Clinical Study Synopsis

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Date of study report:	21 JUL 2010
Study title:	Phase I/II study to investigate the safety, tolerability, efficacy, and pharmacokinetics of ZK 219477 in combination with cisplatin as first-line therapy in chemotherapy-naïve subjects with extensive-disease (ED) stage small-cell lung cancer (SCLC)
Sponsor's study number:	91495 (310101)
NCT number:	NCT00359359
EudraCT number:	2006-000067-29
Sponsor:	Bayer HealthCare
Clinical phase:	Phase I/II
Study objectives:	**Phase I part**: Primary objective: • To determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of ZK 219477 in combination with cisplatin • To investigate the safety and tolerability of ZK 219477 in combination with cisplatin Secondary objective: • To investigate the pharmacokinetics of ZK 219477 and cisplatin when given as a combination • To evaluate the antitumor activity of ZK 219477 in combination with cisplatin in subjects with chemotherapy-naive, extensive-disease (ED) stage small-cell lung cancer (SCLC) **Phase II part**: Primary objective: • To evaluate the antitumor activity of ZK 219477 in combination with cisplatin in subjects with chemotherapy-naive, ED stage SCLC Secondary objective: • To investigate the safety and tolerability of ZK 219477 in combination with cisplatin in this subject population • To evaluate the population pharmacokinetics of ZK 219477 and cisplatin
Test drug:	Sagopilone (ZK 219477, BAY 86-5302)
Name of active ingredient(s):	Sagopilone
Dose:	**Phase I part** (dose escalation/de-escalation): Starting dose of 12 mg/m^2 body surface area (BSA) followed by 16 mg/m^2 or 9 mg/m^2 depending on

	the incidence of DLTs. Further dose steps included 19 mg/m^2 and 22 mg/m^2. As a rule, dose increases were only allowed if no more than 1 out of 6 subjects experienced a DLT during the first course. **Phase II part**: The recommended Phase II dose was the MTD defined in phase I part. **Both parts**: The study drug ZK 219477 was administered in combination with a fixed dose of cisplatin (75 mg/m^2 as a 1-h infusion after the ZK 219477 infusion on Day 1).
Route of administration:	Intravenous (IV) infusion over 3 h
Duration of treatment:	**Phase I part:** For dose escalation, safety data for each cohort was reviewed after all subjects in the cohort had received one dose and further followed for at least 3 weeks after dosing. Dose escalation continued until MTD was reached. Generally, subjects received 2-6 courses at 3-week intervals; in the event of sustained clinical benefit, more than 6 treatment courses were permitted. **Phase II part:** ZK 219477 IV on Day 1 every 3 weeks in combination with cisplatin IV 75 mg/m² on Day 1 every 3 weeks (3 weeks defined as 1 cycle); treatment for 2-6 cycles (prolongation of treatment if indicated).
Reference drug:	Not applicable
Indication:	Small-cell lung cancer
Diagnosis and main criteria for inclusion:	• Adult patients (≥18 years of age) with histologically or cytologically proven SCLC • Stage of extensive disease defined by the presence of distant lesions • At least 1 unidimensionally measurable lesion (suitable for modified Response Evaluation Criteria in Solid Tumors [modRECIST] evaluation) • No prior chemotherapy for SCLC; no prior radiotherapy for SCLC (except radiation of brain metastases); and no prior surgical resection within 4 weeks prior to inclusion • Adequate function of major organs and systems • Use of highly effective birth control methods in females of child-bearing potential
Study design:	This was a prospective, open, multicenter Phase I/II study. The study was conducted in 2 parts; Phase I and Phase II. Phase I part was a dose-escalation phase, wherein MTD was identified. Phase II part was mainly focused on assessment of subjects for safety, efficacy, and PK at the MTD identified in the Phase I part of the study.
Methodology:	The study comprised of screening phase followed by 6 treatment cycles

