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.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare	
Study Number:	91374 (307971)	NCT00160069 EudraCT No.: 2005-000586-19
Study Phase:	II	
Official Study Title:	Prospective, multicenter, randomized, independent-group, open-label phase-II study to investigate the efficacy and safety of 3 regimen with 2 doses of ZK 219477 (16 mg/m^2 body surface area as 3-hour infusion or 22 mg/m^2 body surface area as 30-minute or 3-hour infusion) as second-line therapy in patients with Stage IIIB or Stage IV non-small-cell lung cancer (NSCLC)	
Therapeutic Area:	Oncology	
Test Product		
Name of Test Product:	Sagopilone (ZK 219477, BAY 86-5302)	
Name of Active Ingredient:	Sagopilone	
Dose and Mode of Administration:	Dose: Treatment arm A: 16 mg/m^2 body surface area (BSA) (maximum dose of 32 mg), every 3 weeks Treatment arm B and C: 22 mg/m^2 BSA (maximum dose of 44 mg), every 3 weeks Mode of administration: Treatment arm A and B: Intravenous (IV) infusion over 3 h Treatment arm C: IV infusion over 0.5 h	
Reference Therapy/Placebo		
Reference Therapy:	None	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	Treatment with the study drug was given in 2 to 6 courses at 3-week intervals; in the event of sustained clinical benefit, more than 6 treatment courses were permitted.	
Studied period:	Date of first subject's first visit:	03 AUG 2005
	Date of last subject's last visit:	15 APR 2009
Premature Study Suspension / Termination:	Not applicable	
Substantial Study Protocol Amendments:	Amendment No. 1, dated 20 JUN 2005 incorporated the following changes: • The starting dose of ZK 219477 was reduced from 22 mg/m^2 (maximum 44 mg) to 16 mg/m^2 (maximum 32 mg)	

	• The tubings of infusion line were to be rinsed with sodium chloride solution for 15 min (instead of 10 min) using the study drug administration flow rate
	• Change of dosing modifications for management of toxicity:
	  • Grade 2 neurotoxicity: If symptoms resolved to Grade 0-1, the treatment would be restarted at 12 mg/m^2 instead of 16 mg/m^2 as previously stated.
	  • Grade 3 neurotoxicity: If symptoms resolved to Grade 0-1, the treatment would be restarted at 12 mg/m^2 or 9 mg/m^2 (investigator discretion) instead of 16 mg/m^2 as previously stated.
	• All baseline evaluations were to be performed as close as possible to the beginning of treatment, and never more than 4 weeks, instead of 2 weeks, before the beginning of the treatment
	
	Amendment No. 2, dated 18 JUL 2006 incorporated the following changes:
	• Addition of two treatment arms for better evaluation of ZK 219477 efficacy: 22 mg/m^2 as 30 min and 3 h infusion separately
	• Modification of overall study design to three arm, open label, randomized and independent group Phase 2 study (fixed sample design with total sample size for 3 × 38 evaluable subjects)
	• A pharmacokinetic (PK) substudy was added to investigate the PK profile of ZK 219477 when infused over 30 min and over 3 h. Blood samples for PK measurements were to be taken during Courses 1 and 2 having different sampling schedules and analysis of PK profile of ZK 219477 for 30 min and 3 h infusion
	• Exclusion criterion included subjects with history of any other primary malignancy with the exceptions of non-melanoma skin cancer and carcinoma in situ of the cervix
	• Dose reduction steps in case of toxicities were further defined
	
