1. S107 Clinical Study Synopsis: Phase I/II Study of Concurrent Cisplatin, Pemetrexed, and Radiotherapy for Limited Stage Small Cell Lung Cancer (LS-SCLC)

LY231514 (Pemetrexed)

A Phase I/II study of pemetrexed and cisplatin with concomitant radiotherapy in patients with limited-stage SCLC.

Eli Lilly and Company
Protocol H3E-EW-S107
Phase I/II
First patient enrolled: 9 Mar 2007
Last patient enrolled: 20 Dec 2007
Last patient completed (data collection cut-off): 30 May 2008
Date of final report: 30 May 2009

[redacted]

Responsible Medical Officer: [redacted]
Eli Lilly and Company

2. Synopsis

Clinical Study Report Synopsis: Study H3E-EW-S107

Title of Study: Phase I/II Study of Concurrent Cisplatin, Pemetrexed, and Radiotherapy for Limited Stage Small Cell Lung Cancer (LS-SCLC)	
Number of Investigator(s): This multicenter study included 3 principal investigators.	
Study Center(s): This study was conducted at 3 study centers in 2 countries.	
Publication(s) Based on the Study: None at this time	
Length of Study: Date of first patient enrolled: 9 Mar 2007 Date of last patient enrolled: 20 Dec 2007 Date of data collection cut-off: 30 May 2008	**Phase of Development:** I/II
Objectives: The primary objective of the phase 1 part of this study was to determine the recommended phase 2 dose of pemetrexed, cisplatin, and involved-field radiotherapy in the treatment of patients with LS-SCLC. The primary objective of the phase 2 part was to further delineate the activity of this regimen at the recommended dose in terms of overall response rate. The Secondary objectives for the phase 1 part of this study was: (1) To determine the maximum tolerated dose (MTD) of pemetrexed, cisplatin and involved-field radiotherapy. (2) To determine the quantitative and qualitative dose-limiting toxicities (DLT) of pemetrexed in combination with cisplatin and curative thoracic radiotherapy (TRT). (3) To further characterize acute and late toxicities. (4) To document objective best overall response. Secondary objectives for the phase 2 part was: (1) To further characterize acute and late toxicities. (2) To determine complete response rate. (3) To assess time-to-event for: time to progressive disease (TTPD), duration of response, overall survival (OS).	
Study Design: This was a multicenter, open-label, phase 1, dose-escalation study of pemetrexed and cisplatin combined with TRT in patients with LS-SCLC. The study phase 1 was stopped early based on interim results of the GALES trial in December 2007, showing inferior activity of pemetrexed /carboplatin compared to etoposide /carboplatin in extensive SCLC. Phase 2 was planned as an open-label, nonrandomized study with patients receiving the recommended phase 2 dose identified in the phase 1 part of the study.	
Number of Patients: Planned: Up to 24 patients in phase 1 (3-6 patients per cohort) Treated (at least 1 dose): 9 active drug Completed: 7	
Diagnosis and Main Criteria for Inclusion: This study included treatment-naive males and females at least 18 years of age with histological and/or cytological diagnosis of LS-SCLC, without cytological proven malignant pleural effusion, and confined to one hemithorax. Patients were required to have at least one unidimensionally measurable lesion meeting Response Evaluation Criteria in Solid Tumors (RECIST) criteria, ECOG performance status 0 to 1, minimal risk for radiation pneumonitis and able to drain third space fluids , adequate organ function and an estimated life expectancy of at least 12 weeks. No prior chemo- or thoracic radiotherapy was allowed, and no concurrent administration of any other antitumor therapy.	

Study Drug, Dose, and Mode of Administration: Pemetrexed 400 to 500 mg/m^2 and cisplatin 75 mg/m^2 administered intravenously (iv), combined with TRT 50 to 62 Gy.
Supplementation with oral folic acid (350 to 1000 µg) starting 5 to 7 days prior to the first dose of pemetrexed and continuing daily until 3 weeks after the last dose of pemetrexed.
Vitamin B12 (1000 µg) intramuscular injection, starting 1 to 2 weeks prior to first dose of pemetrexed and repeated approximately every 9 weeks until 3 weeks after the last dose of pemetrexed.
Dexamethasone (4 mg taken orally, twice per day) on the day before, the day of, and the day after each dose of pemetrexed for rash prophylaxis.

