2. S079 Synopsis

Clinical Study Report Synopsis: Study H3E-IT-S079

Title of Study: Phase II Trial of Neoadjuvant ALIMTA plus Cisplatin followed by Surgery and Radiation in the Treatment of Pleural Mesothelioma	
Number of Investigator(s): This multicenter study included four principal investigators.	
Study Center(s): This study was conducted at four study centers in one country.	
Publication(s) Based on the Study: None at this time.	
Length of Study: Date of first patient enrolled: 15 June 2005 Date of last patient completed: 10 February 2010	**Phase of Development:** II
Objectives: The primary objective of this trial was to determine the event-free survival (EFS) of patients with clinical stage I, II, or III (T1-3 N0-2) pleural mesothelioma treated with pre-operative chemotherapy (ALIMTA plus cisplatin), surgery (EPP) and hemithoracic radiation. The secondary objectives were: to determine the 1- and 2- year disease free survival and median survival, to determine complete pathological response rate, to determine clinical response rate measured by radiological assessment, to characterize the quantitative and qualitative toxicities of chemotherapy, surgery and radiation in this patient population, to determine the pattern of relapse (local versus metastatic), to measure time-to-event efficacy variables including: time to objective tumor response for responding patients, time to progressive disease and overall survival**.**	
Study Design: This is a Phase II, open-label, multi-center study to determine the effectiveness and feasibility of a multi-modality approach to the treatment of malignant pleural stage I to III mesothelioma. Patients were to be treated with ALIMTA plus cisplatin followed by extrapleural pneumonectomy, with post-operative radiation.	
Number of Patients: Planned: 53 Screened: 56 Enrolled: 54 Treated (at least 1 dose): 54 Completed: 22	
Diagnosis and Main Criteria for Inclusion: Patients with clinical stage I, II, or III (T1-3 N0-2) pleural mesothelioma. Main criteria for inclusion were: • Performance status of 0 to 1 on the ECOG performance status schedule. • No prior systemic chemotherapy. • No previous surgical resection of mesothelioma. • No previous radiation therapy. • Estimated life expectancy of at least 12 weeks. • Adequate bone marrow reserve: absolute neutrophil (segmented and bands) count (ANC) $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and hemoglobin ≥ 9 g/dL. • Hepatic: bilirubin ≤ 1.5 times the upper limit of normal ($\times$ ULN), alkaline phosphatase (AP), aspartate transaminase (AST) and alanine transaminase (ALT) $\leq 3.0 \times$ ULN. • Renal: calculated creatinine clearance (CrCl) ≥ 45 mL/min based on the standard Cockroft and Gault formula or on measured glomerular filtration rate (GFR). • Pulmonary function tests: FEV1 >0.8, DLCO >35% of predicted postoperative FEV1 (ppoFEV1) ABG predicted postoperative pCO_2 <50. • Adequate cardiac function test. • Female patients of child-bearing potential must test negative for pregnancy at the time of enrollment based on a serum pregnancy test. Male and female patients must agree to use a reliable method of birth control during and for 3 months following the last dose of study drug.	

- Patients must sign an informed consent document.
- At least 18 years of age.

Study Drug, Dose, and Mode of Administration:
Patients were to be treated with ALIMTA plus cisplatin followed by extrapleural pneumonectomy, with post-operative radiation as follow:

Pre-operative Chemotherapy
ALIMTA: 500 mg/m^2 iv infusion administered on Day 1 of each 21 day cycle.
Cisplatin: 75 mg/m^2 iv infusion administered on Day 1 of each 21 day cycle, after ALIMTA infusion.
Supportive treatnments were:
Folic acid: Oral dose daily beginning approximately 1 to 2 weeks prior to the first dose of ALIMTA, and continuing daily until 3 weeks after the last dose of ALIMTA.
Vitamin B12: 1000 µg intramuscular injection. Approximately 1 to 2 weeks prior to the first dose of ALIMTA, and approximately every 9 weeks until 3 weeks after the last dose of ALIMTA.
Dexamethasone: 4 mg, orally twice per day (or equivalent) should be taken on the day before, the day of, and the day after each dose of ALIMTA/cisplatin, unless clinical contraindications exist.

