2. H3E-XM-S092 Synopsis

Clinical Study Report Synopsis: Study H3E-XM-S092

Title of Study: Treatment with Alimta® (Pemetrexed) and cisplatin as neoadjuvant therapy in non-small-cell lung cancer	
Number of Investigators: This multicenter study included 6 principal investigators.	
Study Centers: This study was conducted at 6 study centers in one country.	
Publication(s) Based on the Study: None at this time.	
Length of Study: Date of first patient enrolled: 28 February 2006 Date of last patient completed study: 20 December 2007	**Phase of Development:** II

Objectives:

- Primary Objetive:
  - To determine the objective response rates (complete and partial responses) obtained with this regimen for neoadjuvant therapy in patients with stage T3-4N0M0 and IIIA NSCLC
- Secondary Objetives:
  - To determine the surgical resectability rate
  - To determinate the complete pathologic remissions rate after surgery
  - To determine toxicity
  - To determine relapse-free survival
  - Pharmacogenomic determinations and their correlation with the response rate obtained and relapse-free survival
  - To determine the objective response rate using PET and its correlation with the objective response rate obtained using CT and with the pathological response

Study Design:

This is an open-label Phase II study, in which there is no control arm.

Number of Subjects/Patients:

Planned: 44 patients
Randomized: Not Applicable
Treated (at least 1 dose): 10 patients
Completed: 10 patients

Diagnosis and Main Criteria for Inclusion:
Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Inclusion Criteria:

- Diagnosis of non-small-cell carcinoma of the lung
- Patients with locally advanced disease or metastatic disease, candidates to surgery after evaluation by oncologist and thoracic surgeon
- Tumour with possibility of curative surgery
- At least one uni-dimensionally measurable lesion
- Adequate pulmonary function to perform the planned surgical resection

Exclusion Criteria:

- Active infection (at the investigator's discretion)
- Pregnancy or breast-feeding
- Serious concomitant illness at the investigator's discretion
- Previous diagnosis of malignant disease
- They have received treatment during the last 30 days with a drug, other than the study drug, that has not received regulatory approval for any indication at the time of their entry in the study

Study Drug, Dose, and Mode of Administration:
Pemetrexed 500 mg/m2, intravenous (IV), every 21 days x 3 cycles in combination with Cisplatin 75 mg/m2, intravenous (IV), every 21 days x 3 cycles

Comparator, Dose, and Mode of Administration: Not Applicable

Duration of Treatment:
3 cycles of 21 days.
Pemetrexed 500 mg/m2, intravenous (IV), every 21 days x 3 cycles in combination with Cisplatin 75 mg/m2, intravenous (IV), every 21 days x 3 cycles

Variables:

Efficacy:

- Treatment Response: Best response recorded from the start of treatment until disease progression/recurrence using Response Evaluation Criteria In Solid Tumors (RECIST) criteria that defines when participants improve ("respond"), stay the same ("stable"), or worsen ("progression") during treatment
- Pathologic Remissions After Surgery: The status of the pathological response was evaluated on the basis of the original results of the histopathological examination of the tumour samples resected. A complete pathological response was defined as the absence of any viable tumour cell in the tumour samples obtained for histological examination
- Relapse-Free Survival: Results for this outcome measure were not analyzed because the trial stopped early due to low enrollment.

Safety:

- Reported Adverse Events

Statistical Evaluation Methods:

Efficacy:

The sample size of the Phase II study has been calculated on the basis of the expected efficacy of the treatment, using the Simon tables optimized for an error α=0.05 and an error β=0.20. It is expected that the treatment regime designed will be well tolerated and will produce responses in approximately 55% (P1) of patients, with P0= 35%. With these forecasts, it will be necessary to include 44 patients: if 20 or fewer of the 44 patients present responses the treatment regime will be considered to present an activity of less than 55 % with a 20% probability of error.

For descriptive analysis, the results of qualitative variables will be presented as absolute and relative frequencies and quantitative variables by means of statistics with the central trend and dispersion (mean, median, standard deviation and range), calculating the limits of the 95% confidence interval when necessary.

