

Summary ID# 10105

Clinical Study Summary: Study H3E-SB-S089 Primary Objective (Acute Phase)

A Randomized Phase 2 Study of Pemetrexed in Combination with Cisplatin or Carboplatin as Adjuvant Chemotherapy in Patients with Completely Resected Stage Ib or II Non-Small Cell Lung Cancer

Date summary approved by Lilly: 16 October 2008

Title of Study: A Randomized Phase 2 Study of Pemetrexed in Combination with Cisplatin or Carboplatin as Adjuvant Chemotherapy in Patients with Completely Resected Stage Ib or II Non-Small Cell Lung Cancer	
Investigator(s): In this multicenter study with 18 sites all investigators entered subjects into the study.	
Study Center(s): This study was conducted at 18 study centers in three countries.	
Length of Study: Date of first patient enrolled: 21 December 2005 Date of last patient completed acute phase +30-d FU: 12 November 2007 Availability of long-term time- to-event data: planned for 2011	Phase of Development: 02
Objectives: The primary objective of this study is: <ul style="list-style-type: none"> To assess the feasibility of an adjuvant chemotherapy of pemetrexed, in combination with either cisplatin or carboplatin in patients with completely resected stage Ib or IIa/IIb non-small cell lung cancer (NSCLC). The secondary objectives of the study are: To characterize the quantitative and qualitative potential toxicities and the necessity of dose reductions and cycle delays due to toxicities of either treatment arm. <ul style="list-style-type: none"> To assess time to event efficacy parameters in both treatment arms including <ul style="list-style-type: none"> 3-year overall survival. 3-year disease-free survival. To assess biomarkers relevant to pemetrexed and disease state and their correlation to clinical outcome (including 3-year overall survival, 3-year disease-free survival and toxicity). 	
Study Design: Multicenter, open-label, sequential (Simon 2-stage), two-arm, randomized parallel Phase 2 study of pemetrexed (Pem) combination therapy with either cisplatin (Cis) or carboplatin (Carbo) as adjuvant chemotherapy in patients (outpatients) with completely resected NSCLC.	
Number of Patients: Planned: 106 patients (pts.), 53 patients (pts) per treatment (Tx) -arm Randomized/Enrolled (ITT): Total 122 pts., Pem+Cis: N=63, Pem+Carbo: N=59* Randomized/Treatment received: Total 118 pts., Pem+Cis: N=64, Pem+Carbo: N=54 Evaluable for feasibility: Total 118 pts., Pem+Cis: N=64, Pem+Carbo: N=54 Protocol completed: Total 94/118 (79.7%), Pem+Cis: N=46/64 (71.9%), Pem+Carbo: N=48/54 (88.9%) *1 pt. randomized to Pem+Carbo was accidentally treated with Pem+Cis, 4 pts. did not start Pem+Carbo treatment due to patient-/physician decision.	
Diagnosis and Main Criteria for Inclusion: Patients with histologically confirmed, completely resected Stage Ib or II NSCLC, ≥ 18 yrs of age, with adequate organ function, ECOG performance status ≤ 1 , and no serious concomitant systemic disorders.	
Study Drug, Dose and Mode of Administration: Patients were randomly assigned 1:1 to either: Pemetrexed (500 mg/m ²) i.v. + cisplatin (75 mg/ m ²) i.v. d1 q3weeks (wks) for 4 cycles <u>or to</u> Pemetrexed (500 mg/m ²) i.v. + carboplatin (AUC 5) i.v. d1 q3wks for 4 cycles All patients received concomitant folic acid and vitamin B ₁₂ supplementation therapy.	
Reference Therapy, Dose and Mode of Administration: not applicable	

Duration of Treatment:**Four cycles of 21 days each**

Pemetrexed on Day 1 of each cycle in combination with

Cisplatin on Day 1 of each cycle **or**

Carboplatin on Day 1 of each cycle

usual 3-week (21-day) cycle could be extended (next dose delayed) up to 42 days, e.g. for toxicity reasons or scheduling conflicts.

