2. S109 Synopsis

Clinical Study Report Synopsis: Study H3E-SB-S109

Title of Study: A Randomized Phase 2 Study of Pemetrexed in Combination with Cisplatin or Carboplatin in the First Line Therapy of Advanced NSCLC
Number of Investigators: This multicenter study included 15 investigators.
Study Centers: This study was conducted at 15 study centers in one country (Germany).
Publications Based on the Study: Schuette W, Groeschel A, Sebastian M, Andreas S, Mueller T, Schneller F, Guetz S, Leschinger M, Buettner H, Reck M. 2009. Pemetrexed in combination with cisplatin or carboplatin in the first line therapy of locally advanced or metastatic non-small cell lung cancer: a randomized, two-arm, parallel, open-label, multicentric phase 2 study [Abstract]. Eur J Cancer 7 (Suppl): 528.
Length of Study: Date of first patient visit: 24 November 2006 Date of last patient completed: 20 April 2009
Objectives: **Primary Objective:** to assess progression free survival (PFS) in patients with advanced NSCLC of stage IIIb or IV undergoing first line chemotherapy (Tx) with pemetrexed (Pem) in combination with cisplatin (Cis) or carboplatin (Carbo). **Secondary Objectives:** to assess • Overall survival including 1-year survival rate • Objective tumor response rate (according to RECIST criteria) • Time to treatment failure • Assessment of potential toxicities and the necessity of dose reductions and cycle delays due to toxicities The primary efficacy analysis and safety evaluation were performed 6 months after enrollment of the last study patient, the secondary efficacy analysis was performed 12 months after enrollment of the last study patient.
Study Design: A two-arm, randomized, non-comparative parallel group, open-label, Phase 2 multicenter study of Pem as 1st line combination therapy with either Cis) or Carbo in stage IIIb or IV NSCLC patients (pts). Randomization (1:1) was stratified by stage of disease (pts were not additionally stratified by center as planned in the protocol due to the unexpectedly high number of study centers).
Number of Patients: Planned: Total=130, Pem+Cis=65, Pem+Carbo=65 Randomized: Total=133, Pem+Cis=66, Pem+Carbo=67 Treated (at least 1 dose): Total=130, Pem+Cis=65, Pem+Carbo=65 Treatment and protocol complete (of pts random.): Total=60 pts (45.1%), Pem+Cis=28 (42.4%), Pem+Carbo=32 (47.8%)
Diagnosis and Main Criteria for Inclusion: Pts with cytologically and/or histologically confirmed NSCLC stage IIIb or IV; no previous systemic chemotherapy for NSCLC (previous adjuvant therapy allowed if it has been more than one year since the end of adjuvant therapy) at least one unidimensionally measurable lesion meeting Response Evaluation Criteria in Solid Tumors (RECIST), adequate organ function (especially renal, hepatic, bone marrow reserve); ECOG performance status ≤ 1 and no serious concomitant systemic disorder

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 q3 weeks (wks) for 6 cycles or to
Pemetrexed (500 mg/m^2) i.v. + carboplatin (AUC 6) i.v. d1 q3 weeks for 6 cycles
All patients received folic acid and vitamin B_{12} supplementation and dexamethasone prophylaxis.

Duration of Treatment: Six cycles of 21 days each. Cycle delay(s) up to 42 days post last study drug administration and a maximum of 2 dose reductions according to pre-defined criteria were permitted.

Variables:
Primary Outcome: The detailed definition of the primary outcome measure was the progression-free survival (PFS) rate at 6 months, tested independently for each Tx arm. The PFS rate was defined as the rate of progression-free surviving pts at 6 months from the date of randomization and was determined using the distribution of overall PFS times (estimate based on exponential distribution).

