2. S103 Synopsis

Approval Date: 05-Nov-2012 GMT

Clinical Study Report Synopsis: Study H3E-MC-S103

Title of Study: A Randomized Phase 2 Study Comparing Erlotinib-Pemetrexed, Pemetrexed alone, and Erlotinib alone, as Second-Line Treatment for Non-Smoker Patients with Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer

Number of Investigators: This multicenter study included 33 principal investigators.

Study Centers: This study was conducted at 33 study centers in 8 countries/regions.

Publication Based on the Study: None at this time.

Length of Study:	**Phase of Development:** 2
Date of first patient enrolled: 15 November 2007 Date of last patient discontinued: 15 January 2012	

Objectives:

The primary objective

To compare an erlotinib-pemetrexed combination with pemetrexed alone, and erlotinib alone, in terms of progression-free survival (PFS) in non-smoker patients with locally advanced or metastatic (Stage IIIA, IIIB, or IV) nonsquamous non-small cell lung cancer (NSCLC) who have failed first-line chemotherapy treatment.

The secondary objectives

1) To conduct the above comparisons in terms of:

- tumor response rate
- disease control rate (percentage of randomized patients with best response of stable disease, partial response, complete response)
- overall survival (including 1-year survival rates)
- safety and adverse events (AEs) profile (including Common Terminology Criteria for Adverse Events [CTCAE] grades for laboratory and nonlaboratory adverse events)
- association between epidermal growth factor receptor (*EGFR)* and methylthioadenosine phosphorylase (*MTAP)* genotype, and clinical outcome to treatment
- time-to-worsening of symptoms using the Lung Cancer Symptom Scale (LCSS)

2) To compare pemetrexed alone with erlotinib alone in non-smoker patients with locally advanced or metastatic (Stage IIIA, IIIB, or IV) nonsquamous NSCLC who have failed first-line chemotherapy treatment in terms of PFS and all the other items stated above.

Study Design: multicenter, open-label, randomized, parallel, three-arm Phase 2 study

Number of Patients:

Planned: 237 patients, randomized in 1:1:1 to one of the three treatment arms: erlotinib-pemetrexed (ERL+PEM), erlotinib (ERL), or pemetrexed (PEM).

Randomized: 81 (ERL+PEM), 82 (ERL), 84 (PEM).

Treated (at least 1 dose): 78 (ERL+PEM), 82 (ERL), 81 (PEM).

Completed: 9 (ERL+PEM), 19 (ERL), 11 (PEM). (No fixed number of treatment cycle. Patients continued to receive study therapy until one of the reasons for discontinuation of study drug were met. The non-squamous subjects who have completed 18 months from randomization were recorded as completed here.)

Diagnosis and Main Criteria for Inclusion:

Male and female non-smoker (having smoked <100 cigarettes in their lifetime) patients ≥18 years of age with locally advanced or metastatic nonsquamous NSCLC, who had failed only one prior chemotherapy regimen, ≥1 measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST) 1.0, and Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2 were eligible.

Erlotinib-Pemetrexed or Erlotinib or Pemetrexed, Dose, and Mode of Administration (Figure S103.2.1):

ERL+PEM: pemetrexed 500 mg/m^2, given intravenously on Day 1 plus erlotinib 150 mg, given orally once per day on Day 2 through Day 14 of a 21-day cycle.

ERL: erlotinib 150 mg, given orally once per day of a 21-day cycle.

PEM: pemetrexed 500 mg/m^2, given intravenously on Day 1 of a 21-day cycle.

All patients receiving pemetrexed also received dexamethasone, folic acid and vitamin B12 supplementation.

Duration of Treatment:

3 weeks per cycle; patients continued to receive study therapy until one of the reasons for discontinuation of study drug were met. (See Protocol section 4.3.1)

Variables:

Efficacy: PFS, tumor response rate (TRR), disease control rate (DCR), and overall survival (OS) (including 1-year survival rates).

Quality of Life Measure: Time-to-worsening of symptoms (TWS) were assessed using the patient-rated LCSS.

Safety: AEs, CTCAE ratings, chemistry and hematology assessments, key concomitant medications, and physical examinations.

Bioanalytical: Formalin-fixed, paraffin-embedded tumor tissue samples (previously taken to diagnose the patient's disease) were obtained from patients consenting to participate, and genetic material derived from these samples were tested for aberrations within EGFR.

Statistical Evaluation Methods:

The study was powered on a global comparison of PFS across the three treatment groups of ERL+PEM combination, ERL alone and PEM alone. In total, 237 patients were planned with a 1:1:1 ratio to observe 213 progression events. This sample size provided at least 80% power to reject the null hypothesis that all treatment arms were equal, provided that the maximum difference in hazard ratio (HR) between treatment arms was 0.67, assuming an overall two-sided alpha significance level of 0.2 and 10% censoring.

