## CLINICAL STUDY SYNOPSIS

**Title of Study:** A Randomized, Open-Label Study of Oral CEP-701 Administered in Sequence With Standard Chemotherapy to Patients With Relapsed Acute Myeloid Leukemia (AML) Expressing FLT-3 Activating Mutations

**Investigators and Study Centers (Institutional Review Boards):** The study was conducted at 52 centers in the United States (24 centers); Poland (8 centers); Italy (4 centers); Australia, Germany, and Israel (3 centers each); Canada and Spain (2 centers each); and New Zealand, Russia, and Sweden (1 center each). A complete list of investigators and their affiliations is included in Appendix A. Institutional Review Boards are listed in Appendix B. A summary of auditing activities is provided in Appendix C. Available data from this study were reviewed by an Independent Data Monitoring Committee (IDMC) on 30 January 2007 and 8 January 2008. On each occasion, the IDMC recommended that the study continue as planned.

**Publication (reference):** Levis M, Smith BD, Beran M, Baer MR, Erba HP, Cripe L, et al. A randomized, open-label study of lestaurtinib (CEP-701), an oral FLT3 inhibitor, administered in sequence with chemotherapy in patients with relapsed AML harboring FLT3 activating mutations: clinical response correlates with successful FLT3 inhibition [abstract]. Blood 2005;106:403.

**Study Period:** 21 January 2004 to 2 June 2009 (data cut-off); last follow-up visit 13 January 2010

**Phase of Development:** 2

**Primary Objective:** The primary objective of the study was to determine whether lestaurtinib treatment given in sequence with induction chemotherapy increased the proportion of patients with relapsed acute myeloid leukemia (AML) who achieved a second complete remission (CR) or a CR with incomplete platelet count recovery (CRp).

**Secondary Objectives:** The secondary objectives of the study were to determine the following:

- overall survival
- event-free survival
- remission duration (for patients who achieved a CR or a CRp [CR/CRp])
- the proportion of patients who achieved an outcome of CR, CRp, or partial remission (PR)
- the proportion of patients who maintained an outcome of CR/CRp up to day 113
- the proportion of patients who achieved an outcome of CR/CRp after crossing over to treatment with lestaurtinib
- the safety and tolerability of lestaurtinib treatment administered in sequence with chemotherapy throughout the study
- the pharmacokinetics of lestaurtinib treatment at specified time points
- lestaurtinib inhibitory activity in plasma by means of an fms-like tyrosine kinase 3 (FLT3) ex vivo bioassay and cell assay at specified time points

**Number of Patients (Planned and Analyzed):** For this study, 220 patients were planned to be enrolled; data from 224 patients were analyzed for efficacy and data from 220 patients were analyzed for safety.

**Diagnosis and Criteria for Inclusion:** Patients were included in the study if all of the following inclusion criteria were fulfilled at the baseline visit:

- The patient had cytological confirmation of AML.
- The patient had relapsed disease following first CR of a duration of 1 month (30 days) to 24 months (730 days). The time from first relapse to study entry (start of first course of induction chemotherapy) was no longer than 30 days.
- The patient had confirmed FLT3 activating mutation positive status after point of initial relapse.
- The patient was aged 18 years or older.
- Written informed consent was obtained.
- The patient was able to understand and comply with study restrictions.
- The patient had no comorbid conditions that would limit life expectancy to less than 3 months.
- The patient had an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 1, or 2.
- Women were neither pregnant nor lactating, and either of nonchildbearing potential or using adequate contraception with a negative pregnancy test at study entry.

**Criteria for Exclusion:** Patients were excluded from participating in this study if 1 or more of the following criteria were met:

- The patient had bilirubin levels greater than 2 times the upper limit of normal (ULN) or alanine transaminase or aspartate transaminase levels greater than 3 times the ULN.
- The patient had serum creatinine concentrations greater than 1.5 mg/dL.
- The patient had resting ejection fraction of the left ventricle less than 45% (only applied to patients scheduled to receive mitoxantrone/etoposide/cytarabine [MEC]).
- The patient had untreated or progressive infection.
- The patient had any physical or psychiatric condition that might compromise participation in the study.
- The patient had known central nervous system involvement with AML.
- The patient had any previous treatment with a FLT3 inhibitor.
- The patient required current treatment for the human immunodeficiency virus (HIV) with protease inhibitors.
- The patient had active gastrointestinal ulceration or bleeding.
- The patient used an investigational drug that was not expected to be cleared by the start of lestaurtinib treatment.

**Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number:** Lestaurtinib was supplied in 20-mL amber glass vials or in 4-oz amber glass bottles (100 mL fill) as a clear yellow oral solution at a concentration of 25 mg/mL in a nonaqueous vehicle of polysorbate 80 NF and propylene glycol USP (50:50). The formulation in amber glass bottles also contained butylated hydroxanisole. Immediately prior to administration, lestaurtinib was diluted in juice. The following juices are approved for use to administer lestaurtinib: grape, pineapple, apple, V8® 100% vegetable, cranberry, and orange (with pulp and pulp free).

For patients randomly assigned to receive standard chemotherapy plus sequential lestaurtinib, lestaurtinib was administered at a dosage of 80 mg bid starting 2 days (48 hours) after the last administration of the first course of induction chemotherapy, which was day 7 of the study if the first course of chemotherapy was completed as scheduled. (Study day 1 was the first day of the first treatment of the first course of chemotherapy.) Under no circumstances was lestaurtinib coadministered with any course of chemotherapy. If a second course of chemotherapy was given, treatment with lestaurtinib stopped 3 days (72 hours) before the first administration of the second course of chemotherapy. Treatment with lestaurtinib recommenced 2 days (48 hours) after the last administration of chemotherapy in the second course.

Patients randomly assigned to chemotherapy alone who demonstrated a partial remission (PR) at the outcome assessment could have received sequential lestaurtinib therapy at a dosage of 80 mg bid until the completion of the treatment period on day 113. The dosage of lestaurtinib was reduced to 60 mg bid at any time for any patient receiving lestaurtinib if the 80 mg bid dosage was not well tolerated; return to 80 mg bid was permitted if tolerance improved. Patients who did not tolerate 60 mg bid of lestaurtinib were withdrawn from the study.

The dosage could be increased to 100 mg bid for patients randomly assigned to the lestaurtinib treatment group in the following circumstances:

- patients tolerated lestaurtinib treatment at 80 mg bid well and met the criteria for a second course of chemotherapy. In this case, lestaurtinib could be administered at 100 mg bid after the washout period following completion of the second course of chemotherapy.
- patients tolerated lestaurtinib treatment at 80 mg bid well and achieved a PR at the outcome assessment. In this case, lestaurtinib could be administered at 100 mg bid after the outcome assessment.

Lestaurtinib was supplied as an oral solution (batches 00004C5a, 03127C5a, 06C016A501, 06C021A501, and 07C006A501).

**Other Study Drugs and Dosage:** One of 2 combinations of induction chemotherapy for AML was administered for 5 days to every enrolled patient. The choice of chemotherapy combination was based upon the duration of CR prior to study entry.

***MEC Induction Chemotherapy*** (for patients with duration of first CR of 1 month [30 days] to 6 months [180 days]):

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|---|---|
| Mitoxantrone | 8 mg/m$^2$/day for 5 days (study days 1 to 5 inclusive) administered intravenously in normal saline by slow intravenous (iv) push over 5 minutes |
| Etoposide | 100 mg/m$^2$/day for 5 days (study days 1 to 5 inclusive) administered intravenously in normal saline over 1 hour beginning immediately after mitoxantrone administration |
| Cytarabine (AraC) | 1 gram/m$^2$/day for 5 days (study days 1 to 5 inclusive) administered intravenously in normal saline over 1 hour beginning immediately after etoposide administration (longer infusion times have been reported to increase the risk of cerebellar toxicity) |

***High Dose Cytarabine (HiDAC) Induction Chemotherapy*** (for patients with duration of first CR of more than 6 months [181 days] to 24 months [730 days]):

| | |
|---|---|
| Cytarabine (AraC) | 1.5 g/m$^2$ twice daily for 5 days (study days 1 to 5 inclusive) administered intravenously in normal saline over 1 to 3 hours. This dosage might have been reduced to 1.5 g/m$^2$ once daily for patients older than 65 years. |

Patients could receive up to 2 courses of induction chemotherapy depending upon the results of the aplasia assessment made after the first course of induction chemotherapy (day 15±2 days). Patients in whom aplasia (<5% cellularity) was not induced, but who had a reduction in peripheral or bone marrow leukemic blasts, could receive a second course of the same regimen as the first induction chemotherapy provided that they met the following criteria:

- ECOG performance scores did not exceed 2
- bilirubin levels did not exceed 2 times ULN
- ALT and AST levels did not exceed 3 times ULN
- serum creatinine levels did not exceed 1.5 mg/dL
- bone marrow cellularity exceeded 20% with more than 5% myeloblasts
- resting ejection fraction was at least 45% for patients receiving MEC

Patients randomly assigned to chemotherapy alone received the second course of induction chemotherapy as soon as clinically indicated; patients randomly assigned to receive chemotherapy plus sequential lestaurtinib had lestaurtinib withheld for 3 days (72 hours) before the start of the second 5-day course of chemotherapy and resumed lestaurtinib treatment 2 days (48 hours) after the final administration of the second course of chemotherapy.