For survival analysis, the Kaplan-Meier model will be applied

Safety:

The safety measures to be applied in this study include physical examinations and laboratory tests (haematology, biochemistry and creatinine clearance). The toxicity of patients prior to each cycle will be evaluated using version 3.0 of the scale of common toxicity criteria (CTC) drafted by the National Cancer Institute (NCI) (Cancer Therapy Evaluation Program, 1998)

Summary:

- Baseline Characteristics, Patient Population:

	Pemetrexed + Cisplatin
Number of Participants:	
Started	10
Completed	10
Age:	
Continuous [units: years] Mean ± Standard Deviation	61.6 ± 8.2
Gender:	
Male [units: participants]	6
Female [units: participants]	4
Region of Enrollment:	
Spain [units: participants]	10
Study Specific Characteristic [Eastern Cooperative Oncology Group Functional Status]	
0 - Fully Active [units: participants]	8
1 - Ambulatory, Restricted Strenuous Activity [units: participants]	2
2 - Ambulatory, No Work Activities [units: participants]	0
3 - Partially Confined to Bed, Limited Self Care [units: participants]	0
4 - Completely Disabled [units: participants]	0
Study Specific Characteristic [Race/Ethnicity]	
Caucasian [units: participants]	10
Study Specific Characteristic [Body Mass Index]	
[units: kilograms per square meters] Mean ± Standard Deviation	27.1 ± 4.3
Study Specific Characteristic [Corporal Surface (Body Surface Area)]	
[units: square meters] Mean ± Standard Deviation	1.8 ± 0.2
Study Specific Characteristic [Height]	
[units: meters] Mean ± Standard Deviation	1.6 ± 0.1
Study Specific Characteristic [Weight]	
[units: kilograms] Mean ± Standard Deviation	72.8 ± 12.2

- Efficacy outcome measures:

Primary Outcome Measure: Treatment Response	**Pemetrexed + Cisplatin**
Number of Participants Analyzed	10
Treatment Response: Complete Response [units: participants] Partial Response [units: participants] Incomplete Response/Stable Disease [units: participants] Progressive Disease [units: participants] Not Evaluable [units: participants]	 0 5 4 1 0
Secondary Outcome Measure: Pathologic Remissions After Surgery	
Number of Participants Analyzed	7
Pathologic Remissions After Surgery Complete Remission - Yes [units: participants] Complete Remission - No [units: participants]	 5 2
Secondary Outcome Measure: Relapse-Free Survival	
Number of Participants Analyzed	0
Relapse-Free Survival [units: months] Mean ± Standard Deviation	Results not analized

- Safety:

	Pemetrexed + Cisplatin		
Serious Adverse Events	**number of subjects at risk**	**number of events**	**number of subjects affected**
Total Number of Subjects Affected			1
Infections and infestations Urinary tract infection	 10	 1	 1
Other Adverse Events Reporting Frequency Threshold: 10%			
Total Number of Subjects Affected			8
Blood and lymphatic system disorders Leukocytosis Leukopenia Neutrophilia	 10 10 10	 1 1 1	 1 1 1
Gastrointestinal disorders Abdominal Distension Constipation Diarrhoea Nausea Vomiting	 10 10 10 10 10	 1 1 1 5 2	 1 1 1 4 2
General disorders Fatigue Mucosal inflammation Pyrexia	 10 10 10	 1 1 2	 1 1 1
Infections and infestations Candidiasis Respiratory tract infection	 10 10	 1 1	 1 1

Investigations			
Alanine aminotransferase increased	10	2	2
Aspartate aminotransferase increased	10	2	2
Haemoglobin decreased	10	1	1
Platelet count increased	10	1	1
Metabolism and nutrition disorders			
Diabetes mellitus	10	1	1
Nervous system disorders			
Motor dysfunction	10	1	1
Paraesthesia	10	1	1
Respiratory, thoracic and mediastinal disorders			
Cough	10	3	3
Dysphonia	10	1	1
Productive cough	10	1	1
Rhinorrhoea	10	1	1
Skin and subcutaneous tissue disorders			
Rash	10	2	2
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain	10	1	1

Conclusions:
Trial was stopped early due to low enrollment, because of that the results presented are descriptive, and the relapse-free survival outcome measure was not analyzed.
The pharmacogenomic secondary objective cannot be analized due to the very limited number of samples and their poor quality: only 2 samples were received and the amount and quality of both were very poor.
No publications are planned in the future because of the low unrepresentative number of patients.