The primary objective of this study was to compare the ERL+PEM combination with ERL alone, and ERL+PEM combination with PEM alone, in terms of PFS. A multivariate Cox regression model (Cox 1972) was used to estimate treatment group differences adjusted for baseline prognostic factors :gender (male vs female), race (east asia vs non-east asia), ECOG PS (0-1 vs 2) and histology subtype (adenocarcinoma vs non-adenocarcinoma). Primary analysis was conducted by first performing a global comparison of PFS across all three arms. Pairwise comparisons between combination arm vs. each single agent arm alone (comparison between single agent arms were secondary) were then conducted under the global model, given the global null hypothesis was rejected at 2-sided 0.2 significance level. Note that pairwise comparisons would not had been conducted if the global test was not rejected and statistical significance was claimed only if both the pairwise and global null hypotheses were rejected at a 2-sided 0.05 significance level. (Figure S103.2.2) The Qualified Intention to Treat (Q-ITT) population was the primary analysis population, which was defined as all patients, with nonsquamous histology, who were randomized to therapy.

As supportive analyses, an univariate Cox model with assigned treatment as the only cofactor in the model was used to estimate the unadjusted hazard ratio. Kaplan-Meier analyses were performed (Kaplan and Meier 1958). Kaplan-Meier curves were generated, and medians, quartiles, survival rates at appropriate time points, and corresponding 95% CIs were calculated. Unadjusted comparisons on PFS across treatment arms were conducted using both log-rank and Wilcoxon tests.

Statistical Evaluation Methods (cont.):
The analyses of the secondary time to events endpoints (eg. overall survival) were analogous to those used to analyze the primary endpoint. Tumor response rates (TRR) and disease control rates (DCR) were analyzed mainly using multivariate logistic regression models.

Quality of life analyses included Cox regressions of TWS. Time-to-worsening of symptoms was assessed using the patient-rated LCSS (LCSS; Hollen et al. 1994). The LCSS data were also analyzed using linear mixed models and summarized descriptively by baseline and cycle.

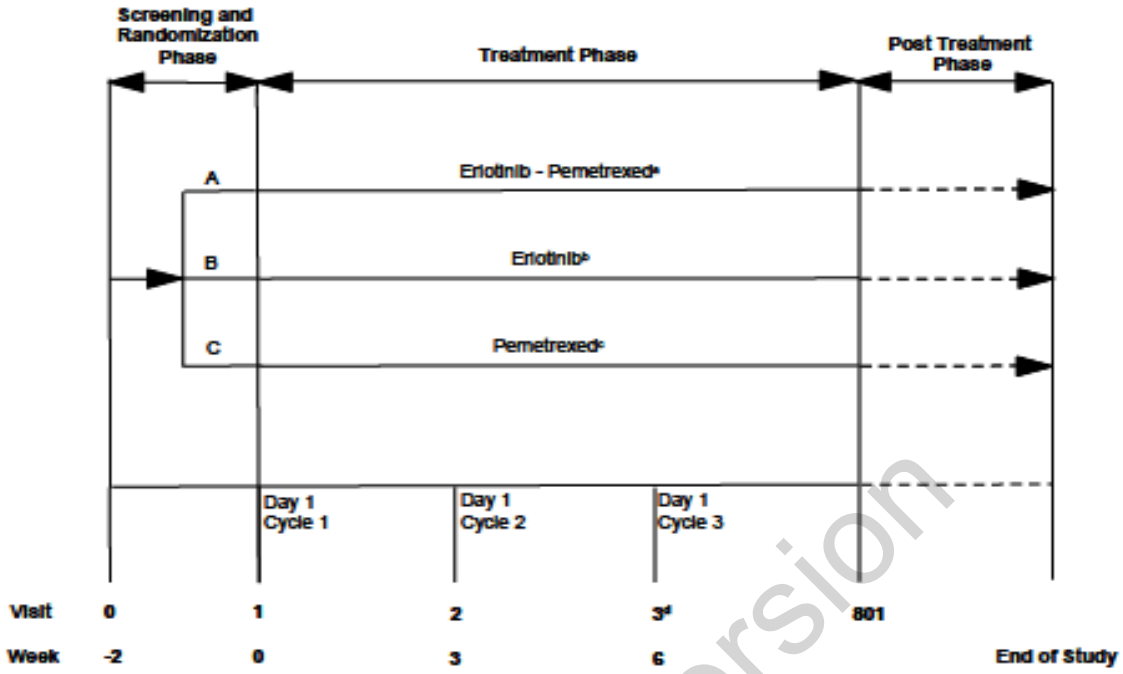
Descriptive statistics were generated to summarize the EGFR test results and the baseline characteristics of the population who provided EGFR samples. Efficacy analyses of PFS were conducted on this population using multivariate Cox regression models. Forest plots were used to present the subgroup analyses results.

Safety endpoints were mainly analyzed on nonsquamous patients who received at least one dose of study therapy and according to the treatment they received in the first cycle. Safety analyses included summaries of the incidence of AEs by maximum CTCAE Grade (version 3.0). The incidences of AEs across treatment arms were compared using Fisher's exact tests.

Change of Analysis:
In protocol, association between *MTAP* genotypes and clinical outcome to treatment was listed as one of the secondary objectives. Due to budget constraints, *MTAP* testing was not done and this analysis was removed.

The primary censoring rule of PFS followed the FDA guideline Table A [Refer to http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf]. Additional sensitivity analysis of PFS with a simpler censoring rule (ITT censoring rule that censor patient without baseline assessment or patients not known to have died or with status of progressive disease at the data inclusion cutoff date for analysis) was conducted after the delivery of the draft outputs.

