2. S102 Synopsis

Clinical Study Report Synopsis: Study H3E-MC-S102

<table>
<tr><td colspan="2">Title of Study: A Phase 2 Study of Pemetrexed versus Pemetrexed plus Erlotinib in Second-Line Treatment in Patients with Nonsquamous NSCLC</td></tr>
<tr><td colspan="2">Number of Investigators: This multicenter study included 24 investigators.</td></tr>
<tr><td colspan="2">Study Centers: This study was conducted at 24 study centers in 5 countries.</td></tr>
<tr><td colspan="2">Publication(s) Based on the Study: None at this time.</td></tr>
<tr><td>Length of Study:
Date of first patient enrolled: 11 April 2007
Date of last patient completed: The primary analysis cut-off date was determined as 27 July 2010; Trial: Planned for 31 August 2011 (1 patient still on study so this is the expected last patient visit or when this remaining patient is expected to have had the postdiscontinuation 30-day follow-up visit completed).</td><td>Phase of Development: 2</td></tr>
<tr><td colspan="2">Objectives:
The primary objective was to evaluate progression free survival (PFS) between pemetrexed 500 mg/m² every 3 weeks plus erlotinib 150 mg daily and pemetrexed 500 mg/m² every 3 weeks when given as second-line therapy for the treatment of locally advanced or metastatic nonsquamous non-small cell lung cancer (NSCLC). The original protocol was to evaluate both squamous and nonsquamous histological subgroups and was amended (Protocol Amendment (a) approved 01 August 2008) and narrowed to nonsquamous NSCLC after study initiation based upon other study efficacy results that demonstrated a treatment-by-histology effect for pemetrexed, showing a benefit to patients with other than predominantly squamous NSCLC (Peterson et al. 2007; Scagliotti et al. 2008; Ciuleanu et al. 2009). All enrolled patients with squamous NSCLC were allowed to continue to receive pemetrexed if, in the opinion of the investigator, they were receiving benefit from the treatment. Both histological subgroup data are reported where applicable or meaningful in this synopsis to provide complete results and to further support the benefit of pemetrexed in nonsquamous NSCLC.
The secondary objectives were to assess and compare the following variables in both treatment arms:
• Safety and adverse event (AE) profile
• Response rates
• Disease control rates
• Time to treatment failure (TTTF)
• Overall survival (OS) including 1-year survival rates</td></tr>
</table>

Approval Date: 08-Apr-2011 GMT

Study Design: This multicenter, randomized, Phase 2, open-label, parallel trial comparing pemetrexed versus pemetrexed plus erlotinib in patients with locally advanced or metastatic nonsquamous NSCLC (Stage IIIA, IIIB, or IV) who had been treated with 1 prior chemotherapy regimen. Eligible patients were randomized 1:1 to either pemetrexed 500 mg/m^2 every 3 weeks (Arm A) or pemetrexed 500 mg/m^2 every 3 weeks and erlotinib 150 mg daily (Arm B). Assignment to treatment groups was determined by a computer - generated random sequence using an interactive voice response system (IVRS). The randomization was stratified by: 1) Performance status (0 to 1 versus 2) and 2) Smoking history (nonsmoker patients OR <15 pack year history of smoking OR quit smoking over 25 years prior versus more than 15 pack year history of smoking and have smoked within the last 25 years). Patients in both arms received premedication with dexamethasone, vitamin B12, and folic acid according to the pemetrexed label. There was a follow-up period of 12 months after the last patient entered treatment.

The change of the primary analysis population to nonsquamous patients occurred prior to the data lock for the primary objective and did not impact the method of randomization. All patients with 'nonsquamous' NSCLC will form the analysis populations as detailed later in this section. Data related to squamous NSCLC, that is, patients with squamous NSCLC entered before the protocol amendment excluding them, will be excluded from all analyses for both efficacy and safety.

