Clinical Study Synopsis

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Date of study report:	15 DEC 2009
Study title:	Prospective, multicenter, randomized, independent-group, open-label Phase II study to investigate the efficacy, safety, and tolerability of 4 regimen with 3 doses of ZK 219477 (16 and 12 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) in patients with metastatic breast cancer
Sponsor's study number:	91464 (309544)
NCT number:	NCT00288249
EudraCT number:	2005-003216-30
Sponsor:	Bayer HealthCare
Clinical phase:	Phase II
Study objectives:	Primary objective: To investigate the efficacy of 4 regimen with 3 doses of ZK 219477 in patients with metastatic breast cancer in progression following a maximum of 2 previous regimen of chemotherapy. Previous chemotherapy must have not included taxanes and vinca alkaloids. Secondary objective: To evaluate the safety and tolerability of 4 regimens with 3 doses of ZK 219477.
Test drug:	Sagopilone (ZK 219477, BAY 86-5302)
Name of active ingredient(s):	Sagopilone
Dose:	**Arm A**: 16 mg/m^2 body surface area (BSA) (maximum dose of 32 mg) as 3- h intravenous (IV) infusion **Arm B**: 12 mg/m^2 BSA (maximum dose of 24 mg) as 3-h IV infusion **Arms C:** 22 mg/m^2 BSA (maximum dose of 44 mg) as 0.5-h IV infusion **Arm D**: 22 mg/m^2 BSA (maximum dose of 44 mg) as 3-h IV infusion
Route of administration:	IV infusion
Duration of treatment:	Two to six courses at 3-week intervals, each course consisted of IV infusion on a single day; in the event of sustained clinical benefit, more than 6 treatment courses were allowed to be administered.
Reference drug:	Not applicable
Indication:	Metastatic breast cancer
Diagnosis and main criteria for inclusion:	• Females aged ≥18 years with histologically proven (at diagnosis), metastatic breast cancer, giving written informed consent, with at least 1 unidimensionally measurable lesion (suitable for the modified Response Evaluation Criteria in Solid Tumors [mRECIST] evaluation),World

	Health Organization (WHO) performance status of 0-1, with progression of disease following a maximum of two previous steps of chemotherapy, including treatments in an adjuvant or neo-adjuvant setting • No previous taxane or vinca alkaloid treatment and no more than 1 non-cytotoxic therapy (biologic agents), no radiotherapy, chemotherapy, or immune/biologic therapy within 3 weeks prior to first dose of ZK 219477, adequate recovery from previous surgery, radiation, and chemotherapy • Adequate function of major organs and systems ▪ Hematopoietic: Hemoglobin ≥10 g/dL; WBC ≥3000/mm^3; absolute neutrophil count ≥1500/mm^3; platelet count ≥100000/mm^3 ▪ Hepatic/Renal: Bilirubin within normal limits; aspartate aminotransferase/alanine aminotransferase (AST/ALT) ≤5 times the upper limit of normal (ULN), creatinine ≤2 mg/dL ▪ Cardiovascular: No New York Heart Association (NYHA) class III or IV heart failure; no unstable angina pectoris; no arrhythmia needing continuous treatment; no other uncontrolled concurrent illness • Negative pregnancy test at enrollment (females of childbearing potential only) and agreement to use highly effective contraception methods (intra-uterine contraceptive device [IUCD], condoms, oral contraceptives, or other adequate barrier contraception) in females of child-bearing potential
Study design:	This was a prospective, multicenter, randomized, independent-group, open-label, Phase 2 study to investigate the efficacy, safety, and tolerability of 4 regimen with 3 doses of ZK 219477 (16 and 12 mg/m^2 BSA as a 3-h infusion or 22 mg/m^2 BSA as a 0.5-h or 3-h infusion) in subjects with metastatic breast cancer. Randomization was done between Arms A, B, C, and D mentioned above. In total, a minimum of 15 and a maximum of 27 evaluable subjects were recruited for each arm. **Step 1**: Fifteen evaluable subjects with results other than "unknown" for "best overall response" per arm. If at least 5 subjects show response, Step 2 was initiated within the respective treatment arm. **Step 2**: Twelve additional evaluable subjects per arm with results other than "unknown" for "best overall response."
Methodology:	Each subject after screening was scheduled to receive one infusion of ZK 219477 every 3 weeks; each infusion corresponded to one treatment course. If deemed necessary (e.g., due to toxicity) an infusion may be postponed by up to 2 weeks; for each subject, only one such postponement was allowed during the whole study. During the main part of the study, 2-6 treatment courses were planned for each subject, with prolongation of treatment if indicated. The conduct of each course was similar, with 3 visits