Additional analyses of EGFR were performed for exploratory purposes.



a Pemetrexed (500 mg/m2, Day 1) - erlotinib (150 mg/day, Day 2 through Day 14)
b Erlotinib (150 mg/day)
c Pemetrexed (500 mg/m2, Day 1)
d Subsequent cycles should follow the same guidelines as Cycles 1-3. Patients may continue to receive study therapy until one of the reasons for discontinuation of study drug were met (see Protocol Section 4.3.1).

Figure S103.2.1. Illustration of study design for Protocol H3E-MC-S103.

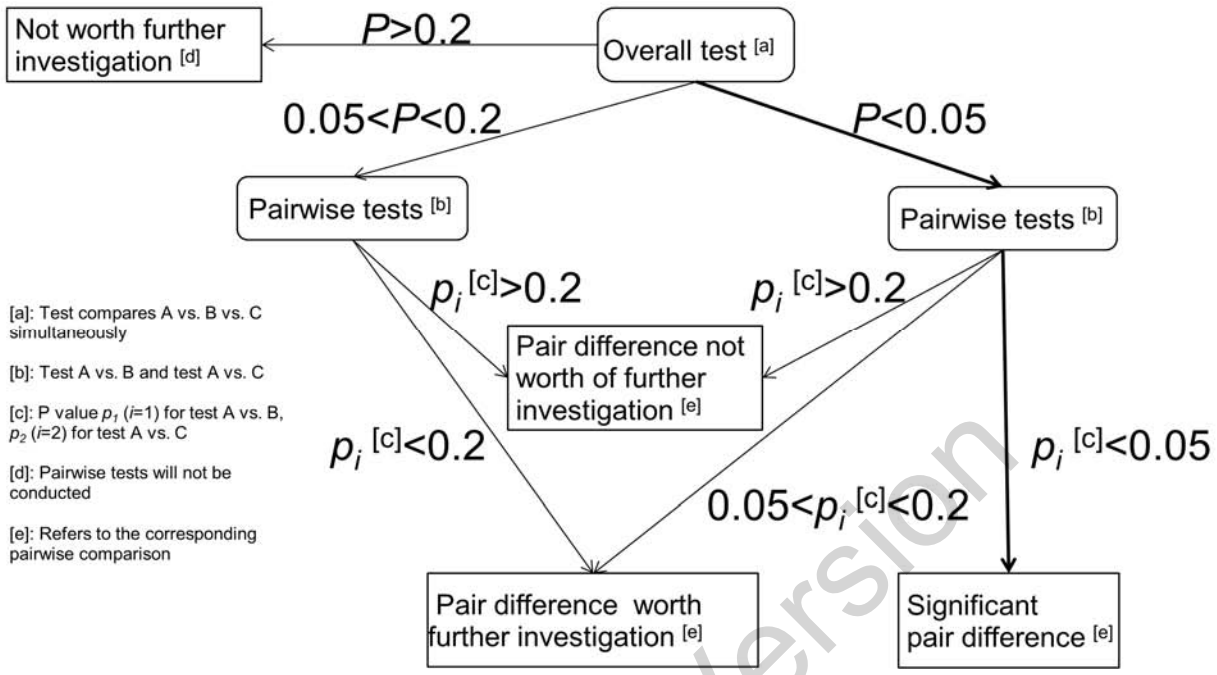
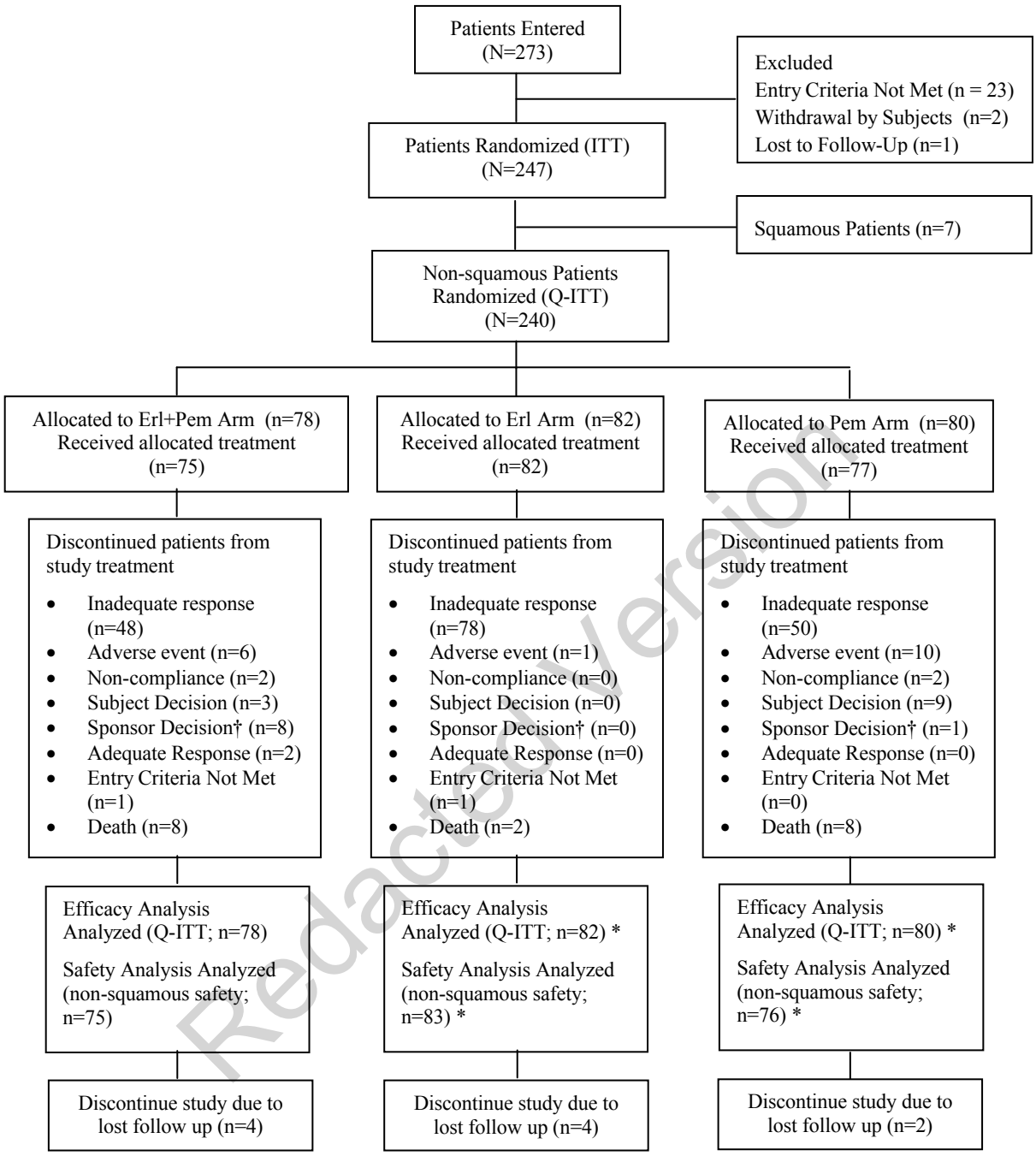