Number of Patients:

Planned (prior to amendment (a): Approximately 150 patients (75 in each arm)

Randomized: 211 Overall (105 Arm A, 106 Arm B); 165 Nonsquamous (86 Arm A; 79 Arm B); 46 Squamous (19 Arm A, 27 Arm B)

Treated (at least 1 dose): 159 Nonsquamous (83 Arm A, 76 Arm B); 45 Squamous (19 Arm A; 26 Arm B)

Completed: 112 Nonsquamous (64 Arm A, 48 Arm B); 36 Squamous (15 Arm A, 21 Arm B)

Diagnosis and Main Criteria for Inclusion: Male or female patients at least 18 years of age with a histological or cytological diagnosis of nonsquamous NSCLC with locally advanced or metastatic disease (Stage IIIA, IIIB, or IV at entry) that was not amenable to curative therapy and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 were eligible for this study. Patients must have failed 1 prior platinum-based chemotherapy regimen and were eligible for further chemotherapy following progression of their disease. Prior radiation therapy to <25% of the bone marrow was allowed (excluding whole pelvis or chest for the treatment of NSCLC) if completed at least 4 weeks prior to study enrollment. Both smokers and nonsmokers were eligible; however, patients were strongly advised not to smoke during the course of the study. Previous treatment with therapies not specifically directed to the human epidermal receptor (HER) axis (such as sorafenib and bevacizumab) was allowed, provided the targeted therapy was initiated concurrently with chemotherapy as part of first-line treatment, had been discontinued for at least 2 weeks prior to enrollment, and the patient had recovered from acute toxic effects of therapy.

Test Product, Dose, and Mode of Administration:

Pemetrexed 500 mg/m^2, administered intravenously (IV) every 3 weeks, plus erlotinib 150 mg/day, given orally.

Reference Therapy, Dose, and Mode of Administration:

Pemetrexed 500 mg/m^2, administered IV every 3 weeks

Duration of Treatment: Patients in both treatment arms received pemetrexed 500 mg/m^2 IV over 10 minutes on day 1 of every 21-day cycle. Patients in Arm B also received erlotinib 150 mg orally every day beginning on day 1 of the first cycle. In addition, all patients received pretreatment with folic acid, vitamin B12, and dexamethasone according to the pemetrexed labeling information. Patients were treated until intolerable toxicity or disease progression.

Variables:

Efficacy: PFS, assessed by and radiological Response Evaluation Criteria in Solid Tumors (RECIST 1.0 criteria, every second cycle), was defined as the time from the date of randomization to the first date of objectively determined (by computed tomography scan or magnetic resonance imaging) progressive disease (PD) or death from any cause. With regard to secondary variables, best response was determined from the sequence of responses assessed, including complete response, partial response, best response of stable disease, and PD. Overall survival time was measured from the date of randomization to the date of death from any cause. TTTF was defined as the time from date of randomization to the first date among death from any cause, PD, or study treatment discontinuation due to any reason other than "protocol complete" or "satisfactory response."

Safety: The safety and AE profile (including Common Terminology Criteria for Adverse Events [CTCAE Version 3.0; NCI 2006] grades for laboratory and nonlaboratory AEs) of each treatment regimen were recorded.

Evaluation Methods:

Efficacy: Efficacy analyses were conducted on the data from all randomized patients with nonsquamous NSCLC who received at least 1 dose of pemetrexed or erlotinib. For each treatment arm, the Kaplan-Meier (KM) technique was used to estimate the PFS curve. The PFS (primary outcome) obtained for the 2 treatment arms was compared using the log-rank test statistic with 1-sided alpha of 0.20. The Cox regression method was used for further exploration of data to take into account covariates (smoking status, gender and ECOG 0 to 1 versus 2). The sample size of approximately 150 randomized patients was chosen to allow for the observance of 134 events, resulting in a power of 80% to reject the null hypothesis of no treatment effect against a 1-sided alternative hypothesis at a level of significance of 20% if a true improvement in PFS of 1 month between treatment groups or a PFS hazard ratio of approximately 0.744 was assumed. These assumptions for planning of the study were based on a 15-month accrual period and a maximum length of follow-up of 27 months. Response rates and disease control rates were reported by treatment group, including 95% confidence intervals (CIs), and compared using a 1-sided Fisher's exact test. If treatment effects were opposite to the direction planned for the 1-sided tests, 2-sided tests were reported instead to avoid underreporting of possibly relevant treatment effects. Secondary time-to-event outcomes (observed distributions of OS and TTTF) were analyzed using Kaplan-Meier techniques, log-rank test, and Cox regression methods.