Surgery: Extrapleural Pneumonectomy
The surgery were performed on all patients unless there was (1) objective evidence of progression of disease or (2) deterioration of functional status occurred. Surgery should occurr at least 3 weeks post last dose of chemotherapy, to a recommended maximum interval of 8 weeks. Before surgery cardio-pulmonary functions were assessed.

Hemi-thoracic Radiation Therapy:
All patients who underwent a complete surgical resection received radiation therapy starting 4 – 8 weeks after EPP. Radiation therapy could be extended to 12 weeks post EPP.
Due to potentially toxicity related deaths the study protocol was amended by reducing the post-surgery radiation dose administered to patients: a total of 54 Gy in 30 fractions of 1.8 Gy per day (for the 21 patients enrolled before the protocol amendment) and a total of 50.4 Gy in 28 fractions of 1.8 Gy per day (for the 33 patients enrolled after the amendment) had to be administered.

Supplied from package lot

ALIMTA	CISPLATIN
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	
COMMERCIAL VIAL	

Duration of Treatment:
A cycle was defined as an interval of 21 days. A cycle comprised of one treatment of ALIMTA plus cisplatin Day 1. A total of 3 cycles were given.

Variables:

Efficacy: Primary end-point of the study was the EFS. Secondary efficacy parameters include: 1- and 2-year progression-free survival (the same as disease-free survival in this study), complete pathological response rate, overall survival (OS) time to objective tumor response (TTR), response rates and time to progressive disease. Local versus metastatic relapse pattern was not assessed because the CRF does not discriminate between local and metastatic recurrence.

Safety: Adverse Events, transfusions, vital signs (pulse rate, SBP, DBP, weight, BSA (m2), ECOG Performance Status), laboratory parameters (hematology and biochemistry), cardiac function tests and pulmonary test.

Statistical Evaluation Methods:

Sample size: assuming a 1-year EFS rate of about 30%, 53 patients had to be enrolled in this study. The sample size was adequate to obtain an expected 95% confidence interval (CI) width around the 1-year EFS rate of about +/- 12%.

Efficacy: Primary end-point of the study was the EFS.

A subject was defined event-free if she/he did not show a progression of disease, did not die as a result of any cause and did not early discontinue the treatment. Subjects without an assessment at 1-year (due to whatever reason) were considered as not-event-free. The 1-year and 2-year progression-free survival rates and the corresponding 95% confidence interval are provided.

Kaplan-Meier curves and confidence interval for 25th, median and 75th percentiles time were estimated for time-to-event variables.

Objective tumor response rate was collected at each visit. The best objective tumor response rate was summarized.

Efficacy analysis was performed on the full analysis set (FAS), defined as all enrolled patients meeting the following criteria:

- Histologic or cytologic diagnosis of malignant pleural mesothelioma.
- No prior or concurrent systemic chemotherapy, immunotherapy, or biological therapy.
- For clinical response, presence of measurable or evaluable disease.
- Treatment with at least one dose of ALIMTA/cisplatin.

For objective tumor response, the analysis set is the set of responding patients, that is patients with CR or PR.

Safety: Safety analysis was performed on Safety Population. All patients who received at least one dose of ALIMTA or cisplatin were evaluated for safety. All TEAEs were assigned to a preferred term (PT) and were classified by system organ class (SOC) according to MedDRA dictionary version 12.1. Tables with TEAEs categorized by SOC and PT were produced for all TEAEs, all TESAEs, related-TEAE, related TESAEs, grade I-IV episodes of TEAEs.

Summary statistics were provided for vital signs at each visit. Changes from baseline to each visit were calculated and summarized.

For each laboratory variable the change from baseline to each visit after baseline was calculated. Summaries for laboratory values at each visit and change from baseline were provided. A shift table showing values classified as lower, normal and upper based on Reference Ranges from baseline to each visit was also produced.

Summary statistics were provided for cardiac and pulmonary tests at each visit.

Summary:

Study population:
Fifty-six patients were screened for this study and fifty-four patients were enrolled in this study. The study population included 54 adult patients with clinical stage I, II, or III (T1-3 N0-2) pleural mesothelioma.