	Amendment No. 3, dated 26 SEP 2007, incorporated the following changes:
	• Biomarker analysis added as an optional module for assessing biomarker profile of ZK 219477
	• Method for the cranial tumor scan [cranial computed tomography (CT) or magnetic resonance imaging (MRI)] at the screening visit changed and a pre-study scan was acceptable if taken not ≥ 4 weeks before the first infusion
	• Follow-up (FU) of all subjects with possibly drug-related toxicities of common toxicity criteria (CTC) Grade ≥ 2 (except alopecia) persisting at end-of-study (EOS) and followed-up until recovery, baseline status or stabilization for a maximum of 6 months following the last dose of study

	drug • After study drug treatment completion, independent of the reason for study termination, subjects were followed-up every 3 months (except if the subject has withdrawn consent) to determine overall survival status and third-line therapy for up to 6 months • Modification of secondary objectives to include duration of complete response (CR) or partial response (PR) as 'overall response', time to disease progression, progression free survival (PFS), and overall survival (OS) and time-to-event variables to be analyzed by Kaplan-Meier product limit method • Addition of an enzyme inhibitor (Pefabloc SC®) to sample containers for PK analyses of ZK 219477 for maintaining the stability of study drug in human serum at room temperature or at − 80°C • If drug-related toxicities ≥ Grade 2 resolved to Grade 0-1 within the next 5 weeks after the last infusion, treatment was to be restarted at next lower dose level or at the same dose level at the discretion of the investigator • Two treatment postponements were allowed during the study Amendment No. 4, dated 04 MAR 2008, incorporated the following changes: • Response Evaluation Criteria in Solid Tumors (RECIST) criteria was adapted to published RECIST criteria. An algorithm defined for "best overall response" Stable Disease (SD), and "best overall response" PR and CR • Calculation basis of primary analysis set (PAS) changed from full analysis set (FAS) to per protocol set (PPS) • Major protocol violators to be replaced to maintain 38 evaluable subjects for each treatment arm and only subjects that terminated the study before the first efficacy evaluation (Course 2) due to study drug related toxicity were excluded from replacement • Definition of secondary variables (time to progression [TTP], PFS, OS) modified to suggest that the measurements were to be done from randomization • The first interim analysis was to be scheduled after the last subjects EOS visit, which was 21-28 days after the last treatment • Abnormal laboratory values to be considered as adverse events (AEs) only if they meet predefined criteria
Study Center(s):	The study was conducted across 12 centers in Germany.
Methodology:	This was a prospective, three-arm, open-label, randomized multi-center, independent-group Phase II study (proof of concept). At screening visit (within 4 weeks before the first visit), subject's characteristics demographics, history of NSCLC, medical/surgical history, World Health Organization (WHO)

	performance status, and vitals were collected. A cranial CT scan was also performed. The subjects were scheduled to receive 1 infusion of the study drug every 3 weeks; each infusion corresponds to 1 treatment course. The subjects received a minimum of 2 and a maximum of 6 treatment courses, more than 6 courses were allowed if subject derived clinical benefit. Tumor response was assessed radiographically every 2 courses by CT scan and/or MRI. The scans were evaluated; the overall response was computed and was combined to give the "best overall response." World Health Organization performance status was assessed pre-infusion, on the first day of every treatment course and at EOS visit (3-4 weeks after last dose of the study drug). AEs were monitored throughout the study period. Neurological score (Scottish Gynaecological Cancer Trials Group [SGCTG] Neurotoxicity Score) were assessed at screening, on Day 1 of every treatment course prior to the infusion, and at EOS visit, and also at FU visit for subjects with toxicities, Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 (6 months after EOS visit). Physical examination and vital signs were assessed on the first day of ea ch treatment course prior to the infusion and at EOS and additionally at FU visit for subjects with toxicities CTCAE Grade ≥2. Electrocardiogram (ECG) was performed on Day 1 of every treatment course post-infusion and at EOS. Blood samples for laboratory examinations (serum chemistry, hematology, coagulation, and urinalysis) were collected at every visit, while urine specimens were obtained on the first and third visit of first 5 treatment courses, first visit of Course 6, EOS visit, and FU visit for subjects with toxicities CTCAE Grade ≥2.
Indication/Main Inclusion Criteria:	**Indication:** Carcinoma, Non-small-cell lung cancer **Main inclusion criteria**: • Adult subjects (≥18 years) with histologically or cytologically proven NSCLC, Stage IIIB or Stage IV • At least 1 unidimensionally measurable lesion (suitable for modified version of the RECIST [modRECIST] evaluation) • WHO performance status 0-1 • Treatment failure of 1 previous platinum-based chemotherapy regimen • Adequate recovery (excluding alopecia) from previous surgery, radiation, and chemotherapy • Adequate function of major organs and systems, and survival expectation of ≥3 months • Time period since prior radio-, chemo-, or immunotherapy ≥3 weeks • No brain metastases requiring whole-brain irradiation • No history of any other primary malignancy with the exceptions of non-melanoma skin cancer and carcinoma *in situ* of the cervix • Use of highly effective birth control methods in females of childbearing potential and negative pregnancy test at enrollment