Safety: Safety analyses were conducted on the data from all randomized patients with nonsquamous NSCLC who received at least 1 dose of pemetrexed or erlotinib. Safety summaries included the incidence of AEs by maximum CTCAE grade (occurring during the study treatment period or within 30 days of the last dose of study treatment); study treatment discontinuations due to AEs; deaths; serious adverse events (SAEs); SAEs with outcome of death; SAEs possibly related to study treatment; treatment-emergent adverse events (TEAEs); hospitalizations; and use of key concomitant medications or growth factors. In addition, exploratory/descriptive analysis of the squamous subtype were conducted..

Summary:

Summary of Protocol Violations for Both Subtypes:

For patients with at least 1 protocol violation in the nonsquamous subtype group Table S102 2.1 provides all the inclusion and exclusion reasons for protocol violations and summarizes the most relevant protocol violations for the categories of incorrect dose modification and protocol specific. Patients of the squamous subtype showed a similar pattern of protocol violations as described in Table S102 2.1.

Table S102 2.1 Summary of Significant Protocol Violations Nonsquamous Subtype (Randomized and Treated Population)

	Pemetrexed	Pemetrexed + Erlotinib	Total
Parameter [n (%)]	**(N=83)**	**(N=76)**	**(N=159)**
Protocol inclusion/exclusion criteria	8 (9.6)	13 (17.1)	21 (13.2)
Alanine transaminase (ALT) >3 times the upper limit of normal (>5 x ULN if liver has tumor involvement)	1 (1.2)	1 (1.3)	2 (1.3)
Alkaline phosphatase (AP) >3 times the upper limit of normal (>5 x ULN if liver has tumor involvement)	1 (1.2)	2 (2.6)	3 (1.9)
Aspartate transaminase (AST) >3 times the upper limit of normal (>5 x ULN if liver has tumor involvement)	1 (1.2)	1 (1.3)	2 (1.3)
Bilirubin >1.5 times the upper limit of normal	1 (1.2)	0	1 (0.6)
Calculated creatinine clearance <45 mL/min based on Cockcroft and Gault Formula	3 (3.6)	4 (5.3)	7 (4.4)
No measurable lesion meeting RECIST criteria at baseline	1 (1.2)	0	1 (0.6)
Patient does not have appropriate diagnosis for inclusion in the study or have missing diagnosis[a]	2 (2.4)	4 (5.3)	6 (3.8)
Platelets <100 x 10^9/L at baseline visit	0	1 (1.3)	1 (0.6)
Prior radiotherapy was not completed at least 4 weeks before study enrollment	2 (2.4)	1 (1.3)	3 (1.9)
Serum creatinine ≥1.5 times the upper limit of normal	1 (1.2)	0	1 (0.6)
Incorrect dose modification			
Grade 3 to 4 adverse event (except nausea and vomiting) is recorded in adverse event form and treatment is not delayed	4 (4.8)	13 (17.1)	17 (10.7)
Nadir ANC < 0.5 x 109/L and dose administered more than 80% full dose in mg/m² for pemetrexed	2 (2.4)	10 (13.2)	12 (7.5)
Patient did not take vitamin supplementation according to the protocol	8 (9.6)	23 (30.3)	31 (19.5)
Protocol – specific			
Progressive disease without discontinuation of the study	4 (4.8)	6 (7.9)	10 (6.3)
Tumor assessment not performed prior to Day 1 of Cycle 3, Cycle 5, etc[b] ...	8 (9.6)	13 (17.1)	21 (13.2)
Chemistry not assessed within 7 days prior to cycle 1 or within 3 days prior to each cycle > 1	22 (26.5)	19 (25.0)	41 (25.8)
Hematology not assessed within 7 days prior to cycle 1 or within 3 days prior to each cycle > 1	20 (24.1)	16 (21.1)	36 (22.6)

Abbreviations: ANC = absolute neutrophil count; RECIST = Response Evaluation Criteria in Solid Tumors ; ULN = upper limit of normal.

[a] Subtype of lung cancer is unknown in these patients.

[b] Assessment has been done but not prior day 1. Assessments were to continue prior to Day 1 every other cycle.