	scheduled per course, except for Course 6 (only 2 visits scheduled). End-of-study visit was scheduled 3-4 weeks after last study dose was administered. Follow-up evaluations were done for selected subjects only. Subjects who had no evidence of tumor progression or symptomatic deterioration at the end of follow-up entered long-term follow-up phase (approximately every 6 months until progressive disease [PD]). Tumor scans (spiral computed tomography [CT], magnetic resonance imaging [MRI], CT with contrast] were performed for efficacy assessment at screening, and every 2 cycles thereafter until tumor progression. Second radiological assessment was done 6 weeks after the first assessment to confirm complete response (CR) or partial response (PR). Adverse events (AEs) were monitored throughout the study for safety assessment.
Study center(s):	The study was conducted at 25 centers in 11 countries: 2 centers in Austria:, 1 center in Belgium, 3 centers in Bulgaria, 5 centers in France, 1 center in Germany, 4 centers in Italy, 2 centers in Slovakia, 1 center in Slovenia, 2 centers in Spain, 3 centers in Poland, 1 center in United Kingdom.
Publication(s) based on the study (references):	None at the time of report creation.
Study period:	Study Start Date: 13 DEC 2005 Study Completion Date: 15 JAN 2009
Early termination:	The study did not meet its primary endpoint in 3 of the 4 treatment arms. None of the treatment arms met stage 1 criteria for efficacy (≥5 responders); therefore the study was prematurely terminated after enrollment of subjects.
Number of subjects:	Planned: 60-108 subjects (15-27/treatment arm) Analyzed: 82 subjects
Criteria for evaluation	
Efficacy:	• Primary efficacy variable: The proportion of subjects with either CR or PR according to the mRECIST criteria as best overall response after 6 courses of therapy (i.e., before Course 7). • Secondary efficacy variables ▪ Response duration (defined as the 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 PD was documented) ▪ Time to progression (defined as time from the start of study treatment to the first objective evidence of tumor progression, symptomatic deterioration, or death from cancer) ▪ Progression-free interval • Time to death
Safety:	Adverse events were coded by using Medical Dictionary for Regulatory

	Activities (MedDRA), Version 10.0. AEs were classified per seriousness, and causal relationship to study drug. The intensity of the AE was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. Other safety variables included vital signs (body temperature, heart rate, systolic and diastolic blood pressure), neurotoxicity score (Scottish Gynaecological Cancer Trials Group [SGCTG] Neurotoxicity Score), 12-lead ECG, and laboratory examinations (serum chemistry, hematology, coagulation, urinalysis).
Statistical methods:	Analysis sets: The statistical analysis was done using full analysis set (FAS) that included all subjects assigned to study treatment, safety set (SAF) that included all FAS subjects with at least one intake of study drug, per protocol set (PPS) that included all FAS subjects with no major protocol deviation, and primary analysis set (PAS) that included all FAS subjects for whom the primary efficacy variable was assessable. Demographics and baseline characteristics: Descriptive statistics and/or frequency tables were used as appropriate. Efficacy: The efficacy variables were analyzed in the FAS, in the PPS, and in the PAS. The analysis of the primary efficacy variable in the PAS was considered as primary analysis. Due to the sequential study design (Simon's two-stage design), it was ensured that the PAS consisted of exactly 15 subjects per group for the first step and exactly 12 subjects per group in the second step, if applicable. The primary efficacy analysis included testing a null hypothesis that the overall tumor response rate was ≤0.25 versus an alternative hypothesis that the overall tumor response rate was >0.25 (one-sided type-one error probability of 0.10 and type-two error rate of 0.20; i.e., 80% power). No type-one error adjustment for multiplicity was done. The target response rate ("good response") was 0.45. In addition, the response probabilities and the 80% confidence interval (CI) were calculated. As an exploratory measure, a corresponding 90% CI for differences in response rates between the treatment arms 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% confidence intervals (95% CI) were calculated for each treatment arm separately and overall. According to Simon's two-stage design, an interim analysis was performed when the overall tumor response data was available from the evaluable Step-1 subjects, 15 subjects of the PPS per arm. Safety analysis: The SAF was used for the analyses of the safety variables. Safety variables were summarized by descriptive statistics and/or frequency tables.
Substantial protocol changes:	Protocol Amendment No. 1 from 03 JUL 2006 introduced the following change - Addition of 2 treatment arms. In order to find the optimum regimen in terms of efficacy, tolerability, and convenience, 2 treatment arms were added to the present study: Arm C: 22 mg/m² of ZK 219477 as a 30-min IV