	(3 visits per cycle on Day 1, 8, and 15 for first 5 treatment cycle, i.e., Visits 1-15). The last treatment cycle has visits on Day 1 and 8 (Visits 16 and 17) and end of study (EOS) visit (Visit 18) was performed 3-4 weeks after the last administered dose. A follow-up visit was also conducted 3 months after EOS in the subjects who have shown toxicities Common Toxicity Criteria (CTC) Grade ≥2. **Dose-escalation requirements**: In the dose-escalation (Phase I part) portion of the study, subjects were enrolled in cohorts. The planned dose range was from 9 mg/m^2 to 22 mg/m^2. Safety data for each cohort was reviewed after all subjects in the cohort have received one dose and been followed for at least 3 weeks after dosing. Dose escalation was continued until MTD was reached. Doses were escalated until DLT was observed in 2 of 6 subjects. The MTD was the dose level at which no more than 1 out of 6 subjects experienced a DLT. Subjects participating in the Phase I part of the study who appear to benefit from treatment can receive additional cycles at the dose level at which they were treated. There was no intra-subject dose escalation. **Efficacy assessment:** Tumor scans were performed radiographically by computed tomography [CT] and/or magnetic resonance imaging [MRI] every 2 cycles. Tumor response was evaluated on Day 15 of Courses 2, 4 and 6. Complete response (CR) or partial response (PR) had to be confirmed with a 2nd radiological assessment not less than 4 weeks after the first assessment **Pharmacokinetic sampling:** Serial blood samples were drawn during and after the infusions across Cycles 1 and 2: • For ZK 219477: 0, 0.25, 1, 2, 3 h (5 min prior to the end of the ZK 219477 infusion); 3 h 15 min, 3 h 30 min, and 4 h 15 min, 5 h 30 min, 7, 10, 24, 48, 72, 96, 168, 336 h after the beginning of the ZK 219477 infusion. • For cisplatin: 0, 15 min, 1 h (5 min prior to the end of the cisplatin infusion); 1 h 30 min, 2 h 15 min, 3 h 45 min, 6 h 45 min, 20 h 45 min after the beginning of the cisplatin infusion. In addition samples for the determination of cisplatin were also taken at 4-5 h after start of ZK 219477 infusion in Cycle 1 and 3.5-4 h after start of ZK 219477 infusion in Cycle 2. **Safety assessments**: Adverse events (AEs) were monitored throughout the study. **Other assessments**: Optional pharmacogenomic sampling was done.
Study center(s):	The study was conducted at 3 study centers in Germany.
Publication(s) based on the study (references):	None at the time of report creation.

Study period:	Study Start Date: 31 JUL 2006 Study Completion Date: 17 AUG 2009
Early termination:	The study was terminated after the completion of the Phase I part in connection with the sponsor's decision to put the development of ZK 219477 on hold.
Number of subjects:	Planned: 46 Subjects (12 Subjects in Phase I part and 34 Subjects in Phase II part) Analyzed: 26 Subjects

Criteria for evaluation

Efficacy: Tumor response was defined as objective response (CR or PR) according to the modRECIST criteria. Each evaluation comprised of 3 variables: (1) target lesions, (2) non-target lesions, and (3) new lesions. Based on the results for target lesions, non-target lesions, and new lesions, the investigator assessed each evaluation for the "overall response" and among all time-points evaluated, best overall response was reported.

Phase I part: No primary efficacy variable was defined for the Phase I part. The secondary efficacy variable was the proportion of subjects with either CR or PR according to the modRECIST criteria as "best overall response" after 6 courses of therapy (i.e., before Course 7)..

Phase II part: The primary efficacy variable was proportion of subjects with either CR or PR as "best overall response". Secondary efficacy variables were time to progression (TTP), progression free survival (PFS), overall survival (OS) and response duration (i.e., duration of CR or PR).

Safety: The primary safety variable was the occurrence of DLTs. The toxicity grading was performed according to the CTC grades ranging from 0 (no signs of toxicity) to 4 (most severe signs of toxicity). The AEs were coded according to the common terminology criteria for adverse events (CTCAE 3.0) and AEs were classified according to their seriousness, severity (mild, moderate, severe), relationship to investigational product. Neurological score (Scottish Gynecological Cancer Trials Group [SGCTG] Neurotoxicity Score), incidence of abnormal findings in measurements of vital parameters (body temperature, heart rate, systolic and diastolic blood pressure), ECG, and laboratory findings (serum chemistry, hematology, coagulation, urinalysis) were also evaluated.

