Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Date of study report:	21 NOV 2008
Study title:	Phase-II study to investigate the efficacy and safety of ZK 219477 as first-line therapy in chemotherapy naive patients with extensive disease (ED) stage small-cell lung cancer (SCLC)
Sponsor's study number:	91375
NCT number:	NCT00299390
EudraCT number:	2005-000597-53
Sponsor:	Bayer HealthCare
Clinical phase:	Phase II
Study objectives:	Primary objective: To investigate the efficacy of ZK 219477 in chemotherapy naive subjects with ED SCLC (proof of concept) Secondary objective: To investigate the safety and tolerability of the above treatment
Test drug:	Sagopilone (BAY 86-5302, ZK 219477)
Name of active ingredient(s):	Sagopilone
Dose:	16 mg/m^2 (maximum 32 mg)
Route of administration:	3-h intravenous (i.v.) infusion
Duration of treatment:	One infusion every 3 weeks; up to six infusions
Reference drug:	Not applicable
Indication:	SCLC
Diagnosis and main criteria for inclusion:	• Histologically or cytologically proven SCLC in subjects aged 18 years and above • Stage of extensive disease defined by the presence of distant metastases • At least one unidimensionally measureable lesion • World Health Organization (WHO) performance status 0-1 • No previous SCLC-related chemotherapy • No previous SCLC-related surgery • No previous radiotherapy (excepting for brain metastasis) • Adequate function of major organs and systems ▪ Nervous system ✓ No grade 2 or greater peripheral neuropathy

	▪ Cardiovascular ✓ No symptomatic congestive heart failure ✓ No unstable angina pectoris ✓ No arrhythmia needing continuous treatment ▪ No other uncontrolled concurrent illness
Study design:	Prospective, single-arm, open-label, multicenter, phase II proof of concept study
Methodology:	Subjects were scheduled to receive one infusion of ZK 219477 every 3 weeks; each infusion corresponded to one treatment course. Subjects were to receive a minimum of two and a maximum of six courses of treatment. In case of sustained clinical benefit, the treatment could have been continued after mutual consultation between the investigator and sponsor. The study was divided into six treatment courses. The conduct of each course was similar, with three visits scheduled per course. Each infusion was to start 3 weeks after the preceding infusion. If deemed necessary (e.g., due to toxicity), an infusion was allowed to be postponed for up to 2 weeks; for each subject, only one such postponement was allowed during the whole study. Tumor response was assessed radiographically after every two courses by computed tomography (CT) scan and/or magnetic resonance imaging (MRI) as clinically appropriate. Evaluations were based on a modified version of the Response Evaluation Criteria in Solid Tumors (modRECIST; the modification includes the addition of "unknown" as an additional response category). WHO performance status was determined starting from screening, first day of each course, and at the end of the study (EOS; 3-4 weeks after last study drug administration). Follow-up visit was conducted 3 months after EOS in all subjects with toxicities of common toxicity criteria (CTC) grade ≥2. Safety and tolerability were monitored throughout the study.
Study center(s):	The study was conducted at four centers in Germany
Publication(s) based on the study (references):	None at the time of report creation
Study period:	**Study Start Date:** 24 APR 2006 **Study Completion Date:** 17 APR 2007
Early termination:	The primary objective of the study was to demonstrate the efficacy of ZK 219477 by showing that the response rate based on the "best overall response" according to modRECIST criteria was significantly higher than 35% using Simon's two-stage statistical design. To proceed to the second stage, it was necessary to demonstrate that at least 5 of the first 12 subjects