Study Objectives:	Primary objective: • To investigate the efficacy of 3 regimens of ZK 219477 in platinum-pretreated subjects with NSCLC (proof of concept). Secondary objective: • To evaluate the safety and tolerability of the 3 regimens of ZK 219477, duration of CR or PR as 'overall response', time to disease progression, overall survival (time to death), progression free survival.
Evaluation Criteria:	Efficacy: **The primary 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). **The secondary efficacy variables** included: • Response duration: Defined as the time between the first date that the measurement criteria for CR or PR as "overall response" was met (whichever status is recorded first) and the first date that recurrence or overall response of progressive disease (PD) was documented • Time to tumor progression: Defined as the time between date of randomization and establishment of tumor progression or death from the tumor • Progression free survival: Defined as time between date of randomization and establishment of tumor progression or death • Time to death: Defined as time between date of randomization and death Different methods (spiral CT, CT with contrast, or MRI) were used for scanning tumors. The results of the tumor scans were evaluated using modRECIST. WHO performance status was also assessed. Safety: **Adverse events:** All AEs were assessed and documented by the investigator according to their seriousness, intensity (or severity), pattern, and relationship to the study drug (not related, unlikely, possible, probable, or definite).The severity was evaluated using the National Cancer Institute (NCI)'s CTCAE Version 3. **Peripheral neuropathies/neurotoxicities** were assessed using SGCTG neurotoxicity score. The first segment was a patient neurological questionnaire where the subject provided details on potential tingling/numbness, burning/discomfort, and weakness for feet and/or fingers. Based on this, the investigator performed structured neurological assessment which included 2-point discrimination, Romberg test, tendon reflexes, and vibration test. **Safety evaluation** also included laboratory examinations (serum chemistry, hematology, coagulation, and urinalysis), 12-lead ECG, and vital signs such as body temperature, systolic blood pressure (SBP) and diastolic blood pressure (DBP), and heart rate.

Statistical Methods:	Efficacy was evaluated using the following analysis sets: • Full analysis set (FAS): All subjects who were assigned to the study treatment • Per protocol set (PPS): All FAS subjects with no major protocol deviations • Primary analysis set (PAS): All FAS subjects for whom the primary efficacy variable was assessable The study was designed to demonstrate a lack of effect of ZK 219477 compared with a response rate of 20% (called "good response"). In general, all variables measured on a metric scale were presented by descriptive statistics; categorical and binary variables were displayed using frequency tables. Safety was analyzed using safety analysis set (SAF) which included all FAS subjects who received at least 1 dose of the study drug. Efficacy: The primary efficacy variable was analyzed by applying a null hypothesis which was tested with a one-sided type-one error probability of α=10% at a power of 80%. No type-one error adjustment for multiplicity was done. The null hypothesis was rejected, if ≤4 subjects in each arm were classified as responders. The response rate and its confidence interval (CI) were calculated. Frequency tables by treatment arm and in total were given by time point for overall assessment of response. For all time-to-event variables, Kaplan-Meier estimates for survival probabilities including 95% CIs were calculated within each treatment arm separately and overall. Duration of CR or PR as "overall response" was tabulated. Safety: The incidence rates of AEs and serious adverse events (SAEs) were summarized using descriptive statistics and/or frequency tables. All the AEs were coded using Medical Dictionary for Regulatory Affairs (MedDRA), Version 12, system organ class (SOC) and graded using NCI's CTCAE Version 3.0.
Number of Subjects:	**Planned**: 38 evaluable subjects (ie, results other than “unknown” for “best overall response”) per treatment arm **Analyzed**: 128 subjects