Clinical pharmacology: Pharmacokinetics: The parameters evaluated for both ZK 219477 and cisplatin included maximum (peak) plasma concentration (C_{max}), area under the concentration-time curve, extrapolated to infinity (AUC), AUC from zero time to t_{last}, where t_{last} was the last time point with measurable concentration for individual formulation (AUC[0-t_{last}]), time to reach maximum concentration (t_{max}), terminal disposition rate constant (λ_z [K_{el}]), terminal half-life ($t_{½}$), total body clearance (CL), volume of distribution at steady state (V_{SS}), and mean residence time (MRT).

	Other: Optional pharmacogenomic evaluation included assessment of deoxyribonucleic acid (DNA) methylation.
Statistical methods:	Analysis sets: Full analysis set (FAS) included all subjects assigned to study treatment, safety set (SAF) included all FAS subjects with at least one intake of study drug, per protocol set (PPS) included all FAS subjects with no major protocol deviation, primary analysis set (PAS) included all FAS subjects for whom the primary efficacy variable was assessable. The efficacy variables were analyzed in the FAS, in the PPS, and in the PAS. The SAF was used for the analyses of the safety variables. The FAS was used for the display of all other variables. Demographics and baseline characteristics: Descriptive statistics and/or frequency tables were used as appropriate. Efficacy analysis: Descriptive statistics (e.g., mean, standard deviation [SD], minimum, maximum for continuous data; frequency tables for categorical data) were provided per dose level and overall efficacy variables. No formal hypothesis testing regarding efficacy was performed for the Phase I part of the study. No inferential statistics or statistical comparisons were planned; therefore, no alpha level was specified. Subjects who experienced a DLT were listed. Time-to-event parameters (time to progression and response duration) were analyzed by means of the Kaplan-Meier product limit method. Safety analysis: Descriptive statistics and/or frequency tables were used.
Substantial protocol changes:	Protocol Amendment No 1 from 20 JUL 2007 introduced: • Continuation of dose escalation in the Phase I part of the study and inclusion of Phase I subjects treated at the MTD level into the Phase II efficacy and safety evaluation • Changes of the method for the cranial tumor scan at the screening visit • Tumor scans to be provided to the sponsor within the Phase II part of the study • The safety follow-up for subjects with toxicities CTC Grade ≥ 2 persisting at EOS were to be followed up until recovery, baseline status, or stabilization for a maximum of 6 months following the last dose of study drug • Change of the sample container for PK analyses of ZK 219477 (an enzyme inhibitor was added to the sample container) and subsequently changes in sample handling for PK analyses Protocol Amendment No 2 from 22 JUL 2008 introduced: • Additional dose steps (including de-escalation) within the Phase I part • Definition of algorithm for “best overall response” for SD

- Replacement of major protocol violators to ensure that the PPS contains exactly 34 subjects. Toxicity was specified as reason for replacement
- The PFS and OS as new secondary efficacy variables, TTP, PFS and OS measured from date of assignment to treatment
- First interim analysis after "Last Patient First Treatment" Phase I Part, second interim analysis after "Last Patient Last Treatment" (LPLT), end of efficacy observation period limited to 12 months after LPLT
- Abnormal laboratory values are only considered as adverse events if they meet predefined criteria

Subject disposition and baseline

A total of 28 subjects were screened and 26 of them were assigned to treatment (SAF). Six subjects were treated at a dose of 12 mg/m^2, 7 at a dose of 16 mg/m^2, 7 at a dose of 19 mg/m^2, and 6 at a dose of 22 mg/m^2. All subjects in the SAF were also included in the PPS.

Thirteen subjects (50.0%) withdrew from study medication before Course 6, with the drop-out rate increasing with the dose administered (1 subject in the 12 mg/m^2 arm and all 6 subjects in the 22 mg/m^2 arm). One subject in the 19 mg/m^2 arm withdrew his consent and another subject in this arm died before Course 6. The remaining 11 subjects prematurely discontinued treatment due to AEs, 7 of them because of peripheral neuropathy.

The subjects' mean (±SD) age was 60.2 ± 9.2 years (median: 61.5 years; range: 43-74). Two thirds (65.4%) of the study participants were men, and all subjects were of Caucasian origin.

In accordance with the eligibility criteria for this study, all subjects were diagnosed with extensive disease. One subject in the 19 mg/m^2 dose group had received prior radiotherapy for his brain metastases, which was allowed per protocol. All but 1 subject in the 19 mg/m^2 dose group had undergone a surgical procedure for SCLC (mostly a biopsy) before study entry.

