2. S095 Synopsis

Clinical Study Report Synopsis: Study H3E-MC-S095

Title of Study: Phase II Study of Concurrent Carboplatin, Pemetrexed, and Radiotherapy for Limited Stage Small Cell Lung Cancer	
Number of Investigator(s): This multicenter study included 2 principal investigators.	
Study Center(s): This study was conducted at 2 study centers in 2 countries.	
Publication Based on the Study: None at this time.	
Length of Study: Date of first patient enrolled: 20 Sep 2007 Date of last patient enrolled: 28 Dec 2007 (early study termination) Date of data collection cut-off: 20 Dec 2008	**Phase of Development:** II
Objectives: The primary objective was to estimate the overall response rate after treatment with pemetrexed + carboplatin and concurrent radiation in patients with limted-stage small cell lung cancer (LS-SCLC). Secondary objectives included progression free survival (PFS), 1-year overall survival (OS), duration of response, complete response (CR) rate, safety and acute and late toxicities.	
Study Design: This was an open-label, single-arm, phase II study of pemetrexed and carboplatin combined with thoracic radiotherapy in patients with LS-SCLC. Patients were to receive four 3-weekly treatment cycles and followed up until progression or latest 15 months after last patient received study therapy. The study was stopped early based on interim results of the GALES trial in December 2007, showing inferior activity of pemetrexed /carboplatin compared to etoposide/carboplatin in extensive SCLC.	
Number of Patients: Planned: up to 47 Treated (at least 1 dose): 4 Completed: 2	
Diagnosis and Main Criteria for Inclusion: This study included males and females at least 18 years of age with histological and/or cytological diagnosis of LS-SCLC, without cytological proven malignant pleural effusion, and confined to one hemithorax. Patients were required to have at least one unidimensionally measurable lesion meeting Response Evaluation Criteria in Solid Tumors (RECIST) criteria, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1, adequate organ function and an estimated life expectancy of at least 12 weeks. No prior chemo- or thoracic radiotherapy was allowed, and no concurrent administration of any other antitumor therapy.	
Study Drug, Dose, and Mode of Administration: Pemetrexed 500 mg/m^2 and carboplatin (target AUC 5) intravenous infusion combined with radiotherapy (50 Gy cumulative dose). Patients were administered folic acid, vitamin B_{12} supplementation, and dexamethasone prophylaxis according to the pemetrexed label during the study. Package lot CT numbers: [redacted]	
Reference Therapy/Comparator, Dose, and Mode of Administration: None	

Duration of Treatment:
All patients first received 2 cycles of induction treatment with pemetrexed 500 mg/m^2 and carboplatin (target AUC 5 IV infusion) (Cycles 1 and 2), on day 1 of each 21-day cycle.
At the end of Cycle 2 patients received 2 additional cycles of combination chemotherapy with concurrent radiotherapy (Cycles 3 and 4), if the following criteria were met: (a) a complete or partial response or stabilization, (b) performance status <2, (c) no residual toxicity ≥2 according the NCI CTCAE scoring, (d) study drug administered at full dose during induction chemotherapy, (e) minimal risk for radiation pneumonitis as defined by a V_{20} of <36% and able to drain third space fluids.
Radiotherapy was administered after chemotherapy, starting on day 1 of cycle 3 (2 Gy per fraction, 5 fractions/week) and continuing for 5 weeks or until a cumulative dose of 50 Gy was reached.

Variables:
Efficacy: Tumor response was measured according to RECIST guidelines version 1.0. The primary efficacy endpoint was overall response rate. Secondary measures were duration of response, PFS, 1-year OS, complete response rate.
Safety: Safety measures were adverse event according to CTC (NCI, version 3.0), acute and late radiation morbidity scoring criteria (RTOG) for acute and late toxicities, lung function, ECG.

Statistical or Other Evaluation Methods:
Efficacy & Safety:
As only 4 patients were enrolled in the study, only a basic evaluation of safety and efficacy has been conducted. Summary statistics were replaced by listings and no statistical analysis performed.

Summary:

Patient disposition and demographics
A total of 4 patients were entered into the study. All caucasian, male, with ECOG performance status 1. Age between 51 to 70 years.

Patient exposure
All 4 patients received at least one cycle of induction chemotherapy. Two patients completed treatment (2 induction cycles and 2 cycles with concurrent radiotherapy). Two patients received one treatment cycle and had to discontinue the study due to sponsor decision (early study termination).

There were no dose adjustments for pemetrexed or carboplatin. Both radiotherapy treated patients received the total dose of 50 Gy.

Primary efficacy endpoint
The study was stopped too early to assess the primary endpoint. The best overall response was 1 PR and 1 SD, the other 2 patients were not evaluable.

Safety
The related grade 3/4 treatment emergent adverse events are shown in Table 1.

Table 1: Treatment emergent CTC grade 3/4 toxicities possibly related to study therapy and/or procedure

CTCAE grade 3*, n(%)	**N=4**
Patients with at least one related TEAE with CTC grade ≥ 3	*2 (50%)*
Neutropenia	2 (50%)
Platelet count decreased	1 (25%)

* there were no grade 4 CTCAEs reported

There were no serious adverse events reported.
There were 2 deaths due to study disease that occurred more than 90 days after start of radiotherapy.

One of the 2 radiotherapy treated patients experienced acute toxicity of RTOG grade 1-3 (mild, moderate, severe). The grade 3 toxicities were neutropenia in cycle 3, and decreased hematologic WBC, platelets, hemoglobin and hematocrit count in cycle 4. There were no late RTOG toxicities.

Conclusions:

- This study was stopped early based on interim results of the GALES trial in December 2007, showing inferior activity of pemetrexed /carboplatin compared with etoposide/carboplatin in extensive SCLC.
- The study was stopped too early to conclude on primary or secondary outcomes.
- The limited observation of adverse events does not raise any safety concerns.