A Phase II, Double-blind, Placebo-controlled, Randomised Study to Assess the Efficacy and Safety of ZD4054 in Combination with Pemetrexed (Alimta®) vs Pemetrexed Alone in Patients with Non-small Cell Lung Cancer who Have Failed One Prior Platinum-based Chemotherapy Regimen

Study dates: First patient enrolled: 12 August 2008
Last patient last visit*: 28 January 2010
Data cut-off date used for analysis of overall survival: 17 January 2010
*Study is ongoing, last patient last visit date given for data reported in this Clinical Study Report

Phase of development: Therapeutic exploratory (II)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centres

The study was conducted at 14 investigational centres in Bulgaria (3 sites), the Czech Republic (2 sites), France (2 sites), Romania (3 sites), and Ukraine (4 sites).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1   Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
To demonstrate an improvement in survival for the combination of zibotentan plus pemetrexed compared to pemetrexed alone in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) without predominantly squamous histology after failure of first line anti-cancer therapy.	Time to death
Secondary	**Secondary**
The efficacy of zibotentan in combination with pemetrexed versus pemetrexed alone for the treatment of patients with NSCLC who have failed first line cancer therapy by the assessment of disease progression. Progression was defined as any of the following: – Objective disease progression measured using Response Evaluation Criteria In Solid Tumours (RECIST) and/or clinical progression on or before the Mandatory Tumour Assessment Visit (MTAV; 19 August 2009 ± 3 days). – Death from any cause	Disease progression
The safety and tolerability of zibotentan in combination with pemetrexed for the treatment of NSCLC by review of adverse events (AEs) and laboratory parameters.	AEs and laboratory parameters.

Additional exploratory objectives of the study are described in the Clinical Study Report; however the results will be reported separately.

Study design

This was a double-blind, placebo-controlled, 2-arm, parallel group, 1:1 randomised study. Following baseline assessments, a total of 66 patients with advanced NSCLC with non-squamous histology were randomised in a 1:1 ratio to receive either zibotentan 10 mg once daily in combination with pemetrexed 500 mg/m^2 or pemetrexed 500 mg/m^2 with placebo to match zibotentan.

Target subject population and sample size

Male or female patients, aged 18 years or older, with histologically or cytologically confirmed locally advanced or metastatic NSCLC on entry into study, where the histology was not predominantly of squamous type were included in this study. Patients also needed to require

treatment that met 1 of the following criteria: a) had progressed following 1 prior platinum-based chemotherapy regimen for locally advanced or metastatic disease, or b) had progressed within 6 months of adjuvant platinum-based chemotherapy.

A total of 64 patients were planned to be entered (32 in each treatment group); 66 patients were randomized and were analysed for efficacy and safety (zibotentan: 30 patients; placebo: 36 patients).

Sample size calculation was based on the following: A study with at least 80% power to detect a true hazard ratio (HR) of 0.50 at the 2-sided 20% significance level would require approximately 38 death events. Assuming a median survival of 8 months for pemetrexed (Hanna et al 2004), recruitment of 64 patients in 9 months would be expected to yield approximately 38 death events after approximately 12 months following randomisation of the last patient. Time to death and safety variables were analysed when this target number of deaths was reached.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Patients were randomised to receive either pemetrexed 500 mg/m^2 with zibotentan 10 mg, or pemetrexed 500 mg/m^2 with placebo matching zibotentan. Zibotentan and matching placebo, both manufactured by AstraZeneca were given orally once daily. Pemetrexed was given by intravenous infusion over 10 minutes every 21 days according to the manufacturer's guidelines.

The batch numbers for zibotentan were 2000112246/52640B07, 2000112295/52642G07, 2000115453/60623H08, 2000115455/60662F08, 2000115457/60667B08, 2000117043/61727F08, and 2000117047/61730A08.

The batch numbers for placebo were 2000112786/52954D07, 2000115388/60604B08, and 2000116199/61023I08.

Duration of treatment

Patients could receive study medication until the data cut-off (DCO) for survival, estimated to be 12 months after the last patient was randomised. Patients who were still receiving study treatment after the closure of the database could continue to do so if, they had not progressed and, in the opinion of the investigator, were continuing to receive benefit from treatment

Statistical methods

The primary objective of assessing efficacy of zibotentan in combination with pemetrexed versus pemetrexed alone for the treatment of patients with NSCLC was achieved by comparing time to death (TTD) between treatment groups. Time to death was calculated from the date of randomisation to date of patient death from any cause. Patients who had not died at the time of the DCO were censored at the last date the patient was known to be alive. The analysis for survival was performed using a Cox proportional hazards regression model on an ITT basis, with the EXACT method to control for ties. The model allowed for the effect of

treatment. The estimated HR was reported together with appropriate confidence interval (CI) and p-value.