Figure S103.2.2. Primary analysis interpretation flow chart

Summary:

Of the 273 patients entered, a total of 247 patients were enrolled into the study (Figure S103.2.3). Of the enrolled patients, 240 patients were qualified with nonsquamous histology (Q-ITT) and were used as the primary population for analysis as required by protocol amendment (b) approved on 5 May 2008. The efficacy and safety results summarized below are for non-squamous patients only, unless otherwise stated. The main baseline characteristics for the ERL+PEM /ERL/PEM treatment arm were: female 74.4%/65.9%/56.3%; median age 55.8/53.9/55.9 years; East Asian race 52.6%/59.8%/53.8%; ECOG PS 0-1 91.0%/92.7%/95.0%; adenocarcinoma subtype 92.3%/92.7%/96.3%; stage IV at entry 92.3%/82.9%/85.0%. Table S103.2.1 showed summary of baseline prognostic factors in Q-ITT population.

Of the 240 patients with nonsquamous histology, 234 patients received at least one dose of treatment and were used for the safety analyses.



†: The patients in study for at least 18 months since randomization and still on study treatment when study closed.

*: The fact that one patient was assigned to Pemetrexed (singe) but received Erlotinib (singe) at first cycle leads to the discrepancy of patients for efficacy and safety analysis.

Figure S103.2.3. Patient disposition.

Table S103.2.1. Summary of Baseline Prognostic Factors

(Q-ITT Population)

Parameter	Pemetrexed + Erlotinib (N=78)	Erlotinib (N=82)	Pemetrexed (N=80)	Total (N=240)
Race (East Asian Race vs. Non-East Asian) [n (%)]				
Number of Patients	78	82	80	240
East Asian Race[a]	41 (52.6)	49 (59.8)	43 (53.8)	133 (55.4)
Non-East Asian	37 (47.4)	33 (40.2)	37 (46.3)	107 (44.6)
Gender (Male vs. Female) [n (%)]				
Number of Patients	78	82	80	240
Male	20 (25.6)	28 (34.1)	35 (43.8)	83 (34.6)
Female	58 (74.4)	54 (65.9)	45 (56.3)	157 (65.4)
ECOG Status (0/1 vs. 2/3) [n (%)]				
Number of Patients	78	82	80	240
ECOG Status 0/1	71 (91.0)	76 (92.7)	76 (95.0)	223 (92.9)
ECOG Status 2/3	7 (9.0)	6 (7.3)	4 (5.0)	17 (7.1)
Histological subtype (Adenocarcinoma vs. Non-adenocarcinoma) [n (%)]				
Number of Patients	78	82	80	240
Adenocarcinoma	72 (92.3)	76 (92.7)	77 (96.3)	225 (93.8)
Non-adenocarcinoma	6 (7.7)	6 (7.3)	3 (3.8)	15 (6.3)

Primary Efficacy Measures

The primary efficacy endpoint was the PFS. Of 240 randomized nonsquamous patients, there were 193 patients with death or progression events. The total PFS censor rate was 19.6% for Q-ITT population. A statistically significant difference in PFS was found across the 3 arms (global p=0.003), with ERL+PEM significantly better than both single agents (HR [95% CI] for ERL+PEM vs. ERL was 0.57 [0.40, 0.81], p=0.002; for ERL+PEM vs. PEM was 0.58 [0.39, 0.85], p=0.005). No statistically significant difference was noted between ERL and PEM (HR [95% CI]=0.99 [0.70, 1.40], p=0.959). Median PFS (95% CI) was 7.4 months (4.4, 12.9) in ERL+PEM, 3.8 (2.7, 6.3) in ERL and 4.4 (3.0, 6.0) in PEM. Figure S103.2.4 showed the Kaplan-Meier graph of the PFS by treatment group for the Q-ITT population.

