Title of Trial: Randomized, phase II, open-label controlled study of two different doses and schedules of EMD 72000 (matuzumab) in combination with pemetrexed, or pemetrexed alone, as secondline treatment in subjects with Stage IIIB/IV non-small cell lung cancer (NSCLC) and progressive disease (PD) on or after first-line treatment with a platinum analogue in combination with either taxanes, gemcitabine or vinorelbine.

Investigational Product: Matuzumab

Trial No.: EMD 72000-031

Trial Dates:

Trial Initiation Date: 16 August 2005

Trial Completion Date: 16 July 2007

Development Phase: Phase 2

Publication (reference): None

Study Objectives:

Primary objective:

The primary objective of this study was to determine the tumor response rate (as assessed by the Independent review committee [IRC]) of two different regimens of matuzumab in combination with pemetrexed in comparison to pemetrexed alone in subjects with Stage IIIB/IV NSCLC.

Secondary objectives:

- Tumor response rate (as assessed by the investigator)
- Overall survival
- Time to tumor progression (Progression-free survival [PFS])
- Duration of response
- Safety and tolerability
- Quality of life (QoL).

Additional objectives of this study included evaluation of the following:

- Human anti-humanized antibody (HAHA) (Groups B and C only)
- Pharmacokinetics (PK) of matuzumab (Groups B and C only)
- Epidermal growth factor receptor (EGFR) mutation analysis and association of EGFR mutations with tumor response
- EGFR detectability by immunohistochemistry (IHC) and its association with tumor response.

Methodology: Subjects were centrally randomized and stratified by best response to first-line chemotherapy and time from completion of previous chemotherapy to randomization and assigned to one of three treatment arms as follows:

- Group A: pemetrexed alone
- Group B: pemetrexed plus matuzumab (800 mg intravenous [i.v.] every week)
- Group C: pemetrexed plus matuzumab (1600 mg i.v. every 3 weeks).

Pemetrexed (500 mg/m2 i.v.) was administered according to a 3-week cycle in each group.

Subjects in both groups were evaluated for tumor response every 6 weeks during study treatment, regardless of any treatment delays, until PD. The overall response rate was based on the assessment of at least one bi-dimensional lesion on images obtained by either computed tomography (CT) or magnetic resonance imaging (MRI). An IRC conducted a blinded radiological review of the images of all subjects to determine response and response duration using criteria based on a separate charter. Responses were classified according to the modified World Health Organization (WHO) criteria.

Upon occurrence of PD, all study treatment was to be discontinued and the end of treatment (EoT) visit was to be performed.

The end of study (EoS) visit took place at least 6 weeks after EoT, unless the subject was to receive further anti-cancer treatment in which case the EoS visit took place at least 28 days after the EoT but prior to the start of further anti-cancer treatment. After the EoS visit, survival follow-up visits were performed every 3 months.

Routine safety assessments were performed throughout the study. QoL was assessed for both treatment groups.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Inclusion criteria:

For inclusion in the study, all of the following inclusion criteria had to be fulfilled:

- Written informed consent provided prior to any screening procedure
- Male or female, ≥ 18 years of age
- Histologically or cytologically confirmed diagnosis of NSCLC
- Demonstrated PD on or after first-line chemotherapy for Stage IIIB/IV disease. The first-line therapy had to consist of platinum-based regimens in combination with taxanes, gemcitabine or vinorelbine. Stage IIIB subjects had to have measurable disease (tumor) without clinically significant pleural effusion unless the pleural effusion could be effectively drained prior to admission into the study
- A chemotherapy-free interval of at least 3 weeks between the end of first-line chemotherapy and start of study treatment
- At least one measurable lesion according to the modified WHO criteria