Study Results

Results Summary — Subject Disposition and Baseline

A total of 128 subjects were screened and randomized (44 subjects to the 16 mg/m^2 [3 h] arm, 41 subjects to the 22 mg/m^2 [0.5 h] arm, and 43 subjects to the 22 mg/m^2 [3 h] arm; see Table 1). All but 1 subject in the 22 mg/m^2 (3 h) arm, who died from PD prior to treatment start, received at least 1 infusion of ZK 219477. Forty-seven subjects (36.7%) withdrew from the study medication before Course 6, with the highest drop-out rate of 41.5% in the 22 mg/m^2 (0.5 h) dose arm. The most frequent primary reason for premature discontinuation was the occurrence of AEs (33 subjects or 25.8%), mostly peripheral neuropathy. Five subjects (3.9%) withdrew their consents, 3 subjects (2.3%) died, and 6 subjects (4.7%) discontinued for other reasons. In addition, 40 subjects (31.3%) discontinued treatment because of PD.

Table 1: Disposition of subjects

Analysis set	16 mg/m^2 (3-h) N (%)	22 mg/m^2 (0.5-h) N (%)	22 mg/m^2 (3-h) N (%)
Full analysis set (FAS)	44 (100.0)	41 (100.0)	43 (100.0)
Safety analysis set (SAF)	44 (100.0)	41 (100.0)	42 (97.7)
Per protocol set (PPS)	44 (100.0)	40 (97.6)	42 (97.7)
Primary analysis set (PAS)	38 (86.4)	37 (90.2)	38 (88.4)

The mean age of the FAS was 61.4 ± 7.4 years (median: 62.5 years; range: 42-76 years). Two-thirds (64.8%) of the study participants were men, and all subjects were of Caucasian origin. The majority of the subjects (90.6%) were current or previous smokers with a median number of 1 cigarette pack per day. As per protocol, all subjects entered the study with Stage IIIB (14.1%) or Stage IV (85.9%) NSCLC according to the tumor node and metastasis (TMN) staging system. In 92 subjects (71.9%), the tumor was located centrally at first diagnosis, and in 50% of these subjects the tumor was an adenocarcinoma. All subjects had received prior first-line chemotherapy with a platinum-based regimen for NSCLC. Prior immunotherapy was reported in single cases only. Fifty-five subjects (43.3%) had received prior radiotherapy. Thirty-two subjects (72.7%) in the 16 mg/m^2 (3 h) arm, but only 24 subjects (58.5%) and 21 subjects (50.0%) in the 22 mg/m^2 (0.5 h) and 22 mg/m^2 (3 h) arms, respectively, presented with a WHO performance status 1 at screening. The remaining subjects had a WHO performance status 0. Besides this numerical imbalance, the 3 treatment arms were similar with regard to all other baseline and disease characteristics.

All of the 128 randomized subjects were included in the FAS. The safety analysis was based on the SAF, which excluded 1 subject in the 22 mg/m^2 (3 h) arm who died from PD before his first infusion. In addition to this subject, 1 subject in the 22 mg/m^2 (0.5 h) arm was excluded from the PPS because of major protocol deviations (history of cervix carcinoma at screening). The PAS included the first 38 evaluable subjects each from the 16 mg/m^2 (3 h) and 22 mg/m^2 (3 h) arms and the 37 evaluable subjects from the 22 mg/m^2 (0.5 h) arm.