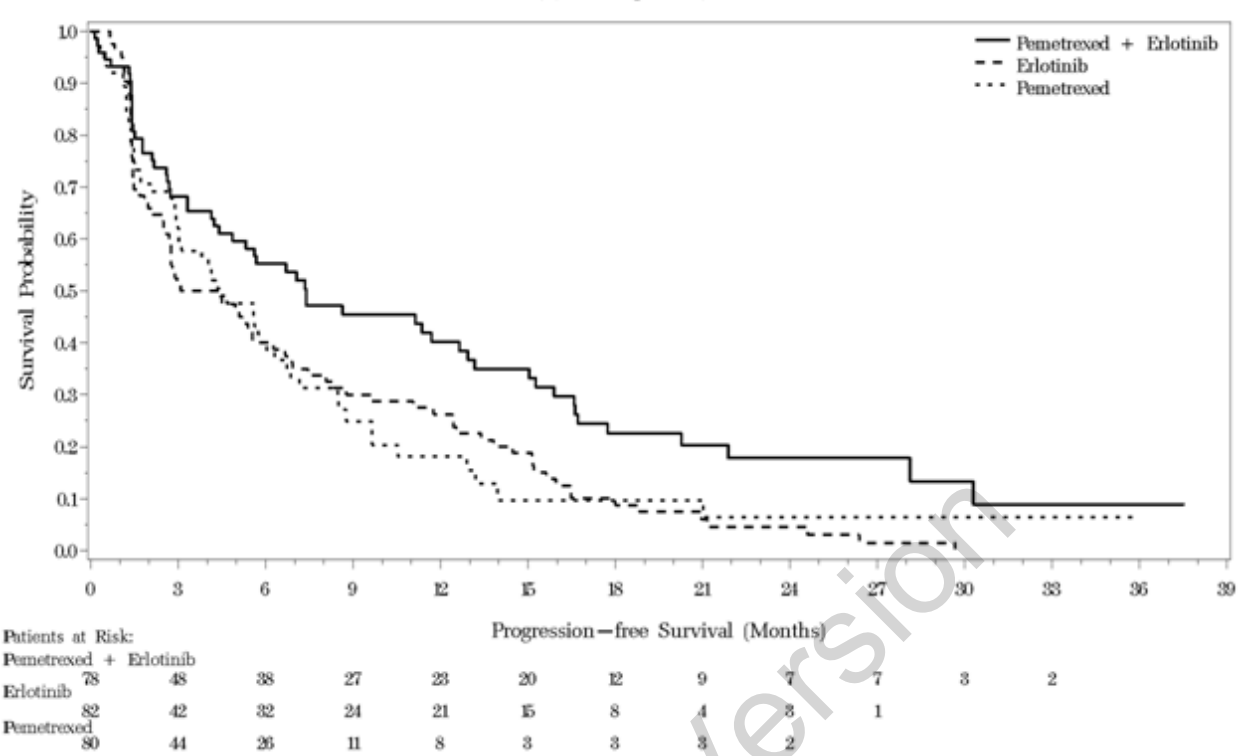


Figure S103.2.4. Kaplan-Meier graph of Progress-free survival by treatment group (Q-ITT Population).

Secondary Efficacy Measures

Of 240 patients entered, there were 130 patients with death events. The total OS censor rate was 45.8% for Q-ITT population. No statistically significant difference in OS was found across the 3 arms (global p=0.194). No statistically significant difference was noted between ERL+PEM and either single agent (HR [95% CI] for ERL+PEM vs. ERL was 1.08 [0.69, 1.67], p=0.747; for ERL+PEM vs. PEM was 0.75 [0.49, 1.13], p=0.168). Also, no statistically significant difference was noted between ERL and PEM (HR [95% CI]=1.44 [0.94, 2.21], p=0.094) (Figure S103.2.5). Median OS (95% CI) was 20.5 months (17.1, 25.0) in ERL+PEM, 22.8 (18.2, 29.5) in ERL and 17.7 (11.8, 25.3) in PEM. The 12 months survival rate (95% CI) (%) was 69.2 (57.1, 78.6) for ERL-PEM, 65.5 (53.6, 75.1) for ERL, and 60.6 (47.8, 71.1) for PEM. There was a statistically significant difference in TRRs observed between the 3 arms (overall P<0.001): The TRR was 44.7% (33.3%, 56.6%) for ERL+PEM (n=34), 29.3% (19.7%, 40.4%) for ERL (n=24), and 10.0% (4.4%, 18.8%) for PEM (n=8). There was no statistically significant difference for DCR among three arms (overall P=0.306): the DCR was 64.5% (52.7%, 75.1%) for ERL+PEM, 52.4% (41.1%, 63.6%) for ERL, and 56.3% (44.7%, 67.3%) for PEM.

