2. Synopsis

Clinical Study Synopsis: Study H3E-IT-S105

Title of the study: Pemetrexed monochemotherapy in patients with locally advanced or metastatic Non Small Cell Lung Cancer. A pilot study to define the best dosing schedule for a planned phase II randomized trial

Investigators: one principal investigator in Italy

Study centers: one investigational study site in Italy

Publication (reference): Not applicable

Length of study: 23 months Date first patient enrolled: 06 September 2006; Date last patient completed: 15 September 2008	**Phase of development:** II

Objectives:

The primary objective of the trial was to assess which is the proper time interval between Pemetrexed and Gemcitabine administration to optimize the synergism between the two drugs in the treatment of patients with advanced NSCLC. The secondary objectives of this study were to assess tumor response rate (RECIST criteria) and toxicity of the investigational medicinal product.

Study design:

This was a pilot, phase II, open-label trial aimed to define the best time interval between the administration of the first (Pemetrexed) and second (Gemcitabine, not given) drug. Treatment was to be administered until progression of the disease, unacceptable toxicity or patient refusal.

Number of patients (total and in each arm):

Planned: 19; Treated: 19; Completed: 6

Diagnosis and main criteria for inclusion:

- Histologically or citologically proven IIIB and IV NSCLC;
- Absence of symptomatic uncontrolled brain metastasis;
- Not suitable for platinum containing regimens if chemo-naïve or pre-treated with regimens not containing Gemcitabine or Pemetrexed;
- Age ≥ 18 years;
- Performance status ≤ 2 on the ECOG Scale;
- A life expectancy of at least 12 weeks;
- Adequate bone marrow: platelets ≥ 100 000 cells/L, ANC ≥ 1.5 x 10^9 cells/L, Hb ≥ 9 g/dL;
- Hepatic: total bilirubin ≤ 1.5 times the upper limit of normal (x ULN), alkaline phosphatase (AP), aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3 x ULN (AP, AST, and ALT ≤ 5 x ULN is acceptable if liver has tumor involvement);
- Renal: calculated creatinine clearance (CrCl) ≥ 45 mL/min based on the standard Cockroft and Gault formula or on measured glomerular filtration rate (GFR);
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule;
- Patients had to sign an Informed Consent Document.

Test product, dose and mode of administration, batch no:

The therapeutic regimen of this study was a monochemotherapy with Pemetrexed.

The dosing schema for Pemetrexed and supportive treatments was as follows:

- Pemetrexed 500 mg/m^2 in 10-minute IV infusion was administered on day 1 every 14 days in the first 12 patients, and on day 1 every 21 days in the other 7 patients;
- Folic Acid: 450 µg orally per day was recommended beginning 1-2 weeks prior to first dose of Pemetrexed and continuing while the patient remained on study;
- Vitamin B12: 1000 µg IM prior to the first dose of Pemetrexed and repeated every 9 weeks while the patient remained on study;
- Dexamethasone 4 mg or equivalent corticosteroid taken orally twice per day on the day before, the day of, and the day after each dose of Pemetrexed to prevent rash;

Dose and schedule modifications were planned according to standard algorhythms.

Used batches of Pemetrexed are detailed in Appendix 16.1.6.

Duration of treatment: Treatment should have been administered until documented disease progression, unacceptable toxicity, or patient refusal for a maximum of 6 cycles (18 weeks). A cycle was defined as the administration of the drug every three weeks.

Reference therapy, dose and mode of administration, batch no: Not applicable.

Variables:

Efficacy:

Primary variables: dCK and hENT expression on normal lymphocytes in cycle 1, cycle 2 and cycle 3 at various intervals (1, 2, 4, 6, 24 and 48 hours; 8 days optional) after Pemetrexed administration.

Secondary variables: Tumor response (RECIST criteria): objective tumor response, duration of overall response, duration of stable disease, time to progression.

Safety: adverse events and adverse drug reactions, vital signs (weight, BSA, SBP, DBP, heart rate, temperature and ECOG Performance Status) and laboratory parameters (hematology, serum chemistry and urinary creatinine clearance).