In the FAS, a total of 354 courses with infusions were administered (128 at a dose of 16 mg/m^2, and 226 at dose of 22 mg/m^2). The median number of infusions per arm was 2 (range: 1-6 infusions). The median values of the individual mean doses were as planned, i.e., 16 mg/m^2 and 22 mg/m^2, respectively.

Postponements of at least 1 treatment course due to AEs were necessary in 1 subject (2.3%) in the 16 mg/m^2 (3 h) arm, in 3 subjects (7.3%) in the 22 mg/m^2 (0.5 h) arm, and in 7 subjects (16.3%) in the 22 mg/m^2 (3 h) arm. Only 9.1% of the subjects in the 16 mg/m^2 (3 h) arm, but 24.4% subjects in the 22 mg/m^2 (0.5 h) and 21.4% in the 22 mg/m^2 (3 h) arm had at least 1 dose reduction after Course 1. In most cases, the dose was reduced due to AEs.

Results Summary — Efficacy

The primary efficacy variable, the proportion of responders (CR or PR as best overall response after 6 treatment courses or end of treatment), was analyzed in the 113 subjects in the PAS. Only 2 subjects each in the 16 mg/m^2 (3 h) and the 22 mg/m^2 (0.5 h) arms (5.3% and 5.4%, respectively) and 4 subjects (10.5%) in the 22 mg/m^2 (3 h) arm had confirmed PR as best response. None achieved CR. Thus, the null hypothesis (probability of response is ≥20%) was rejected in all treatment arms, because at least 5 confirmed responders per arm would have been necessary to conclude success. About half of the subjects in each arm achieved SD as best overall response. A summary

of the best overall response is shown for the PAS in Table 2.

Table 2: Best overall response (according to modRECIST) at the end of Course 6 or end of treatment (primary analysis set)

Treatment arm	Response category	N	n (%)	Estimated response rate	80% confidence interval [a]
16 mg/m^2 (3-h)	Response (CR + PR)	38	2 (5.3)	0.0526	[0.0217, 0.1266]
	CR		0 (0.0)		
	PR		2 (5.3)		
	SD		20 (52.6)		
	PD		12 (31.6)		
	ND/UNK/NA		4 (10.5)		
22 mg/m^2 (0.5-h)	Response (CR + PR)	37	2 (5.4)	0.0541	[0.0223; 0.1302]
	CR		0 (0.0)		
	PR		2 (5.4)		
	SD		18 (48.6)		
	PD		14 (37.8)		
	ND/UNK/NA		3 (8.1)		
22 mg/m^2 (3-h)	Response (CR + PR)	38	4 (10.5)	0.1053	[0.0467; 0.1929]
	CR		0 (0.0)		
	PR		4 (10.5)		
	SD		18 (47.4)		
	PD		12 (31.6)		
	ND/UNK/NA		4 (10.5)		

[a] Calculated using the method by Blyth-Still-Casella
CR = complete response, PR = partial response, SD = stable disease,
PD = progressive disease, ND/UNK/NA = not done/unknown/not available

There were no additional responders in the FAS or PPS. A further 2 subjects in the 16 mg/m^2 (3 h) arm of the FAS had PD.

The analysis of the secondary efficacy variables was performed in the FAS and the PPS, as per protocol. All secondary time-to-event variables were analyzed using the Kaplan-Meier product limit method. As shown in Table 3, the estimated median time to tumor progression, the median time of progression-free survival, and the median time to death were similar across all treatment arms both in the FAS and the PPS.

Due to the low number of responders (see Table 2), statistical evaluation of the duration of response was not performed.