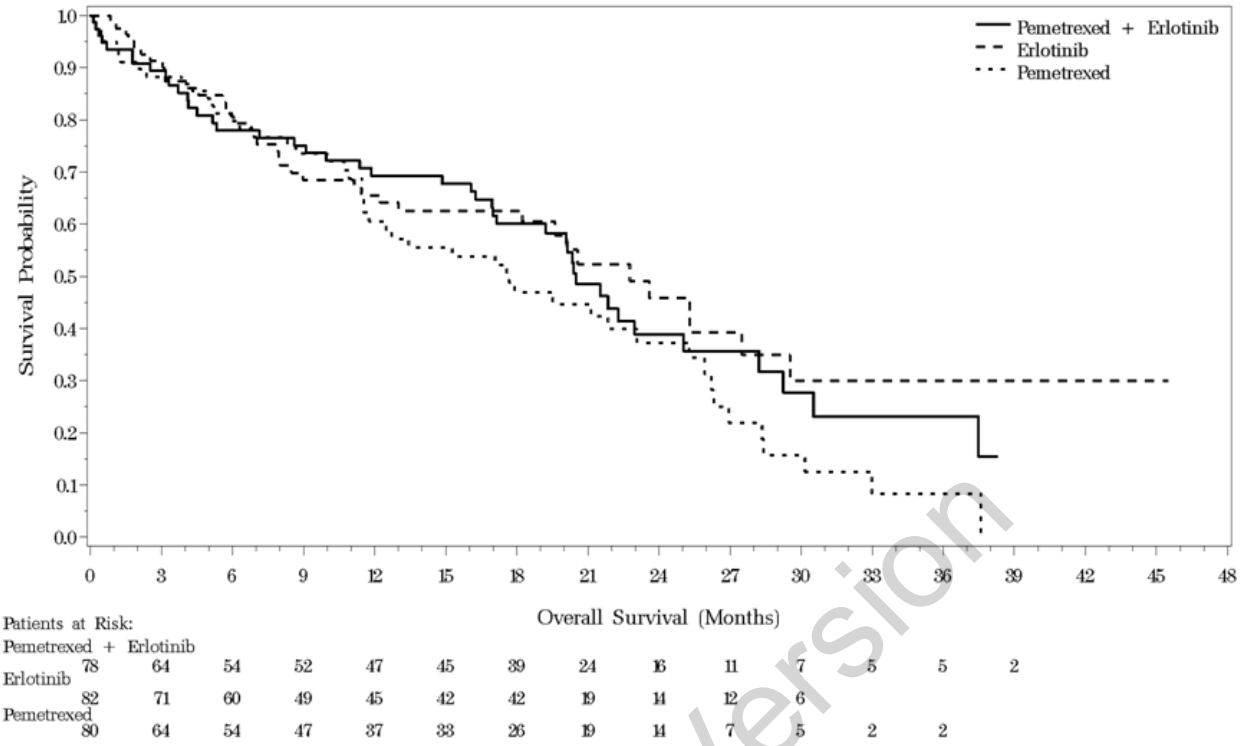


Figure S103.2.5. Kaplan-Meier graph of overall survival by treatment group (Q-ITT Population).

For LCSS, there was no statistically significant difference for change from baseline among three arms. Although there was no statistically significant difference for each individual item for TWS, ERL+PEM and PEM may have better TWS of any of the 6 LCSS symptom-specific items than ERL, which need further confirmation.

For EGFR analysis, 53 patients of 240 Q-ITT population provided samples. Of them, 43 were able to detect the EGFR status; 10 were unable to detect the EGFR status due to insufficient DNA or discrepant block ID. For the 43 patients with valid EGFR samples, 24 patients were detected with mutations in EGFR (12 with deletions in Exon 19- RUO-CL, 11 with L858R- RUO-CL, and 1 with G719X- RUO-CL) and 19 patients were detected without EGFR mutations. East Asian and females were slightly over represented in the EGFR analyzable population; considering the small sample size, the population was similar to Q-ITT in baseline characteristics (Table S103.2.2). The efficacy results in EGFR-sample provided patients comparing the treatments are consistent with those based on Q-ITT. Subgroup analyses of PFS and OS were conducted on subgroups defined by EGFR positive (patients with any mutation detected), EGFR negative (patients without mutations detected), and unknown (patients without EGFR samples or without valid EGFR samples) (Figure S103.2.6).

Table S103.2.2. Baseline Characteristics Comparison Between EGFR analyzable population and Q-ITT population

Patients with valid EGFR samples	Pem+Erl (N=17)	Erl (N=14)	Pem (N=12)	Total (N=43)
East Asian	58.8%	85.7%	75.0%	72.1%
Gender (Female)	76.5%	78.6%	66.7%	74.4%
Q-ITT population	**Pem+Erl (N=78)**	**Erl (N=82)**	**Pem (N=80)**	**Total (N=240)**
East Asian	52.6%	59.8%	53.8%	55.4%
Gender (Female)	74.4%	65.9%	56.3%	65.4%

