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:	16 DEC 2008
Study title:	Randomized, multicenter, prospective two-arm, open-label Phase II study to investigate the efficacy and safety of two ZK 219477 i.v. infusions (3-hour infusion of 16 mg/m^2 versus 0.5-hour infusion of 16 mg/m^2) in patients with recurrent ovarian cancer progressing during, or within 6 months of the end of platinum-based chemotherapy
Sponsor's study number:	91447
NCT number:	NCT00246688
EudraCT number:	2005-000635-15
Sponsor:	Bayer HealthCare
Clinical phase:	Phase II
Study objectives:	Primary objective: To investigate the efficacy of ZK 219477 in subjects with recurrent ovarian cancer progressing during or within 6 months of the end of platinum-based chemotherapy (proof of concept). Secondary objectives: To investigate the safety and tolerability of the above treatment. To assess the impact of the infusion duration on the tolerability of ZK 219477.
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:	Intravenous (i.v.) infusion
Duration of treatment:	One infusion every 3 weeks; up to six infusions (approx. 18 weeks)
Reference drug:	Not applicable
Indication:	Recurrent, platinum pre-treated ovarian cancer
Diagnosis and main criteria for inclusion:	Females aged 18 years or over, histologically proven cancer of any of the following types: epithelial ovarian cancer, peritoneal cavity cancer, fallopian tube cancer, up to two previous chemotherapies; the most recent must have been a platinum-containing therapy, progression of disease or symptomatic relapse during or within 6 months of previous therapy, 4 weeks or more since prior radiotherapy or chemotherapy, 3 weeks or more since prior immunotherapy, adequate recovery from previous surgery, radiotherapy, and chemotherapy (excluding alopecia), survival expectation of 3 months or more.
Study design:	The study was conducted in a prospective, randomized, two-arm, open-label, multi-center design.

Methodology: Eligible subjects having completed the screening assessment were randomly assigned to one of the two parallel treatment arms on a 1:1 basis. In order to assess the impact of the infusion regimen on the tolerability of ZK 219477, the following treatment regimens were evaluated:

- Arm 1: 16 mg/m^2 ZK 219477 given as a 3-h infusion (maximum dose 32 mg)
- Arm 2: 16 mg/m^2 ZK 219477 given as a 0.5-h infusion (maximum dose 32 mg)

In both treatment arms, subjects were scheduled to receive one infusion of ZK 219477 every 3 weeks; each infusion corresponded to one treatment course. Subjects received a minimum of two and a maximum of six treatment courses. Subjects with stable disease at the first response evaluation received further treatment if this was considered appropriate by the treating physician. In the event of sustained clinical benefit, treatment was continued for longer after mutual consultation of the investigator and the sponsor.

Tumor response was assessed at regular intervals by the following methods, depending on the measurability of the subject's disease:

- Subjects with measurable disease: Objective response according to a modified version of the Response Evaluation Criteria in Solid Tumors (modRECIST) as assessed radiographically by computed tomography (CT) scan and/or magnetic resonance imaging (MRI), as clinically appropriate.
- Subjects without measurable disease: Serum Cancer Antigen 125 (CA 125) response according to the Gynaecological Cancer Intergroup (GCIG) criteria (defined as a decrease of CA 125 levels of at least 50% compared to baseline).

Simon's two-step design was applied to both treatment arms independently (optimal design variant). For each arm, this implied the following: 13 subjects were to be treated initially. If ≤1 responder (response per modRECIST or CA 125 50% response) was found at this first step, the study was terminated; if ≥2 responders were found in either arm, that arm was to accrue a further 21 subjects. The overall results of each arm were to be considered positive if ≥6 responders were found among the total of 34 subjects.

For each subject, the screening visit took place within 2 weeks of the first dose of study drug. On Day 1 of each course, study drug was administered. The end of study (EOS) visit was conducted approximately 3-4 weeks after the last administration of study drug. All subjects with possibly drug-related toxicities of Common Terminology Criteria (CTC) Grade ≥ 2 persisting at EOS were followed up for a maximum of 3 months after the EOS visit until recovery or stabilization. Subjects who had no evidence of tumor