- Archived tissue or cytology sample available for the determination of EGFR expression
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Life expectancy > 12 weeks
- Adequate baseline organ functions, defined as follows:
  - Serum creatinine ≤ 1.5 × upper limit of normal (ULN)
  - In case of borderline values for serum creatinine, creatinine clearance must be ≥ 45 mL/min
  - Total bilirubin < 1.5 × ULN
  - Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 2.5 × ULN (Subjects with liver metastases should have had ALT/AST < 5 × ULN)
  - Absolute neutrophil count (ANC) ≥ 1,500/mm3
  - Platelet count ≥ 100,000/mm3
  - Hemoglobin level ≥ 10 g/dL
- If procreative potential (male or female), willingness to use effective contraceptive methods for the duration of treatment and continuing for 2 months after the last dose. Subjects of procreative potential were defined as any fertile male, or any female who had experienced menarche and who was not postmenopausal (defined as age-related amenorrhea ≥ 12 months) or who had not undergone successful surgical sterilization (hysterectomy or bilateral oophorectomy).

Exclusion criteria:

Subjects were not eligible for this study if they fulfilled one or more of the following exclusion criteria:

- Radiotherapy or major surgery within 30 days prior to the start of study treatment
- Prior treatment with an EGFR-directed therapy or with EGFR signal transduction inhibitors
- Prior treatment with pemetrexed
- Pregnant (confirmed by beta human chorionic gonadotrophin [β-hCG]) or lactating female
- Weight loss > 10% within 12 weeks prior to the start of study treatment
- Documented or symptomatic brain metastases or leptomeningeal disease
- Myocardial infarction within 6 months prior to the start of study treatment, uncontrolled congestive heart failure, or any current New York Heart Association class III or IV cardiovascular disorder despite treatment
- Presence of a ≥ grade 2 pre-existing skin disorder (except for alopecia)
- Previous diagnosis of autoimmune disease with significant organ involvement
- Concurrent malignancies or invasive carcinomas diagnosed within the past 5 years, except for adequately treated basal cell carcinoma of the skin or in situ carcinoma of the cervix
- Any significant disease that, in the investigator's opinion, should have excluded the subject from the study
- History of significant neurological or psychiatric disorder (e.g. dementia, seizures, or bipolar disorder)

- History of drug abuse within 6 months prior to the start of study treatment
- Known conditions that require concurrent treatment with a non-permitted drug
- Presence of a contraindication to the study treatment(s) according to the current IB for matuzumab and the labeling for pemetrexed
- Known hypersensitivity to the study treatment or any of its components
- Participation in another clinical study within 30 days prior to the start of study treatment.
- Legal incapacity or limited legal capacity.

Study Treatment: Matuzumab, supplied in vials of 200 mg of lyophilized anti-body.

Matuzumab 800 mg i.v. infusion weekly (Group B) or 1600 mg i.v. infusion every 3 weeks (Group C) administered over a 1-hour period.

Duration of treatment: Subjects were to receive study treatment until PD, occurrence of unacceptable toxicity or subject withdrawal.

Reference therapy: Pemetrexed chemotherapy was administered in accordance with the approved product labeling, by a 10-minute i.v. infusion in Groups A, B, and C as follows:

- 500 mg/m^2 every 3 weeks.

Criteria for Evaluation:

- Baseline characteristics and demographics
- Objective response based on the IRC assessment
- Safety data: Adverse events (AEs), serious adverse events (SAEs), deaths and clinical laboratory investigations

Statistical Methods:

The Screening population was defined as all subjects who provided informed consent and demographic and/or baseline screening assessments regardless of their randomization or treatment status. The Intent-to-treat (ITT) and the Safety populations were defined as all subjects who were randomized and received at least one dose of matuzumab or pemetrexed. Subjects in this population were analyzed according to the treatment group to which they were randomized. The Per protocol (PP) population was defined as all randomized subjects with at least one post-baseline tumor assessment who received at least two cycles of study treatment, except in case of death or PD and had no major protocol violation.

The primary efficacy variable was the confirmed best tumor response rate based on response assessments carried out by the IRC.