Demographics:
The Full Analysis Population included 7 females (13.0%) and 47 males (87.0%). The mean age was 61.8 ± 8.1 years (median 63, range 39-75). Staging at entry was stage T1 in 13 (24.1%) patients, stage T2 in 12 (22.2%) patients and T3 in 29 (53.7%) patients.

Patient Disposition:
Twenty-two (40.7% of total) patients completed the study, whereas 32 (59.3%) prematurely discontinued. The causes of early discontinuation were: adverse events (1 patient, 1.9%), death (11 patients, 20.4%), lack of efficacy (16 patients, 29.6%), physician decision (1 patient, 1.9%), protocol violation (2 patients, 3.7%) and subject decision (1 patient, 1.9%).
All enrolled subjects (n=54) were included in both the Safety and Full Analysis Population.
Of the 54 enrolled patients, 21 were enrolled before the protocol amendment and 33 after the amendment.

Efficacy:

Event-Free-Survival (EFS)
Overall, the median EFS was 6.9 months (95% CI: 5.0 to 10.5). Median EFS was higher in patients enrolled after the protocol amendent (median=8.1 months; 95% CI: 4.1 to 19.7) than in those enrolled before the amendment (median=6.3 months; 95% CI: 3.3 to 10.5).

One-year and 2-year EFS Rate
Overall, 18 patients (33.3%; 95% CI: 21.1% to 47.5%) were event-free after 1 year and 13 patients (24.1%; 95% CI:13.7% to 36.0%) were event-free after 2 years. The 1-year EFS rate was higher in patients enrolled after the protocol amendment(39.4%; 95% CI: 22.9% to 57.9%) than in those enrolled before the amendment (23.8%; 95% CI: 8.2% to 47.2%). Also, the 2-year EFS rate was higher in patients enrolled after the amendment (30.3%; 95% CI: 15.9% to 46.1%) compared to those enrolled before the amendment (14.3%; 95% CI: 3.6% to 32.1%).

Complete Pathological Response
Pathological response was evaluated at the time of surgery (EPP). Resected tissue or pleural fluid were sent for pathological and histological evaluation. Of the 45 patients that underwent surgery only 13 were evaluated for pathological response, of which 12(22.2% of the full analysis population) had complete pathological response.

Progression-Free Survival (PFS)
Median PFS was 8.6 months (95% CI: 6.3 to 14.4). Median PFS was higher in patients enrolled after the protocol amendment (median=11.9 months; 95% CI: 6.9 to 26.9) than in those enrolled before the amendment (median= 6.6 months; 95% CI: 5.0 to 11.0).

One-year and 2-year PFS rate
The 1-year and 2-year PFS rate is 40.7% (95% CI: 27.7% to 53.4%) and 31.5% (95% CI: 19.7% to 43.9%) respectively. For the 1-year PFS, the rate is higher after the amendment 48.5% (95% CI: 30.8% to 64.1%) when compared to the rate before the amendment (28.6%; 95% CI:11.7% to 48.2%). Similarly, for the 2-year PFS, the rate is higher after the amendment (39.4%; 95% CI: 23.1% to 55.4%) when compared to the rate before the amendment 19.1% (95% CI: 5.9% to 37.7%).

Overall-Survival (OS)
The median OS was 15.5 months (95% CI: 11.0 to NA [the upper limit was not reached]). Median OS was 12.6 months (95% CI: 6.9 to 20.1) for patients enrolled before the protocol amendment while for patients enrolled after the protocol amentdment the median was not reached. The 25th percentile of the overall survival after the amendment was 8.1 months (95% CI: 5.1 to 14.6) and the median OS before the amendment is 6.6 months (95% CI: 6.1 to 11.0).

Time–to-tumor-response (TTR)
The median TTR was 4.8 months (95% CI: 2.5 to .8.0). Median TTR was higher in patients enrolled after the protocol amendent (median = 7.6 months; 95% CI: 4.1 to 8.9) than in those enrolled before the amendment (median=2.8 months; 95% CI: 1.4 to 5.1).