	included in the study showed response to the treatment. Since only 1 of the first 10 subjects responded to the study treatment, it was decided to stop the trial due to lack of efficacy.
Number of subjects:	**Planned:** 32 subjects **Analyzed:** 10 subjects
Criteria for evaluation	
Efficacy:	Primary endpoint: Response to treatment according to the modRECIST (complete response [CR] or partial response [PR]) Secondary efficacy variables • Time to progression: Time from the start of study treatment to the first objective evidence of tumor progression, symptomatic deterioration, or death from cancer • Response duration: Time between the first date that confirmed CR or PR was established as "overall response" and the first date that recurrence or overall response of progressive disease (PD) was documented
Safety:	Adverse event (AE) assessment based on the Common Toxicity Criteria for Adverse Events (CTCAE), Scottish Gynecological Cancer Trials Group (SGCTG) neurotoxicity score, standard laboratory measurements, vital signs, and electrocardiogram (ECG)
Statistical methods:	Simon's two-step (optimal) design was used. This design ensured the specified error probabilities (alpha, beta) and minimized the average sample size in case of poor response probabilities. Step 1: Twelve evaluable subjects (i.e., results other than unknown for "best overall response"). Step 2: If the results for the first 12 evaluable subjects met the predefined criterion (i.e., $\geq$ 5 responders), recruitment would continue until a total of 32 evaluable subjects were available. Time-to-event parameters (i.e., time-to-progression of disease and response duration) were to be analyzed using the Kaplan-Meier product limit method. Tumor response rates were to be summarized at each evaluation time point. Toxicities were assessed using CTCAE (Version 3.0). Safety variables were summarized by means of descriptive statistics and/or frequency tables as appropriate.
Substantial protocol changes:	The study was conducted according to final study protocol from 28 NOV 2005.

Subject disposition and baseline

Altogether 11 subjects were screened. One subject discontinued during the screening period due to hepatitis C infection and 10 subjects were allocated to treatment.

These 10 Caucasian subjects consisted of eight males and two females with a mean age of 65.4 years. All the subjects had a history of smoking with a mean pack-year history of 43.2. Nine of the 10 subjects had extensive disease and one subject had no distant metastases (only pleural effusion). Eight subjects had stage T4 SCLC (per Tumor classification system [T=primary tumor, M=distant metastases, N=regional lymph nodes]) and two subjects had stage T2 disease; one subject had nodule stage N1, four subjects had nodule stage N2, and five subjects had nodule stage N3. Overall six subjects had pulmonary and five subjects had hepatic metastases. One subject in the category "other" had involvement of the cervical lymph nodes.

Altogether seven subjects completed the study treatment and three subjects prematurely discontinued; two subjects discontinued due to AEs (one subject due to polyneuropathy and another subject due to pneumonia), and one subject due to other reasons (due to a decision of the investigator since the subject had stable disease after cycle 1). One subject entered the follow-up period.

Five subjects were found to have had abnormal bone scan findings at screening. These included one subject with multiple metastases of the spine, pelvis, and chest; one subject with metastases of the right dorsal rib; one subject with a suspicion of bone metastases of the thorax and thoracic spine; one subject with bone metastases of the cranium. Eight of the 10 subjects in the study had abnormal findings in their medical and surgical history. All subjects reported taking concomitant medication at the screening visit

The most common baseline findings (those experienced by at least three subjects for any given SOC) included respiratory, thoracic, and mediastinal disorders (10 subjects), general disorders and administration site conditions (five subjects), infections and infestations (three subjects), investigations (three subjects with weight decreased), metabolism and nutrition disorders (three subjects), vascular disorders (three subjects). Most of the baseline findings were of CTC grade 1 or 2 intensity and were ongoing before the start of the study treatment.

Efficacy evaluation

No efficacy analysis was performed (due to early termination of the study because of lack of efficacy).

Safety evaluation

Extent of exposure

Half of the subjects (five subjects) received one course of treatment, four subjects received two courses, and one subject received five courses of treatment.

AEs

More than half of the subjects (six subjects or 60%) had musculoskeletal and connective tissue disorders and nervous system disorders, while five subjects (50%) reported gastrointestinal disorders; four subjects (40%) had general disorders and administration site conditions. Metabolism and nutrition disorders and respiratory, thoracic and mediastinal disorders were reported for three subjects (30%) each, infections and infestations and skin and subcutaneous tissue disorders were reported for two subjects each (20%).

Seven subjects had at least one AE that was considered to be treatment related. The most frequently reported treatment-related AEs reported for three subjects each included nausea, myalgia, peripheral sensory neuropathy, and polyneuropathy (altogether six subjects with neuropathy).

Altogether six subjects in the study had at least one AE that was of CTC grade 1 or 2 intensity, three subjects had at least one AE that was CTC grade 3, and one subject had at least one CTC grade 4 AE. The CTC grade 4 AE involved pneumonia (one subject who did not recover, no study drug relationship). CTC grade 3 AEs included pneumonia (one subject; recovered, no study drug relationship), nausea (one subject; did not recover, study drug related), general physical health deterioration (one subject died, no study drug relationship), anorexia (one subject; did not recover, study drug related), and loss of consciousness (one subject; subject recovered, study drug related).