	progression or symptomatic deterioration at the EOS, and who did not receive any further anti-neoplastic therapy, were scheduled for additional assessments (additional efficacy follow-up) until disease progression. The visits were scheduled by the investigator as clinically indicated. Tumor evaluation (tumor scans by CT or MRI) according to modRECIST criteria was performed at screening and continued every two cycles until tumor progression. Complete response (CR) or partial response (PR) must be confirmed with a second radiological assessment 6 weeks after the first assessment. Blood samples for CA 125 were collected and World Health Organization (WHO) performance status was evaluated at the screening visit, pre-dose on Day 1 of each treatment course, and the EOS visit. For subjects who had no evidence of tumor progression or symptomatic deterioration at the EOS, efficacy parameters (tumor scans, modRECIST, CA 125, and WHO performance) were additionally measured in further efficacy follow-up visits until disease progression. Adverse events (AEs) coded according to common terminology criteria for AEs (CTCAE) were monitored from Day 1 of treatment Course 1 up to follow-up visit. Physical exam findings, blood pressure (BP), heart rate (HR) and neurotoxicity score (by means of Scottish Gynaecological Cancer Trials Group [SGCTG] neurological questionnaire) were measured at screening, Day 1 for each treatment course, at the EOS, and or the follow-up visit, if clinically indicated (neurotoxicity score). 12-lead-electrocardiogram (ECG) was performed at the screening visit, pre-dose and post-dose on Day 1 of each treatment course and the EOS visit.
Study center(s):	There were 14 study centers in the United Kingdom of which 12 were recruiting.
Publication(s) based on the study (references):	Rustin G, Reed N, Jayson GC, Ledermann JA, Adams M, Perren T, et al. A phase II trial evaluating two schedules of sagopilone (ZK-EPO), a novel epothilone, in patients with platinum-resistant ovarian cancer. Ann Oncol. 2011 Nov; 22(11):2411-6.
Study period:	**Study Start Date:** 16 NOV 2005 **Study Completion Date:** 26 JUN 2007
Early termination:	Not applicable
Number of subjects:	**Planned:** 34 subjects **Analyzed:** 63 subjects
Criteria for evaluation	
Efficacy:	Based on modRECIST in subjects with measurable disease and CA 125 levels in subjects with non-measurable disease following variables of

efficacy were measured:

Primary efficacy variable:

- Proportion of responders

  Response was to be established as follows:

✓ Subjects with measurable disease: Best overall response (combined overall response obtained from all time points available for an individual subject) of "PR" or "CR" at any time after the start of study treatment

✓ Subjects without measurable disease: ≥50% reduction in CA 125 levels compared to the pretreatment sample (Baseline, Day 1 pre-infusion).

Secondary efficacy analysis:

- CA 125 response
- Duration of response (time period between the first date that the measurement criteria for CR or PR as "overall response" were met [whichever status was recorded first] and the first date that "progressive disease [PD]" as overall response was documented or other criteria for PD were fulfilled in subjects with measurable disease; time between first date of CA 125 response and first date of CA 125 progression according to the relevant GCIG criteria in subjects without measurable disease)
- Time to disease progression (the time period between randomization and the first assessment of PD)
- Time to death (the time period between randomization and death)
- Progression-free survival (PFS: the time period between randomization and death or disease progression, whichever is recorded first)

Safety: AE assessment based on CTCAE (Version 3.0), standard safety laboratory examinations, 12-lead ECG, neurotoxicity score, WHO performance status

Statistical methods: The study population was divided into the following analysis sets:

Full analysis set (FAS): It included all subjects assigned to study treatment (i.e., who received a randomization number).

Safety analysis set (SAF): It included all randomized subjects who received at least one study drug administration.

Per-protocol set (PPS): It consisted of all valid cases, i.e. all subjects who showed no major protocol deviations.

Primary analysis set (PAS): It included all subjects for whom the primary efficacy variable was assessable.

Within each treatment arm, Simon's two-step design was used independently of the other arm, applying the same assumptions.

Step 1**:** Thirteen evaluable subjects with results other than unknown (UNK)

for "best overall response" per arm were included. If at least two subjects showed response, Step 2 was to be initiated in the respective treatment arm.

Step 2**:** Twenty-one additional evaluable subjects per arm with results other than UNK for "best overall response" were included.

In total, a minimum of 13 and a maximum of 34 evaluable subjects were recruited for each arm.

This design ensured the specified error probabilities (alpha, beta) and minimized the average sample size, should there have been a poor response.

The overall sample size was between 26 and 68 evaluable subjects.

The primary efficacy analysis included testing null hypotheses that the overall tumor response rate was ≤0.10 *versus* an alternative hypothesis that the overall tumor response rate was >0.10 (one-sided type-one error rate of 0.10 and type-two error rate of 0.20; i.e. 80% power) using Simon's two-step optimal design in each treatment arm. The target response rate (called "good response") was 0.25.

Accordingly, if ≥6 of the maximum 34 evaluable subjects per treatment arm showed response, the study outcome was considered as successful for that treatment arm.