Variables:

Efficacy: The primary outcome measure was the feasibility rate. A treatment regimen was considered “feasible” for a patient, if this patient was able to follow the treatment administrations for 4 consecutive cycles as defined per protocol, was alive, and showed no toxicities \geq Grade 3 according to CTCAE criteria (V3.0) 30 days after the last administration of study drugs.

Safety: Adverse events were assessed according to the NCI CTCAE Version 3 and coded by MedDRA dictionary.

Time to event parameters: 3-year survival will be evaluated and reported as soon as data are mature.

- 3-year overall survival.
- 3-year disease-free survival.

Pharmacogenomics: To assess biomarkers relevant to pemetrexed and disease state and their correlation to clinical outcome (including 3-year overall survival, 3-year disease-free survival and toxicity).

Pharmacogenomics data will be evaluated once mature 3-year survival data are available.

Evaluation Methods:

Statistical: Feasibility rate = Number of feasible patients (according to the above definition) divided by the number of qualified patients. The feasibility rate is reported with its binominal 95% confidence interval for both Tx-arms.

The statistical H_0 -hypothesis which needed to be disproven assumed a feasibility rate $\leq 60\%$, that is, either regimen would be considered feasible if the feasibility rate was $> 60\%$. The Simon 2-stage design was employed independently for each of both Tx-arms. Accordingly, $> 12/19$ pts. per Tx-arm in stage 1, and, in case stage 1 could be fulfilled, $> 37/53$ pts. per Tx-arm at the end of stage 2 need to be considered “feasible” to conclude feasibility of either regimen, in this study. As the dynamic of recruitment and the omission of treatment in 4 pts. from Pem+Carbo-treatment led to a remarkably higher number ($n=64$, planned: 53) of pts. actually treated in the Pem+Cis-arm compared to the protocol assumptions, the statistical calculation needed to be adapted. In consequence, $> 38/54$ pts. in the Pem+Carbo group and $> 44/64$ pts. in the Pem+Cis group need to be considered “feasible” to show feasibility of either regimen. Stage 1 criteria for feasibility were met as confirmed by a pre-defined assessment committee through a feasibility review meeting on February 20, 2007.

Safety: Treatment emergent AEs, SAEs and possible relation to study drug or protocol procedure have been reported. AEs leading to early discontinuation and/or dose reduction/cycle delay were reported.

Summary:

This study is a multicenter, open-label, sequential (Simon 2-stage), two-arm, randomized parallel Phase 2 study of pemetrexed (Pem) combination therapy with either cisplatin (Cis) or carboplatin (Carbo) as adjuvant chemotherapy in patients (outpatients) with completely resected non small cell lung cancer (NSCLC).

Overall, 122 patients (pts.) have been enrolled in 3 European countries. Of these 122 pts. enrolled and randomized, 4 pts. randomized to Pem+Carbo did not start treatment due to patient- (n=1) or physician decision (n=2), or protocol violation (n=1). In total, 118 pts. were treated (at least 1 dose of study drug), 64 of these with Pem+Cis, 54 with Pem+Carbo.

Patient Demographics:

All pts. treated except 2 (1 per Tx-arm each) were Caucasians. Mean age (SD) of patients was 60 years (± 7.8) [Pem+Cis] and 59 years (± 7.3) [Pem+Carbo]. Patients' age ranged from 43 to 75 years.

Basic demographics [Pem+Cis / Pem+Carbo]: 77% (49/64 pts.) / 72% (39/54 pts.) were male; 89.1% (57/64 pts.) / 94.4% (51/54 pts.) did ever smoke. The most common tumor types at initial pathological diagnosis were 'adenocarcinoma of the lung' 43.8% (28/64 pts.) / 38.9% (21/54 pts.) and 'squamous carcinoma of the lung' 37.5% (24/64pts.) / 35.2% (19/54 pts.). Stage of disease prior to tumor resection was: 0%/2% Ia, 42%/44% Ib, 9%/9% IIa, 48%/43% IIb, 0%/2% IIIa. Curative surgery used included: 14%/17% pneumonectomy, 73%/78% lobectomy, 13%/6% bi-lobectomy; i.e. the majority of pts. [85.9%/83.3%] were not pneumonectomized.