Demographics:
A total of 214 patients entered the study and 211 patients were enrolled or randomized to treatment of which 165 patients had nonsquamous histology and 46 had squamous histology. For the squamous group, 45 patients received at least 1 dose of pemetrexed (Arm A) or pemetrexed plus erlotinib (Arm B) and 159 nonsquamous patients received treatment. For the nonsquamous group, 3 each from Arm A and Arm B were randomized but did not receive treatment: Arm A (1 death due to study disease, 1 death due to AE other cause, and 1 patient decision), Arm B (1 AE and 2 due to entry criteria not met)]. A summary of patient demographics and baseline characteristics are provided in Table S102 2.2. A total of 204 patients therefore were considered protocol-qualified for the efficacy and safety analyses sets as each had received at least 1 dose of pemetrexed or pemetrexed + erlotinib.

Table S102 2.2 Summary of the Major Patient Demographics and Baseline Characteristics (Randomized and Treated Population)

	Pemetrexed (N=102)		Pemetrexed + Erlotinib (N=102)		Total Patients Randomized (N=204)	
Demographic/ Parameter	**Nonsquamous (N=83)**	**Squamous (N=19)**	**Nonsquamous (N=76)**	**Squamous (N=26)**	**Nonsquamous (N=159)**	**Squamous (N=45)**
Mean age in years (± SD)	59.8 (±10.25)	63.9 (±9.33)	63.5 (±9.7)	66.1 (±8.58)	61.5 (±10.13)	65.2 (±8.87)
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Sex						
Male	49 (59.0)	19 (100)	46 (60.5)	24 (92.3)	95 (59.7)	43 (95.6)
Female	34 (41.0)	0 (0)	30 (39.5)	2 (7.7)	64 (40.3)	2 (4.4)
Origin						
Caucasian	82 (98.8)	19 (100)	75 (98.7)	26 (100)	157 (98.7)	45 (100)
Hispanic	1 (1.2)	0 (0)	0 (0)	0 (0)	1 (0.6)	0 (0)
West Asian	0 (0)	0 (0)	1 (1.3)	0 (0)	1 (0.6)	0 (0)
ECOG						
0	33 (39.8)	7 (36.8)	33 (44.0)	9 (34.6)	66 (41.8)	16 (35.6)
1	39 (47.0)	7 (36.8)	33 (44.0)	13 (50.0)	72 (45.6)	20 (44.4)
2	11(13.3)	5 (26.3)	9 (12.0)	4 (15.4)	20 (12.7)	9 (20.0)
Stage of Disease at Study entry						
Stage IIIA	3 (3.6)	2 (10.5)	1 (1.3)	0 (0)	4 (2.5)	2 (4.4)
Stage IIIB	10 (12.0)	4 (21.1)	11 (14.5)	5 (19.2)	21 (13.2)	9 (20.0)
Stage IV	70 (84.3)	13 (68.4)	64 (84.2)	21 (80.8)	134 (84.3)	34 (75.6)
Smoking Status						
Ex- smoker	44 (53.0)	12 (63.2)	51 (67.1)	19 (73.1)	95 (59.7)	31 (68.9)
>15 pack-years	60 (92.3)	15 (93.8)	48 (78.7)	25 (96.2)	108 (85.7)	40 (95.2)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; SD = standard deviation.

Efficacy:

Primary Endpoints:

After protocol amendment (a) (approved 01 Aug 2008), simulated predictions of the number of PFS events within the nonsquamous group of patients indicated the minimum of 134 events could not be reached due to drop-outs and lost-to-follow-up patients, even if the follow-up period would have been extended. Therefore, it was decided by Lilly's study team to perform the primary statistical analyses at the end of the 1-year follow-up period instead of performing it when the 134th PFS event occurred. This decision was noted in a note to file according to standard operating procedures. For this new adjusted time of analysis, a maximum number of 128 PFS events were expected resulting in approximately 79% power instead of the planned 80% at 134 PFS events. Using the adjusted time of analysis, the actual number of PFS events that occurred in the nonsquamous group was 130 (70 in the pemetrexed only arm and 60 in the pemetrexed + erlotinib arm) and ultimately the impact on the power and the validity of the results was low.