Table 3: Median time to tumor progression, progression-free survival, and time to death (full analysis set and per protocol set)

Variable	Treatment arm	Point estimate for the median [95% CI][a]	
		FAS N = 128	PPS N = 126
Time to tumor progression [days]	16 mg/m^2 (3-h)	81 [47; 94]	81 [47; 94]
	22 mg/m^2 (0.5-h)	86 [49; 203]	86 [49; 203]
	22 mg/m^2 (3-h)	69 [47; 126]	69 [47; 126]
Progression free survival [days]	16 mg/m^2 (3-h)	76 [44; 92]	76 [44; 92]
	22 mg/m^2 (0.5-h)	85 [47; 142]	86 [47; 142]
	22 mg/m^2 (3-h)	69 [47; 126]	69 [47; 126]
Time to death [days]	16 mg/m^2 (3-h)	223 [148; 371]	223 [148; 371]
	22 mg/m^2 (0.5-h)	197 [118; 216]	197 [123; 302]
	22 mg/m^2 (3-h)	201 [128; 236]	201 [139; 236]

[a] Kaplan-Meier-Product limit method.

In accordance with the observed lack of efficacy, the subjets' WHO performance status had deteriorated to Grade 3 at maximum in 39 subjects (30.7%) by EOS. Improvements were only seen in 3 subjects in the 22 mg/m^2 (0.5 h) arm.

Results Summary — Safety

A brief summary of the number of subjects with AEs during the treatment period is given in Table 4.

Table 4: Number of subjects with adverse events during the treatment period (safety analysis set)

Type of AE	16 mg/m^2 (3-h) N=44 n (%)	22 mg/m^2 (0.5-h) N=41 n (%)	22 mg/m^2 (3-h) N=42 n (%)
Any AE	40 (90.9)	40 (97.6)	42 (100.0)
Any related AE	34 (77.3)	36 (87.8)	36 (85.7)
Any AE leading to withdrawal from study drug	8 (18.2)	11 (26.8)	14 (33.3)
Any AE indicating neurotoxicity	25 (56.8)	36 (87.8)	31 (73.8)
Any AE of CTCAE grade ≥3	19 (43.2)	24 (58.5)	20 (47.6)
Any related AE of CTCAE grade ≥3	8 (18.2)	16 (39.0)	14 (33.3)
Any SAE	12 (27.3)	12 (29.3)	15 (35.7)
Any fatal SAE (other than fatal PD)	1 (2.3)	2 (4.9)	0 (0.0)

Eighty-eight subjects (68.8%) in the SAF died (29/44 in the 16 mg/m^2 [3 h] arm, 30/41 in the 22 mg/m^2 [0.5 h] arm, and 29/42 in the 22 mg/m^2 [3 h] arm). Fourteen of these subjects (7 in the 16 mg/m^2 arm, 5 in the 22 mg/m^2 [0.5 h] arm, and 2 in the 22 mg/m^2 [3 h] arm) died during the survival follow-up period. Eighty-four died from PD, which was not to be reported as an SAE. The other 4 subjects died from lung embolism, cardiac failure, hemoptysis, and an unknown cause.

A total of 39 subjects (30.7%), 12/44 (27.3%) subjects in the 16 mg/m^2 (3 h) arm, 12/41 (29.3%) subjects in the 22 mg/m^2 (0.5 h) arm, and 15/42 (35.7%) subjects in the 22 mg/m^2 (3 h) arm, experienced at least 1 SAE during the study. The pattern of SAEs in all study subjects was quite diverse. The highest incidences of SAEs by system organ class were seen for general disorders and administration site conditions (13 subjects); respiratory, thoracic, and mediastinal disorders (11 subjects) and nervous system disorders (7 subjects); and by preferred term for dyspnea (5 subjects), fatigue (4 subjects), edema peripheral, pulmonary embolism, dizziness, and chest pain (3 subjects each).

Eight subjects (1 each in the 16 mg/m^2 [3 h] and in the 22 mg/m^2 [0.5 h] arms and 6 subjects in the 22 mg/m^2 [3 h] arm) experienced SAEs which were considered by the

investigators to be at least possibly related to ZK 219477. With the exception of drug-related herpes zoster, which occurred in 2 subjects, all other drug-related SAEs occurred only in single cases.