**Reference Therapy Dose, Mode of Administration, and Administration Rate:** Not applicable

**Method of Blinding:** This was a randomized, open-label study with no blinding. Patients were stratified by duration of first CR (1 month to 6 months vs more than 6 months to 24 months). Within each stratum, eligible patients were randomly assigned, using an interactive voice response system (IVRS), to receive induction chemotherapy with or without sequential treatment with lestaurtinib. The IVRS used a minimization procedure to bias randomization towards balance between the 2 treatment groups with respect to center and age (less than 50 vs at least 50 years old) based upon the balance of previously assigned patients and an element to ensure randomization (Pocock and Simon 1975). This minimization procedure was used separately for both strata.

**Duration of Treatment:** Patients participated in the study for a 16-week treatment period with a 2-week follow-up visit. A further follow-up period occurred for up to 2 years or until the patient died.

**General Design and Methodology:** This was a randomized, open-label study designed to compare the proportion of patients with relapsed AML expressing FLT3 activating mutations who achieved an outcome of CR/CRp from induction chemotherapy with and without sequential treatment with lestaurtinib, and to assess the safety and tolerability of lestaurtinib treatment given in sequence with chemotherapy in this patient population. Informed consent was obtained from each patient at a screening visit before any procedures were performed to determine eligibility for the study. The following information was collected or procedures conducted at the screening visit: demographic data, details of original cancer diagnosis (World Health Organization [WHO] AML and French-American-British [FAB] AML classifications), medical history including cancer treatment history, physical examination, vital signs measurements (systolic and diastolic blood pressure, pulse, and body temperature), pregnancy test for women of childbearing potential, clinical laboratory tests (serum chemistry, hematology, and urinalysis), ECOG performance status, 12-lead electrocardiogram (ECG), multiple gated acquisition (MUGA) scan or echocardiogram (ECHO) for patients scheduled to receive mitoxantrone, bone marrow aspirate and biopsy, and determination of allogeneic transplant candidacy. Patients returned to the study center within 14 days after screening for the baseline visit, at which the following procedures were conducted: review of inclusion/exclusion criteria, physical examination, vital signs measurements (systolic and diastolic blood pressure, pulse, and body temperature), clinical laboratory tests (hematology and serum chemistry) if more than 48 hours after the screening visit, determination of ECOG performance status, collection of blood samples for pharmacokinetic and pharmacodynamic analyses (only for patients scheduled to receive lestaurtinib), and adverse event and concomitant medication recording. All patients began the study on study day 1 with a course of MEC or HiDAC induction chemotherapy that extended through day 5. Patients randomly assigned to receive chemotherapy plus sequential lestaurtinib began taking lestaurtinib on study day 7, or 2 days (48 hours) after the completion of chemotherapy.

Patients could receive up to 2 courses of induction chemotherapy, depending upon the results of the aplasia assessment after the first course of induction chemotherapy (day 15±2 days). Patients with aplasia at the aplasia assessment continued their randomized course of treatment without interruption and did not receive a second course of chemotherapy. Patients without aplasia who had a reduction in peripheral or bone

marrow leukemic blasts could receive a second course of induction chemotherapy provided that they met the criteria described above.

An outcome assessment was performed after the final course of induction chemotherapy at the earliest occurrence of 1 of the following:

- peripheral white blood cell and platelet counts returned to normal
- leukemic blasts were detected in the peripheral blood
- 42 days (±2 days) elapsed from the first administration of the final course of chemotherapy

A bone marrow aspirate and biopsy were obtained to verify an outcome of CR, CRp, or PR. No response (NR) could be verified by bone marrow aspirate and biopsy or evidence of circulating leukemic blasts.

Patients with an outcome of CR/CRp remained in their randomly assigned treatment groups and completed the treatment period on day 113 (±2 days). All patients with an outcome of PR received sequential lestaurtinib therapy, and completed the treatment period on day 113 (±2 days). Patients who showed progressive disease or no reduction in peripheral or bone marrow leukemic blasts withdrew from the study once this determination was made. All patients requiring additional chemotherapy for either induction or consolidation were required to withdraw from the study. A final bone marrow aspirate and biopsy were obtained on day 113 (±2 days) to assess durability of response. For patients receiving lestaurtinib, the last administration of lestaurtinib was on day 113 (±2 days).

Study procedures and assessments are described in detail in the protocol (Appendix D). At weekly visits beginning on day 8, at biweekly visits between day 42 (outcome assessment) and day 113 (last administration of lestaurtinib) or withdrawal from treatment, and at the initial follow-up visit (day 127 or 14 days after withdrawal from treatment), safety assessments included physical examination, vital signs measurements (systolic and diastolic blood pressure, pulse, and body temperature), ECOG performance status, serum chemistry and hematology evaluations, and information on adverse events and concomitant medication use. At the aplasia and outcome assessments, blood samples for pharmacokinetic and pharmacodynamic analyses were also collected. Additional assessments on day 113 were 12-lead ECGs, MUGA scans or ECHOs for patients who received mitoxantrone, and urinalysis. A follow-up period extended for up to 2 years after the initial follow-up visit or until a patient died. During this period, telephone contacts/visits occurred every 2 months. Data for the following were collected after discontinuation of protocol-specified treatment: subsequent AML treatment, AML status, and survival (ie, including cause of death and date of death). Patients who participated in this study may have elected to continue, or begin, receiving treatment with lestaurtinib by enrolling into extension study C0701a/501/ON/US.

**Primary Efficacy Measure(s) and Endpoint(s):** The primary efficacy variable for this study was an outcome of CR/CRp, summarized by the proportion of patients who achieved an outcome of CR/CRp. The outcome assessment was performed at a weekly visit when peripheral white blood cell and platelet counts had returned to normal, or leukemic blasts were detected in the peripheral blood, or 42 days (±2 days) had elapsed

from the first administration of the final course of chemotherapy, whichever occurred first.

**Secondary Efficacy Measures and Endpoints:** The secondary efficacy variables and endpoints were as follows:

- overall survival, defined for all patients, measured from the date of randomization until death from any cause
- event-free survival, defined for all patients, measured from the date of randomization to 1 of the following events: failure to achieve a reduction in myeloblasts meeting the criteria for response (CR, CRp, or PR), withdrawal from the study for disease progression, or death from any cause, whichever occurred first
- remission duration, defined only for patients who achieved an outcome of CR/CRp, measured from the date of CR/CRp by blood count recovery and bone marrow examination to the date of AML relapse
- outcomes of CR, CRp, and PR summarized by the proportions of patients with outcomes of CR, CRp, and PR at the outcome assessment
- outcome of CR/CRp maintained up to day 113 summarized by the proportion of patients who maintained this outcome up to day 113
- outcome of CR/CRp after crossover to lestaurtinib treatment after the outcome assessment summarized by the proportion of patients who achieved a response of CR/CRp after crossover

The definitions of response were based on the recommendations of the International Working Group to Standardize Response Criteria and Treatment Outcomes for Therapeutic Trials in Acute Myeloid Leukemia (Cheson et al 2003) and modified for this study.

**CR:** A patient had an outcome of CR if all of the following conditions were met:

- less than 5% myeloblasts in a bone marrow sample containing marrow spicules and at least 200 nucleated cells. (If spicules were absent from the sample, a repeat bone marrow biopsy was performed to ensure sufficient sampling.)
- no myeloblasts in the bone marrow sample containing Auer rods
- no evidence of extramedullary disease
- no persistence of a unique phenotype (by flow cytometry) identical to that found in the pretreatment specimen
- normal values for absolute neutrophil count (at least 1000/µL), platelet count (at least 100 000/µL), and an absence of peripheral myeloblasts. The patient was independent of transfusions.

**CRp:** A patient had an outcome of CRp if all the conditions for CR were met except that the number of platelets was less than 100 000/µL. In addition, the patient had not had a platelet transfusion in the 7 days prior to the designation of a CRp or, if transfused within the past 7 days, the patient's platelet count was independently rising.

**PR:** A patient had an outcome of PR if he or she failed to meet the criteria for CR/CRp, but there was a decrease of at least 50% in the percentage of myeloblasts to 5% to 25% in the bone marrow sample. Thus, if the pretreatment bone marrow blast percentage was

50% to 100%, the percentage of myeloblasts had decreased to a value between 5% and 25%; if the pretreatment myeloblast percentage was 10% to less than 50%, then the percentage of myeloblasts had decreased by at least half.

**NR:** A patient had an outcome of NR if the criteria for CR, CRp, and PR were not met or if there was evidence of circulating leukemic blasts.

**Safety Variables:** Safety and tolerability were assessed by evaluating the following: reported adverse events, including deaths, other serious adverse events, and withdrawals attributed to adverse events; clinical laboratory test results (serum chemistry, hematology, and urinalysis); vital signs measurements (systolic and diastolic blood pressure, pulse, and body temperature); MUGA scan/ECHO results for patients receiving mitoxantrone; ECG and physical examination findings; ECOG performance status; and concomitant medication usage. AML disease progression was monitored as part of the efficacy assessments for this study and was not to be treated as an adverse event unless it was considered severe or life-threatening. Likewise, abnormal clinical laboratory and urinalysis values were not to be treated as adverse events unless the finding resulted in treatment that was nonroutine for patients with AML or was considered clinically significant in the context of AML by the investigator.