	infusion and Arm D: 22 mg/m² of ZK 219477 as a 3-h IV infusion. Protocol Amendment No. FRA 01 from 07 MAR 2006 introduced the following change - Addition of an electromyogram examination including a nerve conduction study to better evaluate the peripheral neuropathy possibly induced by ZK 219477. This amendment was applicable only to France.

Subject disposition and baseline

A total of 88 subjects were screened for inclusion in the study. Six subjects failed screening, leading to a total of 82 randomized subjects (15 subjects in the 12 mg/m^2 arm, 27 subjects in the 16 mg/m^2 arm, 22 subjects in the 22 mg/m^2 0.5-h arm, and 18 subjects in the 22 mg/m^2 3-h arm), who received at least 1 infusion of ZK 219477 (FAS). All of the 82 treated subjects were included in the FAS and in the SAF. One subject each in the 12 mg/m^2 arm, 16 mg/m^2 arm, and 22 mg/m^2 0.5-h arm and 2 subjects in the 22 mg/m^2 3-h arm were excluded from the PPS because of major protocol violations. The PAS included the first 15 evaluable subjects each in the 16 mg/m^2, 22 mg/m^2 0.5 h, and the 22 mg/m^2 3-h arms, and the remaining 14 evaluable subjects in the 12 mg/m^2 arm, since only 14 subjects were assigned to the PPS in this arm.

The mean age of the FAS population was 58.4 ± 9.2 years (median: 58.5 years; range: 33–76 years). All but 1 subject (98.8%) were of Caucasian origin. At initial diagnosis, about half of the subjects (47.6%) had an invasive ductal carcinoma, and the disease stage according to the International Union Against Cancer (UICC) scale ranged between stage I (18.3%) and stage IV (12.2%), with the majority of subjects (67.1%) presenting with a stage I to IIB disease. At screening, all subjects had advanced disease. Almost all (93.9%) of the subjects had already undergone previous drug treatment for breast cancer, i.e., 6.1% (n=5) of all subjects had not received prior drug treatment. Also, 84.0% had received prior radiotherapy, and 93.9% had undergone surgery or endoscopic procedures. The subjects' WHO performance status at screening was 0 (in 46.3%) or 1 (in 50.0%). One subject (1.2%) in the 12 mg/m^2 arm had a WHO performance status 2, and in 1 subject each in the 12 mg/m^2 and the 22 mg/m^2 0.5-h arms the assessment of the WHO performance status was not done. The distribution of the WHO performance status was overall well balanced among the treatment arms. Only in the 16 mg/m^2 arm were markedly more subjects Grade 1 (63.0%) than Grade 0 (37.0%). In addition to the 11 subjects who discontinued the study due to PD, a further 36 subjects (43.9%) withdrew from study medication before Course 6. One of the subjects withdrew consent; all others terminated the study because of AEs (mostly peripheral neuropathy). The highest drop-out rates of about 60% occurred in the two 22 mg/m^2 arms.