Response rate and 95% confidence intervals (CIs) were calculated for the proportion of responders.

An analysis for progression-free survival (PFS) censoring non-progressing subjects at the date when last known to be progression-free was performed. Kaplan-Meier curves were plotted from the data. Median time to PD with corresponding 95% CIs were derived from Kaplan-Meier estimates.

Subjects who achieved PR or CR but for whom subsequent PD was not observed during the study were censored at the time when the subject was last known to be non-progressing (last visit date).

Survival time was defined as the number of months between the date of randomization and date of death. Subjects who were alive were censored at the time when last known to be alive. The survival curve was plotted using Kaplan-Meier estimates, from which median survival times and 95% CIs were determined.

The time to response in months was determined for subjects whose best response was either CR or PR. It was defined as the time from randomization until the date of best response.

Results:

Subject Disposition: A total of 148 subjects were included in the study (Safety/ITT population); 50 subjects in Group A, 51 subjects in Group B and 47 subjects in Group C. Forty-four subjects in Group A (88%) and in Group B (86%) and 42 subjects (86%) in Group C were included in the PP population.

At the time of the data cut-off, seven subjects (5%) were still on treatment and 141 subjects (95%) were discontinued. The most frequent reasons for discontinuation were PD (96 subjects, 65%) which occurred at a similar percentage in each treatment group, AEs (nine subjects [6%]: five subjects [10%] in Group A, three subjects [6%] in Group B, and one subject [2%] in Group C) and deaths (eight subjects [5%]: one subject [2%] in Group A, one subject [2%] in Group B and six subjects [13%] in Group C).

Efficacy Results:

Subjects were treated with pemetrexed (500 mg/m2 i.v. every 3 weeks) alone (Group A), or in combination with matuzumab 800 mg i.v. every week (Group B) or with matuzumab 1600 mg i.v. every 3 weeks (Group C).

The primary analysis of objective response, assessed by the IRC based on the primary analysis set (PP population), did not reveal any statistically significant difference between the pooled groups treated with matuzumab in combination with pemetrexed (Groups B + C) compared to the control group (Group A) (Objective response rate 11% vs 5%, p-value 0.3315).

Based on the Safety/ITT population a higher frequency in objective response rate was observed in Group B (eight subjects, 16% [95% CI 7 to 29]) compared to Group A (two subjects, 4% [95% CI 1 to 14]) and to Group C (one subject, 2% [95% CI 0 to 11]) basedon IRC assessment. The investigator assessment showed the same trend in favor of Group B.

Regarding PFS time similar results were observed in the individual treatment groups with respect to median PFS time (2.7 months [95% CI 1.6 to 4.4 months] in Group A, 2.3 months [95% CI 1.5 to 3.8 months] in Group B, and 2.5 months [95% CI 1.4 to 2.9 months] in Group C) and hazard ratio (0.96 [95% CI 0.59 to 1.56] for Group B vs Group A and 1.46 [95% CI 0.90 to 2.38] for Group C vs Group A).

The preliminary overall survival time results revealed a trend in favor of Group B vs Group A with regard to both the median survival time (12.4 months [95% CI 8.8 months, upper range not yet evaluable] vs 7.9 months [95% CI 7.2 to 9.9 months]) and the hazard ratio was 0.67 (95% CI 0.37 to 1.21). In Group C, the median survival time was 5.9 months (95% CI 3.6 to 7.2 months) and the hazard ratio was 1.66 (95% CI 0.97 to 2.86) compared to Group A.

Subgroup analysis by prior chemotherapy revealed that subjects who had not responded to prior therapy did not have any objective response to study treatment in any treatment group. Analyses by time from end of prior chemotherapy to randomization indicated that subjects who had a treatment free interval 3 months or more before randomization had a similar or better objective response to study treatment.

Safety Results:

The safety data were generally consistent with the existing safety profile of the study medication. Overall, there were no major differences between treatment groups with regard to frequency, type or severity of AEs experienced.