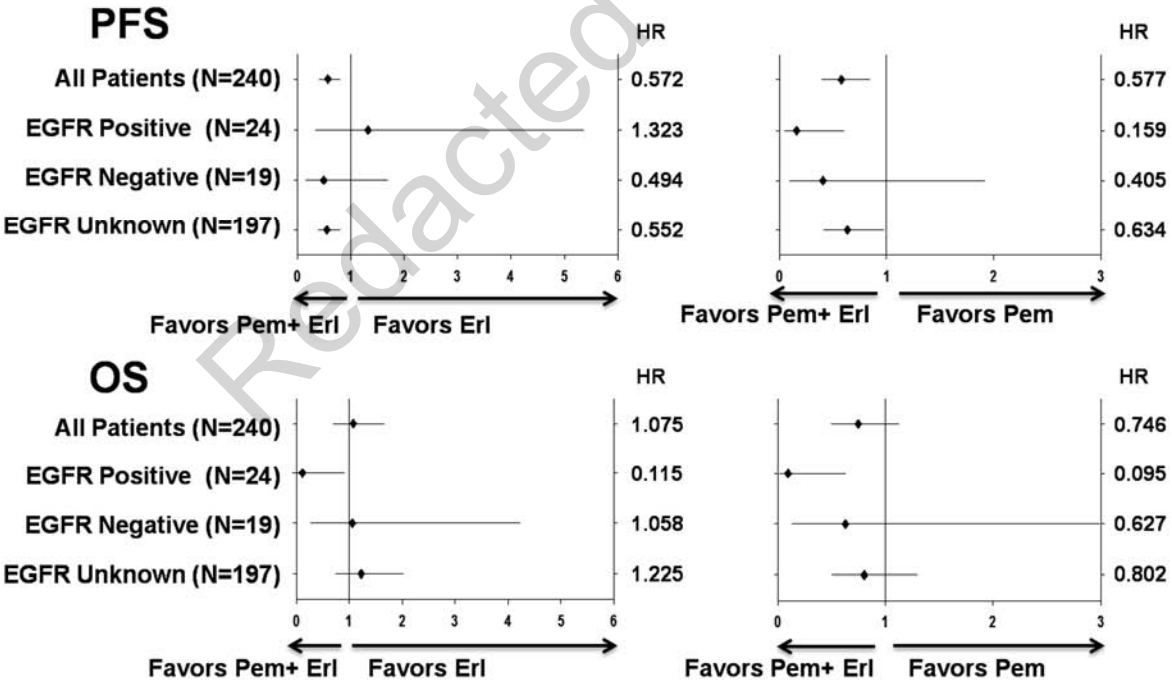


Figure S103.2.6. Forest plots of EGFR subgroups

Exploratory Analyses:

Subgroup analyses of PFS and OS were conducted on selected clinical baseline characteristics.

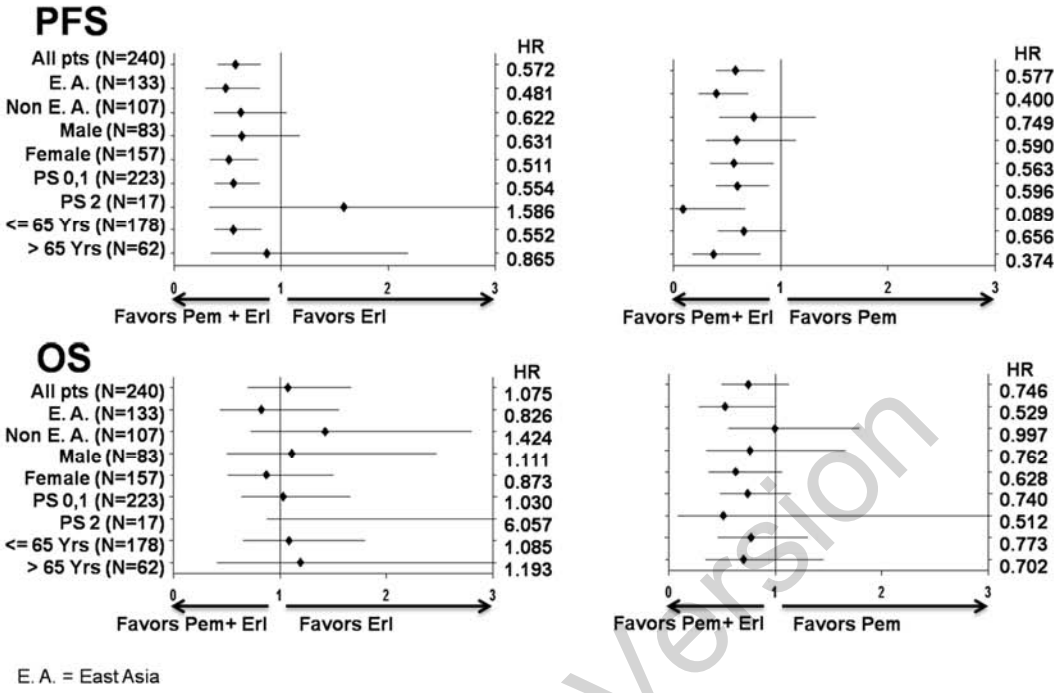


Figure S103.2.7. Forest plots of other clinical subgroups

Safety:

The median number of cycles received for ERL was 8.0 in ERL+PEM arm and 4.0 in ERL arm. The median number of cycles received for PEM was 8.0 in ERL+PEM arm and 6.0 in PEM arm. Drug compliance was ensured for PEM by administration restriction; compliance for ERL was 88% in ERL+PEM arm and 97.6% in ERL arm. Table S103.2.3 showed the overview of possible drug related adverse events. Overall, three arms had similar situation. ERL+PEM arm and PEM arm showed higher toxicity incidence rate compared with ERL arm, and most of the AEs were clinically manageable. For drug related TEAE, there were 5 patients having CTCAE grade 5 AEs (death). Two of them were from ERL+PEM treatment arm and 3 of them were from PEM arm (ERL+PEM arm: 2 Sepsis; PEM arm: 1 Neutropenia, 1 Hepatitis acute, and 1 sudden death with unknown reason). Seventy-seven patients had at least one TEAE with CTCAE grade 3/4, which was 60.0% (n=45) in ERL+PEM, 12.0% (n=10) in ERL and (n=22) 28.9% in PEM arm. Study drug-related grades ¾ toxicities (in ≥5% of patients) in ERL+PEM/ERL/PEM were neutropenia (24.0%/0%/13.2%), anemia (10.7%/0%/9.2%), leukopenia (12.0%/0%/7.9%), lymphopenia (12.0%/0/6.6%), rash (8.0%/6.0%/0), and diarrhea (9.3%/0/0).