Estimates of the response rates and their confidence intervals (CIs) as well as a corresponding CI for rate differences were given. Time to progression was analyzed using the Kaplan-Meier product limit method. Other efficacy data were summarized as appropriate.

According to Simon's two-step design, an interim assessment was performed when the overall tumor response data were available from the 26 (13 per arm) evaluable Step 1 subjects.

Safety variables were summarized by means of descriptive statistics and/or frequency tables as appropriate. No subgroup analyses were planned; all analyses were performed separately for each treatment arm.

Substantial protocol changes:

Amendment 1 from date 08 AUG 2006 introduced the following changes:

- The addition of French study centers and logistical changes necessitated by this.
- The exclusion of subjects with mucinous tumors or clear cell tumors.
- The exclusion of subjects with a platinum-free treatment interval of >6 months.
- Additional guidance on specific toxicities and neurotoxicity.
- Further clarification of the scans required for the study.
- Further clarification of the use of CA 125 measurements to determine response in accordance with the GCIG definition published on 17 MAR 2004 in the *Journal of the National Cancer Institute* (JNCI).

- Further details on the collection, storage, and analysis of pharmacokinetic blood samples.
- Further clarification on events to be considered as serious AEs (SAEs).

Amendment 2 from date 02 NOV 2006 introduced the following changes:

- Changes to dose modification for the management of toxicity, allowing investigators to continue giving study drug at a dose of 16 mg/m^2 after a Grade 2 or 3 neurotoxicity
- Changes to the procedure for drug accountability
- Correction of an ambiguity in the text concerning the premature termination of one study arm.

Subject disposition and baseline

A total of 74 subjects were screened for inclusion in the study, leading to a total of 63 who were randomized and treated with ZK 219477. All subjects received the same dose of ZK 219477 (16 mg/m^2 body surface area [BSA], once every 3 weeks) in one of two regimens: as a 3-h infusion in Arm 1 (38 subjects) and as a 0.5-h infusion in Arm 2 (25 subjects). All 63 subjects had recurrent ovarian cancer progressing during or within 6 months of the end of platinum-based therapy.

In total, 48 subjects completed study medication according to protocol and 15 subjects discontinued study medication prematurely. All subjects who received at least one dose of study medication were followed for the duration of the study.

The two treatment arms were comparable with respect to demographic and baseline characteristics. The 63 (1 Asian and 62 Caucasian women) randomized and treated subjects (mean age 60.4 ± 8.8 years, range 43-83 years) were included in the FAS and in the SAF. Due to protocol deviations, only 57 subjects were included in the PPS. The PAS included 47 subjects (the first 13 evaluable subjects from each arm of the first step of the study and the next 21 evaluable subjects from Arm 1 of the second step of the study).

In total, 31 (81.6%) subjects in the 3-h arm and 22 (88.0%) subjects in the 0.5-h arm reported previous diseases or surgeries. The two treatment arms were comparable with respect to history of ovarian cancer, based on histopathologic type and FIGO staging. All subjects had been diagnosed with either epithelial ovarian cancer (52 subjects), peritoneal cavity cancer (3 subjects), or fallopian tube cancer (8 subjects). The majority of subjects (41/63) were stage IIIC on the FIGO staging system at first diagnosis.

All 63 (100%) subjects had previously been treated with chemotherapy for ovarian cancer. Of these, 27 (42.9%) had received one therapy and 36 (57.1%) had received two therapies. All 63 subjects had received prior platinum therapy, and 33 (86.8%) subjects in the 3-h arm and 21 (84.0%) subjects in the 0.5-h arm had also received taxane therapy. The time between the last dose of platinum therapy and the start of treatment ranged from 28 to 217 days. Two subjects were treated more than 28 weeks (196 days + 14-day window) after the last dose of platinum therapy. Four subjects (all in the 3-h arm) had also

been treated with hormone therapy. Only one subject (in the 3-h arm) had received radiotherapy as prior therapy (22 days before start of treatment). Surgery (including endoscopic procedures) had been given as prior therapy to 27 (71%) subjects in the 3-h arm and to 20 (80.0%) subjects in the 0.5-h arm.

The two treatment arms were comparable with respect to baseline findings, and nearly all subjects (61/63; 96.8%) had at least one event. The subjects in the 3-h arm tended to have more events per subject than those in the 0.5-h arm. The MedDRA system organ classes (SOCs) most commonly cited were gastrointestinal disorders (45/63; 71.4%), nervous system disorders (34/63; 54.0%), general disorders (24/63; 38.1%), musculoskeletal and connective tissue disorders (23/63; 36.5%), and metabolism and nutrition disorders (19/63; 30.2%). The most frequently recorded baseline findings were constipation (19/63; 30.2%), abdominal pain (13/63; 20.6%), fatigue (12/63; 19.0%), and hypertension (11/63; 17.5%).