The FAS (equals SAF) underwent a total of 297 treatment courses, thereof 285 with infusions. No subject in the 22 mg/m^2 arms received more than 6 infusions. The maximum numbers of infusions in the other 2 dose groups were 9 in 1 subject in the 12 mg/m^2 arm and 8 in 1 subject in the 16 mg/m^2 arm. There was no consistent pattern among the treatment arms with regard to the numbers of infusions actually administered, but most of the subjects received between 2 and 4 infusions. A total of 15 subjects (18.4%) received 6 or more infusions. No subject in the 12 mg/m^2 arm and 1 subject each in the 16 mg/m^2 and the 22 mg/m^2 3 h arms required a dose reduction with the first 5 treatment courses. However, in 7 of the 22 subjects (32.8%) in the 22 mg/m^2 0.5-h arm the dose had to be reduced during this period. The mean individual mean doses in the different dose arms were 11.8 ± 0.6 mg/m^2 (12 mg/m^2 arm), 15.9 ± 0.4 mg/m^2 (16 mg/m^2 arm), 21.1 ± 1.7 mg/m^2 (22 mg/m^2 0.5-h arm), and 21.9 ± 0.6 mg/m^2 (22 mg/m^2 3-h arm). Thus, the mean dose intensities in the different arms were consistently >98%.

Efficacy evaluation

Primary variable: The primary efficacy variable, the proportion of responders (CR or PR as best overall response after 6 treatment courses), was analyzed in the 59 subjects in the PAS. No subject in the PAS achieved CR. Only the 22 mg/m^2 0.5-h arm achieved 5 responders (33.3%), which was the minimum number of responders necessary in stage 1 to proceed with stage 2 of Simon's two-stage design.

As a supportive analysis, the response rates were also analyzed in the FAS and in the PPS. In the FAS, PR as best response was documented for 2 additional subjects (1 in the 16 mg/m^2 arm, the other in the 22 mg/m^2 3-h arm). One of these subjects (16 mg/m^2 arm; PPS) was enrolled after the 15th evaluable subject was available for the PAS, and the second subject (22 mg/m^2 3-h arm; FAS) was not valid for efficacy, because of a major protocol deviation (violation of inclusion/exclusion criteria). Therefore, the response rates in the 22 mg/m^2 3-h arm were 3 in the PPS and 4 in the FAS. Based on the response rates, the response probabilities (with 80% CI) and the differences (with 95% CI) between the two lower dose arms (16 mg/m^2 arm minus 12 mg/m^2 arm) and the two 22 mg/m^2 arms (22 mg/m^2 3-h arm minus 22 mg/m^2 0.5-h arm) were calculated for the PAS. A summary of the best overall response is shown for the PAS, PPS, and FAS in Table 1.

The data displayed in Table 2 show that a response probability of >25% was only to be expected in the 22 mg/m^2 0.5-h arm (33.3%; 95% CI: 20.0%-51.4%). In all other arms, the response probabilities were <25%. Thus, the null hypothesis of a response probability of >25% was not rejected in these arms. Although the criterion for continuation in step 2 was met in the 22 mg/m^2 0.5-h arm, it had already been decided to close this arm due to the level of neurotoxicity observed with this regimen. The differences in the response probabilities between the two low-dose arms and between the two high-dose arms were statistically not relevant, because the 90% CI for the difference included zero in both comparisons.

Table 1: Best overall response (according to mRECIST) at the end of Course 6 (PAS, PPS, and FAS)

Treatment arm	Response category	PAS N = 59 n (%)	PPS N = 77 n (%)	FAS N = 82 n (%)
12 mg/m^2 3-h	Response (CR + PR)	0 (0.0)	0 (0.0)	0 (0.0)
	CR	0 (0.0)	0 (0.0)	0 (0.0)
	PR	0 (0.0)	0 (0.0)	0 (0.0)
	SD	5 (35.7)	5 (35.7)	5 (33.3)
	PD	9 (64.3)	9 (64.3)	9 (60.6)
	ND/UNK/NA	0 (0.0)	0 (0.0)	1 (6.7)
16 mg/m^2 3-h	Response (CR + PR)	2 (13.3)	3 (11.5)	3 (11.1)
	CR	0 (0.0)	0 (0.0)	0 (0.0)
	PR	2 (13.3)	3 (11.5)	3 (11.1)
	SD	6 (40.0)	10 (38.5)	10 (37.0)
	PD	6 (40.0)	11 (42.3)	11 (40.7)
	ND/UNK/NA	1 (6.7)	2 (7.4)	3 (11.1)
22 mg/m^2 0.5-h	Response (CR + PR)	5 (33.3)	5 (23.8)	5 (22.7)
	CR	0 (0.0)	0 (0.0)	0 (0.0)
	PR	5 (33.3)	5 (23.8)	5 (22.7)
	SD	7 (46.7)	9 (42.9)	10 (45.5)
	PD	3 (20.0)	6 (28.6)	6 (27.3)
	ND/UNK/NA	0 (0.0)	1 (4.8)	1 (4.5)
22 mg/m^2 3-h	Response (CR + PR)	3 (20.0)	3 (18.8)	4 (22.2)
	CR	0 (0.0)	0 (0.0)	0 (0.0)
	PR	3 (20.0)	3 (18.8)	4 (22.2)
	SD	8 (53.3)	8 (50.0)	9 (50.0)
	PD	4 (26.7)	4 (25.0)	4 (22.2)
	ND/UNK/NA	0 (0.0)	1 (6.3)	1 (5.6)