Efficacy evaluation

No primary efficacy variable was defined for the Phase I part of the study.

The proportion of responders (CR or PR as best overall response after 6 treatment courses or end of treatment) was analyzed as a secondary efficacy variable.

Two subjects each in the 12 mg/m^2, 16 mg/m^2, and the 22 mg/m^2 dose groups, and 6 subjects in the 19 mg/m^2 dose group had confirmed PR as best overall response. None achieved confirmed CR (1 subject in the 19 mg/m^2 group showed unconfirmed CR after Course 4).

Thus, 12 subjects (46.2%) in total were classified as responders. Three subjects (1 in the 12 mg/m^2 dose group and 2 in the 16 mg/m^2) developed PD during the first 6 courses.

Table 1: Best overall response (confirmed responses according to modRECIST) at the end of Course 6 or end of treatment (SAF)

Response category	12 mg/m^2 N = 6 N (%)	16 mg/m^2 N = 7 N (%)	19 mg/m^2 N = 7 N (%)	22 mg/m^2 N = 6 N (%)	Total N = 26 N (%)
Response (CR + PR)	2 (33.3)	2 (28.6)	6 (85.7)	2 (33.3)	12 (46.2)
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	2 (33.3)	2 (28.6)	6 (85.7)	2 (33.3)	12 (46.2)
SD	2 (33.3)	2 (28.6)	0 (00.0)	3 (50.0)	7 (26.9)
PD	1 (16.7)	2 (28.6)	0 (00.0)	0 (00.0)	3 (11.5)
ND/UNK/NA	1 (16.7)	1 (14.3)	1 (14.3)	1 (16.7)	4 (15.4)

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, ND/UNK/NA = not done/unknown/not available

Note: Response was clearly dose-dependent, even though there was the same number of responders in the highest dose group as in the lowest two. The difference was that PR in 3 subjects in the highest dose group after Course 2 could not be confirmed because the subjects discontinued the study due to neuropathy before Course 4. A summary of the confirmed best overall response is shown in Table 1. The corresponding data for unconfirmed best overall response are shown in Table 2.

Table 2: Best overall response (unconfirmed responses according to modRECIST) at the end of Course 6 or end of treatment (SAF)

Response category	12 mg/m^2 N = 6 N (%)	16 mg/m^2 N = 7 N (%)	19 mg/m^2 N = 7 N (%)	22 mg/m^2 N = 6 N (%)	Total N = 26 N (%)
Response (CR + PR)	2 (33.3)	3 (42.9)	6 (85.7)	5 (83.3)	16 (61.5)
CR	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	1 (3.8)
PR	2 (33.3)	3 (42.9)	5 (71.4)	5 (83.3)	15 (57.7)
SD	2 (33.3)	1 (14.3)	0 (00.0)	0 (00.0)	3 (11.5)
PD	1 (16.7)	2 (28.6)	0 (00.0)	0 (00.0)	3 (11.5)
ND/UNK/NA	1 (16.7)	1 (14.3)	1 (14.3)	1 (16.7)	4 (15.4)

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, ND/UNK/NA = not done/unknown/not available

Safety evaluation

A total of 77 courses with infusions were administered (29 at a dose of 12 mg/m^2, 31 at dose of 16 mg/m^2, 29 at a dose of 19 mg/m^2, and 8 at a dose of 22 mg/m^2). The median number of infusions per dose group ranged between 3 (22 mg/m^2 dose group) and 6 (16 mg/m^2 dose group). The mean values of the individual mean doses were 12.0 ± 0.0 mg/m^2 in the 12 mg/m^2 arm, 15.7 ± 0.6 mg/m^2 in the 16 mg/m^2 arm, 18.8 ± 0.6 mg/m^2 in the 19 mg/m^2 arm, and 21.5 ± 0.9 mg/m^2 in the 22 mg/m^2 arm. No subject received more than 6 treatment courses. Postponements of at least 1 treatment course due to AEs were necessary in 9 subjects (34.6%). Two subjects in the 16 mg/m^2 dose group, 1 subject in the 19 mg/m^2 dose group, and 2 subjects in the 22 mg/m^2 dose group had at least 1 dose reduction after Course 1. All dose reductions were due to AEs.