Adverse events occurred in almost all subjects (145 subjects, 98%) in the Safety/ITT population.

Overall, 130 subjects (88%) had a treatment-related AE; these AEs were more frequent in Group B (47 subjects, 92%) and Group C (44 subjects, 94%) than in Group A (39 subjects, 78%). The most frequent treatment-related AE was nausea (49 subjects, 33%), which occurred more frequently in Group B (20 subjects, 39%) than in Group A (15 subjects, 30%) and Group C (14 subjects, 30%). Of the 98 subjects who were treated with matuzumab, 88 subjects had an AE assessed as possibly related to matuzumab; 46 subjects (90%) in Group B and 42 subjects (89%) in Group C. The most frequent matuzumab related AEs were rash (34 subjects, 23%), fatigue (30 subjects, 20%), nausea (25 subjects, 17%) and dermatitis acneiform (16 subjects, 11%).

A total of 27 subjects experienced CTC grade 3 or 4 matuzumab-related AEs; these occurred to a similar extent in Group B (14 subjects, 27%) and Group C (13 subjects, 28%). The most frequent CTC grade 3 or 4 AE was fatigue (five subjects, 3%), which occurred more frequently in Group B (four subjects, 8%) than in Group C (one subject, 2%).

Overall 25 subjects (17%) experienced a treatment-related SAE; these occurred more frequently in Group A (nine subjects, 18%) and Group C (11 subjects, 23%) than in Group B (five subjects, 10%). The most frequent treatment-related SAE was febrile neutropenia, which occurred in five subjects (3%); one subject (2%) in Group A and Group B and three subjects (6%) in Group C.

Overall 27 subjects (18%) had an AE that resulted in treatment discontinuation; 10 subjects (20%) in Group A, nine subjects (18%) in Group B, and eight subjects (17%) in Group C. The most frequent were deep vein thrombosis (three subjects, 2%), which occurred in one subject (2%) in each treatment group, and pneumonia (three subjects, 2%), which occurred in two subjects (4%) in Group A and one subject (2%) in Group B. Nine subjects (6%) were discontinued from study due to AEs; five subjects (10%) in Group A, three subjects (6%) in Group B and one subject (2%) in Group C; individual AEs occurred in no more than one subject, respectively.

Deaths: Sixteen subjects died within 30 days of the last administration of study drug: three subjects in Group A, five subjects in Group B and eight subjects in Group C. Seven subjects died due to AEs: one subject in Group A died due to sepsis, two subjects in Group B died due to respiratory failure and exsanguination, respectively, and four subjects in Group C died due to pneumonia and respiratory failure, renal failure, hemorrhage and pulmonary embolism, respectively.

Conclusion:

The primary analysis did not result in a statistically significant difference in objective response between the pooled matuzumab treatment groups (matuzumab at a weekly dose of 800 mg or 1600 mg every three weeks combined with pemetrexed 500 mg/m2 every three weeks) compared to the control group (pemetrexed 500 mg/m2 every three weeks alone) for second-line treatment of EGFR-expressing Stage IIIB/IV NSCLC.

Efficacy analysis on the individual treatment groups, revealed a clear trend in favor of Group B (matuzumab 800 mg i.v. every week in combination with (pemetrexed every three weeks) with regard to objective response rate and preliminary median overall survival time compared to the control group (Group A, pemetrexed every three weeks alone). Considering the 3-weekly administration schedule of matuzumab (matuzumab 1600 mg i.v. every 3 weeks) in combination with pemetrexed, no trend for a treatment benefit was seen compared to the control group (Group A, pemetrexed every three weeks alone). However, with regard to PFS time no relevant differences between treatment groups were observed.

Overall, there were no major differences between treatment groups with regard to the safety data. There is no evidence that co-administration of both drugs aggravates the safety profile of the individual therapies.