Phase 1 was a dose-escalation study: Three to six patients were to be treated in each cohort. A maximum of 4 cohorts were planned. The dose of pemetrexed and radiotherapy was to be increased in a stepwise manner depending on the observed toxicity.
Cohort 1:
pemetrexed 400 mg/m^2, cisplatin 75 mg/m^2, radiotherapy 50 Gy in 25 QD fractions of 2 Gy in 5 weeks
Cohort 2:
pemetrexed 500 mg/m^2, cisplatin 75 mg/m^2, radiotherapy 50 Gy in 25 QD fractions of 2 Gy in 5 weeks
Cohort 3:
pemetrexed 500 mg/m^2, cisplatin 75 mg/m^2, radiotherapy 56 Gy in 28 QD fractions of 2 Gy in 5.5 weeks
Cohort 4:
pemetrexed 500 mg/m^2, cisplatin 75 mg/m^2, radiotherapy 62 Gy in 31 QD fractions of 2 Gy in 6.2 weeks

CT lot number: [redacted]

Reference Therapy/Comparator, Dose, and Mode of Administration: None

Duration of Treatment: The planned duration of treatment, in absence of DLT, was up to 4 cycles (each 3-4 weeks).
All patients first received the induction chemotherapy, one cycle of pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 intravenously on day 1 of the 21-day cycle. Pemetrexed was given as a 10 minute iv infusion. Cisplatin was administered as an iv infusion over 120 minutes beginning 30 minutes after the infusion with pemetrexed. Patients had to recover fully from the first cycle of induction chemotherapy before continuing with the concurrent chemoradiation cycles.
In cycle 2 and 3, patients received pemetrexed and cisplatin followed by TRT administered 2 hours after chemotherapy, if they met all of the following criteria: (a) performance status <2, (b) no residual toxicity ≥2 according the CTCAE scoring, (c) study drug administered at full dose during induction chemotherapy.
During Cycle 4, pemetrexed 500 mg/m^2 in combination with cisplatin 75 mg/m^2 was to be administered on day 1 of the 21-day cycle.

Variables:

Efficacy: The primary efficacy endpoint for phase 1 was the determination of the recommended dose of pemetrexed, cisplatin, and involved-field radiotherapy. The primary endpoint for phase 2 was the overall response rate with the recommended dose. Secondary efficacy endpoints included MTD, DLT, best overall response, complete response rate, and duration of response, TTPD, OS.

Safety: Secondary endpoints included MTD, DLT, and acute and late toxicities (according to RTOG scoring criteria, Radiation Therapy Oncology Group). Late toxicity was defined as the adverse event, which occurs >90 days after start of the radiotherapy. Safety measures used in this study included: toxicities assessed according to Common Toxicity Criteria (CTCAE Version 3), performance status and weight, ECG, hematology, blood chemistry, creatinine clearance, lung function.

Evaluation Methods:

Efficacy & Safety:

As only 9 patients were enrolled in the study, only a basic statistical evaluation of safety and efficacy has been conducted. Summary statistics on adverse events are provided.

Summary:

Patient disposition and demographics

A total of 9 patients were entered into the study. All Caucasian, 6 male, 3 female. Seven patients with ECOG performance status 1 and two with PS 0. Age between 50 to 80 years. Their baseline forced expiratory volume in 1 second was in the range of 43% to 90%.

Three patients were entered into cohort 1: Two completed all 4 cycles, one discontinued at cycle 4 due to lack of efficacy.

Six patients entered cohort 2: One completed all 4 cycles, three discontinued due to adverse events (two at cycle 1, one at cycle 2), two discontinued in the first cycle due to sponsor decision when the study was early terminated. Three discontinued patients were to be replaced to have more evaluable patients.

All 9 patients received at least one cycle of induction chemotherapy. Five patients received at least 1 cycle of TRT. Four patients received the maximum of 4 cycles of study therapy.

Efficacy and primary outcome measures

The study was stopped too early to assess the primary endpoint of recommended dose for phase 2, or estimate MTD.

The objective best overall response in cohort 1 (N=3) was 2 PR, 1 PD, and in cohort 2 (N=6) 1 PR, other patients were not estimable.

Safety

Three patients in cohort 2 discontinued due to adverse events after 1 or 2 treatment cycles (renal failure, femoral artery occlusion, peripheral sensory neuropathy).