**Pharmacokinetics:** Plasma concentrations of lestaurtinib were determined from blood samples taken during the study only for patients receiving lestaurtinib. For patients receiving lestaurtinib, blood samples were collected in the morning before the administration of chemotherapy on day 1, immediately before the first administration of lestaurtinib on day 15 of each course of treatment, on the day of the outcome assessment, and, when possible, at the point of treatment failure.

**Pharmacodynamics:** The inhibitory activity of lestaurtinib in plasma was measured via an ex vivo bioassay for FLT3 and an assay of FLT3 phosphorylation status in blood cells only for patients receiving lestaurtinib. Protein quantification assays were performed if an adequate sample was available. Blood samples for the determination of the inhibitory activity of lestaurtinib were collected in the morning before the administration of chemotherapy on day 1, immediately before the first administration of lestaurtinib on day 15 of each course of treatment, on the day of the outcome assessment, and, when possible, at the point of treatment failure.

The sensitivity of bone marrow leukemic myeloblasts to lestaurtinib–mediated FLT3 inhibition was determined by in vitro assay in the screening bone marrow aspirate sample if sufficient sample volume was obtained.

**Statistical Considerations:** The statistical methods applied were as stated in the amended protocol and described in the sections below. All data were processed and summarized by the use of SAS® Version 9.1.3. All statistical tests were 2-tailed at the 0.05 level of significance. Details of the methodology are expanded in the statistical analysis plan that was approved before the data were summarized (Appendix E).

**Sample Size and Power Considerations:** A common odds ratio of 2.33 was assumed as effect size in both strata. Such an odds ratio would be obtained, for instance, if response rates improved from 15% to 29% in the MEC stratum and from 30% to 50% in the

HiDAC stratum. On the basis of the approach of Nam (1992) for stratified 2x2 tables, 220 patients yielded a power of 80%, using a 2-sided test with an alpha of 5%. A simulation over the full binomial sample space, on the basis of the stratified Mantel-Haenzel test, yielded a power of 84%. For the secondary variable of overall survival, a hazard ratio of 1.5 was assumed. On the basis of the log-rank test, deaths of 197 patients needed to occur to yield a power of 80%.

**Data Handling Conventions:** Definitions and rules for handling data were as follows:

- Definition of Analysis Sets: The intent-to-treat (ITT) analysis set includes all patients who were randomly assigned to a treatment group, regardless of whether or not the patient received any study drug. The safety analysis set includes all patients in the ITT set who received 1 or more doses of induction chemotherapy or lestaurtinib. The evaluable set includes all patients in the safety analysis set who fulfilled all inclusion criteria and no exclusion criteria and had no protocol violations or deviations related to the primary endpoint or study drug compliance. The sensitivity analysis set includes ITT patients, excluding the first 44 enrolled patients. Data from these 44 patients were summarized and presented at an American Society of Hematology conference in October 2005. The pharmacokinetic and pharmacodynamic analysis set includes all patients in the safety analysis set who were randomly assigned to receive lestaurtinib and had pharmacokinetic or pharmacodynamic values at 1 or more time points during the study.
- Rules and Definitions: Baseline is the last observation prior to the first dose of induction chemotherapy. Endpoint for analyses and summaries is the last observed postbaseline data observation. Descriptive statistics for continuous variables include n, mean, standard deviation, standard error (SE) of the mean, median, minimum, and maximum. Descriptive statistics for categorical variables include patient counts and percentages. Strata were determined by the duration of the patient's first CR. Stratum 1 consisted of those patients with a first CR duration of 1 to 6 months (30 to 180 days). These patients received MEC for induction chemotherapy. Stratum 2 consisted of those patients with a first CR duration of more than 6 to 24 months (181 to 730 days). These patients received HiDAC for induction chemotherapy. Summary statistics are provided for the observed data only in safety analyses. Patients without a known efficacy response during the study were treated as nonresponders. There was no imputation of missing values except for dates that had incomplete information (eg, only the month and year). For partial dates of AML diagnosis, prior complete remission, and relapse, day was estimated as the middle (day 15) of the month, if the month and year were available, or middle (1 July) of the year, if only the year was available. If month and year were provided for dates used in calculating durations for survival analyses, including overall survival, event-free survival, and remission duration, the day was imputed to be the first day of the month. Listings present the partial dates.
- Study Days and Visit Windows: Study days were numbered relative to the first day of dosing. The start of treatment (day 1) was defined as the date on which a patient received the first dose of induction chemotherapy, as recorded on the Chemotherapy Administration page of the CRF. Days were numbered relative to study start (ie, ..., –2, –1, 1, 2, ..., with day 1 being the start of induction chemotherapy and day –1 being

the day before the start of induction chemotherapy). No windowing schemes were applied to the data.

**Study Population:** The ITT set of patients was used for all study population summaries unless otherwise noted. Summaries are presented by duration of first CR and randomized treatment group at study entry.

**Disposition of Patients:** Data for patients who were screened; patients who were screened, but not randomized; patients who were randomized; patients who were randomized, but not treated; patients in the safety, evaluable, sensitivity, and pharmacokinetic/pharmacodynamic analysis sets; crossover patients; patients who completed the treatment phase; patients who withdrew from the treatment phase; patients who died; and patients who enrolled in the open-label extension phase were summarized using descriptive statistics. Data for patients who withdrew from the study were summarized by reason for withdrawal using descriptive statistics.

**Demographic and Baseline Characteristics:** Patient demographic characteristics at baseline were examined to assess the baseline comparability of the randomized treatment groups. The continuous variables of patient age, weight, height, body mass index (BMI), and body surface area were summarized using descriptive statistics. Treatment groups were compared for all continuous variables using an analysis of variance (ANOVA) with treatment group as a factor. The categorical variables of patient sex, age group, and race were summarized using descriptive statistics for each category. Categories for missing data are provided where applicable. Treatment groups were compared for all categorical variables using a Pearson's chi-square test (or Fisher's exact test if cell sizes were too small).

Other patient characteristics were also examined to assess the baseline comparability of the randomized treatment groups. The continuous variables of duration of first remission, months since AML diagnosis, and time since prior AML relapse were summarized using descriptive statistics for continuous variables. The categorical variables of duration of first remission (1-180, >180 days), baseline ECOG score, cytogenetics performed, French-American-British (FAB) AML classification, age of AML onset (<50, ≥50 years), previous therapies (yes, no), World Health Organization (WHO) classification, and FLT3 mutation were summarized using descriptive statistics for each category. Categories for missing data are provided where applicable. In addition, the number of patients randomly assigned at each study center is included.

Allogeneic transplant candidacy, human leukocyte antigen (HLA) typing, reasons for not being a candidate, incidence of abnormalities in medical history, and the incidence of abnormal physical examination findings at baseline were summarized with descriptive statistics for each category. The incidence of bone marrow transplant history and the incidence of normal and abnormal ECG findings at baseline were also summarized with descriptive statistics.

All prior and concomitant medications were coded according to WHO Drug. Therapeutic classes were grouped into broader categories (eg, analgesics, hypertensive). The incidence of prior medications was summarized with descriptive statistics by therapeutic class. Prior medications included all medications taken prior to the first day of study

drug treatment, and concomitant medications included all medications taken during study participation.

**Primary Efficacy Analyses:** The primary efficacy variable, an outcome of CR/CRp summarized by the proportion of patients who achieved CR or CRp within each treatment group, was compared using the Mantel-Haenzel chi-square test with duration of first CR (30 to 180 days or 181 days to 730 days) and age group (<50 years or ≥50 years) as the stratification factors at a 2-sided alpha of 5% for the primary analysis. Odds ratio, its 95% confidence interval, and p-value are reported. Patients in the control group (chemotherapy alone) who achieved PR, crossed over to treatment with lestaurtinib, and then achieved a CR/CRp were counted in the control group.

A logistic model using age, duration of first CR, treatment, WHO classification, and age-by-treatment and duration of first CR-by-treatment interactions was fitted. If there were no significant interactions identified at alpha=0.15, a main effects model was fitted, and a point estimate and 95% confidence interval for the common odds ratio of treatment were calculated. In addition, the 95% exact confidence interval, based on the binomial distribution, was calculated for the primary efficacy variable for each treatment group.

