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: An Open-Label, Randomized Phase 2 Study of ABT-869 in Combination with mFOLFOX6 (Oxaliplatin, 5-Fluorouracil, and Folinic Acid) Versus Bevacizumab in Combination with mFOLFOX6 as Second-line Treatment of Subjects with Advanced Colorectal Cancer		
Coordinating Investigator: Bert O'Neil, MD UNC School of Medicine Physician's Office Building 170 Manning Drive CB # 7305 Chapel Hill, NC 27599		
Study Sites: 46 sites in the United States, Australia, Belgium, Brazil, Canada, Czech Republic, Spain, Greece, South Korea, New Zealand, Poland, Portugal, Romania, and Russia participated in the study.		
Publications: One abstract was published for this study.		
Studied Period (Years): First Subject First Visit: 22 October 2008 Last Subject Last Visit: 07 May 2012	**Phase of Development:** 2	
Objectives: The primary objective of the study was to assess if the addition of oral linifanib to mFOLFOX6 (5-fluorouracil, folinic acid, and oxaliplatin) could prolong progression-free survival (PFS) compared with bevacizumab plus mFOLFOX6 as second-line treatment in subjects with advanced colorectal cancer. The secondary objectives of the study were to evaluate overall survival and additional efficacy endpoints, as well as the safety and tolerability of the combination. The tertiary objectives were to evaluate quality of life and performance status.		

Methodology:

This was a Phase 2, open-label, randomized, active-controlled, multicenter study of the efficacy and tolerability of linifanib (ABT-869) in combination with mFOLFOX6 versus bevacizumab in combination with mFOLFOX6 in subjects with advanced colorectal cancer in the second-line metastatic therapy setting. Study Day 1 was defined as the first day of mFOLFOX6 administration for patients in the lead-in cohort, and Study Day 1 was defined as the first day of linifanib or bevacizumab in combination with FOLFOX6 for patients in the randomized portion of the study. A lead-in cohort of 6 subjects was to be monitored for 2 cycles (1 cycle was defined as 14 days) of 0.15 mg/kg once daily (QD) linifanib and mFOLFOX6 combination therapy to assess the pharmacokinetic (PK) interactions and the safety of the combination. Dosing of mFOLFOX6 began on Cycle 1 Day 1 and linifanib dosing began on Cycle 1 Day 3 (to determine PK for linifanib and mFOLFOX6). Subjects continued to dose linifanib daily (Days 1 to 14 of every 14-day cycle thereafter). Subjects continued to receive mFOLFOX6 on Day 1 of every 14-day cycle thereafter.

All subjects in the randomized portion of the study were to receive standard mFOLFOX6 on Day 1 of every 14-day cycle. Subjects randomized to the bevacizumab group were to receive10 mg/kg bevacizumab on Day 1 of every 14-day cycle. Subjects randomized to the linifanib groups were to begin dosing either 7.5 mg or 12.5 mg linifanib on Cycle 1 Day 1 and continued dosing daily (Days 1 to 14 of every 14-day cycle).

Baseline radiographic tumor assessments were to be conducted within 21 days prior to Study Day 1.

Subjects who experienced toxicities due to study treatment (linifanib, mFOLFOX6, or bevacizumab) 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.

Linifanib or bevacizumab was to continue as a single agent following the completion of mFOLFOX6 therapy until disease progression or toxicities prohibited further continuation. For those subjects who continued on linifanib monotherapy after discontinuing mFOLFOX6 therapy, the dose of linifanib could have been increased, based on the investigator's evaluation of the subject's tolerability of linifanib.

Number of Subjects (Planned and Analyzed):

Overall, 135 subjects were planned. Eleven subjects enrolled in the lead-in cohort, but only 9 subjects received linifanib and were included in the pharmacokinetic (PK) and safety analyses. For the randomized portion, 148 subjects were randomized and included in the efficacy analyses; 147 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 advanced colorectal cancer 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 mFOLFOX6 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), 5-fluorouracil, and oxaliplatin.

Safety:

Adverse events, laboratory assessments, vital signs, and physical examinations.

Statistical Methods

Efficacy:

The primary efficacy analysis was a comparison of PFS (radiographic progression, clinical progression, or death) distributions between the bevacizumab group and each of the linifanib groups using Kaplan-Meier methodology and stratified log-rank test. Stratification was done by prior radiotherapy (yes versus no) and prior bevacizumab (yes versus no). In addition, stratified Cox proportional hazard models were used on PFS to test for treatment effect.

The secondary efficacy analysis of OS compared the distribution of time to death for the bevacizumab group compared with each of the linifanib groups using Kaplan-Meier methodology and the stratified log-rank test. Stratification was done by prior radiotherapy (yes versus no) and prior bevacizumab (yes versus no).

Pharmacokinetic:

The effects of co-administration of mFOLFOX6 on linifanib PK were addressed by analyzing the Cycle 2 Day 1 (linifanib with mFOLFOX6) and Cycle 1 Day 14 (linifanib alone) linifanib PK variables, including T_{max}, C_{max}, AUC, and C_{min}. A PK variable was transformed if the transformed variable provided a more nearly symmetric probability distribution. An analysis of variance (ANOVA) was performed by including subject and day as classification variables. In effect, this was equivalent to a paired t-test. Within the framework of ANOVA for C_{max} and AUC, a 95% confidence interval (CI), as well as the point estimate, was provided for the ratio of the central value on the day of mFOLFOX6 dosing (Cycle 2 Day 1) to the central value for linifanib administered alone (Cycle 1 Day 14).