Table S103.2.3. Overview of Possible Drug Related Adverse Events (Safety Population for Non-squamous Patients Only)

Parameters	Pemetrexed + Erlotinib (N=75) n (%)	Erlotinib (N=83) n (%)	Pemetrexed (N=76) n (%)	Total (N=234) n (%)	P-value [a] (P + E vs. E)	P-value [a] (P + E vs. P)	P-value [a] (P vs. E)
Patients with at least one TEAE	66 (88.0)	66 (79.5)	51 (67.1)	183 (78.2)	0.198	0.003	0.105
Patients with at least one TEAE with CTCAE Grade 3/4	45 (60.0)	10 (12.0)	22 (28.9)	77 (32.9)	<.001	<.001	0.010
Patients with at least one CTCAE Grade 3/4 AE	46 (61.3)	10 (12.0)	22 (28.9)	78 (33.3)	<.001	<.001	0.010
Patients who had at least one SAE	13 (17.3)	4 (4.8)	10 (13.2)	27 (11.5)	0.019	0.505	0.092
Patients with at least one lab toxicity AE	45 (60.0)	6 (7.2)	30 (39.5)	81 (34.6)	<.001	0.015	<.001
Patients with at least one lab toxicity AE with CTCAE Grade 3/4	34 (45.3)	1 (1.2)	19 (25.0)	54 (23.1)	<.001	0.011	<.001
Patients with at least one haematological lab toxicity AE	37 (49.3)	2 (2.4)	24 (31.6)	63 (26.9)	<.001	0.032	<.001
Patients with at least one haematological lab toxicity AE with CTCAE Grade 3/4	29 (38.7)	0	18 (23.7)	47 (20.1)	<.001	0.054	<.001
Patients with at least one non-haematological lab toxicity AE	22 (29.3)	4 (4.8)	14 (18.4)	40 (17.1)	<.001	0.130	0.011
Patients with at least one non-haematological lab toxicity AE with CTCAE Grade 3/4	7 (9.3)	1 (1.2)	4 (5.3)	12 (5.1)	0.027	0.368	0.194
Patients with at least one non-lab toxicity AE	61 (81.3)	65 (78.3)	41 (53.9)	167 (71.4)	0.695	<.001	0.001
Patients with at least one non-lab toxicity AE with CTCAE Grade 3/4	21 (28.0)	9 (10.8)	8 (10.5)	38 (16.2)	0.008	0.007	1.000
Patients who discontinued due to non-serious AE	4 (5.3)	1 (1.2)	3 (3.9)	8 (3.4)	0.191	0.719	0.349
Patients who discontinued due to SAE	0	0	1 (1.3)	1 (0.4)	N/A	1.000	0.478
Patients who died on therapy	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Parameters	Pemetrexed + Erlotinib (N=75) n (%)	Erlotinib (N=83) n (%)	Pemetrexed (N=76) n (%)	Total (N=234) n (%)	P-value [a] (P + E vs. E)	P-value [a] (P + E vs. P)	P-value [a] (P vs. E)
Patients who died within 30 days of last dose of study therapy	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: N = total population size; n = number of patients; AE = adverse event; SAE = serious adverse event; TEAE = treatment emergent adverse event; P + E = Pemetrexed + Erlotinib; E = Erlotinib; P = Pemetrexed.

Note: Treatment-emergent adverse events (TEAEs) are defined as events that first occur or worsen after the first dose of study drug. All adverse events are summarized by a patient starting to experience at least one AE of each category within the specified timeframe of on study therapy or within 30 days of the last dose. MedDRA Version is 14.1. CTCAE Version is 3.0.

[a] The P-value was based on Fisher's Exact test.

Conclusions:

This multicenter, open-label, randomized, three-arm Phase 2 study compared erlotinib-pemetrexed, pemetrexed alone, and erlotinib alone, as second-line treatment for non-smoker patients with locally advanced or metastatic nonsquamous NSCLC. The following conclusions were drawn:

- ERL+PEM significantly improved PFS compared to ERL or PEM alone; no statistically significant differences were noted between ERL and PEM in terms of PFS.
- No statistically significant differences were observed in OS across the 3 arms.
- ERL+PEM had higher TRR than ERL or PEM alone, and ERL had higher TRR than PEM.
- There was no statistically significant difference in DCR among three arms.
- ERL+PEM seemed more toxic than ERL or PEM alone, but was still clinically manageable. The safety findings and AEs reported were consistent with prior ERL or PEM studies.
- The efficacy results in EGFR-provided patients comparing the treatments are consistent with those based on Q-ITT.
- Exploratory analysis suggested ERL+PEM may provide benefits across different clinical and biomarker subgroups.