**Secondary Efficacy Analyses:** Secondary efficacy variables were analyzed as follows:

- Overall survival, defined for all patients, was measured from the date of randomization until death from any cause. Overall survival was described and estimated by duration of first CR, age group, and overall using the Kaplan-Meier method. Median survival time and its 95% confidence interval were calculated using the method of Brookmeyer and Crowley (1982). The logrank test stratified by age group (<50 vs. ≥50) and duration of first CR served as the primary method of comparing survival results. In addition, a Cox proportional hazard regression model including age, duration of first CR, WHO classification, 2 time-dependent covariates (bone marrow/stem cell transplants and treatment crossover to lestaurtinib), and treatment were used to assess the treatment effect. The constant hazard ratio overtime assumption for the Cox proportional hazard model was checked using log(-log(survival)) plotted against the log(time). If the assumption was violated, the data should be interpreted with caution. For a patient who was not known to have died by the time of the analysis data cutoff, observation of overall survival was censored on the date the patient was last known to be alive or on the cutoff date, whichever occurred first. Data from patients in the chemotherapy alone group who received lestaurtinib treatment after the outcome assessment were analyzed as being in the chemotherapy alone group. The overall survival analyses were performed when the deaths of 197 patients needed for statistical power were obtained. This is considered the primary analysis time point.
- Event-free survival, defined for all patients, was measured from the date of randomization to 1 of the following events: failure to achieve a PR, CRp, or CR; withdrawal from the study for disease progression; or death from any cause, whichever occurred first. For a patient who did not have any of the aforementioned events and withdrew from the study for reasons other than disease progression (eg, to receive a stem cell or bone marrow transplant), the observation of event-free survival was censored on the date of withdrawal. However, if an event occurred for this

patient after the date of withdrawal, event-free survival was measured from the date of randomization to the date of this event. For a patient maintaining a response with no events by the end of the 2-year follow-up period, observation of event-free survival was censored on the date the patient was last known to be event free. Event-free survival was analyzed using the Kaplan-Meier method as described for overall survival. A sensitivity analysis for event-free survival was also performed. Patients who did not have disease progression during the treatment period of the study, but who had progression or died during the follow-up period were censored at the date of withdrawal from the study.

- Remission duration, defined only for patients who achieved an outcome of CR/CRp, was measured from the date of CR/CRp until the date of AML relapse as determined by investigators. Remission duration was analyzed using the Kaplan-Meier method as described for overall survival.
- Outcome of CR, CRp, or PR: The proportion of patients with CR, CRp, or PR was calculated as the number of patients achieving CR, CRp, or PR during treatment divided by the number of patients in the analysis set. Patients in the control (chemotherapy only) group who achieved PR, crossed over to treatment with lestaurtinib, and then achieved a CR/CRp were counted in the control group. This variable was analyzed using the Mantel-Haenzel chi-square test, as described for the primary endpoint.
- Outcome of CR/CRp maintained up to day 113: The proportion of patients who achieved a response of CR/CRp at the outcome assessment and maintained it up to day 113 was calculated as the number of patients who achieved a response of CR/CRp at both the outcome assessment and day 113 divided by the number of patients in the analysis set. This proportion was summarized by duration of first CR and treatment group using the Mantel-Haenzel chi-square test, as described for the primary endpoint.
- Outcome of CR/CRp achieved after crossing over to treatment with lestaurtinib: Patients not receiving sequential lestaurtinib treatment prior to the outcome assessment who achieved a response of PR at the outcome assessment may have crossed over and begun receiving lestaurtinib. The proportion of these patients who achieved a CR/CRp after crossing over was calculated as the number of patients who achieved a CR/CRp after crossover divided by the number of patients who crossed over. The proportion was analyzed using descriptive statistics for categorical variables.

**Safety Analyses:** The safety analysis set was used for all safety analyses. The overall safety and tolerability of lestaurtinib were assessed throughout the study by the monitoring of adverse events and the following additional safety variables:

- clinical laboratory tests at every study visit and endpoint
- vital signs measurements at every study visit and endpoint
- electrocardiography findings at endpoint
- MUGA/echocardiogram results at day 113
- ECOG performance status scores at every study visit and endpoint

For continuous variables, descriptive statistics are provided for actual values and changes

from baseline to each visit. For categorical variables, patient counts and percentages are provided. Descriptive summaries of patients with serious adverse events, patients who withdrew from treatment because of adverse events, and patients with potentially clinically significant abnormal laboratory, vital signs, or body weight values on the basis of predefined criteria are also provided. Concomitant medication usage and supportive care, including transfusions, were also monitored throughout the study.

Duration of treatment (days) was calculated as the number of days on study drug and summarized with descriptive statistics and categorically as follows: <15, 15 to 30, 31 to 43, 44 to 85, and >85 days. Shifts in dosage received for patients treated with lestaurtinib were summarized using descriptive statistics. Relative dose intensity (%) was calculated for each patient as (total actual dose taken [mg] during the study divided by total initially planned dose [mg])x100 and summarized as both categorical (<85%, and ≥85%) and continuous variables using descriptive statistics, where the total initially planned dose was calculated as number of planned doses x 80 mg. The number of chemotherapy courses received and the total dose (mg) of the specific chemotherapy agent received were summarized using descriptive statistics. Study drug administration was summarized for the overall study.

The incidence of adverse events was summarized with descriptive statistics by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Patients were counted only once in each system organ class category, and only once in each preferred term category. For the summary by severity, patients were counted at the greatest severity. For the summary by relationship, patients were counted at the closest relationship to study drug. Summaries are provided for all adverse events (overall and by severity [NCI CTC grade]), adverse events determined by the investigator to be treatment-related (defined as possibly, probably, and definitely related or missing), treatment-related adverse events by severity, serious adverse events, and adverse events causing withdrawal from the study. In addition, summaries are presented for adverse events that occurred prior to the outcome assessment and after the outcome assessment. Listings for all adverse events, serious adverse events, adverse events leading to withdrawal, and signs and symptoms are presented.

Laboratory data (chemistry and hematology) are provided for baseline, each study visit, and endpoint. Separate listings for all laboratory data and for NCI CTC-graded laboratory data are provided. Two sets of analyses were performed as follows:

- Change from baseline: Laboratory data for each test variable were summarized with descriptive statistics for each study visit and endpoint. This presentation of laboratory data includes a summary for the change from baseline for each of these visits. If multiple repeat laboratory values within a visit were available, only the last value was used in the analysis.
- Shifts from the baseline: Shift tables from baseline to each visit and endpoint for worst NCI CTC grade values and from baseline to worst grade overall are presented. All the data, including the repeat observations or evaluations from unscheduled visits, were used in this analysis.

Summary statistics for vital signs values are provided for baseline, each study visit, and endpoint. Actual values and changes from baseline to each visit and endpoint and the

incidence of potentially clinically significant abnormal values for selected vital signs were also summarized with descriptive statistics. The incidence of potentially clinically significant changes (increase or decrease ≥7%) from baseline in body weight was summarized using proportions and counts. Separate listings of all vital signs and patients with potentially clinically significant abnormal vital signs measurements are provided.

A shift table from baseline to endpoint for ECG findings is presented as a contingency table. Summary statistics for ECG interval measurements are provided for baseline and endpoint. Actual values and changes from baseline to endpoint were summarized for ECG variables with descriptive statistics. A listing of all ECG findings is provided.

Ejection fraction data from MUGA scans/echocardiograms were summarized with descriptive statistics. A listing of all ejection fraction data is provided.

Abnormal physical examination findings at baseline were summarized with descriptive statistics. A listing of all physical examination findings is provided.

All concomitant medications were coded using the WHO Drug dictionary. The incidence of concomitant medications was summarized with descriptive statistics by Anatomical Therapeutic Chemical (ATC) class and preferred term.

ECOG performance status was assessed at each visit after screening. Shifts from baseline to outcome assessment and endpoint were summarized. A listing of ECOG data collected at all visits is provided.

Listings of supportive care, diagnostic procedures, and blood product usage are provided.

**Changes in the Conduct of the Study or Planned Analyses:** There were 5 amendments to the protocol and 2 administrative letters for this study; a summary of changes is provided with the protocol (Appendix D). Changes relative to all amendments are reflected in the methods described in this report.

Major changes to the protocol, all of which were made by Amendment 4, dated 23 May 2006, were as follows:

- the primary endpoint was changed from CR alone to CR plus CRp
- the sample size was increased from 120 to 220 patients
- overall survival was ranked as the most important secondary endpoint

These major changes were made following discussions with the Food and Drug Administration (FDA) concerning the primary endpoint and after estimates of response rates in the target population were revised on the basis of an early analysis of data from 44 patients using the primary endpoint of CR. The statistical analysis plan was revised following these protocol modifications. An algorithm for testing both response and overall survival was added, preserving alpha in each case at a level of 5% (2-sided). To address concerns regarding the interpretation of statistical significance in a study that was modified after an early analysis, the statistical analysis plan also includes a sensitivity analysis excluding patients whose tumor response data were known when the primary endpoint was changed. The statistical analysis plan, dated 14 December 2006, was provided to the FDA on 26 January 2007 (Serial No. 0160). Additional minor changes

have been made since then for clarity and improvement of data presentation. The statistical methods used by Cephalon for the analysis and reporting of data from the study are those stated in the amended statistical analysis plan (Statistical Analysis Plan with Amendment 1, dated 26 February 2009) (Appendix E).

Additional changes to the planned analyses were as follows:

- The protocol section 9.7.1 and the amended statistical analysis plan section 7.2.2 include initiation of chemotherapy for disease progression as 1 of the criteria for determining event-free survival. Data were not available to determine the reason for the initiation of chemotherapy; therefore, this criterion was not used in the event-free survival analysis.
- The remission duration analysis described in protocol section 9.7.2 and in the amended statistical analysis plan section 7.2.3 was changed. Remission duration was analyzed using the Kaplan-Meier method as described for overall survival.
- A sensitivity analysis for event-free survival was performed, although it was not specified in the protocol or the amended statistical analysis plan. Data from patients who did not have disease progression during the treatment period of the study, but who had progression or died during the follow-up period were censored at the date of withdrawal from the study.