In addition to the subjects who prematurely terminated the study due to PD, 33 subjects (26.0%) (8 [18.2%] in the 16 mg/m^2 [3 h] arm, 11 [26.8%] in the 22 mg/m^2 [0.5 h] arm, and 14 [33.3%] in the 22 mg/m^2 [3 h] arm) discontinued the study drug because of AEs, 26 of whom (20.5%) due to polyneuropathy and related neurological disorders.

A total of 122 subjects (96.1%) experienced at least 1 AE during the treatment period, and 58/70 subjects (82.9%) had at least 1 AE during follow-up. The highest incidences (≥20%) of AEs were observed for polyneuropathy (53.5%), fatigue (27.6%), constipation (26.0%), and nausea (22.8%). In 106 subjects (83.5%), at least 1 AE was rated as drug-related. Drug-related AEs mostly referred to nervous system disorders (71.7%). In 46.5% of the subjects, the maximum intensity of an AE was CTCAE Grade 1 or 2, 40.9% of the subjects experienced AEs of CTCAE Grade 3, 4.7% of CTCAE Grade 4, and 3.9% of CTCAE Grade 5. Thus, 49.6% subjects experienced AEs of CTCAE Grade 3 or higher. Adverse events of CTCAE Grades ≥ 3 that occurred in at least 3 subjects were: polyneuropathy (21 subjects), fatigue (6 subjects), dyspnea (6 subjects), peripheral sensory neuropathy (4 subjects), herpes zoster (3 subjects), and paresthesia (3 subjects).

AEs indicating neurotoxicity were expected to be the most clinically relevant events in the study. The overall incidence of AEs indicating neurotoxicity was 72.4%. It was highest (87.8%) in the 22 mg/m^2 (0.5 h) arm, followed by the 22 mg/m^2 (3 h) arm (73.8%) and the 16 mg/m^2 (3 h) arm (56.8%). Most of these AEs were rated as drug-related. Sixty-one subjects (48.0%) experienced AEs indicating neurotoxicity of a maximum intensity of CTCAE Grade <3 and 31 subjects (24.4%) of CTCAE Grade ≥3. In 1 subject (2.4%) in the 22 mg/m^2 (0.5 h) arm (1 case of polyneuropathy) and in 2 subjects (4.8%) in the 22 mg/m^2 (3 h) arm (1 case each of neuralgia and polyneuropathy), the AEs indicating neurotoxicity were of CTCAE Grade 4. An influence of the type of prior chemotherapy (taxane, vinca alkaloids, carboplatin, and cisplatin) or pre-existing neurotoxicological baseline findings on the occurrence of AEs indicating neurotoxicity was not observed.

Hematological AEs of clinical significance were observed infrequently (7.1%). Only 3 cases of anemia and 1 case each of leukopenia and thrombocytopenia were rated as drug-related. Most of the hematological AEs were of CTCAE Grades 1 or 2. Two subjects (1.6%) in the 22 mg/m^2 arms developed anemia of CTCAE Grade 3. None of the hematological AEs were of CTCAE Grades 4 or 5.

No clinically consistent trends were observed for any laboratory parameter in any of the 3 treatment arms. Most laboratory abnormalities were of CTC Grade 1 or 2. Most changes were from CTC Grade 0 to CTC Grades 1 or 2. All treatment arms were equally affected by changes. Changes in hematology laboratory parameters to CTC Grade 4 occurred only with neutrophils (1 subject in the 22 mg/m^2 [0.5 h] arm) and creatinine (1 subject in the 22 mg/m^2 [3 h] arm). Changes to CTC Grade 3 occurred in less than 20% of the subjects per parameter and treatment arm.

According to the overall ECG interpretation, 11 subjects (9.6%) entered the study with abnormal ECG findings, but only in 2 subjects in the 22 mg/m^2 (3 h) arm were the abnormal findings of clinical relevance. By the end of the study, the number of subjects with abnormal ECG findings had decreased to 4 (4.3%) 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.