Evaluation Methods:

Statistical:

Summary statistics was calculated for original values of dCK and hENT, for the relative differences from baseline to each planned time, for the peak-values and for the relative-difference-at-peak, by cycle. The 95% CI for the mean peak value and for the relative difference at mean peak was calculated, respectively for cycle 1, cycle 2 and cycle 3. A frequency table showing the distribution of time-to-peak was produced, by cycle. The 95% CI was also calculated for each category, respectively for cycle 1, cycle 2 and cycle 3. Furthermore, a multivariate repeated-measures analysis of variance on dcK and hENT values (original values and relative differences) was performed using two-repeated within-subjects factors: cycle and time. The following effects were tested: the within-subjects main effect of cycle, the within subjects main effect of time and the within-subjects interaction effect of cycle*time.

Explorative analyses were performed in order to investigate the relationship between dCK/hENT values (baseline pre-dose values and peak values within each cycle) and the following variables: demographic characteristics, drugs administered, tumor response and safety variables (vital signs and laboratory parameters). Relationship between dcK/hENT values and continuous variables was assessed using a linear regression analysis, performed separately for each cycle. Relationship between dcK/hENT values and categorical variables was assessed using the Kruskal-Wallis non-parametric one-way ANOVA, separately for each cycle.

Descriptive statistics was provided for objective tumor response, duration of overall response and duration of stable disease. Moreover, time to progression was evaluated. The response rate and its 95% CI was provided. Kaplan-Meier curves and CI for median time was estimated for the duration of stable disease and for time to progression.

All adverse events were assigned to a preferred term (PT) and were classified by system organ class (SOC) according to the MedDRA dictionary. Tables with AEs categorized by SOC and PT were also produced for all AEs, drug-related AEs, AEs leading to dose modification or treatment discontinuation, SAEs, grade I to grade IV AEs, episode of AE.

Summary statistics was provided for weight, BSA, SBP, DBP, heart rate, temperature and ECOG Performance Status at each visit. Changes from baseline to each visit were calculated.

For each laboratory variable, the change from baseline to each visit after baseline was calculated. A shift table showing values classified as lower, normal and upper based on reference ranges from baseline to each visit was also produced.

Summary:

Study population:

The study population included 19 adult patients with histologically or citologically proven IIIB and IV NSCLC.

Demographics:

The ITT population included 11 males (57.9% of total) and 8 females (42.1%). The mean age was 69.2 ± 8.90 years (median 69, range 51-83). Staging at study entry was stage IIIB in 4 (21.1%) patients (all treated with the 2-weekly regimen) and stage IV in the other 15 (78.9%).

Patient disposition:

Six (31.6% of total) subjects completed the study, whereas 13 (68.4%) were prematurely discontinued. Adverse events (7 patients, 36.8%) and disease progression (4 patients, 21.1%) were the most common causes of early withdrawal.

Of the 19 enrolled patients, 12 used the 2-weekly regimen and 7 used the 3-weekly regimen of Pemetrexed (i.e. were enrolled before and after the amendment).

Efficacy :

dCK and hENT expression:

A marked and statistically significant ($p<0.001$) increase from pre-dose in mean values of dCK expression was observed after 1, 2, 24 and 48 hours (irrespective of the cycle), compared to a smaller but significant increase after 4 hours ($p = 0.030$) and no substantial changes after 6 hours post-dose. Similarly to dCK, a marked and statistically significant ($p<0.001$) increase from pre-dose in mean values of hENT expression was observed after 1, 2, 24 and 48 hours (irrespective of the cycle), compared to no substantial changes in values after 4 and 6 hours post-dose.

There were no substantial differences in changes from pre-dose of dCK and hENT expression measured in any cycle between the two used dose regimens.

Most of patient reached the dCK peak after 1 and 2 hours post-dose at any cycle (13/19 patients in cycle 1, 11/17 in cycle 2 and 11/15 in cycle 3), while there were no substantial differences between the examined time points in the time of hENT peak (apart from cycle 3, when 7/15 patients peaked at 24 hours post-dose). The results in the PP population were consistent with those observed in the ITT analysis.

Explorative analyses:

A statistically significant effect was observed in relation with weight, hemoglobin and RBCs count for baseline or peak dCK or hENT, which varied across cycles, whereas there were no substantial correlations with the other investigated parameters (demographic characteristics, drugs administered, vital signs and laboratory parameters). Similarly, there were no significant effects of tumor progression and type of tumor (squamous or non-squamous) on dCK or hENT expression, apart from a statistically significant effect observed at cycle 3 for baseline values of dCK in relation with histological type of tumor.