During the course of the study, 1 subject in the 19 mg/m^2 dose group experienced 2 confirmed DLTs. Documentation of DLTs was done in a general comment field on the CRF. The subject had developed neutropenic sepsis (CTCAE Grade 5) and thrombocytopenia (CTCAE Grade 4) and died 11 days after his first infusion. Both events were rated as possibly drug-related and confirmed as DLTs. The events in 3 other subjects, which were documented by the investigators as DLTs, could not be confirmed either by the investigator or the sponsor. The recommended Phase II dose was established at 19 mg/m^2 for

ZK 219477 in combination with cisplatin. A brief summary of the number of subjects with AEs during the study is given in Table 3 below.

Table 3: Number of subjects with AEs during the study (SAF)

Type of AE	12 mg/m^2 N = 6 N (%)	16 mg/m^2 N = 7 N (%)	19 mg/m^2 N = 7 N (%)	22 mg/m^2 N = 6 N (%)
Any AE	6 (100.0)	7 (100.0)	7 (100.0)	6 (100.0)
Any related AE	5 (83.3)	7 (100.0)	7 (100.0)	6 (100.0)
Any AE leading to withdrawal from study drug	1 (16.7)	2 (28.6)	2 (28.6)	6 (100.0)
Any AE indicating neurotoxicity	3 (50.0)	5 (71.4)	6 (85.7)	5 (83.3)
Any AE of CTCAE grade ≥3	5 (83.3)	6 (85.7)	5 (71.4)	6 (100.0)
Any related AE of CTCAE grade ≥3	2 (33.3)	4 (57.1)	4 (57.1)	4 (66.7)
Any SAE	5 (83.3)	1 (14.3)	3 (42.9)	4 (66.7)
Any fatal SAE (other than fatal PD)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)

Seven subjects (26.9%) died. Thereof, one subject in the 19 mg/m^2 dose group died from sepsis in leukopenia and the remaining 6 subjects (2 each in the 12 mg/m^2, 16 mg/m^2, and 22 mg/m^2 dose groups) died from PD, which was not to be reported as a serious adverse event (SAE). A total of 13 subjects (50.0%) experienced at least 1 SAE during this study. There was no apparent relationship between the incidence of SAEs and the ZK 219477 dose. The highest incidence was seen with nervous system disorders (6 subjects or 23.1%). SAEs which occurred in at least 3 subjects (>10% of the total group) were pneumonia (n=3) and syncope (n=3).

Two subjects in the 22 mg/m^2 dose group and 1 subject each in the 12 mg/m^2 and in the 19 mg/m^2 dose groups experienced SAEs which were considered by the investigators to be at least possibly related to ZK 219477. All drug-related SAEs occurred only in single cases. In addition to the subjects who prematurely terminated the study due to PD, 11 subjects (42.3%) discontinued study drug because of AEs, 7 of whom (26.9%) due to polyneuropathy and related neurological disorders. Six of these 7 subjects were treated at a dose of 19 mg/m^2 or 22 mg/m^2. All subjects (100.0%) experienced at least 1 AE during the study. The highest incidences (≥30%) of AEs were observed for peripheral neuropathy (73.1%), nausea (61.5%), vomiting (50.0%), fatigue (46.2%), constipation (46.2%), insomnia (42.3%), decreased appetite (42.3%), hypokalemia (38.5%), diarrhea (34.6%), vertigo (34.6%), and headache (34.6%).

In all but 1 subject (96.2%) at least 1 AE was rated as drug related. Drug-related AEs mostly referred to nervous system disorders (84.6%), in particular peripheral neuropathy (73.1%). In 4 subjects (15.3%), the maximum intensity of an AE was CTCAE Grade 1 or 2, 16 subjects (61.5%) experienced AEs of CTCAE Grade 3, 5 subjects (19.2%) of CTCAE Grade 4 and 1 subject (3.8%) of CTCAE Grade 5. Thus, 22 subjects (84.6%) experienced AEs of CTCAE Grade 3 or higher. AEs of CTCAE grades ≥3 that occurred in at least 3 subjects (>10%) were: peripheral neuropathy (n=6), fatigue (n=6), syncope (n=4), leukopenia (n=3), pneumonia (n=3), decreased appetite (n=3), dehydration (n=3), hyperglycemia (n=3), and hypocalcaemia (n=3). In 14 subjects (53.8%), at least 1 AE of CTCAE Grade 3 or higher was rated as drug related. The most frequent drug-related AE of CTCAE Grade 3 or higher was peripheral neuropathy (23.1%).