Patient scores in the SGCTG neurological questionnaire were similar in the 3 treatment arms. The total mean scores increased over the course of the study, from 1.5 ± 2.0 (median 1.0) at screening to 7.7 ± 3.7 (median 7.0) at the EOS, indicating some

worsening of neurological symptoms. The worsening was numerically more pronounced in the 22 mg/m^2 arms (median changes: 7.0 in the 22 mg/m^2 [0.5 h] arm and 10.0 in the 22 mg/m^2 [3 h] arm) than in the 16 mg/m^2 (3 h) arm (median change: 5.0).

The mean DBP and SBP varied in each arm across treatment courses. The minimum mean DBP for 16 mg/m^2 was noted on Course 5 (Day 1) at 70 mmHg (standard deviation: ±10.00; n=5) and the maximum mean DBP was noted on FU visit at 76.1 mmHg (standard deviation: ± 9.32; n=7). The minimum mean DBP for 22 mg/m^2 (30 min infusion) was noted on Course 5 (Day 1) at 67 mmHg (standard deviation: ± 10.95; n=5) and the maximum mean DBP was noted on Course 3 (Day 1) at 76.8 mmHg (standard deviation: ± 6.54; n=18). The minimum mean DBP for 22 mg/m^2 (3 h infusion) was noted on EOS visit at 72.4 mmHg (standard deviation: ± 10.32; n=36) and the maximum mean DBP was noted on Course 6 (Day 1) at 83.3 mmHg (standard deviation: ± 5.77; n=3). The minimum mean SBP for 16 mg/m^2 was noted on Course 5 (Day 1) at 118 mmHg (standard deviation: ± 24.90; n=5) and the maximum mean SBP was noted on FU visit at 133.7 mmHg (standard deviation: ± 19.16; n=7). The minimum mean SBP for 22 mg/m^2 (30 min infusion) was noted on Course 6 (Day 1) at 116.3 mmHg (standard deviation: ± 11.09; n=4) and the maximum mean SBP was noted on Course 2 (Day 1) at 128.6 mmHg (standard deviation: ± 16.53; n=31). The minimum mean SBP for 22 mg/m^2 (3 h infusion) was noted on Course 4 (Day 1) at 115.4 mmHg (standard deviation: ± 13.39; n=12) and the maximum mean SBP was noted on Course 2 (Day 1) at 128.9 mmHg (standard deviation: ± 16.40; n=32).

Heart rate was within the normal range of 60-100 beats per minute (bpm) across the treatment cycles in all the 3 treatment arms.

Overall, 1 out of 128 subjects (0.8%; in treatment arm A) was reported with an AE of Grade 0 "body temperature increased" at the baseline.

Conclusion(s)

This study did not meet its primary endpoint. The response rates in all treatment arms were too low to conclude success. The most common adverse events were polyneuropathy, fatigue, constipation, and nausea. The incidence of adverse events indicating neurotoxicity was markedly higher in the 22 mg/m^2 arms than in the 16 mg/m^2 arms. Both efficacy and neurotoxicity appear to be dose-dependent. In conclusion, this study indicated that ZK 219477 as second-line therapy had limited activity in subjects with advanced non-small-cell lung cancer who had failed previous treatment with a platinum-based chemotherapy.

Publication(s):	Heigener DF, von Pawel J, Eschbach C, Brune A, Schmittel A, Schmelter T, Reck M, Fischer JR. Prospective, multicenter, randomized, independent-group, open-label Phase II study to investigate the efficacy and safety of three regimens with two doses of sagopilone as second-line therapy in patients with Stage IIIB or IV non-small-cell lung cancer. Lung Cancer. 2013 Jun;80(3):319-25. doi: 10.1016/j.lungcan.2013.02.007. Epub 2013 Mar 20.

Date Created or Date Last Updated:	17 OCT 2014	Date of Clinical Study Report:	29 APR 2010