The primary objective analysis cut-off date after the last patient enrolled was 27 July 2010. For the nonsquamous histology group, the median PFS time was statistically significantly longer with the combined therapy (Arm B) than the single therapy (Arm A): 2.9 months for Arm A and 3.2 months for Arm B (log-rank one-sided p=.0047; hazard ratio (HR) of 0.63; 95% CI: 0.483 to 0.897), which met the primary objective of the trial. For the squamous subtype, patients did not show an improvement in median PFS between the 2 treatment arms (3.8 months for Arm A and 3.4 months for Arm B [log-rank 2-sided p=0.1699 with a HR of 1.56; 95% CI: 0.822 to 2.960]). The Cox regression analysis, adjusted for covariates, confirms a statistically significant treatment difference in PFS for the nonsquamous subtype patients, with the adjusted PFS HR estimated to be 0.64 (95% CI: 0.442 to 0.928; p=.0185). In squamous patients, a higher adjusted PFS hazard rate was estimated for combination therapy compared to mono-therapy (HR=2.47; 95% CI: 1.054 to 5.772; p=.0375). The KM curve of PFS for the nonsquamous group is shown in Figure S102 2.1.

The 3-, 6-, and 12-month nonsquamous PFS rates were 42.4%, 22.7%, and 3.5 %, respectively, for Arm A, and 57.2%, 31.5%, and 18.8%, respectively, for Arm B. The 3-, 6-, and 12-month squamous PFS rates were 67.7%, 28.2%, and 5.6 %, respectively, for Arm A, and 60.7%, 13.0%, and 0%, respectively, for Arm B.