Hematological AEs of CTCAE Grade 3 or higher occurred in 6 subjects (23.1%). These were leukopenia (n=3), anemia (n=2), neutropenia (n=1), and thrombocytopenia (n=1). One case of leukopenia was of CTCAE Grade 4. One case of neutropenic sepsis was of CTCAE Grade 5.

AEs indicating neurotoxicity were expected to be the most clinically relevant events in the study. The overall incidence of AEs indicating neurotoxicity was 73.1%. It was highest (85.7%) in the 19 mg/m^2 dose group, followed by the 22 mg/m^2 dose group (83.3%), the 16 mg/m^2 dose group (71.4%), and the 12 mg/m^2 dose group (50.0%). With the exception of 1 case of hypoesthesia, all other AEs indicating neurotoxicity were rated as drug related. Thirteen subjects (50.0%) experienced AEs indicating neurotoxicity of a maximum intensity of CTCAE Grade 1 or 2, and 6 subjects (23.1%) of CTCAE Grade 3. Neurotoxicities of CTCAE Grade 4 did not occur.

No clinically consistent trends were observed for any laboratory parameter in any of the 4 treatment arms. Most laboratory abnormalities were of CTC Grade 0 or 1. Most changes were from CTC Grade 0 to CTC Grades 1 or 2. All treatment arms were equally affected by changes. Changes in laboratory parameters to CTC Grade 4 occurred only with neutrophils (1 subject in the 16 mg/m^2 arm), platelets (1 subject in the 22 mg/m^2 arm), fibrinogen (1 subject in the 19 mg/m^2 arm), and calcium (1 subject in the 16 mg/m^2 arm). Changes to CTC Grade 3 occurred in more than 2 subjects per parameter and treatment arm with leukocytes (3 subjects in the 16 mg/m^2 arm) and neutrophils (4 subjects in the 16 mg/m^2 arm).

According to the overall ECG interpretation, 10 subjects (40.0%) entered the study with abnormal ECG findings, but these were of clinical relevance in only 2 subjects. By the end of the study, the number of subjects with abnormal ECG findings had decreased to 9 (47.7%) and none of the abnormal findings were of clinical relevance. Besides the 2 cases at screening, none of the abnormal ECG findings recorded during the study were assessed as being of clinical relevance.

In accordance with the course of disease, the subjects' WHO performance status had deteriorated from Grade 0 or 1 at screening to Grade 3 or 4 in 7 subjects (29.2%) by the end of the study. Deteriorations to Grade 3 occurred in the 16 mg/m^2 arm only (3 subjects or 42.9%). No subject deteriorated to Grade 4.

Due to the small number of subjects in this study, data regarding the subject scores in the SGCTG neurological questionnaire were only listed and were not analyzed.

Clinical pharmacology evaluation

The study was terminated after the completion of the Phase I part in connection with the sponsor's decision to put the development of ZK 219477 on hold. PK report is not available

Other evaluations

Pharmacogenomic sub-study: Despite analysis of a large number of cell lines and xenograft tumor models, it has so far not been possible to define a set of methylation markers that correlate with response of solid tumors to therapy with ZK 219477 or other epothilone derivatives. It was therefore not possible to pursue the analysis of pharmacogenetic markers in plasma DNA as originally planned for this study.

Overall conclusions

The study was terminated after the completion of the Phase I part in connection with the sponsor's decision to put the development of ZK 219477 on hold. The 19 mg/m^2 dose arm had the highest tumor

response rate of 86% (confirmed responses) and offered the optimum balance between efficacy and tolerability.

The most common AEs were peripheral neuropathy, nausea, vomiting, fatigue, constipation, insomnia, and decreased appetite. The incidence of AEs indicating neurotoxicity was higher in the 19 mg/m^2 and in the 22 mg/m^2 arms than in the 12 mg/m^2 and 16 mg/m^2 arms. In conclusion, this study indicated that ZK 219477 in combination with cisplatin as first-line therapy had significant activity in chemotherapy-naïve subjects with ED stage SCLC. The recommended Phase II dose was established at 19 mg/m^2 for ZK 219477 in combination with cisplatin at the standard dose of 75 mg/m^2.