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

Table 2: Response probability and differences between low-dose arms and high-dose arms (PAS)

Treatment arm	Response probability [80% confidence interval][a]	Difference [90% confidence interval][b]
12 mg/m^2 3-h	0.0000 [0.0000; 0.1309]	0.1333 [-0.1669; 0.4838]
16 mg/m^2 3-h	0.1333 [0.0553; 0.2822]	
22 mg/m^2 0.5-h	0.3333 [0.2003; 0.5137]	-0.1333 [-0.4427; 0.1967]
22 mg/m^2 3-h	0.2000 [0.1041; 0.3636]	

[a] Blyth-Still-Casella method.
[b] Differences: 16 mg/m^2 3-h minus 12 mg/m^2 3-h and 22 mg/m^2 3-h minus 22 mg/m^2 0.5-h

Secondary variables: 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 as well as the median progression-free interval (both analyses yielded nearly identical results for both variables) were numerically longer in the 22 mg/m^2 dose arms than in the lower dose arms. However, the differences were not statistically relevant because of the largely overlapping 95% CI both in the FAS and the PPS. As a consequence of the early termination of this study, no reliable results were obtained for time to death. Due to the low number of responders (see Table 1), no statistical evaluation of the duration of response was performed.

Table 3: Median time to tumor progression and progression-free survival (FAS and PPS)

Variable	Treatment arm	Point estimate for the median [95% CI][a]	
		FAS N = 82	PPS N = 77
Time to tumor progression [days]	12 mg/m^2 3-h	56 [42; 84]	62 [42; 126]
	16 mg/m^2 3-h	82 [41; 196]	82 [41; 196]
	22 mg/m^2 0.5-h	199 [52; 202]	199 [49; 202]
	22 mg/m^2 3-h	126 [83; 270]	100 [78; 270]
Progression free survival [days]	12 mg/m^2 3-h	56 [42; 84]	62 [42; 126]
	16 mg/m^2 3-h	79 [41; 196]	82 [41; 196]
	22 mg/m^2 0.5-h	199 [52; 202]	199 [49; 202]
	22 mg/m^2 3-h	126 [83; 270]	100 [78; 270]

[a] Kaplan-Meier-Product limit method.

Safety evaluation

An overview of the AEs in this study is shown in Table 4 below. Eleven subjects (13.4%) died. Thereof, 3 (20%) belonged to the 12 mg/m^2 arm, 3 (11.1%) to the 16 mg/m^2 arm, 4 (18.2%) to the 22 mg/m^2 0.5-h arm, and 1 (5.6%) to the 16 mg/m^2 3-h arm. Nine of them died from PD, 1 subject (16 mg/m^2 arm but not treated) died from congestive heart failure before any study drug was given, and in 1 subject (22 mg/m^2 0.5 h arm), the exact cause of death was unknown (death during follow-up, 173 days after last dose of study drug, while on a regimen of doxorubicin; no SAE reported; the investigator suspected bleeding in the lungs or gastrointestinal tract). A total of 13 subjects (15.9%) experienced at least 1 SAE during this study. One additional SAE (febrile neutropenia) occurred in a subject in the 22 mg/m^2 3-h arm during the follow-up. The pattern of SAEs in study subjects was diverse. SAEs that occurred in more than 1 subject were asthenia (1 subject each in the 12 mg/m^2 and in the 16 mg/m^2 arms, and 2 subjects in the 22 mg/m^2 0.5-h arm), dehydration (1 subject each in the 16 mg/m^2 and 22 mg/m^2 0.5-h arms), and peripheral neuropathy (peripheral sensory neuropathy in 1 subject, and peripheral sensory neuropathy in combination with peripheral motor neuropathy in another subject; both in the 16 mg/m^2 arm).

