based on radiographic and clinical progression by the investigator. There were no statistically significant dose group differences within either ethnicity subgroup for time to disease progression. In addition, there were no statistically significant differences between ethnicity subgroups overall or within each of the dose groups.

Efficacy Results (Continued): No statistically significant difference was observed between the 2 dose groups in overall survival in ITT analysis set subjects. A statistically significant dose group difference in overall survival was observed for Asian subjects but not for non-Asian subjects. Among Asian subjects, median survival time was 454 days (14.9 months) in the 0.10 mg/kg dose group compared to 158 days (5.2 months) in the 0.25 mg/kg dose group ($P = 0.002$ for log-rank test, and $P = 0.004$ for Cox proportional hazards model). Presumably, this difference may be due to dissimilar baseline characteristics of these subgroups. Of note, among Asian subjects, higher proportions of subjects in the 0.10 mg/kg dose than in the 0.25 mg/kg dose group had an ECOG performance score of 0 (26.1% versus 7.7%) and had locally advanced disease rather than metastatic disease (13.0% versus 0%).

Dose group differences in PFS and overall survival were evaluated within subgroups defined by age, sex, baseline ECOG score, smoking history, number of prior systemic therapies, and region. The only statistically significant dose group difference in PFS was observed in females, with longer median PFS in the 0.25 mg/kg dose group (113 days, 3.7 months) than in the 0.10 mg/kg dose group (61 days, 2.0 months). The only statistically significant dose group difference in overall survival was observed in ex-USA subjects, with longer median overall survival in the 0.10 mg/kg dose group (377 days, 12.4 months) than in the 0.25 mg/kg dose group (234 days, 7.7 months).

Within each dose group, changes in EORTC QLQ-C30 scores from Baseline to the Final Visit indicated worsening of symptoms and global health status/quality of life, and improvement in functioning, with the 0.25 mg/kg dose group showing greater improvement than the 0.10 mg/kg dose group. Mean ECOG performance status worsened from Baseline to Final Visit within each dose group ($P < 0.001$), with no statistically significant difference between dose groups. However, the quality of life and performance status analyses were based on an observed case analysis and not all subjects in the ITT analysis set.

Safety Results:

A review of all adverse events, laboratory variables, vital sign data, and multi-gated acquisition (MUGA) findings show that linifanib was generally well tolerated and exhibited a favorable safety profile in subjects with non-small cell lung cancer.

Main Portion of the Study:

One hundred thirty-eight (99.3%) subjects experienced at least 1 treatment-emergent adverse event. Overall, the adverse events most frequently reported (by 20% or more of subjects) were fatigue, decreased appetite, diarrhea, hypertension, nausea, cough, palmar-plantar erythrodysesthesia syndrome, proteinuria, headache, and vomiting. The adverse event profile was consistent with the expected effects of vascular endothelial growth factor/platelet-derived growth factor (VEGF/PDGF) inhibitors seen in nonclinical or other clinical studies of linifanib or the underlying malignancy and its complications.

The most frequently reported severe (grade 3 or 4) adverse events considered by the investigator possibly or probably related to linifanib were hypertension, palmar-plantar erythrodysesthesia syndrome, fatigue, decreased appetite, asthenia, diarrhea, stomatitis, and proteinuria. These events likely represent known class effects of linifanib and other agents in the VEGF/PDGF tyrosine kinase inhibitor class or progressive disease or complications of the malignancy.

The most frequently reported serious adverse events were non-small cell lung cancer and pneumonia and were likely due to progressive disease or complications of the malignancy/underlying lung disease. The majority of serious adverse events reported were considered not or probably not causally related to study drug.

Safety Results (Continued):

Main Portion of the Study (Continued):

Thirty-one subjects died within 30 days after the last dose of linifanib, and another 3 died more than 30 days after the last dose of linifanib but the adverse events that resulted in death were treatment-emergent. Twenty-seven deaths were attributed to disease progression/non-small cell lung cancer, and 1 death each was attributed to acute myocardial infarction, death, sudden death (cardiac arrest), chronic obstructive pulmonary disease, pulmonary embolism, pulmonary hemorrhage, and respiratory distress. Four of the deaths were considered possibly or probably related to linifanib (pulmonary hemorrhage [with alternative etiology of possible progression of disease], death, sudden death [on post-treatment Day 24], and acute myocardial infarction [on post-treatment Day 8 after discontinuation due to cough and dyspnea]). Eighty additional subjects died more than 30 days after the last dose of linifanib.