The number of patients with progression events occurring on or before the intermediate mandatory tumour assessment visit (MTAV) was compared between the treatment groups using a logistic regression model with a complementary log-log function and including a factor for treatment group. An additional analysis taking account of the timing of a progression event was performed in support of the progression event count analysis.

Analyses were performed on an ITT basis using the ITT analysis set; the ITT set was also used for safety analyses.

There were no formal statistical analyses for safety and tolerability. The treatment groups were compared descriptively using summary statistics and percentage counts.

Subject population

A total of 66 patients were randomized; 30 patients to the zibotentan group and 36 patients to placebo. All randomized patients received at least one dose of study medication. A total of 26 patients (86.7%) in the zibotentan group and 32 patients (88.9%) in the placebo group discontinued the study prior to the DCO. As of the date of DCO (17 January 2010), there were 8 patients who continued on study therapy as they were deriving clinical benefit as judged by the investigator.

Imbalances between treatment groups in demographic, key characteristics, and disease characteristics included: sex, smoking status, time since diagnosis of advanced disease, and number and location of distant metastatic sites. These imbalances between treatment groups were not considered to impact the results of the study.

Summary of efficacy results

- At the DCO, a total of 44 deaths had occurred, 20 (66.7%) in the zibotentan group and 24 (66.7%) in the placebo group. There was no evidence of a difference between treatment groups in TTD (HR = 1.13; 80% CI: 0.77 to 1.67; p-value = 0.69).

- There was no evidence of a difference between treatment groups in the percentage of patients with a disease progression event (defined as objective disease progression, clinical disease progression, or death) on or before the MTAV. The HR was 0.78 (80% CI: 0.52 to 1.18; p-value = 0.44). An additional sensitivity analysis assumed that the 5 patients without an MTAV in the zibotentan group had progressed and the 2 patients in the placebo group without an MTAV had not progressed; the HR was 1.26 showing that the primary analysis was potentially biased in favour of the zibotentan group.

Summary of safety results

- The mean duration of exposure to IP was similar for the 30 patients in the zibotentan group (135.5 days) and the 36 patients in the placebo group (138.5days); the mean duration of exposure to pemetrexed was also similar between the zibotentan and placebo group (134.6 days and 136.5 days, respectively).

- The majority of patients reported at least 1 AE in both treatment groups (zibotentan: 76.7%; placebo: 69.4%). The most frequently reported AEs in both treatment groups was anaemia, followed by nausea and peripheral oedema in the zibotentan group. As expected based on the pharmacology of zibotentan, a higher incidence of nausea, peripheral oedema, and headache were observed in the zibotentan group compared with the placebo group. Other preferred terms not previously observed in clinical studies with zibotentan with a higher incidence in the zibotentan group compared with placebo included increased brain natriuretic peptide and rash. Neither of these preferred terms was associated with withdrawal of study treatment. In 2 patients for each of the events of increased brain natriuretic peptide and rash, the events were considered causally related to zibotentan by the investigator.

- A higher percentage of patients in the zibotentan group had a causally-related AE, as assessed by the investigator (26.7%) compared with the placebo group (8.3%). Only 1 patient had a causally-related AE that led to permanent withdrawal of zibotentan (headache).

- A lower percentage of patients in the zibotentan group had an SAE during the study (4 patients, 13.3%) compared with placebo (7 patients, 19.4%); none of the SAEs were considered causally-related to IP. A total of 4 patients, 2 in each treatment group, had an SAE that led to death (zibotentan group: pancytopenia, dyspnoea; placebo group: febrile bone marrow aplasia, upper gastrointestinal haemorrhage).

- The majority of AEs were CTCAE Grade 1 or 2. A lower percentage of patients in the zibotentan group had an AE with CTCAE Grade 3 or higher during the study (8 patients, 26.7%) compared with placebo (12 patients, 33.3%).

- As expected in this patient population, there was some reduction in haemoglobin and neutrophil/white cell counts consistent with commencement of chemotherapy together with a number of variations in clinical chemistry values outside the normal range, but no apparent meaningful differences between treatment groups were noted.