# Clinical Study Report Synopsis: Study H6Q-MC-JCBT

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| **Title of Study:** A Phase 2 Double-Blind Randomized Study of Oral Enzastaurin HCl versus Placebo Concurrently with Pemetrexed (Alimta®) as Second-Line Therapy in Patients with Advanced or Metastatic Non-Small Cell Lung Cancer | |
| **Number of Investigators:** This multicenter study included 23 principal investigators. | |
| **Study Centers:** This study was conducted at 23 study centers in 6 countries. | |
| **Publications Based on the Study:** None at this time. | |
| **Length of Study:**<br>Date of first patient visit: 17 September 2007<br>Date of last patient completed: 01 October 2008 | **Phase of Development:** 2 |

**Objectives:** The primary objective of this study was to compare pemetrexed plus enzastaurin when given in a twice-daily (BID) dosing schedule versus pemetrexed plus placebo BID in terms of the progression-free survival (PFS) of patients receiving second-line therapy for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC).

The secondary objectives of this study were to assess and compare the following variables between treatment arms:

- time-to-event variables, including:
  - overall survival (OS)
  - time to worsening of symptoms (TWS)
  - duration of disease control (DDC)
- disease control (best response of stable disease [SD], partial response [PR], or complete response [CR])
- tumor response (best response of PR or CR)
- the safety and adverse event profile (including Common Terminology Criteria for Adverse Events [CTCAE v3.0, NCI 2006] grades for laboratory and nonlaboratory adverse events)
- maximum improvement over baseline score for each item of the Lung Cancer Symptom Scale (LCSS)
- biomarkers relevant to enzastaurin, pemetrexed, the disease state, and the clinical outcome.

**Study Design:** Study JCBT was a Phase 2, double-blind, randomized, multicenter study of pemetrexed plus enzastaurin in comparison to pemetrexed plus placebo, after treatment with 1 prior chemotherapy regimen, in patients with locally advanced or metastatic NSCLC (Stage IIIA, IIIB, or IV) that was not amenable to curative therapy.

Eligible patients were randomly assigned to receive either pemetrexed plus enzastaurin (Arm A) or pemetrexed plus placebo (Arm B). All patients received supplemental folic acid and vitamin B12 as stated in the pemetrexed label. For the purposes of treating this patient population, study treatment (Arm A or Arm B) continued until evidence of progressive disease. Safety was assessed through the evaluation of laboratory and nonlaboratory adverse events using the National Cancer Institute (NCI) CTCAE (v3.0; NCI 2006). Patient-reported symptoms and health-related quality of life (HRQoL) were assessed using the patient scale of the LCSS.

All sites were to participate in the collection of whole blood, plasma, and serum samples for translational research (TR), unless prohibited by local regulations.

**Number of Patients**:
Planned: 160
Randomized: 160: 80 Arm A; 80 Arm B
Treated (at least 1 dose): 79 Arm A, 80 Arm B

**Diagnosis and Main Criteria for Inclusion:** Histologic or cytologic diagnosis of NSCLC with locally advanced or metastatic disease (Stage IIIA, IIIB or IV at entry) not amenable to curative therapy; progressive disease after 1 prior systemic cytotoxic chemotherapy regimen for advanced disease; at least 1 measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines; Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; discontinuation of all previous systemic therapies for cancer (including targeted agents such as bevacizumab) for at least 2 weeks prior to enrollment; previous radiation therapy (including thoracic radiation) was allowed to 25% of the bone marrow but was limited and must not have included whole pelvis radiation; estimated life expectancy of at least 8 weeks.

**Test Product, Dose, and Mode of Administration:**
Pemetrexed 500 mg/m$^2$, given intravenously on Day 8 every 21 days. Enzastaurin tablets – Day 1: loading dose of 9 tablets of oral enzastaurin (375 mg TID; total dose, 1125 mg), Days 2-28: 2 tablets (250 mg) of oral enzastaurin BID (total daily dose, 500 mg).

**Comparator, Dose, and Mode of Administration:** Pemetrexed 500 mg/m$^2$, given intravenously on Day 8 every 21 days. Placebo capsules – Day 1**:** loading dose of 9 tablets of oral placebo, Days 2-28**:** 2 tablets of oral placebo BID.

**Duration of Treatment:**
Patients were to continue on study medication until evidence of progressive disease or unacceptable toxicity.