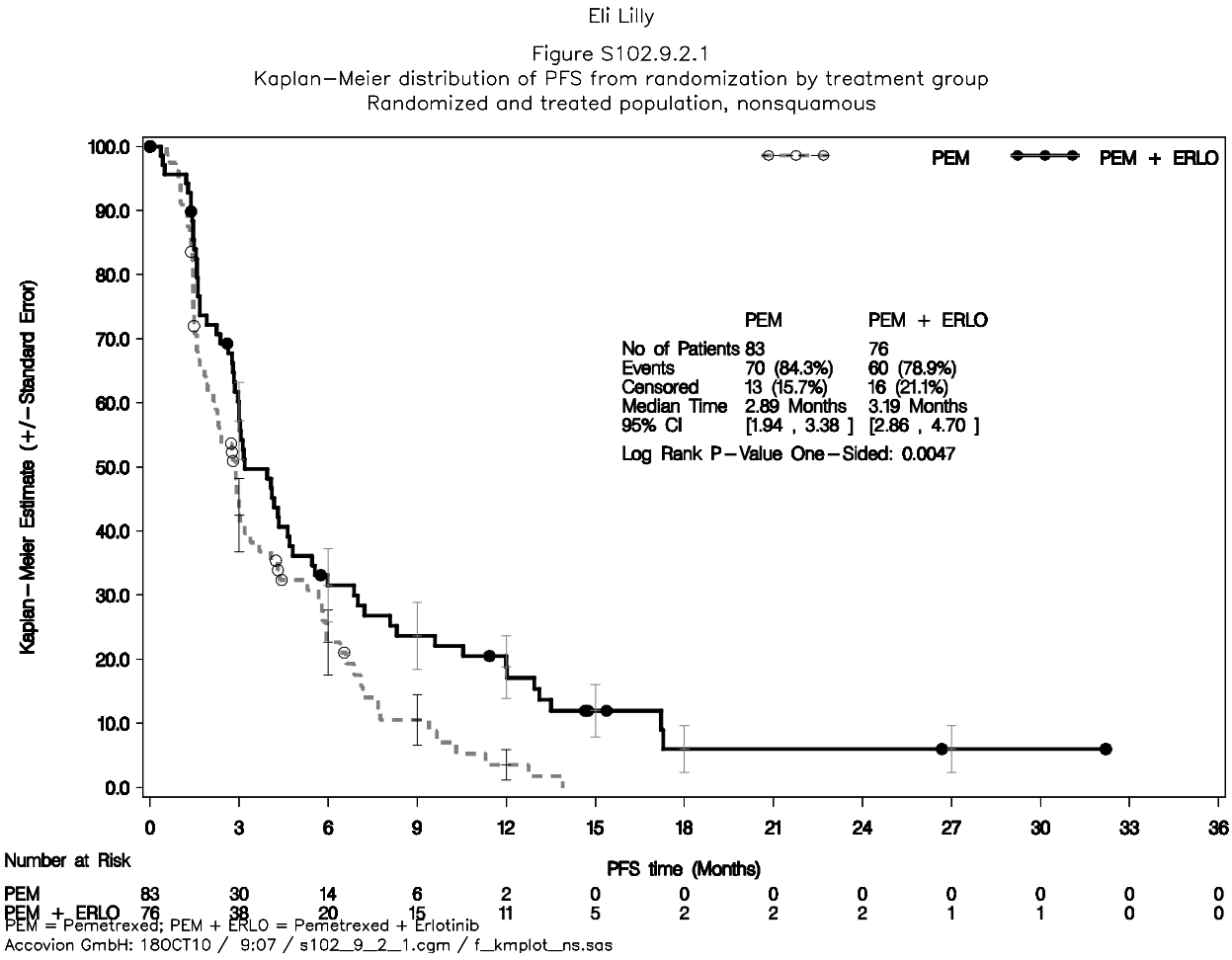

Figure S102 2.1 **Kaplan-Meier distribution of PFS from randomization by treatment group, nonsquamous (randomized and treated population). The vertical lines denote ± standard errors.**

Secondary Endpoints: (Table S102 2.3)

Table S102 2.3 Summary of Secondary Endpoints Both Subtypes (Randomized and Treated Population)

	Pemetrexed (N=102)		Pemetrexed + Erlotinib (N=102)			
Secondary Endpoint	**Nonsquamous (N=83)**	**Squamous (N=19)**	**Nonsquamous (N=76)**	**Squamous (N=26)**	**Hazard Ratio [95% CI][a]**	**p-value**
Median OS (months) (95% CI)	7.8 (5.2 , 10.4)	7.7 (5.1 , 14.5)	11.8 (8.1 , 16.6)	8.5 (4.7 , 9.5)	NS: 0.68 [0.465,0.981] SQ: 1.25 [0.667,2.335]	0.0190[b] 0.4880[c]
OS rates 1-year (%) (95% CI)	34.1 (23.8 , 44.5)	42.1 (20.3 , 62.4)	49.4 (37.2 , 60.3)	30.8 (14.6 , 48.5)	---	---
OS rates 2-year (%) (95% CI)	13.7 (6.5 , 23.3)	15.8 (3.9 , 34.9)	26.8 (15.6 , 39.2)	9.6 (1.8 , 25.4)	---	---
Complete response[d], N (%)	0 (0)	0 (0)	1 (1.3)	0 (0)	---	---
Partial response[d] , N (%)	9 (10.8)	2 (10.5)	12 (15.8)	1 (3.8)	---	---
Stable disease[d], N (%)	34 (41.0)	8 (42.1)	29 (38.2)	14 (53.8)	---	---
TRR, N (%)	9 (10.8)	2 (10.5)	13 (17.1)	1 (3.8)	---	NS: 0.1808[e] SQ; 0.9317[e]
DCR , N (%)	43 (51.8)	10 (52.6)	42 (55.3)	15 (57.7)	---	NS: 0.3909[e] SQ: 0.4859[e]
Median TTTF (months) (95% CI)	2.4 (1.7 , 2.9)	3.0 (1.6 , 4.1)	3.0 (2.2 , 4.0)	2.9 (1.6 , 3.7)	NS: 0.64 [0.457,0.887] SQ: 1.20 [0.655,2.196]	NS: 0.0034 SQ: 0.5535[c]

Abbreviations: --- = not available; CI = confidence interval; DCR = disease control rate (best response of complete response, partial response, or stable disease); NS = nonsquamous; OS = overall survival; SD = stable disease; SQ = squamous; TRR = tumor response rate (best response of complete response or partial response); TTTF = time to treatment failure.

[a] Pemetrexed versus pemetrexed + erlotinib.

[b] One-sided log-rank test.

[c] Two-sided log-rank test.

[d] Best overall response.

[e] p-value is from 1-sided Fisher's exact test.