Five subjects in the 16 mg/m^2 arm and 1 subject each in the other treatment arms experienced SAEs, which were considered by the investigators to be at least possibly related to ZK 219477. These were 1 case each of atrial flutter, dehydration, nausea, orthostatic hypertension, supraventricular arrhythmia, T-wave inversion, vomiting, and febrile neutropenia (during the follow-up period), and 2 cases each of asthenia and peripheral neuropathy. All other SAEs were considered not related or unlikely to be related to ZK 219477.

Thirty-six subjects (43.9%) discontinued the study drug due to AEs and 31 (35.2%) of them due to peripheral neuropathy. The remaining 5 subjects discontinued the study drug due to asthenia (n=1), superior vena cava thrombosis (n=1), mental anguish (n=1), withdrawal of consent due to the AEs asthenia and anorexia (n=1), and cerebrovascular accident (n=1).

All but 4 subjects (95.1%) reported at least 1 AE during the study. About half of the subjects (51.2%) experienced more than 6 AEs, in particular subjects in the 22 mg/m^2 0.5-h arm (68.2%). The highest incidence rates (≥20%) of AEs were observed for peripheral neuropathy (86.6%), asthenia (25.6%), alopecia (23.2%), nausea (22.0%), and myalgia (22.0%). Especially for these AE, there was a general trend for higher incidence rates in the 22 mg/m^2 0.5-h arm.

Table 4: Summary of adverse events during the study (SAF)

Category	12 mg/m^2 3-h N = 15 n (%)	16 mg/m^2 3-h N = 27 n (%)	22 mg/m^2 0.5-h N = 22 n (%)	22 mg/m^2 3-h N = 18 n (%)	Total N = 82 N (%)
Any SAE	2 (13.3)	7 (25.9)	3 (13.6)	1 (5.6)	13 (15.9)
AEs leading to withdrawal from study drug	1 (6.7)	12 (44.4)	12 (54.5)	11 (61.1)	36 (43.9)
Any AE	14 (93.3)	25 (92.6)	22 (100.0)	17 (94.4)	78 (95.1)
CTCAE grade 3	5 (33.3)	8 (29.6)	9 (40.9)	12 (66.7)	34 (41.5)
CTCAE grade 4	1 (6.7)	2 (7.4)	1 (4.5)	1 (5.6)	5 (6.1)
Peripheral neuropathy [1]	10 (66.7)	22 (81.5)	22 (100.0)	17 (94.4)	71 (86.6)
CTCAE grade 3	2 (13.3)	5 (18.5)	7 (31.8)	8 (44.4)	22 (26.8)
CTCAE grade 4	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	1 (1.2)
Hematological AEs	4 (26.7)	1 (3.7)	2 (9.1)	2 (11.1)	9 (11.0)
CTCAE grade 3	2 (13.3)	0 (0.0)	0 (0.0)	2 (11.1)	4 (4.9)

[1] Includes the following MedDRA preferred terms: Coordination abnormal, dysaesthesia, dysgeusia, gait abnormal, hypoaesthesia, hyporeflexia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy, toxic neuropathy.

A total of 47.5% subjects experienced AEs of CTCAE Grades 1 or 2 at maximum; in 41.5%, the maximum intensity of an AE was CTCAE Grade 3; and in 6.1%, the maximum intensity of an AE was CTCAE Grade 4. By far the most frequent AE of CTCAE Grades 3 or 4 was peripheral neuropathy (28.0% or 23 of the 82 subjects), but CTCAE Grade 4 peripheral neuropathy occurred only in 1 subject (16 mg/m^2 arm). The other AEs of CTCAE grades ≥3 occurred in a maximum of 2 subjects per dose arm.