In the 3-h arm 3 subjects experienced non-fatal serious baseline findings. All three subjects remained in the study and started treatment as planned. In the 0.5-h arm no serious baseline findings were reported. Events indicating neurotoxicity were reported in nine (23.7%) subjects in 3-h arm and five (20.0%) subjects in 0.5-h arm at baseline.

Table 1 shows the number of subjects per treatment arm included in each analysis set.

Table 1: Analysis sets

Analysis set	16 mg/m^2 3 h N = 100%	16 mg/m^2 0.5 h N = 100%	Total N = 100%
Full analysis set (FAS)	38	25	63
Per protocol analysis set (PPS)	34	23	57
Primary analysis set (PAS based on FAS)	34	13	47
Primary analysis set (PAS based on PPS)	33	13	46
Safety analysis set (SAF)	38	25	63

Efficacy evaluation

The primary efficacy variable, the proportion of responders, was analyzed in 47 subjects in the PAS based on the FAS (3-h arm: 34 subjects, 0.5-h arm: 13 subjects). A total of six (12.8%) responders were found (3-h arm: 5 subjects, 0.5-h arm: 1 subject). To conclude success in either arm of the study, at least six responders were required in that arm. The response rate was estimated to be 0.1471. The 80% CI for the response rate in the 3-h arm was (0.0830, 0.2427). The response rate was therefore insufficient to conclude success.

The primary efficacy variable was also examined in a post hoc subgroup analysis in the PAS based on the PPS. Of the first 13 evaluable PPS subjects in the 3-h arm, three subjects were classified as responders. Among the next 20 subjects in that arm, three further responders were observed, leading to a total of six responders among 33 evaluable subjects. Based on this, success was concluded for this arm according to Simon’s two-stage procedure.

In the 0.5-h arm, response rates were insufficient to conclude success, since only 1/13 subjects in the first step was classified as a responder.

A secondary analysis was performed to measure tumor response rates among all treated subjects, including those "over-runners" who had been recruited to the 0.5-h arm before its discontinuation. In this analysis, performed in the FAS and PPS, a total of 10 responders were found (as measured by modRECIST or CA 125).

In the majority of subjects, CA 125 levels were elevated from the norm of 0-35 U/mL at baseline and remained elevated throughout the study. A total of 17 subjects (3-h arm: 11, 0.5-h arm: 6) had CA 125 level reductions of at least 50% between baseline and EOS.

For four subjects without measurable disease in the 3-h arm of the study CA 125 measurements were used also in the analysis of the primary efficacy variable. Two of these subjects had reductions in CA 125 levels between baseline and EOS. Among these subjects without measurable disease, a response, confirmed and maintained for at least 28 days, was seen in one subject.

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. Median time to disease progression in the FAS was estimated to be 81 days (95% CI [57 days, 182 days]) for the 3-h arm and 78 days (95% CI [45 days, 137 days]) in the 0.5-h arm. In the PPS, the median time to disease progression was estimated to be 91 days (95% CI [69 days, 212 days]) for the 3-h arm and 78 days (95% CI [45 days, 137 days]) for the 0.5-h arm.

Due to the small number of responders (10 subjects in the PPS), no statistical evaluation of the duration of response was performed. The two treatment arms were comparable, with duration of response ranging from 90 to at least 260 days.

In the FAS, the median time to death was estimated to be 211 days (95% CI [145 days, 340 days]) in the 3-h arm and 269 days (95% CI [157 days, 349 days]) in the 0.5-h arm. In the PPS, the median time to death was estimated to be 211 days (95% CI [143 days, 340 days]) in the 3-h arm and 238 days (95% CI [154 days, 349 days]) in the 0.5-h arm.

The median time of PFS in the FAS was estimated to be 81 days (95% CI [57 days, 182 days]) for the 3-h arm and 68 days (95% CI [42 days, 137 days]) for the 0.5-h arm. In the PPS, the median time of PFS was estimated to be 91 days (95% CI [69 days, 212 days]) for the 3-h arm and 68 days (95% CI [42 days, 86 days]) for the 0.5-h arm.

Safety evaluation

In total, 48 subjects completed the course of study medication per protocol. Of the 15 subjects who discontinued study medication prematurely, 11 withdrew due to AEs, 2 subjects withdrew consent, 1 subject died, and 1 subject discontinued due to another reason (subject's decision).