Tumor response:

The results of best tumor response showed that 1 patient (5.3%) had a partial response, 6 (31.6%) had stable disease, 3 (15.8%) had tumor progression, 1 (5.3%) died prematurely and in 8 (42.1%) the stable disease was not confirmed. Overall, 12 (63.1%; 95% CI: 41.5 to 84.8) patients were not responder and 7 (36.8%; 95% CI: 15.2 to 58.5) were responder. The rate of responders was higher in patients treated with a 3-weekly regimen (57.1%) than in those treated with the 2-weekly regimen (25.0%). The mean (± SE) duration of stable disease (N = 6) was 139.5 ± 18.9 days. The mean (± SE) time to progression (N = 7 patents censored) was 143.5 ± 18.4 days.

Safety :

Adverse events:

All 19 patients (100%) reported at least one AE. Four patients (21.1%) died. SAEs were reported in 5 patients (26.3%). Drug-related AEs (i.e. those AEs that were considered as having a remote, possible, probable, unknown or missing correlation with the study drug) were reported in 18 patients (94.7%). Sixteen patients (84.2%) modified the dose or prematurely terminated the treatment due to AEs. There were no substantial differences in the summary of adverse events between the two used dose regimens.

The most frequently reported drug-related AEs were pyrexia (12 patients, 63.2%), asthenia (9, 47.4%), mucosal inflammation (8, 42.1%), conjunctivitis (6, 31.6%) and dyspnea (6, 31.6%). General disorders and administration site conditions (17 patients, 89.5%) and gastrointestinal disorders (13 patients (68.4%) were the most commonly involved SOCs.

The fatal events and the other non-fatal SAEs were related with tumor progression and worsening of general conditions.

Vital signs:

No statistically or clinically significant changes from baseline to any post-baseline time point were observed for body weight, BSA, blood pressure, heart rate and body temperature.

Laboratory parameters:

The results of hematology showed statistically significant decreases from baseline of mean values of hemoglobin, hematocrit, RBCs count, eosinophils, basophils and lymphocytes, and a general increase of platelets' count, while no substantial changes from baseline were observed for the other variables. The results of hematology expressed with reference to the range of normal values showed that some patients had a decrease during the study of normal baseline values below the lower limit of the normal range for hemoglobin, hematocrit, RBCs count and lymphocytes, and an elevation of normal baseline values above the upper limit of the normal range for neutrophils, while the values of the other variables were generally within the normal range at baseline and at any post-baseline time point.

The results of blood chemistry showed statistically significant decreases from baseline of mean values of total bilirubin, albumin and creatinine clearance, and a general increase of AST, ALT, gamma-GT and LDH, while no substantial changes from baseline were observed for the other variables. The results of blood chemistry expressed with reference to the range of normal values showed that some patients had an elevation of normal baseline values above the upper limit of the normal range for AST, ALT, gamma-GT, LDH and (in a lesser extent) for creatinine clearance and AP, while the values of the other variables were generally within the normal range at baseline and at any post-baseline time point.

ECOG Performance Status:

Most of patients had a grade 1 ECOG PS at any time point. At end of study, 1 patient (5.3%) had grade 0, 7 (36.8%) had grade 1, 7 (36.8%) had grade 2, 3 (15.8%) had grade 3, and the grade was not known in 1 patient (5.3%).

Conclusions:

- dCK and hENT expression induced by Pemetrexed were maximized after 1, 2, 24 and 48 hours post-dose (irrespective of the cycle), compared to little or no effects after 6 and 8 hours. There were no substantial differences in changes from pre-dose measured in any cycle between patients using a 3-weekly or a 2-weekly regimen.

- Some degree of significant correlation was found for baseline or peak dCK or hENT values with relation to weight, hemoglobin and RBCs count.
- Seven patients (36.8%) responded to treatment: the rate of responders was higher in patients treated with a 3-weekly regimen than in those treated every two weeks.
- The results of safety were in line with the expected hematological and non-hematological toxicity profile of Pemetrexed supplemented with dexamethasone/prednisone, folic acid and vitamin B12.