Pemetrexed dose was reduced in one patient in cohort 2 at cycle 2, due to dehydration. Cisplatin dose was reduced in two patients: one in cohort 1 at cycle 4 (due to decreased creatine renal clearance) and the other in cohort 2 at cycle 2 (due to dehydration).

There were no DLTs during TRT and up to 6 weeks after end of treatment, and no radiotherapy interruptions for at least on day because of adverse events.

A total of 2 (67%) patients in cohort 1 and 5 (83%) patients in cohort 2 experienced at least one treatment emergent adverse event (TEAE). Most TEAEs were maximum grade 3. There was only one patient in cohort 1 experiencing drug-related grade 4 lymphopenia and grade 4 hyperglycaemia (not treatment related). A summary of all treatment related CTC grade 3/4 adverse events is shown in Table 1.

Two (67%) patients in cohort 1 experienced esophagitis: One patient reported a serious adverse event (SAE) of grade 2 esophagitis. Another patient had a treatment related adverse event of grade 3 esophagitis, but was able to complete treatment without delay in radiotherapy.

Table 1: Treatment emergent CTC grade 3/4 toxicities possibly related to study therapy and/or procedure

CTCAE grade 3/4, n(%)	Cohort 1 (N=3)	Cohort 2 (N=6)	Total (N=9)
Patients with at least one related TEAE with CTC grade >= 3	*2 (67%)*	*4 (67%)*	*6 (67%)*
Anorexia	2	1	3
Lymphopenia	1	2	3
Dehydration	1	1	2
Neutropenia	1	1	2
Thrombocytopenia	2	0	2
Esophagitis	1	0	1
Anaemia	1	0	1
Leukopenia	1	0	1
Gamma-glutamyltransferase increased	0	1	1
Hyponatraemia	1	0	1
Renal failure	0	1	1
Malaise	1	0	1
Fatigue	0	1	1
Femoral artery occlusion	0	1	1
Peripheral sensory neuropathy	0	1	1

The 5 patients who received radiotherapy experienced acute and late pulmonary toxicity of RTOG grade 0-2 (none, mild, moderate). There was one patient with grade 2 acute pulmonary toxicity in cohort 1, and one with grade 2 late pulmonary toxicity in cohort 2.
The 5 patients who received radiotherapy experienced acute and late esophageal toxicity of RTOG grade 0-2. There were three patients with grade 2 acute esophageal toxicity, and one with grade 2 late esophageal toxicity, all in cohort 1.

A summary of all serious adverse events is shown in Table 2.

Four patients experienced at least one possibly drug-related serious adverse event: one (33%) in cohort 1 (esophagitis grade 2, anaemia grade 3, diverticulitis, malaise) and three (50%) in cohort 2 (sensory neuropathy grade 3, nausea, fatigue, anorexia, dehydration, femoral artery occlusion).

Table 2: Summary of all reported serious adverse events

MedDRA Preferred Term, n (%)	Cohort 1 (N=3)	Cohort 2 (N=6)	Total (N=9)
Patients with at least one serious TEAE	*2 (66.7)*	*4 (66.7)*	*6 (66.7)*
Vomiting	1	1	2
Abdominal pain upper	1	0	1
Nausea	0	1	1
Esophagitis	1	0	1
Diverticulitis	1	0	1
Lung infection	0	1	1
Pneumonia	0	1	1
Fatigue	0	1	1
Malaise	1	0	1
Anaemia	1	0	1
Anorexia	0	1	1
Dehydration	0	1	1
Peripheral sensory neuropathy	0	1	1
Hiccups	1	0	1
Femoral artery occlusion	0	1	1

There were 2 deaths due to study disease (one from each cohort) that occurred more than 6 weeks after treatment discontinuation.

Conclusions:

- The study was stopped early based on interim results of the GALES trial in December 2007, showing inferior activity of pemetrexed / carboplatin compared to etoposide /carboplatin in extensive SCLC.

- The study was stopped too early to conclude on primary endpoint or any efficacy outcome.

- Although the recommended dose of pemetrexed / cisplatin and TRT could not be assessed, the data show that the combination of systemic doses of 500 mg/m^2 pemetrexed and 75 mg/m^2 Cis concurrent with 50 Gy TRT is tolerable.