**Summary of Results**

Figures and summary tables are provided in Appendix F, and individual data listings are provided in Appendix G.

**Patient Disposition and Demography:** In this study, 224 patients with relapsed AML were randomly assigned to treatment (112 patients to treatment with chemotherapy and sequential lestaurtinib and 112 patients to treatment with chemotherapy alone) and comprise the ITT analysis set (Table 1). Duration of first complete remission was 1 to 6 months for 53 patients in each treatment group and more than 6 months to 24 months for 59 patients in each treatment group. The safety analysis set (total 220 patients) includes 111 patients randomly assigned to treatment with sequential lestaurtinib, including 3 patients who received chemotherapy only, and 109 patients randomly assigned to treatment with chemotherapy alone. The evaluable analysis set (total 193 patients) includes 93 patients randomly assigned to treatment with sequential lestaurtinib and 100 patients randomly assigned to treatment with chemotherapy alone. Ninety patients from each treatment group are in the sensitivity analysis set, and 105 patients (sequential lestaurtinib treatment group only) are in the pharmacokinetic/pharmacodynamic analysis set. Fourteen (13%) and 4 (4%) of the patients randomly assigned to the sequential lestaurtinib and to the chemotherapy alone treatment groups, respectively, completed the treatment phase (day 113) of the study. Of the 112 patients who were randomly assigned to receive chemotherapy alone, 7 (6%) patients received sequential treatment with lestaurtinib after the outcome assessment. Following this study, 16 (14%) and 34 (30%) of the patients randomly assigned to the sequential lestaurtinib and chemotherapy alone treatment groups, respectively, enrolled in the open-label extension, study C0701a/501/ON/US.

A total of 206 (92%) patients withdrew from the study (98 [88%] receiving sequential treatment with lestaurtinib and 108 [96%] receiving chemotherapy alone). The time from randomization to termination was longer for the sequential lestaurtinib treatment group than for the chemotherapy alone treatment group. The mean (standard deviation) time to termination was 58.2 (35.72) days (range 4 to 211 days) for patients in the sequential lestaurtinib treatment group and 44.0 (26.06) days (range 1 to 128 days) for patients in the chemotherapy alone treatment group (Adhoc Summary 18). Patients in the sequential lestaurtinib treatment group continued to receive a disease intervention (ie, treatment with lestaurtinib for a mean of 47.6 days [Summary 15.22]) after the 5-day course of induction chemotherapy, whereas patients randomly assigned to the chemotherapy alone treatment group were observed and given supportive care after induction chemotherapy. The most frequent reason for withdrawal from the study was disease progression, which was reported for 38 (34%) patients in the sequential lestaurtinib treatment group and 54 (48%) patients in the chemotherapy alone treatment group. Adverse event was the reason for withdrawal of 29 (26%) patients in the sequential lestaurtinib treatment group and 8 (7%) patients in the chemotherapy alone treatment group. Withdrawal rates due to disease progression and adverse events combined are of similar magnitude in the sequential lestaurtinib (60%) and the chemotherapy alone (55%) treatment groups. The lower rate of withdrawal due to disease progression and the higher rate due to adverse events in the sequential lestaurtinib treatment group may be due to the facts that this was an open-label study and that the categorization of the reason for withdrawal as disease progression or adverse event is a subjective determination by the investigator. If a patient's condition deteriorated, the investigator might have been inclined to classify this as disease progression in patients who received chemotherapy alone and as an adverse event in patients who received treatment with lestaurtinib after chemotherapy.

**Table 1: Disposition of Patients by Duration of First Complete Remission and Treatment Group (All Patients)**

| | Number (%) of patients[a] | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 to 6 months[b] | | >6 months to 24 months[b] | | Total by treatment group | | |
| **Patient disposition** | **With lestaurtinib** | **Chemotherapy alone** | **With lestaurtinib** | **Chemotherapy alone** | **With lestaurtinib** | **Chemotherapy alone** | **Total** |
| Screened | — | — | — | — | — | — | 428 |
| Randomized (ITT analysis set) | 53 (100) | 53 (100) | 59 (100) | 59 (100) | 112 (100) | 112 (100) | 224 (100) |
| Randomized, not treated | 0 | 1 (2) | 1 (2) | 2 (3) | 1 (<1) | 3 (3) | 4 (2) |
| Randomized to lestaurtinib, not treated with lestaurtinib | 1 (2) | N/A | 2 (3) | N/A | 3 (3) | N/A | 3 (1) |
| Safety analysis set | 53 (100) | 52 (98) | 58 (98) | 57 (97) | 111 (>99) | 109 (97) | 220 (98) |
| Evaluable analysis set | 46 (87) | 47 (89) | 47 (80) | 53 (90) | 93 (83) | 100 (89) | 193 (86) |
| Sensitivity analysis set | 42 (79) | 45 (85) | 48 (81) | 45 (76) | 90 (80) | 90 (80) | 180 (80) |
| PK/PD analysis set | 51 (96) | 0 | 54 (92) | 0 | 105 (94) | 0 | 105 (47) |
| Crossover patients[c] | N/A | 5 (9) | N/A | 2 (3) | N/A | 7 (6) | 7 (3) |
| Completed treatment phase (day 113) | 3 (6) | 1 (2) | 11 (19) | 3 (5) | 14 (13) | 4 (4) | 18 (8) |
| Enrolled in open-label extension (study C0701a/501/ON/US) | 4 (8) | 12 (23) | 12 (20) | 22 (37) | 16 (14) | 34 (30) | 50 (22) |
| Withdrawn from treatment phase | 50 (94) | 52 (98) | 48 (81) | 56 (95) | 98 (88) | 108 (96) | 206 (92) |
| Adverse event | 15 (28) | 7 (13) | 14 (24) | 1 (2) | 29 (26) | 8 (7) | 37 (17) |
| Consent withdrawn | 3 (6) | 0 | 0 | 0 | 3 (3) | 0 | 3 (1) |
| Protocol violation | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lost to follow-up | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Disease progression | 21 (40) | 23 (43) | 17 (29) | 31 (53) | 38 (34) | 54 (48) | 92 (41) |
| Noncompliance with study drug administration | 0 | 0 | 1 (2) | 0 | 1 (<1) | 0 | 1 (<1) |
| Noncompliance to study procedures | 0 | 0 | 0 | 1 (2) | 0 | 1 (<1) | 1 (<1) |
| No response | 3 (6) | 10 (19) | 4 (7) | 11 (19) | 7 (6) | 21 (19) | 28 (13) |
| Other | 8 (15) | 12 (23) | 12 (20) | 12 (20) | 20 (18) | 24 (21) | 44 (20) |

SOURCE: Summary 15.1, Listing 2, Listing 3.
[a] Percentages are based on the number of patients randomized.
[b] Duration of first complete remission.
[c] Patients began receiving lestaurtinib after the outcome assessment.
ITT=intent to treat; NA=not applicable; PK/PD=pharmacokinetic/pharmacodynamic.

The sequential lestaurtinib and chemotherapy alone treatment groups appear well balanced with regard to the important demographic and baseline characteristics of age (mean 55.2 and 53.1 years, respectively), sex (45% and 47% men, respectively), race (83% and 90% white, respectively), white blood cell count at baseline (27.3 and 29.9 x $10^9$/L, respectively), duration of first CR of 1 to 6 months (47% of each treatment group), and duration of first CR of more than 6 to 24 months (53% of each treatment group) (Table 2). ECOG performance status at baseline appears to be worse for patients in the chemotherapy alone treatment group (35% with a score of 0 [fully active]) than for patients in the sequential lestaurtinib treatment group (48% with a score of 0).

**Table 2: Demographic and Baseline Characteristics by Treatment Group (Intent-to-Treat Analysis Set)**

| Variables | Treatment group: With lestaurtinib (N=112) | Treatment group: Chemotherapy alone (N=112) |
|---|---|---|
| **Age, years** | | |
| n | 112 | 112 |
| Mean | 55.2 | 53.1 |
| SD | 14.17 | 13.72 |
| Median | 58.5 | 53.5 |
| Min, max | 20.0, 81.0 | 21.0, 79.0 |
| **Sex, n (%)** | | |
| Men | 50 (45) | 53 (47) |
| Women | 62 (55) | 59 (53) |
| **Race, n (%)** | | |
| White | 93 (83) | 101 (90) |
| Black | 9 (8) | 7 (6) |
| Asian | 2 (2) | 1 (<1) |
| Pacific Islander | 1 (<1) | 0 |
| Other | 7 (6) | 3 (3) |
| **White blood cell count, $10^9$/L** | | |
| n | 112 | 112 |
| Mean | 27.3 | 29.9 |
| SD | 31.26 | 46.86 |
| Median | 15.6 | 14.4 |
| Min, max | 0.1, 176.3 | 0.2, 371.9 |
| **Duration of first complete remission, n (%)** | | |
| 1 to 6 months | 53 (47) | 53 (47) |
| >6 to 24 months | 59 (53) | 59 (53) |
| **ECOG performance status, n (%)** | | |
| 0 | 54 (48) | 39 (35) |
| 1 | 49 (44) | 63 (56) |
| 2 | 9 (8) | 10 (9) |

SOURCE: Summary 15.2, Summary 15.3, Listing 1, Listing 5, Listing 28, Listing 39.
ECOG=Eastern Cooperative Oncology Group; min=minimum; max=maximum; SD=standard deviation.