Secondary Outcomes

6-month analysis:

- Objective tumor response rate (%) assessed according to RECIST criteria
- Adverse event assessment, patients' disposition to study drugs (median number of cycles received, number of patients with cycle delays, number of dose reductions, median relative dose intensity)

12-month analysis:

- 12-month PFS rate (%), median PFS (months)
- Median overall survival (months) including 1-year survival rate (%)
- Median time to treatment failure (TTF, months); 6-month TTF rate (%)

Statistical Evaluation Methods:
Primary Analysis:

- The primary analysis was the estimation of 6-month PFS rate based on exponential distribution; also the calculation of sample size was based on this assumption. 95% confidence intervals were presented.
- All pts who received at least one dose of any component of the study regimens were included into the analysis of efficacy parameters.
- H_0 hypothesis: 6-month PFS rate $\leq$ 25.0% (median PFS of 3.0 months)
  Alternative: 6-month PFS rate $\geq$ 41.3% (median PFS of 4.7 months);
  with 90% power and at a two-sided significance level of 0.05
- It was planned to recruit 65 pts per Tx arm assuming a censoring rate of 18%, including administrative censoring and pts lost to follow-up, and an accrual time of 18 months.
- The 6-month PFS rate was also calculated together with its 95% confidence interval using Kaplan-Meier techniques.
- An exploratory subgroup-analysis of different histopathological NSCLC subtypes was performed.

Secondary Analysis:

- Time-to-event parameters were calculated using Kaplan-Meier techniques.
- Adverse events were assessed according to the NCI CTCAE Version 3 and coded by MedDRA dictionary. All patients who received at least one dose of one component of study regimen were evaluated for safety.

Summary:

Of 133 pts randomized at 15 German sites, 130 received Tx (97.7%; Pem+Cis/Pem+Carbo: N=65/65). All pts treated were included into the efficacy and safety analyses. Baseline patient- and disease characteristics as well as prognostic factors, like histology and the number and location of metastasis, were well balanced between the Tx arms, and are generally reflective of the collective of pts with advanced NSCLC. The vast majority of pts presented with stage IV disease; 14 pts (10.5%; 5/9) had stage IIIb, 119 (89.5%; 61/58) had

stage IV tumors. (65%/71% of pts were male; median age was 64/63 years. 18.5%/20.0% (Pem+Cis/Pem+Carbo) of pts showed squamous histology, 81.5%/80.0% non-squamous histology, bone metastases were present in 21.5%/16.9%, brain metastases in 3.1%/1.5%.

Results - Efficacy

Primary Objective

The 6-month PFS rates [95% CI]) were 52.8 % [40.3;65.3] in the Pem-Cis and 39.3% [27.8;50.8] in the Pem-Carbo group.

In the histopathological subgroups, the 6-month PFS rates for pts with squamous histology (Pem+Cis/Pem+Carbo) were 34.9% [9.4;60.4]/42.0% [16.8;67.3], for pts with non-squamous histology 57.6% [43.7;71.5]/38.5% [25.6;51.5].

The results of the additional Kaplan-Meier analysis were in the same range as the primary analysis based on the exponential distribution of the 6-month PFS rate, thus illustrating the appropriateness of the assumptions made regarding distribution.

The H_0-hypothesis (6-month PFS rate ≤ 25.0%, median PFS of 3.0 months) could be rejected for both treatment regimens. Both regimens were deemed worth to be carried forward to further investigations.

Overall, the Pem+Cis regimen yielded more favorable results regarding 6-months PFS rate, although no formal comparison between treatment arms was done.

Secondary Objectives

For an overview on the results of secondary outcomes please see Table S109.1.