Patient Disposition:

Patients were randomly assigned 1:1 to either: pemetrexed (500 mg/m²) i.v. + cisplatin (75 mg/m²) i.v. d1 q3wks for 4 cycles or to pemetrexed (500 mg/m²) i.v. + carboplatin (AUC 5) i.v. d1 q3wks for 4 cycles. All patients should receive concomitant folic acid and vitamin B₁₂ supplementation therapy. The normal 3-week (21-day) cycle could be extended (next dose delayed) up to 42 days, e.g. for toxicity reasons, i.e. to give pts. sufficient time to recover, or scheduling conflicts. Further on, the Tx-dose of either compound could be reduced in alignment to a predefined schedule according to protocol within a certain range.

The mean (SD) [median] number of cycles received was 3.4 (± 1) [4.0] in the Pem+Cis arm and 3.9 (± 0.5) [4.0] in the Pem+Carbo arm. Table 1 gives an overview on the number of cycles received and treatment duration.

Table 1. Patient Disposition

Treatment-arm	Pem+Cis		Pem+Carbo	
	N	%	N	%
Patients treated	64	100.0	54	100.0
Patients received at least:				
1 cycle	64	100.0	54	100.0
2 cycles	57	89.1	53	98.1
3 cycles	51	79.7	53	98.1
4 cycles	46	71.9	48	88.9
Pts. with at least 1 cycle delayed	38	59.4	22	40.7
Pts. with dose reductions*	4	6.3	7	13.0

Abbreviations: n = number; N = number of patients; Pts. = Patients; Pem = pemetrexed; Cis = cisplatin; Carbo = carboplatin. *: All dose reductions due to adverse events (AEs).

The main reasons for cycle delay were “scheduling conflicts” [46.9% (30/64) Pem+Cis and 27.8% (15/54) Pem+Carbo], and “Absolute Neutrophil Count (ANC) $<1.5 \times 10^9/L$ ” [14.1% (9/64) Pem+Cis / 11.1% (6/54) Pem+Carbo]. All dose reductions were due to adverse events.

Early Discontinuation:

Early discontinuation occurred in 28.1% (18/64) of pts. in the Pem+Cis Tx-arm and in 11.1% (6/54) of pts. in the Pem+Carbo Tx-arm. Reasons for discontinuation from study treatment (other than protocol completed) were [Pem+Cis / Pem+Carbo]: adverse events 14.1% (9/64) / 5.6% (3/54), subject decision 10.9% (7/64) / 3.7% (2/54), and physician decision 3.1% (2/64) / 1.9% (1/54).

Dose Intensity:

Table 2 presents an overview on the median dose intensity reached and the incidence of dose reductions, per compound. Dose intensity was calculated as (actual mean dose / planned dose) x 100%.

Table 2. Dose Intensity and Incidence of Dose Reduction per Compound

Treatment-arm	Pem+Cis (N=64)	Pem+Carbo (N=54)
Dose Intensity*		
Compound	Median Dose Intensity (%) [25 th ;75 th Percentiles]	
Pemetrexed (%)	98.7 [95.1;100.3]	98.4 [87.7;99.8]
Cisplatin (%)	98.8 [94.5;100.3]	-----
Carboplatin (%)	-----	97.1 [88.0;99.8]
Dose Reductions/Compound	n (%)	
Pemetrexed	3 (4.7)	7 (13.0)
Cisplatin	4 (6.3)	-----
Carboplatin	-----	6 (11.1)

Abbreviations: n = number of patients; N = total population size; Pem = pemetrexed; Cis = cisplatin; Carbo = carboplatin.

*Dose intensity was calculated as (actual mean dose / planned mean dose) x 100%.

Primary Endpoint:

The primary endpoint of this study was to assess feasibility of either regimen as measured by completion of 4 treatment cycles which needed to be performed according to protocol without remaining toxicities \geq Grade 3 at 30 days after the last infusion. Table 3 shows the feasibility rates (%) and reasons for non-feasibility per Tx-arm.