Summaries of abnormal medical history, allogeneic transplant candidacy, bone marrow transplant history, prior and concomitant medications, ECG findings, and abnormal physical examination findings are provided in Appendix F.

**Efficacy Results:** All efficacy analyses were performed on the ITT analysis set, based on randomization group. The primary efficacy variable was also analyzed based on the evaluable and sensitivity analysis sets using randomization group. Patients in the chemotherapy alone treatment group who achieved PR at the outcome assessment, then received treatment with lestaurtinib, and subsequently achieved a CR/CRp, are counted in the chemotherapy alone treatment group.

Analysis of the primary efficacy variable, the proportion (ie, response rate) of patients achieving CR or CRp during the treatment period, based on the ITT analysis set, showed no statistically significant difference between treatment groups (p=0.3453) (Table 3). Likewise, analyses based on the evaluable (Summary 15.10.2) and sensitivity (Summary 15.10.3) analysis sets showed no difference between the treatment groups.

There was an apparent difference between treatment groups with regard to younger patients (ie, patients less than 50 years of age) (Summary 15.11.6). Of the 33 younger patients in the sequential lestaurtinib treatment group, 9 (27%) achieved a CR/CRp compared with 4 (12%) of 34 younger patients in the chemotherapy alone treatment group.

**Table 3: Response Rates by Treatment Group (Intent-to-Treat Analysis Set)**

| Response | Number (%) of patients: With lestaurtinib (N=112) | Number (%) of patients: Chemotherapy alone (N=112) | Odds ratio[a] (with lestaurtinib/ chemotherapy alone) | 95% CI of odds ratio | p-value[b] |
|---|---|---|---|---|---|
| **Distribution of response** | | | | | |
| CR | 19 (17) | 13 (12) | | | |
| CRp | 10 (9) | 10 (9) | | | |
| Partial remission | 19 (17) | 12 (11) | | | |
| No response | 29 (26) | 44 (39) | | | |
| Unknown | 35 (31) | 33 (29) | | | |
| **Responder (CR/CRp)** | 29 (26) | 23 (21) | 1.358 | 0.72, 2.56 | 0.3453 |
| 95% CI[c] | 18.1, 35.0 | 13.5, 29.2 | | | |
| **Not CR/CRp** | 83 (74) | 89 (79) | | | |

SOURCE: Summary 15.10.1, Listing 14.

[a] The odds ratio and 95% CI comparing the proportion of responders in each treatment group are from a Mantel-Haenzel chi-square test stratified by age group and duration of first CR.

[b] The p-value for the treatment comparison is from a Mantel-Haenzel chi-square test stratified by age group and duration of first CR.

[c] Confidence intervals around the proportion of responders are based on the Exact Binomial distribution.

CI=confidence interval; CR=complete remission; CRp=complete remission with incomplete platelet count recovery.

NOTE: Patients randomly assigned to the chemotherapy alone treatment group who achieved CR/CRp after crossover are counted in the chemotherapy alone treatment group.

Analysis of the key secondary efficacy variable, overall survival, showed no statistically significant difference between the treatment groups (p=0.7700) (Table 4).

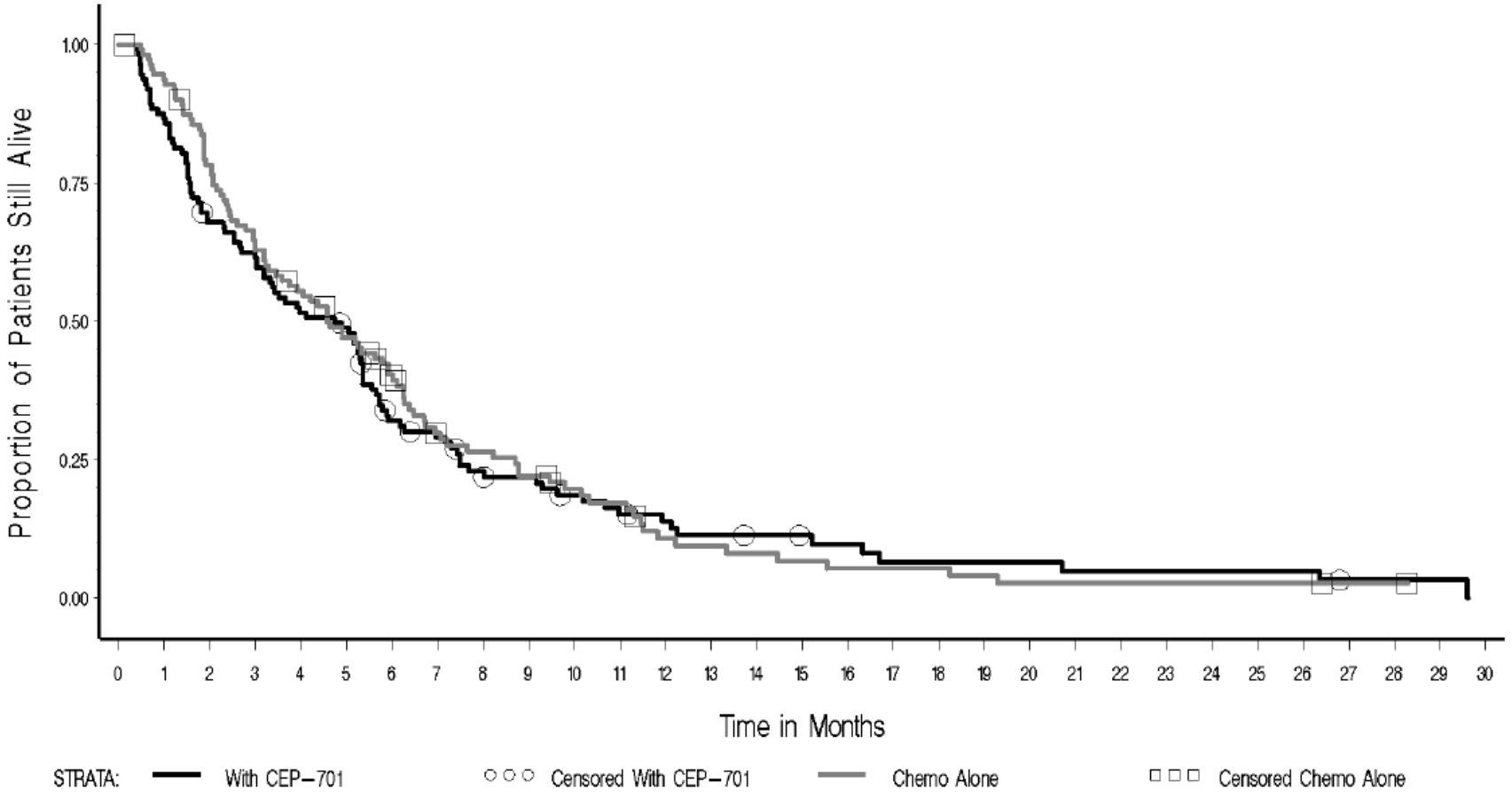
**Table 4: Overall Survival by Treatment Group (Intent-to-Treat Analysis Set)**

| Overall survival | With lestaurtinib (N=112) | Chemotherapy alone (N=112) | p-value[a] |
|---|---|---|---|
| **Patients who died, n (%)** | 100 (89) | 97 (87) | 0.7700 |
| **Patients with censored data, n (%)** | 12 (11) | 15 (13) | |
| **Quartiles (95% CI), months** | | | |
| 25th percentile | 1.56 (1.22, 2.33) | 2.07 (1.87, 2.96) | |
| 50th percentile (median) | 4.73 (3.19, 5.35) | 4.57 (3.29, 5.91) | |
| 75th percentile | 7.49 (5.88, 10.18) | 8.71 (6.37, 10.32) | |
| **Time to onset of event[b]** | | | |
| 2 months | 0.6783 (75) | 0.7826 (86) | |
| 4 months | 0.5155 (57) | 0.5548 (60) | |
| 6 months | 0.3196 (33) | 0.4032 (39) | |
| 8 months | 0.2287 (22) | 0.2643 (24) | |
| 10 months | 0.1855 (16) | 0.1964 (16) | |
| 12 months | 0.1382 (11) | 0.1071 (8) | |
| 14 months | 0.1131 (8) | 0.0803 (6) | |
| 16 months | 0.0969 (6) | 0.0536 (4) | |
| 18 months | 0.0646 (4) | 0.0536 (4) | |
| 20 months | 0.0646 (4) | 0.0268 (2) | |
| 22 months | 0.0485 (3) | 0.0268 (2) | |
| 24 months | 0.0485 (3) | 0.0268 (2) | |
| **Range, patients who died, months** | 0.39, 29.60 | 0.49, 19.28 | |
| **Range, all patients, months** | 0.39, 29.60 | 0.13, 28.29 | |

SOURCE: Summary 15.13, Listing 17.
[a] The p-value was calculated using the log-rank test adjusted for age group and duration of first complete remission.
[b] Time to onset of event was summarized with Kaplan-Meier estimates and (number at risk).
CI=confidence interval.
NOTE: Patients randomly assigned to the chemotherapy alone treatment group who received lestaurtinib treatment after the outcome assessment were counted in the chemotherapy alone treatment group.