The majority of patients (93.9%) experienced at least 1 drug-related AE during the study. The most frequent, expected, drug-related AE in all dose groups was peripheral neuropathy (86.6%). All AEs indicating neurotoxicity referred to peripheral neuropathy and were expected to be the most clinically relevant events in the study. Hematological AEs were relatively uncommon (11.0% in total) and the different types of hematological AEs occurred at frequencies of <5%. In 2 subjects each in the 12 mg/m^2 and 22 mg/m^2 3-h arms, at least 1 hematological AE was of CTCAE Grade 3. No hematological AEs of CTCAE Grade 4 or higher were reported.

No clinically consistent trends were observed for any laboratory parameter in the different 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. Changes to CTC Grade 4 occurred for gamma-glutamyltransferase (1 subject in the 22 mg/m^2 3-h arm) and neutrophils (1 subject each in the 16 mg/m^2 and the 22 mg/m^2 3-h arms). With the exception of gamma-glutamyltransferase, in which 9 of the 82 subjects (11.0%) worsened to CTC Grade 3, changes to CTC Grade 3 in other laboratory parameters occurred only in single cases.

The treatment with ZK 219477 had no apparent influence on vital signs (body temperature, heart rate, and blood pressure). According to the overall interpretation of the ECGs recorded before each study drug administration (available for 70 subjects at screening and for 80 subjects at Course 1/Day 1), 12 subjects entered the study with abnormal findings. At the end of the study, abnormal ECG findings were reported for 11 of the 57 subjects with recordings. There was no consistent pattern with regard to abnormal findings, i.e., some subjects entered the study with abnormal findings, which normalized during the study and others newly developed abnormal findings. In most cases, the abnormalities were transient and occurred on a single occasion only. Besides one case of atrial flutter at screening (22 mg/m^2 0.5-h arm), none of the ECG findings were assessed as clinically relevant. The 3 cardiac SAEs (atrial flutter, supraventricular arrhythmia, and T-wave inversion on the ECG) occurred after study drug administration or at unscheduled visits and were, therefore, not considered in the overall interpretation of the per protocol required ECGs.

Patient scores in the SGCTG neurological questionnaire were similar across the treatment arms. The total mean scores increased over the course of the study, from 0.7 ± 2.4 (median 0.0) at the screening to 9.8 ± 4.8 (median 10.0) at end of the study, indicating a marked worsening of neurological symptoms. The worsening was numerically more pronounced in the two 22 mg/m^2 arms (median changes: 10.0 and 12.5) than in the lower dose arms (median changes: 3.0 and 6.0).

Overall conclusions

This study did not meet its primary endpoint in 3 of the 4 treatment arms. None of the treatment arms using the 3-h infusions (12 mg/m^2, 16 mg/m^2, and 22 mg/m^2 3-h arms) met stage 1 criteria for efficacy (≥5 responders), as only 2 and 3 subjects in the 16 mg/m^2 and 22 mg/m^2 3-h arms of the PAS, respectively, achieved confirmed partial response. Although 5 subjects in the 22 mg/m^2 0.5-h arm showed partial response, recruitment in this treatment arm, too, was prematurely terminated after enrollment of 22 subjects. In the first instance, this was due to the high level of neurotoxicity (peripheral neuropathy) observed with this regimen. The most common AEs were peripheral neuropathy, asthenia, alopecia, nausea, and myalgia. It appeared that subjects in the 22 mg/m^2 arms (especially in the 22 mg/m^2 0.5-h arm) experienced more frequent and more severe peripheral neuropathy than those in the lower dose arms. While the overall safety profile of ZK 219477 was comparable with that reported in other studies, the level of peripheral neuropathy and its impact on the subjects' quality of life was higher than expected. This applied not just to the highest dose level (22 mg/m^2), but also to 16 mg/m^2 given as a 3-h infusion, which was the most extensively investigated regimen in the Phase 2 studies

In conclusion, this study indicated that ZK 219477 had limited activity in taxane- and vinca alkaloid-naïve metastatic breast cancer subjects. Treatment was associated with a considerable level of peripheral neuropathy.