Table 3. Treatment Feasibility

Treatment-arm	Pem+Cis (N=64)		Pem+Carbo (N=54)	
	n	%	n	%
Patients "feasible"	38	59.4	27	50.0
Reasons for Non-feasibility				
Early discontinuation	18	28.1	6	11.1
Lost to follow-up ^a	1	1.6	2	3.7
Remaining Grade 3/4 toxicity ^a	4	6.3	3	5.6
Underdosage ^b	5	7.8	19	35.2

Abbreviations: n = number of patients; N=total population size; Pem = pemetrexed; Cis = cisplatin; Carbo = carboplatin.

Note: Multiple nominations possible

^a 30 days after last dose of study drug.

^b defined as <95% of intended dose

The main reasons for non-feasibility for both regimens [Pem+Cis/Pem+Carbo] were early discontinuation (due to AEs [14.1/5.6%] and patient/physician decision [14.1/5.6%]) and underdosage (<95% of intended dose).

The Pem+Cis treatment schedule was considered feasible in 38/64 pts. (59.4%; 95% CI: 46.4;71.5); the Pem+Carbo treatment schedule was considered feasible in 27/54 pts. (50.0%; 95% CI: 36.1;63.9)]. Thus, neither regimen met the pre-defined feasibility criteria for this study.

Safety

No death occurred in this study. Overall, 97.5% of patients (115/118) experienced at least 1 treatment emergent adverse event (TEAE). Table 4 presents a summary of safety information.

Table 4. Summary of Adverse Event Information

	Pemetrexed + Cisplatin (N=64)	Pemetrexed + Carboplatin (N=54)	Total (N=118)
Patients with at least one TEAE [n (%)]	63 (98.4%)	52 (96.3%)	115 (97.5%)
Patients with at least one TEAE possibly related to SD or PP [n (%)]	58 (90.6%)	47 (87.0%)	105 (89.0%)
Patients with at least one grade 3/4 TEAE [n (%)]	27 (42.2%)	21 (38.9%)	48 (40.7%)
Patients with at least one grade 3/4 TEAE possibly related to SD or PP [n (%)]	20 (31.3%)	15 (27.8%)	35 (29.7%)
Patients with at least one SAE [n (%)]	19 (29.7%)	5 (9.3%)	24 (20.3%)
Patients with at least one SAE possibly related to SD or PP [n (%)]	8 (12.5%)	2 (3.7%)	10 (8.5%)
Patients with at least one AE leading to discontinuation [n (%)]	9 (14.1%)	3 (5.6%)	12 (10.2%)
Patients with at least one AE with outcome death [n (%)] ^a	0 (0.0%)	0 (0.0%)	0 (0.0%)

Abbreviations: TEAE = treatment emergent adverse event; SD = study drug; PP = protocol procedure; SAE = serious adverse event; AE = adverse event; N = total population size; n = number of patients.

^a up to the end of the 30-day post-study follow-up.

Hematologic and Non-hematologic Toxicity

The hematologic as well as the non-hematologic toxicities were low in this study compared to other treatment schedules commonly used in this indication. The only hematologic Grade 3/4 toxicity occurring in $\geq 5\%$ of pts. in at least one Tx-arm was neutropenia (14.1% Pem+Cis / 11.1% Pem+Carbo). The only Grade 3/4 non-hematologic toxicity occurring in $\geq 5\%$ of pts. in at least one Tx-arm was asthenia (6.3% Pem+Cis / 3.7% Pem+Carbo). Table 5 displays an overview on all Grade 3/4 hematologic and non-hematologic toxicities experienced in this study (including laboratory non-hematologic toxicities).