**Variables:**
Efficacy: PFS, OS, DDC, TWS, disease control, tumor response.
Safety: Laboratory and nonlaboratory adverse events (AEs) by maximum CTCAE Grade, discontinuations due to AE or death, deaths, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), transfusions, hospitalizations, use of erythropoietin, G-CSF, or other growth factors.
Translational: Relationship between biomarker expressions ([redacted]) and clinical outcomes (OS and PFS)
Health Outcomes: Lung Cancer Symptom Scale

**Statistical Evaluation Methods:**

Efficacy: The primary endpoint was PFS, defined as the time from the date of randomization to the first date of documented objective progression of disease or of death from any cause. In defining the primary statistical hypotheses for this study, the PFS hazard ratio (HR) of enzastaurin plus pemetrexed over placebo plus pemetrexed was assumed to be approximately constant after randomization. The following were the primary null and one-sided alternative hypotheses for this trial:

- H0: PFS HR = 1.00 (null hypothesis)
- HA: PFS HR < 1.00 (alternative, primary research hypothesis)

This primary statistical test was performed for the final analysis using a nominal one-sided alpha level of 0.2 using a stratified log-rank statistic. The 4 strata were the same as defined for randomization, based on all 4 combinations of values of the following 2 prognostic factors:

- ECOG performance status
  - Baseline score = 0 or 1
  - Baseline score = 2
- Time since last chemotherapy
  - Greater than or equal to 3 months
  - Less than 3 months

The PFS HR was also estimated (with 95% confidence interval) using the Cox proportional hazards model (Cox 1972) with the same stratification and including “treatment arm” as the only covariate.

The sample size of 160 patients allowed for a well-powered final analysis at the point of 25% censoring (120 events). For example, if the true PFS HR was 0.735, there was an 80% chance of rejecting H0 at the nominal one-sided alpha level of 0.2.

For all time-to-event variables, the following analyses were performed:

- The Kaplan-Meier method (Kaplan and Meier 1958) was used to estimate parameters specific to each treatment group. For each variable, Kaplan-Meier graphs were generated, and quartiles and point probabilities were calculated. Interval estimates were calculated using 95% confidence intervals.

- The primary analysis of PFS was repeated for all time-to-event variables (using analogous definitions for the null and alternative hypotheses).
- Additional Cox model analyses (Cox 1972) were conducted, considering other potential prognostic factors as covariates in the model. Among the variables to be considered were (i) prior response to first-line chemotherapy, (ii) use of prior antiangiogenic treatment, (iii) histology, and (iv) gender.

Safety: Safety analyses included summarized counts and rates (per treatment arm) of the incidence of laboratory and nonlaboratory AEs by maximum CTCAE Grade (v3.0, NCI 2006) that occurred during the study treatment period or within 30 days of the last dose of study treatment (summarized based on whether AEs considered drug-related and also regardless of drug relationship).

Translational: Post-hoc analyses were performed to explore the relationship between biomarker expression and clinical outcomes (OS and PFS). Analyses included all randomized patients with signed supplemental consent and at least 1 biomarker expression value (IHC population). All statistical tests were conducted at a 2-sided alpha level of 0.05. The stratified log-rank analyses of OS and PFS on the ITT population were also performed on the IHC population. Spearman's rank correlation coefficient rho ($\rho$) values (Spearman 1904) were calculated to measure the correlation between IHC marker pairs. For biomarkers analyzed by IHC, H-scores were used to dichotomize patients into low- and high-expression subgroups. The association of clinical outcomes with each molecular marker expression level and treatment was assessed by testing interaction and reduced Cox regression models. The interaction model includes terms for treatment, histology (squamous/nonsquamous), marker expression (high/low), treatment by histology interaction, and treatment by expression interaction. The treatment by expression interaction was removed for the reduced model. For each marker and model, the analysis was fit iteratively, testing H-score values from the 25th to the 75th percentile. The optimal fit cut point was identified which maximized the treatment by expression interaction p-value for the interaction model or the marker expression p-value for the reduced model. Significance tests of the association were based on the asymptotic distribution of maximum chi square values (Miller and Siegmund 1982). Treatment-independent analyses were also conducted by combining 2 treatment groups, and fitting Cox regression models on PFS and OS using an interaction model (with terms for histology, marker expression, and their interaction), main effects model (with histology and expression), and a model with only marker expression. The optimal fit cut point was identified which maximized the histology by expression interaction p-value for the interaction model, or the marker expression p-value for the other models. Conclusions were based on the first model in the sequence for which a significant p-value was obtained for the term being optimized. Pre-determined cut points were also used to fit all the above models, where the p-values were calculated using standard chi square distribution. Kaplan-Meier curves were plotted based on cutpoints from the set of analyses.

Health Outcomes: The LCSS data were to be summarized descriptively by baseline and cycle.

Interim Analysis: A planned interim analysis was to occur as soon as possible following the observation of a total of 60 PFS events (disease progression or death due to any cause) among randomized patients. The primary and key secondary endpoints were considered at interim using the same methods described above for the final analysis, with the exception that there were no formal statistical decision rules or hypothesis tests planned for the interim analysis. Results of this planned interim analysis suggested that the combination arm would not meet the primary endpoint of improvement in PFS compared with the control arm. The assessment committee (AC) provided their recommendation to stop Study JCBT to the Lilly physician responsible for the trial on 29 July 2008. The AC recommended stopping the study for futility (lack of efficacy). The study team met via conference call on 01 August 2008 and accepted the AC's recommendation.