Table S109.1. Overview on Secondary Study Results All Patients Treated

	Pem+Cis (N=65)	Pem+Carbo (N=65)
12-month PFS rate (%) [95% CI]	4.2 [0.8,12.7]	1.9 [0.2,9.0]
Median PFS time (months) [95% CI]	6.0 [4.6,7.1]	4.7 [3.4,5.7]
[b]Squamous histology (months) [95% CI]	4.5 [1.6,6.4]	4.6 [3.4,6.3]
[b]Non-squamous histology (months) [95% CI]	6.4 [4.7,7.5]	4.7 [2.9,5.9]
Median overall survival time (months) [95% CI]	11.7 [9.2,14.9]	8.9 [6.0,12.2]
[b]Squamous histology (months) [95% CI]	7.4 [3.5, -]	9.8 [4.4,25.7]
[b]Non-squamous histology (months) [95% CI]	11.9 [9.4,15.2]	8.5 [6.0,13.3]
6-month overall survival rate (%)[95% CI]	77.7 [65.2,86.1]	60.4 [47.3, 71.2]
12-month overall survival rate (%)[95% CI]	47.5 [34.5,59.4]	39.2 [27.2,51.1]
Objective response rate, n responders (all PR) (%)	21 (32.3)	13 (20.0)
Median time to treatment failure[a] (months) [95% CI]	3.0 [2.3,4.6]	3.4 [2.3,4.8]
6-month TTF[a] rate (%) [95% CI]	30.7 [20.0,42.0]	29.2 [18.5,40.6]

[a] Time to treatment failure was defined as the time from the date of study enrollment (randomization) to the first date of disease progression, death due to any cause or early discontinuation of treatment (any reason), whichever occurred first.

[b] Patient numbers (Pem+Cis/Pem+Carbo): Squamous histology N=12/N=13; non-squamous histology N=53/N=52.

Abbreviations: CI= confidence interval; PFS=progression-free survival; PR = partial response; TTF=time to treatment failure.

Results - Safety

Exposure to study drug

Table S109.2 summarizes exposure to study drug, Table S109.3 summarizes reasons for patient discontinuation. 43.1%/50.8% (Pem+Cis/Pem+Carbo) of pts received all 6 Tx-cycles.

Table S109.2. Exposure to Study Medication All Patients Treated

	Pem+Cis (N=65)	Pem+Carbo (N=65)
Number of cycles received, n (%)		
1 cycle	8 (12.3)	1 (1.5)
2 cycles	6 (9.2)	14 (21.5)
3 cycles	4 (6.2)	3 (4.6)
4 cycles	15 (23.1)	8 (12.3)
5 cycles	4 (6.2)	6 (9.2)
6 cycles	28 (43.1)	33 (50.8)
Median number of cycles, n	4	6
Patients with cycle delays	40 (61.5)	41 (63.1)
Number of dose reductions, n (%)[a]	3 (4.6)	16 (24.6)
Median relative dose intensity % [25th,75th percentile]		
Pem	98.2 [92.0, 100.0]	98.6 [91.6, 99.7]
Cis	97.8 [91.6, 99.8]	----------
Carbo	----------	96.3 [83.1, 99.5]

Table S109.3. Reasons for Patient Discontinuation All Patients Randomized

Discontinuations from study medication	Pem+Cis (N=66)	Pem+Carbo (N=67)
Protocol complete[a]	28 (42.4)	32 (47.8)
Adverse event	11 (16.7)	4 (6.0)
Progressive disease	13 (19.7)	20 (29.9)
Lost to follow-up	1 (1.5)	0 (0.0)
Patient/physician decision	10 (15.2)	6 (9.0)
Death[b]	3 (4.5)	5 (7.5)

[a] Includes all patients who completed 6 cycles of treatment and who completed the 30-day follow-up visit.

[b] Includes deaths due to study disease, study drug related deaths, and deaths due to adverse events (other cause), up to 30 days after the last administration of study drug.

Tolerability

An overview on tolerability, hematological and non-hematological toxicities is presented in Table S109.4. No febrile neutropenia was observed. Overall, 3 deaths [1 Pem+Cis/2 Pem+Carbo] were considered study drug related: 1 case of multi-organ failure in the Pem+Cis group, 1 pancytopenia and 1 haemorrhage in the Pem+Carbo group. No death due to AEs unrelated to study drug occurred in the Pem+Cis Tx group; 3 deaths (1 pneumonia, 2 cardiac failures) due to unrelated AEs were reported for Pem+Carbo.