Best Objective-Tumor- Response
Overall, 32 patients (59.3%) showed a complete response (CR), 5 patients (9.3%) a partial response (PR), 12 (22.2%) had stable disease (SD), 3 patients (5.6%) had progression of disease (PD) and for 2 patients (3.7%) tumor response was not assessed.
Response rates according to the protocol amendment were as follow: 13 CR (61.9%) , 2 PR (9.5%), 4 SD (19.0%) and 2 PD (9.5%) for patients enrolled before the amendment and 19 CR (57.6%), 3 PR (9.1%), 8 SD (24.2%), 1 PD (3.0%) and 2 response not assessed (6.1%) for patients enrolled after the amendment.

Time to progressive disease
The median time-to-progression is 14.4 months (95% CI: 9.1 to 26.9). The median time-to-progression is higher in patients enrolled after the amendment (median = 22.5 months; 95% CI: 8.1 to 32.7) compared to the patients before the amendment (median=14.4 months; 95% CI: 5.4 to 25.7).

Safety:

Treatmet Emergent Adverse Events (TEAE)

Overall, 53 patients (98.1%) reported at least one TEAE. Thirty-two (59.3%) patients died. TESAEs were reported in 27 patients (50.0%). Chemotherapy- Related TEAE were reported in 42 patients (77.8%), radiotherapy-related TEAE were reported in 26 patients (48.1%) and both-therapies related TEAE were reported in 4 patients (7.4%). One patient (1.9%) discontinued the study due to a TEAE. Thirty-six patients (66.7%) showed at least one grade III-IV TEAE. Twenty six patients (48.3%) required transfusion.

There were no substantial differences in the summary of adverse events between the subjects enrolled before or after the protocol amendment.

The most commonly involved SOCs were: gastrointestinal disorders (42 patients, 77.8%), general disorders and administration site conditions (30 patients, 55.6%) blood and lymphatic system disorders (29 patients, 53.7%), respiratory, thoracic and mediastinal disorders (29 patients, 53.7%), vascular disorders (26 patients, 48.1%) and cardiac disorders (19 patients, 35.2%).

The most frequently reported TEAEs were: nausea (34 patients, 63.0%), anaemia (28 patients, 51.9%) and hypertension (23 patients, 42.6%).

Cardiac function tests

For stress echocardiogram, all the patients enrolled before or after the amendment had VEF ≥45% both at the baseline and after surgery. For electrocardiogram, 41 patients (83.7%) had normal test results while 8 patients (16.3%) had abnormal results. Stratified results returned that 18 out of 20 patients (90.0%) and 23 out of 29 patients (79.3%) performing electrocardiogram test before or after the amendment respectively, had normal results.

Pulmonary tests

FEV1 test result was >0.8 L at baseline for all patients and for non less than 94% of patients performing the test at following visits. DLCO test result at the baseline was >35% of the predicted postoperative (ppo) FEV1 for all patients. DLCO test performed at following visits generally returned that non less than 85% of patients had DLCO >35% of ppo FEV1. ABG test returned a value <50 either at the baseline or at following visits for all the patients.

Vital Signs

No clinically significant changes from baseline to any post-baseline time point were observed for pulse, SBP, DBP, weight, BSA and ECOG performance status.

Laboratory parameters

The results of hematology showed a general decrease from baseline of mean values of hemoglobin, RBCs count, WBCs count, platelets and neutrophils with no substantial changes from baseline for the other variables.

The results of blood chemistry showed no substantial changes from baseline to visits.

Conclusions:

- The event-free survival of patients with clinical stage I, II, or III (T1-3, N0-2) pleural mesothelioma treated with pre-operative chemotherapy (ALIMTA plus cisplatin), surgery (EPP) and hemithoracic radiation obtained was 6.9 months (95% CI: 5.0 to 10.5). The data demonstrates the feasibility of this trimodality approach. The overall 1-year EFS rate was 33.3% (95% CI: 21.1 to 47.5%) while the 2-year EFS rate was 24.1% (95%CI: 13.7% to 36.0%).
- It is noteworthy that the efficacy parameters were improved once the protocol was amended.
- No relevant differences in the safety data were seen among pre- and post-amendment results.
- The observed results suggested that a reduced post-surgery radiation dose may lead to higher OS and EFS rate as well as improved PFS and TTR. However, this hypothesis should be confirmed by an *ad hoc* designed clinical trial, based on the trimodality approach as defined in the present study.