In total, 39 deaths were reported (21 in the 3-h arm and 18 in the 0.5-h arm), including those reported after EOS. Progression of study disease was given as the cause of death in the majority of cases (14/21 in the 3-h arm and 12/18 in the 0.5-h arm). No deaths were reported to be related to ZK 219477.

A total of 28 subjects (44.4%), 16 in the 3 h arm and 12 in the 0.5 h arm, experienced at least one SAE. A total of 20/28 subjects experienced SAEs that were classed as gastrointestinal disorders. The most frequently reported SAEs by preferred term were ascites (10 subjects), vomiting (7 subjects) and intestinal obstruction (6 subjects).

Two subjects in each arm experienced SAEs that were considered to be at least possibly related to ZK 219477. These were nausea in two subjects, and diarrhea, hypotension, pancytopenia, pain in extremity, paresthesia, pyrexia and vomiting each in one subject. All other SAEs were considered not related or unlikely to be related to ZK 219477.

All subjects reported at least one AE. A total of 61/63 subjects (96.8%) reported at least one AE during the main study and 10/19 subjects (52.6%) reported at least one AE during follow-up. A total of 908 events were reported in all.

The most frequently reported AEs were sensory neuropathy, constipation, nausea, diarrhea, fatigue, vomiting, arthralgia, and pain in extremity.

A total of 59 subjects (93.7%) experienced at least one AE related to study drug (3-h arm: 100%, 0.5-h arm: 84%). In the study population as a whole, sensory neuropathy (73.0%), nausea (36.5%), fatigue (34.9%), and arthralgia (30.2%) were the AEs most frequently considered to be drug related.

Drug-related AEs that occurred considerably less frequently in the 0.5-h arm than in the 3-h arm were pain in extremity and vomiting. Study drug related lethargy and abdominal pain occurred more frequently in the 0.5-h arm. The treatment arms were comparable with regard to the number of other drug-related AEs.

The most common drug-related AEs of CTCAE Grade 3 or higher were sensory neuropathy (10 subjects, 15.9%), pain in extremity (4 subjects, 6.3%) and arthralgia (3 subjects, 4.8%). All other drug-related AEs of Grade 3 or higher occurred in ≤2 subjects.

AEs indicating neurotoxicity were expected to be the most clinically relevant events in the study. The treatment arms were comparable with respect to the number of subjects experiencing AEs indicating neurotoxicity (3-h arm: 76.3%; 0.5-h arm: 72.0% during the treatment period) and nearly all of these events were rated as related to study drug. A difference between the two arms was seen in the intensity of AEs indicating neurotoxicity, which tended to be of greater intensity in the 3-h arm.

No clinically consistent trends were observed for any laboratory parameter in either treatment arm. Up to 12 subjects (approx. 20%) per visit had clinically relevant abnormalities or changes, but these were seen as a reflection of the severity of the subjects' underlying disease. Most laboratory abnormalities were of CTC Grade 1 or 2 toxicity. Most changes were from CTC Grade 0 to CTC Grade 1 or 2. Both treatment arms were equally affected by changes.

Considerable inter-subject variability was recorded for HR and BP, but no notable differences between the two treatment arms were recorded. No pattern of increases or decreases was evident.

The results of physical examinations identified no relevant trends and there were no relevant differences between the two treatment arms.

The overall ECG interpretation was normal in nearly all subjects in both treatment arms throughout the study. Clinically relevant abnormal findings were recorded in only two subjects; both were in the 0.5-h arm and recorded at screening only, with normal findings at the Course 1 visit.

Subject scores in the SGCTG neurological questionnaire were comparable in the two treatment arms. The total mean scores increased over the course of the study, from 2.0 at screening to 6.9 at EOS, indicating some worsening of neurological symptoms.

The scores of majority of subjects on the WHO performance scale remained constant throughout the study and these were mostly Grades 0 and 1. Scores in the two treatment arms were comparable. Over the course of the study the scores of only a small number of subjects improved or deteriorated.

Overall conclusions

- In this study, subjects with platinum-resistant ovarian cancer had confirmed antitumor responses with ZK 219477 treatment, but the target response rate in the primary analysis set based on the full analysis set was not met. In a post hoc subgroup analysis in the primary analysis set based on the per protocol set, the response rate was met in the 3-h treatment arm.

- ZK 219477 was well tolerated in both treatment arms; the majority of adverse events (AEs) were Grade 1 or 2. The most frequently reported AE was sensory neuropathy but only four subjects withdrew from treatment due to this AE.