Overall, seven subjects had at least one study drug related AE. The most frequently reported study drug related AEs involved nervous system disorders and included six subjects. These events were usually of CTC grade 1 or 2 intensity. Peripheral sensory neuropathy was reported in three subjects (two subjects did not recover and one subject was reported to have recovered) and polyneuropathy was reported in three subjects (two subjects did not recover and one subject was reported to have recovered). One case of CTC grade 2 dizziness was reported for one subject (subject did not recover). There was one case of CTC grade 3 loss of consciousness, which resulted in the recovery of the subject.

Three subjects had study drug related gastrointestinal disorders with one subject reported to have had CTC grade 3 nausea and CTC grade 2 vomiting (both did not recover), and CTC grade 1 dysphagia (with recovered as the outcome); two other subjects were reported to have had CTC grade 1 nausea (one subject recovered and the other subject did not recover).

The most common AEs regardless of relationship to study treatment that occurred during this study (those AEs that were documented for at least two subjects) involved myalgia (reported in four subjects); nausea, anorexia, and dyspnea (all reported in three subjects); peripheral sensory neuropathy and polyneuropathy (three subjects each with six subjects altogether); constipation, fatigue, pneumonia, dizziness, and cough (all reported in two subjects).

Deaths

There were three deaths reported during the study: two deaths due to disease progression and one death due to septic cardiovascular and liver failure.

Serious AEs (SAEs)

Altogether three subjects had at least one SAE during the study:

- **Atrial flutter** (CTC grade 2, drug related and recovered), and **pneumonia** (CTC grade 4, not drug related, not recovered) for one subject. Study drug was withdrawn due to pneumonia.

- **General physical health deterioration** (CTC grade 3, not drug related, study drug was withdrawn, with **fatal outcome**) for one subject. This event was considered to be related to disease progression.

- **Pneumonia** (CTC grade 3, not drug related, recovered) and **loss of consciousness** (CTC grade 3, drug related, recovered) for one subject.

Other significant AEs

Study drug was withdrawn for three subjects due to AEs; one subject with general physical health deterioration (CTC grade 3, not drug related, with fatal outcome reported as an SAE), one subject with pneumonia (not drug related, CTC grade 4, reported as an SAE, not recovered). This subject also had CTC grade 2 atrial flutter at this time) and one subject with polyneuropathy (CTC grade 2, treatment related, not recovered).

Clinical laboratory findings

Most of the laboratory values reported over the course of the study were within normal ranges or of CTC grade 1 or 2 toxicity.

CTC grade 3 or 4 laboratory toxicities were reported for five subjects during the study.

- One subject (CTC grade 3 sodium)
- One subject (CTC grade 3 and 4 gamma-glutamyl transferase [GGT], and CTC grade 3 aspartate aminotransferase, platelets, calcium, glucose, and sodium)
- One subject (CTC grade 3 alanine aminotransferase and sodium)
- One subject (CTC grade 3 GGT and CTC grade 3 and 4 calcium)
- One subject (CTC grade 3 and 4 GGT)

These findings mostly reflect the severity of these subjects' underlying disease.

Vital signs and ECG

There were no clinically relevant findings related to vital signs or the ECG examinations.

WHO performance status

At the end of study visit, one subject remained at performance status 0, one subject worsened to performance grade 1 (baseline performance status 0), four subjects remained at performance status 1, and four subjects worsened from performance status 1 at baseline to performance grade 2.

Scottish gynecological cancer trial groups (SGCTG) neurological questionnaire score

The mean scores of the SGCTG neurological questionnaire showed a notable increase at the EOS visit increasing from a mean score of 0.4 at screening to a mean score of 4.2 indicating worsening of neurological symptoms.

Overall conclusions

This study confirmed the known safety profile of ZK 219477 when given as 3-h i.v. infusion at a dose of 16 mg/m^2. Two previously unreported AEs were documented during this study. These included atrial flutter in a subject with a history of myocardial infarction and loss of consciousness reported in one subject during an episode of high fever related to pneumonia. Both subjects recovered from these events. There were no other previously unreported AEs. The overall safety profile of ZK 219477 was considered acceptable in light of the seriousness of the underlying disease of the subjects treated in this study.