Safety: Safety data from 83 and 76 patients with nonsquamous histology randomized and treated in Arm A and Arm B, respectively, were analyzed. In addition, 19 and 26 patients with squamous histology randomized and treated in Arm A and Arm B, respectively, were analyzed.

Discontinuations from AEs for Both Subtypes, Randomized and Treated Patients:
For the nonsquamous subtype, 4 patients (4.8%) in Arm A and 10 patients in Arm B (13.2%) discontinued due to nonserious AEs, regardless of causality. Of these, 3 (3.6%) and 7 (9.2%) were considered possibly related to the study drug. For the squamous subtype, no patients in Arm A and 3 patients in Arm B discontinued due to a nonserious AE, with the 3 in Arm B all considered possibly related to study drug. The most common AE, regardless of causality, leading to discontinuation in the nonsquamous subtype occurred in the blood and lymphatic system disorders for Arm A (3 patients, 3.6%; 1 each of thrombocytopenia, anemia, and leukopenia) and in the infection and infestations category in Arm B (3 patients, 3.9%; 1 each of lung abscess, lung infection, and pneumonia).

Discontinuations from SAEs for Both Subtypes, Randomized and Treated Patients:
A total of 10 (6.2%) of patients discontinued study drug due to SAEs, regardless of causality, in both treatment arms of the nonsquamous subtype; 2 (2.4%) of patients in Arm A and 8 (10.5%) of patients in Arm B. Of these patients who discontinued, 2 patients or all 4.3% in Arm A and 5 patients (6.6%) in Arm B discontinued study treatment due to SAEs that were considered to be possibly related to study drug.

Overall, more possibly drug-related AEs, SAEs, and Grade 3/4 CTCAEs occurred in the pemetrexed + erlotinib arm compared to the pemetrexed only arm for both squamous and nonsquamous subtypes except for the category of gastrointestinal disorders for the patients in the pemetrexed only nonsquamous subtype arm (see Table S102 2.4). Table S102 2.5 describes the specific possibly drug-related Grade 3/4 CTCAE AEs that occurred in greater than 5% of patients in the nonsquamous arms.

Table S102 2.4 Overview of Possibly Drug-Related AEs, Both Subtypes (Randomized and Treated Population)

	Pemetrexed (N=102)		Pemetrexed + Erlotinib (N=102)	
Description of Type of AE	**Nonsquamous (N=83) n (%)**	**Squamous (N=19) n (%)**	**Nonsquamous (N=76) n (%)**	**Squamous (N=26) n (%)**
Patients with at least 1 possibly drug-related AE[a]	58 (69.9%)	14 (73.7%)	72 (94.7%)	24 (92.3%)
Patients with at least 1 possibly drug-related SAE[a]	10 (12.0%)		24 (31.6%)	
Blood and lymphatic system category	4 (4.8%)	3 (15.8%)	17 (22.4%)	4 (15.4%)
Infections and infestations category	1 (1.2%)		4 (5.3%)	
Gastrointestinal disorders category	5 (6.0%)		2 (2.6%)	
Patients with at least 1 drug-related TEAE Grade 3/4 adverse event (laboratory and nonlaboratory combined)[a]	18 (21.7%).	7 (36.8%)	47 (61.8%)	20 (76.9%)
Nonlaboratory: Patients with at least 1 drug-related CTCAE[b] Grade 3/4 adverse event	8 (9.6%)	5 (26.3%).	29 (38.2%)	14 (53.8%)

Abbreviations: AE(s) = adverse event(s); SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Events were coded using MedDRA Version 13.1.

[b] Common Terminology Criteria for Adverse Events.

Table S102 2.5 Possibly Drug-Related Grade 3/4 CTCAE Adverse Events Occurring in >5% of Patients for Nonsquamous Patients (Randomized and Treated Population)

	Pemetrexed (N=102)	Pemetrexed + Erlotinib (N=102)
Possibly Drug-Related Grade 3/4 Adverse Event	**Nonsquamous (N=83)**	**Nonsquamous (N=76)**
Nonlaboratory AEs	**n (%)**	**n (%)**
Rash/desquamation[a]	1 (1.2)	7 (9.2)
Diarrhea	1 (1.2)	4 (5.3)
Febrile neutropenia	2 (2.4)	8 (10.5)
Laboratory AEs		
Hemoglobin	5 (6)	9 (11.8)
Leukocytes	8 (9.6)	18 (23.7)
Neutrophils/granulocytes	8 (9.6)	19 (25)
Platelets	4 (4.8)	11 (14.5)

Abbreviations: AE(s) = adverse event(s); CTCAE = Common Terminology Criteria for Adverse Events.