Table 5. Grade 3/4 Hematologic and Non-hematologic Toxicities

Toxicity (Grade 3/4 TEAE possibly related to SD or PP)	Pemetrexed + Cisplatin (N=64)	Pemetrexed + Carboplatin (N=54)	Total (N=118)
Hematologic toxicities			
Neutropenia	9 (14.1%)	6 (11.1%)	15 (12.7%)
Anaemia	0 (0.0%)	3 (5.6%)	3 (2.5%)
Thrombocytopenia	0 (0.0%)	3 (5.6%)	3 (2.5%)
Febrile neutropenia	0 (0.0%)	2 (3.7%)	2 (1.7%)
Leukopenia	0 (0.0%)	1 (1.9%)	1 (0.8%)
Lymphopenia	1 (1.6%)	0 (0.0%)	1 (0.8%)
Neutrophil count decreased	1 (1.6%)	6 (11.1%)	7 (5.9%)
Haemoglobin count decreased	0 (0.0%)	2 (3.7%)	2 (1.7%)
Platelet count decreased	1 (1.6%)	1 (1.9%)	2 (1.7%)
White blood cell count decreased	0 (0.0%)	2 (3.7%)	2 (1.7%)
Non-hematologic toxicities			
Asthenia	4 (6.3%)	2 (3.7%)	6 (5.1%)
Nausea	3 (4.7%)	0 (0.0%)	3 (2.5%)
Vomiting	3 (4.7%)	0 (0.0%)	3 (2.5%)
Fatigue	0 (0.0%)	2 (3.7%)	2 (1.7%)
Catheter related infection	1 (1.6%)	0 (0.0%)	1 (0.8%)
Gamma-glutamyltransferase increased	1 (1.6%)	0 (0.0%)	1 (0.8%)
Anorexia	1 (1.6%)	0 (0.0%)	1 (0.8%)
Hyperglycaemia	1 (1.6%)	0 (0.0%)	1 (0.8%)
Hyperkalaemia	1 (1.6%)	0 (0.0%)	1 (0.8%)
Psychotic disorder	1 (1.6%)	0 (0.0%)	1 (0.8%)

Abbreviations: TEAE = treatment emergent adverse event; SD = study drug; PP = protocol procedure;
N = total population size.

Adverse Events

Overall, 97.5% of pts. (115/118) experienced at least 1 treatment emergent adverse event (TEAE). Table 6 gives an overview on the most frequently reported TEAEs (ordered according to system organ class).

Table 6. Summary of Most Frequent Treatment Emergent Adverse Events*

	Pemetrexed + Cisplatin (N=64)	Pemetrexed + Carboplatin (N=54)	Total (N=118)
Neutropenia [n (%)]	23 (35.9)	15 (27.8)	38 (32.2)
Anaemia [n (%)]	11 (17.2)	8 (14.8)	19 (16.1)
Thrombocytopenia [n (%)]	3 (4.7)	7 (13.0)	10 (8.5)
Neutrophil count decreased [n (%)]	4 (6.3)	10 (18.5)	14 (11.9)
Platelet count decreased [n (%)]	4 (6.3)	10 (18.5)	14 (11.9)
White blood cell count decreased [n (%)]	2 (3.1)	9 (16.7)	11 (9.3)
Haemoglobin decreased [n (%)]	2 (3.1)	6 (11.1)	8 (6.1)
Alanine aminotransferase increased [n (%)]	0 (0.0)	6 (11.1)	6 (5.1)
Conjunctivitis [n (%)]	1 (1.6)	6 (11.1)	7 (5.9)
Nausea [n (%)]	42 (65.6)	30 (55.6)	72 (61.0)
Vomiting [n (%)]	23 (35.9)	17 (31.5)	40 (33.9)
Constipation [n (%)]	18 (28.1)	8 (14.8)	26 (22.0)
Diarrhea [n (%)]	5 (7.8)	7 (13.0)	12 (10.2)
Fatigue [n (%)]	24 (37.5)	21 (38.9)	45 (38.1)
Asthenia [n (%)]	10 (15.6)	13 (24.1)	23 (19.5)
Anorexia [n (%)]	10 (15.6)	14 (25.9)	24 (20.3)
Headache [n (%)]	8 (12.5)	6 (11.1)	14 (11.9)
Dysgeusia [n (%)]	3 (4.7)	7 (13.0)	14 (11.9)
Cough [n (%)]	7 (10.9)	16 (29.6)	23 (19.5)
Dyspnoea [n (%)]	12 (18.8)	10 (18.5)	22 (18.6)

Abbreviations: N = total population size; n = number of patients.

*All TEAEs occurring in $\geq 10\%$ of patients within at least 1 TX-arm.