2. H3M-XM-S094 Synopsis

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Clinical Study Report Synopsis: Study H3E-XM-S094

Title of Study: Phase I Study of Combination Chemotherapy with Pemetrexed and Cisplatin Concomitant to Radiotherapy Followed by Consolidation Chemotherapy with Pemetrexed in Patients with Inoperable, Locally Advanced Non-Small Cell Lung Cancer

Number of Investigators: This multicenter study included 3 principal investigators.

Study Centers: This study was conducted at 3 study centers in 1 country.

Publication Based on the Study: Cardenal F, Arnaiz MD, Morán T, Jové J, Nadal E, Porta R, et al. Phase I study of concurrent chemoradiation with pemetrexed and cisplatin followed by consolidation pemetrexed for patients with unresectable stage III non-small cell lung cancer. Lung Cancer (2011), doi:10.1016/j.lungcan.2011.01.021.

Length of Study:	**Phase of Development**: Phase I
Date of first patient enrolled: 13 February 2006 Date of last patient completed: 06 August 2010	

Objectives: Primary objective: To determine whether it is possible to administer the combination of pemetrexed and cisplatin at full doses concomitant to standard radical radiotherapy without the dose-limiting toxicity (DLT) exceeding 33% of the patients.

Secondary objectives:

- Evaluation of the tolerance and toxicity of treatment in the form of radiotherapy concomitant to pemetrexed and cisplatin.
- Evaluation of the tolerance and toxicity of consolidation treatment and of complete treatment.
- Evaluation of the response rate obtained following concomitant treatment.
- Evaluation of the time to progression of the disease.
- Evaluation of overall survival.
- Explore the utility of positron emission tomography (PET)/computed axial tomography (CAT) scan with fluorodeoxyglucose (18FDG) in the evaluation of response and in the determination of prognosis.
- Study of the relapse pattern.
- Correlation of the pharmacogenomic determinations to combined treatment response and to prognosis.

Study Design: This was an open-label, phase-I dose escalation feasibility study of concomitant treatment of radiotherapy with pemetrexed plus cisplatin chemotherapy in outpatients with inoperable, locally advanced non-small cell lung cancer (NSCLC) followed by consolidation chemotherapy with pemetrexed. Combination treatment of pemetrexed and cisplatin, concomitant to standard radical chest radiotherapy, was followed by consolidation chemotherapy with pemetrexed (on Day 1, every 21 days). There were 3 cycles for both the concomitant treatment and consolidation chemotherapy stages. For this type of feasibility study, a single arm study without control group and increasing doses of chemotherapy is appropriate.

Number of Patients:

Planned: A maximum of 18 patients (maximal 6 patients per dose level).
Entered: 16 patients
Treated (at least 1 cycle of chemoradiation): 16 patients
Combination treatment completed (3 cycles of chemoradiation): 12 patients
Consolidation treatment completed: 8 patients

Diagnosis and Main Criteria for Inclusion: Patients >18 years of age, with histological or cytological diagnosis of NSCLC with non-resectable stage III disease (except stage IIIB with pleural effusion) and functional class 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG) scale were included in this study..

Study Drug, Dose, and Mode of Administration:
Pemetrexed 500 mg/m^2, given in about 100 mL physiological saline solution as a 10-minute intravenous (i.v.) infusion on Day 1, every cycle of 21 days, for a maximum of 3 cycles.
Cisplatin 60 mg/m^2 for 3 cycles (Dose level 1) as an i.v. infusion (according to usual clinical practice in each center) 30 minutes after the administration of pemetrexed and before radiotherapy on Day 1, and every 21 days. If the maximum tolerated dose (MTD) was not reached, the second dose level was started with 2 cycles of 75 mg/m^2 and a third cycle of 60 mg/m^2 (Dose level 2). Dose level 3, cisplatin 75 mg/m^2 for 3 cycles, was started if MTD was not reached in the Dose level 2.
Radiotherapy (66 Gy) concomitant to chemotherapy was started as soon as possible after diagnosis, following conventional dose fractionation.
Pemetrexed was supplied from package [redacted]

Reference Therapy, Dose, and Mode of Administration: Not applicable

Duration of Treatment:
The planned overall duration of treatment per patient was 9 weeks combination and 9 weeks of consolidation treatment.

Variables:
Efficacy:
- Tumor response rate (including the 95% CI).
- Best response during treatment.
- Time to progressive disease.
- Overall Survival.
- Time to progression-free survival.
- Utility of PET/CAT scan in the evaluation of response and in the determination of prognosis.
- Relapse pattern.