The overall survival analysis was performed after the deaths of 197 patients (100 [89%] patients in the sequential lestaurtinib treatment group and 97 [87%] patients in the chemotherapy alone treatment group). Thirty-nine (35%) patients in the sequential lestaurtinib treatment group and 13 (12%) patients in the chemotherapy alone treatment group died within 30 days of the last dose of study drug (Summary 15.1). This apparent higher incidence rate of early deaths in the sequential lestaurtinib treatment group is misleading because patients in this group received treatment over a longer period of time (ie, throughout the study), while treatment for patients in the chemotherapy alone treatment group stopped on day 5 of the study. A graph of overall survival by treatment group shows no increased early mortality for the sequential lestaurtinib treatment group (Figure 1).

**Figure 1: Overall Survival by Treatment Group (Intent-to-Treat Analysis Set)**

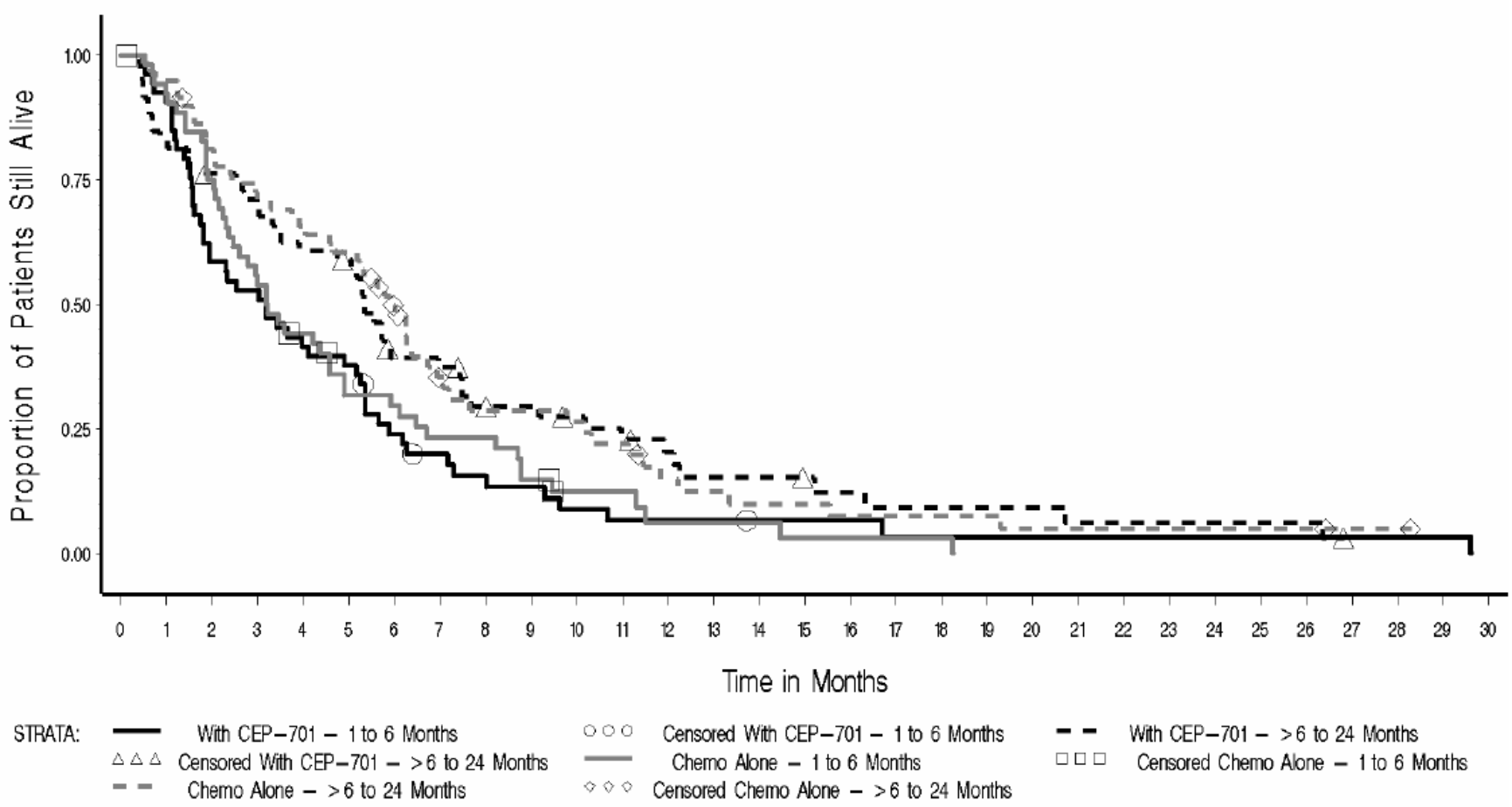



SOURCE: Figure 6.

Analysis of overall survival by duration of first CR shows that survival is better for patients with longer duration of first CR (Figure 2). There is no evidence of an effect of sequential treatment with lestaurtinib compared with treatment with chemotherapy alone.

In order to better understand the apparent lack of efficacy demonstrated in this study, additional exploratory hypotheses were formulated and exploratory analyses were conducted. These analyses confirmed the lack of efficacy. In addition, an analysis was conducted to explore the possibility of a survival effect among patients in the sequential lestaurtinib treatment group who achieved target (ie, ≥85%) FLT3 inhibition; in this analysis, the difference between the treatment groups did not reach statistical significance. The exploratory analyses are provided in Appendix E.

**Figure 2: Overall Survival by Duration of First Complete Remission and Treatment Group (Intent-to-Treat Analysis Set)**




SOURCE: Figure 5.

**Safety Results:** The mean (standard deviation) duration of treatment with lestaurtinib for patients in the sequential lestaurtinib treatment group was 47.6 (35.56) days; the median (range) duration of treatment was 37.5 (3 to 202) days (Summary 15.22). The mean (standard deviation) relative dose intensity of lestaurtinib was 89.0% (14.55%); the median (range) relative dose intensity was 94.2% (43.3 to 120.6%). (NOTE: The duration of treatment and relative dose intensity data exclude zero values for the 3 patients randomly assigned to treatment with sequential lestaurtinib who only received chemotherapy.)

Seven patients randomly assigned to treatment with chemotherapy alone received lestaurtinib after the outcome assessment. For these patients, the mean (standard deviation) duration of treatment with lestaurtinib was 22.9 (18.65) days; the median (range) duration of treatment was 18.0 (3 to 52) days (Summary 15.22). The mean (standard deviation) relative dose intensity of lestaurtinib was 95.6% (7.05%); the median (range) relative dose intensity was 98.1% (80.0% to 100.0%).

A total of 111 patients in the sequential lestaurtinib treatment group and 109 patients in the chemotherapy alone treatment group received the first course of induction chemotherapy (Table 5). Seven patients in each treatment group received a second course of induction chemotherapy. The intensities of the courses of induction chemotherapy were similar for the 2 treatment groups. The mean (standard deviation) durations of treatment with induction chemotherapy were 5.6 (1.52) days for patients in the sequential lestaurtinib treatment group and 5.7 (1.40) days for patients in the chemotherapy alone treatment group; the median (range) durations of treatment were 5.0 (2 to 12) days and 5.0 (4 to 12) days, respectively (Summary 15.23).

**Table 5: Extent of Exposure to the First Course of Induction Chemotherapy (Safety Analysis Set)**

| Variable<br>Statistic | With lestaurtinib (N=111) | Chemotherapy alone (N=109) |
|---|---|---|
| **Total dose of HiDAC cytarabine, g/m$^2$** | | |
| n | 50 | 46 |
| Mean | 13.0 | 13.9 |
| SD | 3.47 | 3.56 |
| Median | 15.0 | 15.0 |
| Min, max | 5.1, 17.5 | 7.4, 28.0 |
| **Total dose of MEC mitoxantrone, mg/m$^2$** | | |
| n | 51 | 55 |
| Mean | 39.6 | 40.0 |
| SD | 1.18 | 3.17 |
| Median | 40.0 | 40.0 |
| Min, max | 33.3, 41.4 | 32.1, 59.9 |
| **Total dose of MEC etoposide, mg/m$^2$** | | |
| n | 51 | 55 |
| Mean | 494.0 | 495.9 |
| SD | 19.47 | 20.92 |
| Median | 500.0 | 500.0 |
| Min, max | 406.1, 510.3 | 401.6, 560.3 |
| **Total dose of MEC cytarabine, g/m$^2$** | | |
| n | 51 | 55 |
| Mean | 4.9 | 4.9 |
| SD | 0.18 | 0.19 |
| Median | 5.0 | 5.0 |
| Min, max | 4.1, 5.1 | 4.0, 5.2 |

SOURCE: Summary 15.23, Listing 20.
HiDAC=high-dose cytarabine; MEC=mitoxantrone/etoposide/cytarabine; min=minimum; max=maximum; SD=standard deviation.