**Summary:**

Results of the planned interim analysis suggested that the combination arm would not meet the primary endpoint of improvement in PFS compared with the control arm. Based on results from the interim analysis, an independent assessment committee (AC) of Lilly experts recommended to stop Study JCBT for futility (lack of efficacy). Although the interim analysis was to take place when 60 PFS events had occurred, enrollment in the study was brisk and was permitted to continue while the interim analysis was being performed. By the time the interim analysis was completed, the trial was fully enrolled (160 patients), and 72 PFS events had occurred. The study report provides the results from the interim analysis only, as the study was halted early due to lack of efficacy.

One hundred seventy patients were entered in this study at 23 sites in 6 countries. Eighty patients were randomized to each arm; the remaining 10 patients were not randomized. For both treatment arms, progressive disease was the most common reasons for discontinuation. Baseline patient demographics were well balanced between the 2 treatment arms. The median age was 62.1 years (range, 34.5 to 81.4 years) for patients on the combination arm and 60.7 years (range, 42.7 to 86.6 years) for patients on the control arm. All patients on both arms, as expected, had received a prior systemic therapy. No important differences in reported prior therapies were noted between the 2 treatment arms.

The Kaplan-Meier estimate of median PFS was 2.96 months (95% confidence interval [CI]: 4.56 to 10.46; range, 1.87 to 3.58 months) on the combination arm and 3.02 months (95% CI: 1.74 to 3.98 months) on the control arm (Table JCBT.7.1). There was no statistically significant difference in PFS between 2 treatment arms (p=.544 from the primary stratified log-rank test). The hazard ratio in PFS for the combination arm versus the control arm is 1.13 (95% CI: 0.77 to 1.65).

The Kaplan-Meier estimate of median OS was 9.63 months in the combination arm and 7.39 months in the control arm. Twenty-seven (33.75%) patients had events (death from any cause) in the combination arm, and 35 patients (43.75%) had events in the control arm.

LCSS scores at baseline were not statistically different between arms. No statistically significant differences in TWS in the LCSS items were noted between the 2 treatment arms, except for a shorter TWS for global HRQoL in the combination arm (p=0.010; Source: kmsurv58). Censoring rates were >50% in the majority of the TWS analyses.

There were no statistically significant differences between the 2 treatment arms in tumor response rates or disease control rates.

For both OS and PFS, none of the IHC markers dichotomized by optimal fit cutoff or a predetermined cutoff value were found to be predictive of treatment effect for TTF1, TS, or FR-alpha in any of the cell compartments investigated. However, there was a significant difference in PFS (HR=0.305, p-value=0.042) for patients with high versus low TS log2 (nuclear/cytoplasm), independent of treatment.

Among notable biomarker interactions, there was a strong inverse correlation between cytoplasmic TS and nuclear TTF1, and a strong direct correlation between membrane FRalpha and nuclear TTF1. There were medium correlations between nuclear TTF1 and cytoplasmic FRalpha, and between nuclear and cytoplasmic TS.

A total of 26 patients died either during the study (3 on combination arm, 6 on control arm) or within 30 days after discontinuation (7 combination arm, 10 control arm). One death in the control arm (neutropenic sepsis) was considered related to study medication. Thirty-three (41.8%) patients on the combination arm and 30 (37.5%) patients on the control arm experienced at least 1 SAE. Fourteen (17.7%) patients on the combination arm and 14 (17.5%) patients on the control arm experienced SAEs that were considered to be possibly related to study drug. On the combination arm, 6 patients (7.6%) discontinued because of nonserious AEs, and 6 patients (7.6%) discontinued because of an SAE. On the control arm, 2 patients (2.5%) discontinued because of a nonserious AE, and 9 patients (11.3%) discontinued because of an SAE. Three patients (3.8%, respectively) in each treatment arm discontinued because of an SAE that was related to study drug. There were no other statistically significant differences in the percentages of study-drug-related AEs between the 2 treatment arms.

**Conclusions:**

- There were no significant differences with regard to any efficacy endpoints between the 2 treatment arms. The addition of enzastaurin to pemetrexed did not correlate to increased efficacy.
- Patients with squamous cell histology had a significantly longer OS in the combination arm compared to the control arm.
- There were no meaningful differences in toxicity profiles between the 2 treatment arms. The addition of enzastaurin did not result in an unexpected or unreasonable safety profile for the 2 agents in combination.
- For the translational research component of this trial, none of the IHC markers dichotomized by optimal fit cutoff or a predetermined cutoff value were found to be predictive of treatment effect for both OS and PFS. There was a strong inverse correlation between cytoplasmic TS and nuclear TTF1 and a strong direct correlation between membrane FRalpha and related to nuclear TTF1.