Safety:
- Feasibility rate of combined radiotherapy and chemotherapy treatment and consolidation treatment with pemetrexed.
- Toxicities including dose-limiting toxicities of combination treatment
- Summary of the rate of adverse events (AEs) and changes in laboratory test parameters.
- List and frequency tables with a classification of the AEs (laboratory or otherwise).
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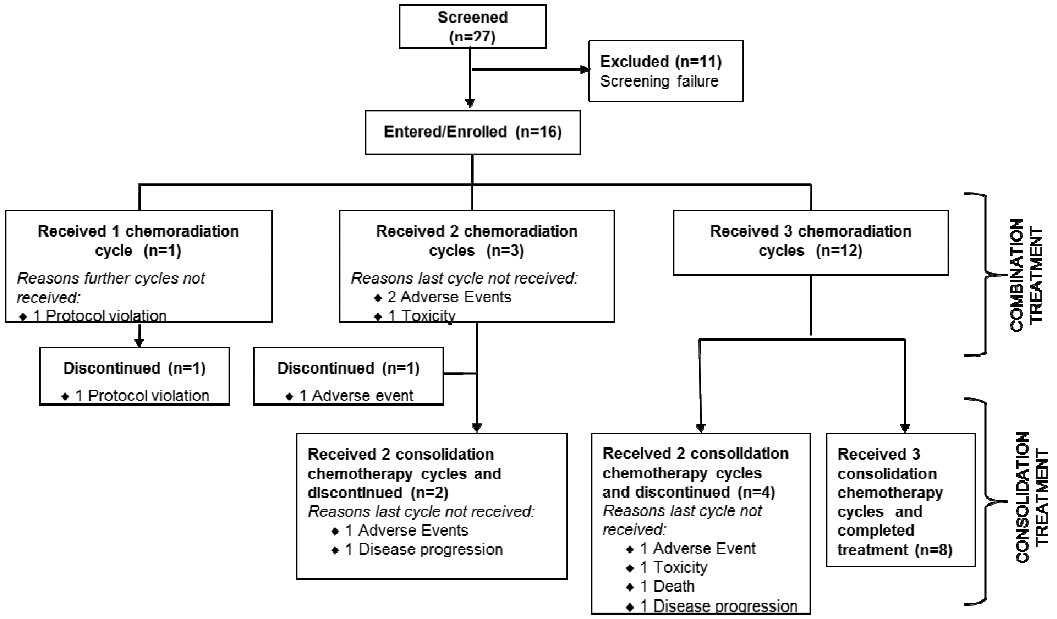
Statistical Evaluation Methods:
Efficacy: The response rate was based on the number of patients with complete response or partial response divided by the number of patients qualified for the efficacy analysis. Kaplan-Meier curves corresponding to time to progression of the disease and overall survival(secondary variables) were plotted to include the quartiles of each variable. All confidence intervals (CIs) for estimated parameters were constructed with a significance level of α=0.05.The results were expressed as the mean, median, and standard deviation (SD) for continuous variables, and as absolute and relative frequencies for qualitative variables.
Safety: The feasibility rate (dose limiting toxicity rate, primary variable) was calculated by dividing the number of patients being able to complete treatment by the number of qualified patients. List and frequency tables with a classification of the AEs (laboratory or otherwise) were created according to maximum toxicity CTC (version 3.0) and their relation to consolidation chemotherapy, as well as the AEs (laboratory or otherwise) according to maximum acute toxicity (RTOG) and their relation to combined treatment.

Summary:

- Of the 27 patients who were screened, 16 (59.3%) entered the study and were assigned to treatment. The study patients were mostly males (12, 75.0%) with a median age of 56.5 years (range 40 to 70 years).

Figure 1: Patient Disposition



- Primary analysis of feasibility: The overall proportion of patients with DLTs for any reason in the study was 12.5%. The combination treatment concomitant to radiotherapy was feasible
- Efficacy outcomes:
    - Response rate (efficacy analysis set):
        - During the combined treatment phase: response rate of 86.7% (partial response in 86.7%, stable disease in 13.3% of patients).
        - During the consolidation phase: response rate of 57.1% (complete response [7.1%], partial response [50.0%], and progressive disease [28.6%] and not done [14.3%]).
        - At the end of treatment (5weeks after completed treatment): 41.7% (partial response [41.7%], progressive disease [33.3%], and not done [25.0%]).
    - Disease progression at the end of the follow up: 60.0%; the 25% level of progression of disease was reached after 5.5 months (95% CI: 4.3 to 18.3 months), and the 50% level of progression of disease after 13.6 months (95% CI: 5.5 to ∞).
    - Death at the end of the follow up: 33.3%; the 25% level of time to death was reached after 17.1 months (95% CI: 4.3 to ∞).
    - Progression free survival at the end of the study follow up: 33.3%; the 25% level of progression or death was reached after 4.4 months (95% CI: 4.0 to 8.8 months), and the 50% level of progression of disease after 8.8 months (95% CI: 5.5 to ∞ months).
    - FDG-PET/CT after consolidation treatment was performed in 12 of 15 patients. According to the investigators clinical assessment criteria, the response by CT scan correlated to PET/CT scan results in all 12 patients.
    - From 15 patients included in the study, progression of the disease was reported in 9. In 6 patients the progression of the disease occurred solely at distant location (outside radiation field), and in 3 at local level (radiation field).

- Safety outcomes: 2 patients (12.5%) died during the study or within 30 days of discontinuation (1 patient due to progression of disease and 1 sudden death) and 3 patients (18.8%) died during in the follow-up period due to disease progression. Serious treatment emergent adverse events (SAEs) were reported for 6 patients (37.5%) with a total number of 12 SAEs. Three patients (18.8%) discontinued treatment due to AEs (serious cholangitis/not related, serious oesophagitis/related, and non-serious ongoing asthenia/related). During the combination phase, 81.3% of patients had at least 1 grade 3/4 toxicity, compared to 14.3% of patients during the consolidation phase. A weight decrease occurred in 3 patients (18.8%) during the course of this study.

Conclusions:

- The study supports that full dose cisplatin and pemetrexed for 3 cycles concurrently with 66 Gy thoracic radiation therapy is feasible for NSCLC patients with unresectable stage III disease and good performance status.
- The concomitant treatment of pemetrexed/cisplatin with radical chemotherapy was feasible at all 3 dose levels (500 mg/m^2 pemetrexed plus 60 mg/m^2, 60/60/75 mg/m^2 and 75 mg/m^2 cisplatin).
- The MTD was not reached in the present study.
- All DLTs were due to Grade 3/4 oesophagitis toxicities.