The adverse events most frequently leading to dose interruptions and dose reductions were hypertension, palmar plantar erythrodysesthesia syndrome, and proteinuria, all of which were adverse events of special interest. Fifty-nine subjects discontinued linifanib due to an adverse event. The most frequently reported adverse events leading to discontinuation were non-small cell lung cancer, disease progression, metastases to central nervous system, and pleural effusion.

Toxicities of hypertension, proteinuria, fatigue, asthenia, diarrhea, thromboembolic events, and skin toxicities were reported in this study, with skin toxicities (54.0% of subjects) and fatigue (48.2%) being the most common, and consistent with effects seen with anti-VEGF agents. Diarrhea was reported for 41.7% of subjects, hypertension was reported for 40.3% of subjects, and proteinuria was reported for 23.0% of subjects. Skin toxicities were frequently reported, with rash (11.5%) being most common. Adverse events meeting criteria for the hand and foot syndrome company MedDRA queries (CMQs) were reported for 34.5% of subjects, with palmar plantar erythrodysesthesia syndrome the most common event (23.7%). These events were generally well tolerated, and no subject discontinued linifanib due to skin toxicity or hand and foot syndrome CMQs. Three subjects discontinued linifanib due to thromboembolic events (1 due to intracardiac thrombus [considered disease progression] and 2 due to pulmonary embolism). One subject each discontinued due to hypertension, proteinuria, and fatigue. No subject discontinued linifanib due to diarrhea.

Clinically meaningful changes in laboratory values were reflective of agents in the anti-VEGF class (increased urine protein:creatinine ratio [UPCR]; proteinuria) or the underlying disease (increases in aspartate aminotransferase [AST], alkaline phosphatase, total bilirubin, and lactate dehydrogenase [LDH]). Small mean increases in systolic and diastolic blood pressures and heart rate and small mean decreases in weight and body temperature were observed in both dose groups, consistent with anti-VEGF effects.

Extension Portion of the Study:

Three subjects ([redacted]) were active in the extension portion of the study. On Study Day 919 Subject [redacted] experienced a serious NCI CTCAE grade 3 adverse event of gastroenteritis that the investigator considered probably not related to linifanib. Study drug was interrupted and the event resolved in 2 days. No other serious adverse events or adverse events ≥ grade 3 were reported during the extension portion of the study. Two subjects ([redacted]) discontinued study due to radiographic disease progression and 1 subject ([redacted]) discontinued because the sponsor discontinued the study.

Conclusions:

Linifanib is a potent and selective VEGF and PDGF receptor tyrosine kinase inhibitor (TKI). In the current study, linifanib was used as second to fourth line therapy. Single-agent linifanib was clinically active in metastatic and advanced NSCLC in the relapsed/refractory setting, with median PFS of 3.6 months, and median OS of 9.0 months. There was no apparent dose relationship for PFS or OS. Linifanib appeared to be more tolerable at the lower dose (0.10 mg/kg), but more active at the higher dose (0.25 mg/kg) in terms of response and degree of tumor size reduction. The adverse event profile and incidence of adverse events observed with linifanib were comparable to those of other multitargeted, small molecule vascular endothelial growth factor receptor (VEGFR) TKIs administered as monotherapy in NSCLC patients. Grade 3 or higher adverse events most often represented known class effects of linifanib or complications of the malignancy or progressive disease, and these events may be managed medically by medications and study drug dose interruptions or reductions. Results of the EORTC QLQ-C30 indicated improvement in functioning within each dose group, with the 0.25 mg/kg dose group showing greater improvement than the 0.10 mg/kg dose group, and worsening of symptoms and global health in both dose groups. Mean ECOG performance status worsened from Baseline to Final Visit in both dose groups, with no statistically significant difference between the 2 dose groups. Baseline concentrations of circulating tumor cells, serum-soluble fragments of cytokeratin 19 (CYFRA), and the inflammatory marker, C-reactive protein (CRP), demonstrated a correlation with both progression-free survival and overall survival. Further evaluation of linifanib monotherapy in patients with advanced NSCLC is warranted, particularly in a biomarker-defined subpopulation.

The safety findings from the extension portion of the study did not alter the safety profile observed in the main portion of the study.