Likewise, the effects of coadministration of linifanib on mFOLFOX6 PK were addressed by analyzing the Cycle 1 Day 1 and Cycle 2 Day 1 mFOLFOX6 PK variables, including T_{max}, C_{max}, and AUC.

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:

No statistically significant differences in PFS were noted for subjects in the bevacizumab group compared with the 7.5 mg or 12.5 mg linifanib groups. A statistically significantly lower OS was noted for the 7.5 mg linifanib group (median OS of 366 days) compared with the bevacizumab group (median OS of 503 days), with a hazard ratio of 1.736 using the Cox Proportional Hazard Model (95% CI: 1.066 – 2.829).

Pharmacokinetic Results:

Plasma concentrations and PK parameter values of linifanib, its inactive metabolite (A-849529), 5-fluorouracil, and oxaliplatin were evaluated for the lead-in cohort. mFOLFOX6 had a negligible effect on linifanib PK. The test/reference ratios of the central values of the dose-normalized linifanib C_{max} and AUC_{24} were close to 1. However, the 90% CI of dose-normalized linifanib C_{max} and AUC_{24} were both outside the 0.80 to 1.25 interval. Linifanib appeared to increase the ratios of central values of 5-fluorouracil C_{max} and AUC_{24} by 31% and 45%, respectively. The 90% CIs of 5-fluorouracil C_{max} and AUC_{24} were outside the 0.80 – 1.25 intervals. The 90% CI of 5-fluorouracil C_{max} was outside both the upper and lower bounds (90% CI of 0.24 – 7.20). The 90% CI of 5-fluorouracil AUC_{24} was outside the upper bound (90% CI of 0.89 – 2.39). It should be noted that there was high variability in 5-fluorouracil C_{max} and AUC_{24} (CV% ranged from 38% to 82%) across all subjects. Linifanib appeared to have a negligible effect on oxaliplatin C_{max} and AUC_{24}. The ratios of the central values and 90% CI of the oxaliplatin C_{max} and AUC_{24} in the presence of linifanib were 1.11 (90% CI of 1.00 – 1.23) and 0.97 (90% CI of 0.83 – 1.14), respectively.

Safety Results:

Overall, when combined with mFOLFOX6, subjects receiving linifanib had more adverse events, including more severe adverse events, than those receiving bevacizumab combined with mFOLFOX6. Specifically, compared with subjects treated with bevacizumab, subjects treated with linifanib had more adverse events with grade ≥ 3 toxicity, more adverse events leading to discontinuation of study drug, and a trend toward more serious adverse events.

Summary/Conclusions (Continued)

Safety Results (Continued):

Compared with the bevacizumab group, the proportions of subjects that experienced thrombocytopenia, hypothyroidism, palmar-plantar erythrodysesthesia syndrome, and rash were greater in the linifanib groups, which is consistent with the known safety profile of linifanib.

Compared with the bevacizumab group, higher proportions of subjects had grade ≥ 3 adverse events of neutropenia and thrombocytopenia in the 7.5 mg and 12.5 mg linifanib groups, and a higher proportion of subjects had grade ≥ 3 adverse events of fatigue, hypokalemia, and palmar plantar erythrodysesthesia syndrome in the 7.5 mg and 12.5 mg linifanib groups, primarily in the 12.5 mg dose group.

Clinically meaningful changes in laboratory values were reflective of agents in the anti-vascular endothelial growth factor class (increased UPCR; proteinuria). Evaluation of laboratory parameters did not show an increase in grade 3 or 4 platelet counts among subjects receiving linifanib. Small mean increases in systolic and diastolic BPs and heart rate and small mean decreases in weight were observed in all treatment groups. The mean decreases in weight were statistically significantly greater for the 12.5 mg linifanib group compared with the bevacizumab group. Reductions in LVEF were greater for the 7.5 mg linifanib group compared with the bevacizumab group on Day 336 and at the final assessment but not at any other time.

Conclusions:

No statistically significant differences in PFS were noted for subjects in the bevacizumab group compared with the 7.5 mg or 12.5 mg linifanib groups.

A statistically significantly lower OS was noted for the 7.5 mg linifanib group (median OS of 366 days) compared with the bevacizumab group (median OS of 503 days), with a hazard ratio of 1.699 using the Cox Proportional Hazard Model (95% CI: 1.065 – 2.710).

The PK of linifanib did not appear to change after co-administration with mFOLFOX6.

C_{max} and AUC_{24} for 5-flourouracil appeared to increase slightly after co-administration with linifanib. However, due to the small number of subjects and high variability in individual subjects, no conclusion could be made about PK interaction.

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

Subjects receiving linifanib had more adverse events, including more severe adverse events, more adverse events leading to discontinuation of study drug, and a trend toward more serious adverse events, than subjects receiving bevacizumab.

The rates of thrombocytopenia and hypokalemia, including grade 3 or 4 events, were higher in subjects treated with linifanib versus bevacizumab. However, these events were generally manageable and led to discontinuation of study drug in only 1 subject. Platelet counts below 50×10^9/L were reported in 3, 2, and 5 subjects treated with mFOLFOX6 combined with bevacizumab, 7.5 mg linifanib, and 12.5 mg linifanib, respectively.

Compared with the bevacizumab group, known VEGF inhibition-related effects of hypothyroidism, palmar-plantar erythrodysesthesia syndrome, and rash were higher in the linifanib-treated group while hypertension and proteinuria were similar.