Every patient who received treatment in this study had at least 1 adverse event (Table 6), and the incidence of NCI CTC grade 3 or 4 adverse events was the same in each treatment group. The incidences of fatal adverse events and serious adverse events were higher in the sequential lestaurtinib treatment group (29% and 55%, respectively) than in the chemotherapy alone treatment group (16% and 45%, respectively). Adverse events leading to withdrawal from lestaurtinib treatment were reported for 27 of the 111 patients in the sequential lestaurtinib treatment group and for 4 of the 7 patients who received lestaurtinib after the outcome assessment. Adverse events that led to the withdrawal of more than 1 patient from treatment with lestaurtinib were nausea (4 patients), renal failure (3 patients), and vomiting, sepsis, muscle spasms, and AML (2 patients each) (Summary 15.29.1).

For the purpose of recording the action taken regarding study drug treatment as a result of adverse events, only lestaurtinib was considered study drug. Therefore, for patients in the

chemotherapy alone treatment group, the action taken was reported as none, and adverse events leading to withdrawal are reported only for patients in the sequential lestaurtinib treatment group and for those in the crossover treatment group who withdrew due to an adverse event while receiving lestaurtinib.

**Table 6: Overview of Adverse Events (Safety Analysis Set)**

| Adverse event category | Number (%) of patients | | |
|---|---|---|---|
| | With lestaurtinib (N=111) | Chemotherapy alone (N=109) | Crossover to lestaurtinib (N=7)[a] |
| Any adverse event | 111 (100) | 109 (100) | 7 (100) |
| Severe adverse events (NCI CTC grade 3 or 4) | 104 (94) | 101 (93) | 6 (86) |
| Adverse events related to lestaurtinib treatment | 98 (88) | NA | 6 (86) |
| Adverse events related to chemotherapy | 110 (>99) | 108 (>99) | 7 (100) |
| Adverse events related to lestaurtinib treatment and chemotherapy | 83 (75) | 3 (3) | 3 (43) |
| Adverse events leading to death | 32 (29) | 17 (16) | 2 (29) |
| Serious adverse events | 61 (55) | 49 (45) | 2 (29) |
| Adverse events leading to withdrawal from lestaurtinib treatment | 27 (24) | NA | 4 (57) |

SOURCE: Summary 15.24.1, Summary 15.26.1, Summary 15.28.1, Summary 15.29.1, Summary 15.30.1, Adhoc Summary 7.1, Listing 21, Listing 22, Listing 23, Listing 49.

[a] The patients in the crossover treatment group are a subset of the patients in the chemotherapy alone treatment group.

NA=not applicable; NCI CTC=National Cancer Institute Common Toxicity Criteria.

NOTE: For the purpose of recording the action taken regarding study drug as a result of adverse events, only lestaurtinib was considered study drug. Therefore, for patients in the chemotherapy alone treatment group, the action taken was reported as none, and adverse events leading to withdrawal are reported only for patients in the sequential lestaurtinib treatment group and for those in the crossover treatment group who withdrew due to an adverse event while receiving lestaurtinib.

Adverse events with an outcome of death were reported for 32 (29%) patients in the sequential lestaurtinib treatment group and 17 (16%) patients in the chemotherapy alone treatment group (Summary 15.30.1). Fatal adverse events reported for more than 1 patient in the sequential lestaurtinib treatment group were AML (6 patients), multiorgan failure and sepsis (4 patients each), and pneumonia and stenotrophomonas sepsis (2 patients each). Fatal adverse events reported for more than 1 patient in the chemotherapy alone treatment group were AML (4 patients) and multiorgan failure (3 patients).

A total of 61 (55%) patients in the sequential lestaurtinib treatment group and 49 (45%) patients in the chemotherapy alone treatment group had at least 1 serious adverse event (Summary 15.28.1). The most frequently (at least 5% of patients) reported serious adverse events for patients in the sequential lestaurtinib treatment group were febrile neutropenia (19 [17%] patients), sepsis (8 [7%] patients), and stomatitis, pneumonia, and AML (6 [5%] patients each). The most frequently reported serious adverse events for patients in the chemotherapy alone treatment group were febrile neutropenia (23 [21%] patients) and AML (5 [5%] patients).

The higher incidence of serious adverse events in the sequential lestaurtinib treatment group as compared with the chemotherapy alone treatment group appears to be due primarily to a higher incidence of events related to infections and infestations (32% vs 21%, respectively). However, there is no corresponding difference between the 2 treatment groups in the occurrence of serious blood and lymphatic system disorders (19% vs 23%, respectively), which can indicate bone marrow depression. The incidence of serious nervous system disorders, primarily cerebral events, is higher in the sequential lestaurtinib treatment group (10%) than in the chemotherapy alone treatment group (2%). The higher incidence of serious adverse events in the sequential lestaurtinib treatment group could be the result of a bias introduced by the study design. Patients randomly assigned to the sequential lestaurtinib treatment group continued to receive a disease intervention (ie, treatment with lestaurtinib for a mean of 47.6 days [Summary 15.22]) after the 5-day course of induction chemotherapy, whereas patients randomly assigned to the chemotherapy alone treatment group were observed and given supportive care after induction chemotherapy. This difference in care may have led to patients in the sequential lestaurtinib treatment group remaining in the study longer, and subsequently having adverse events reported over a longer period of time.

The most frequently reported (more than 50% of patients) NCI CTC grade 3 or 4 adverse events in the sequential lestaurtinib and chemotherapy alone treatment groups were related to blood and lymphatic system disorders (62% and 70%, respectively) and infections and infestations (68% and 60%, respectively) (Adhoc Summary 7.1). In addition, grade 3 or 4 gastrointestinal disorders were reported frequently (38% of patients in the sequential lestaurtinib treatment group and 28% of patients in the chemotherapy alone treatment group).

Narratives for patients who had fatal or nonfatal serious adverse events reported to the Cephalon Global Pharmacovigilance & Epidemiology department are provided in Appendix H. Additional deaths, most due to disease progression, monitored as part of the efficacy assessments, are listed in Listing 49. All of the additional deaths that were not due to disease progression occurred after the initial 14-day follow-up period of the study. Investigators were not required to report serious adverse events that occurred after the 14-day follow-up period unless they were considered at least possibly related to the study drug or study participation.

Few patients had shifts in serum chemistry parameters from NCI CTC grade 0 values at baseline to grade 3 or 4 values at endpoint (Summary 15.33, Summary 15.34.1, and Summary 15.34.2). The most frequent shifts were to low potassium values. Eight patients in the sequential lestaurtinib treatment group and 3 patients in the chemotherapy alone treatment group had shifts from grade 0 values at baseline to grade 3 low values at endpoint.

At least 10 patients in each treatment group had shifts in hematology parameters as follows: white blood cell count shifts from NCI CTC grade 0 values at baseline to grade 4 values at endpoint for 35 patients in the sequential lestaurtinib treatment group and 31 patients in the chemotherapy alone treatment group; absolute neutrophil count shifts from grade 0 values at baseline to grade 4 values at endpoint for 11 patients in the sequential lestaurtinib treatment group and 10 patients in the chemotherapy alone

treatment group; and absolute lymphocyte count shifts from grade 0 values at baseline to grade 3 values at endpoint for 28 patients in the sequential lestaurtinib treatment group and 30 patients in the chemotherapy alone treatment group (Summary 15.35).

Of patients with baseline and postbaseline vital signs, weight, or temperature measurements, 80 (73%) of 110 patients in the sequential lestaurtinib treatment group and 65 (60%) of 109 patients in the chemotherapy alone treatment group had at least 1 potentially clinically significant abnormal value (Summary 15.37). The most frequent (at least 10% of patients) abnormalities in the sequential lestaurtinib treatment group were heart rate of at least 120 bpm and an increase of at least 15 bpm from baseline (21%), increase in weight of at least 7% from baseline (12%), decrease in weight of at least 7% from baseline (47%), and temperature of at least 38.3°C and an increase of at least 1.1°C from baseline (25%). The most frequent abnormalities in the chemotherapy alone treatment group were heart rate of at least 120 bpm and an increase of at least 15 bpm from baseline (14%), increase in weight of at least 7% from baseline (10%), decrease in weight of at least 7% from baseline (31%), and temperature of at least 38.3°C and an increase of at least 1.1°C from baseline (24%).

**Pharmacokinetics Results:** Sample collection information and plasma concentration data are provided in Listing 18, Listing 41, and Listing 42. The bioanalytical report for this study is provided in Appendix I. The plasma concentration data from this study were included in a population pharmacokinetic analysis (report CP-08-001).

**Pharmacodynamics Results:** Analysis of pharmacodynamic data is pending.

**Conclusions:** Overall, patients with relapsed AML expressing FLT3 activating mutations who were in the sequential lestaurtinib treatment group in this study did not have clinical improvement as defined by the protocol compared with patients who were in the chemotherapy alone treatment group, but they also did not have an overall worse clinical outcome. This lack of a clinical benefit from the addition of treatment with lestaurtinib to induction chemotherapy cannot be explained by issues with lestaurtinib treatment compliance, differential dose intensity of chemotherapy in each treatment group, or confounding baseline characteristics.

No clear serious safety signal related to the use of lestaurtinib in conjunction with chemotherapy was identified. The incidence of NCI CTC grade 3 or 4 adverse events was approximately the same in each treatment group; however, the incidence of serious adverse events was higher in the sequential lestaurtinib treatment group than in the chemotherapy alone treatment group. This higher overall incidence seems to be due to higher rates of serious infections, which may be explained by the longer time the patients in the sequential lestaurtinib treatment group were in the study.