[a] Includes Grade 5 as well.

Squamous Subtype: Possibly Drug-Related CTCAE Grade 3/4 Laboratory and Nonlaboratory AEs:

The Grade 3/4 nonlaboratory events that occurred in >5% of the squamous subtype:

- Pemetrexed only arm: nausea, febrile neutropenia, lower extremity muscle weakness, central nervous system cerebral ischemia, motor neuropathy and peripheral arterial ischemia.
- Pemetrexed + erlotinib arm: fatigue, rash/desquamation, mucositis/stomatitis, and febrile neutropenia.

In both treatment arms, the Grade 3/4 laboratory events that occurred in greater than (>) 5% of patients included: hemoglobin, lymphopenia, neutrophils/granulocytes, and platelets. In addition, the pemetrexed + erlotinib arm demonstrated >5% leukocytes.

Summary of Deaths:
A total of 30 deaths were reported on study or within 30 days of discontinuation [nonsquamous: 8 (9.6%) Arm A, 13 (17.1%) Arm B and squamous: 1 (5.3%) Arm A, 8 (30.8%) Arm B]. One death due to study drug toxicity of febrile neutropenia occurred in Arm B of the nonsquamous subtype. No deaths due to study drug toxicity occurred in the squamous subtype. Study disease related deaths occurred in 19 of the nonsquamous subtype (8, 9.6% Arm A and 11, 14.5% Arm B). Study disease related deaths occurred in 7 of the squamous subtype (1, 5.3% Arm A and 6, 23.1% Arm B). Death from AEs included 1 lung abscess in the nonsquamous Arm B and 1 each lobar pneumonia and tracheal obstruction in the squamous Arm B.

Discussion and Conclusions: Study results showed a statistically significant improvement in median PFS (primary endpoint) of approximately 2 weeks when pemetrexed was combined with erlotinib as second-line treatment in patients with nonsquamous NSCLC compared to single-agent pemetrexed. The results pattern shown in the PFS KM curve (Figure S102 2.1) indicated a separation of the curves occurring primarily below 50% (i.e. among patients with the longest PFS times), which is consistent with at least one other erlotinib trial - the Saturn Study (Cappuzzo et al. 2010). This study and Saturn showed a highly significant HR/log-rank yet only a tiny improvement at the median which may suggest that the addition of erlotinib treatment is only beneficial for a subset of patients with advanced NSCLC. Also, among the secondary efficacy endpoints assessed for the nonsquamous subtype, the study showed statistically significant improvements for median OS (4 month improvement for the combination arm) and TTTF while TRR and DCR showed improvements, although non statistically significant, for the combined pemetrexed + erlotinib treated patients when compared to single-agent pemetrexed. In contrast, the squamous subtype did not show improvements in these endpoints. Interpretations of results from the squamous subtype are limited due to the small sample size.

Overall, the combined pemetrexed + erlotinib group experienced more AEs, SAEs and Grade 3/4 CTCAE TEAEs compared to the single-agent pemetrexed group in both histological subtypes. Hematologic (including febrile neutropenia) and rash/desquamation were the most commonly reported possibly drug-related Grade 3/4 CTCAE TEAEs that occurred more in the combination pemetrexed + erlotinib group. One death due to study drug toxicity of febrile neutropenia occurred in Arm B of the nonsquamous subtype.

In conclusion, the study met the primary objective demonstrated by a statistically significant improvement in PFS in the combined therapy of permetrexed and erlotinib when compared to the single therapy of permetrexed in second-line treatment of nonsquamous NSCLC. However, the up to 4 times increased toxicities (Grade 3/4 nonlaboratory and laboratory AEs) recorded on the combination arm requires caution when this combination regimen is considered for further Phase 3 development in second-line treatment.

References

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