Published in final edited form as:

Invest New Drugs. 2008 August ; 26(4): 347–354. doi:10.1007/s10637-008-9135-2.

Phase I dose-escalation study of the thioxanthone SR271425 administered intravenously once every 3 weeks in patients with advanced malignancies

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Summary

This study was performed to determine the dose limiting toxicity (DLT), the recommended phase II dose and the pharmacokinetic profile for SR271425, given over 1 h every 3 weeks. The initial starting dose of SR271425 was 17 mg/m². Patient selection was based on common phase I criteria as well as additional cardiac criteria. Thirty-eight patients were accrued to 16 dose levels from 17 to 1,320 mg/m². Patient characteristics included 24 males and 14 females ages 35–78 with an Eastern Cooperative Oncology Group performance status of 0 (ten patients), 1 (27) and 2 (1). Tumor types were typical for a phase I study. The maximum administered dose was 1,320 mg/m² with two DLTs, both QTc grade 3 prolongation. No drug related hematological toxicity was noted. Grade 1 toxicities included rash, flushing, pruritus, weight loss, diarrhea, hypertension and fatigue. Grade 2 toxicities included yellow discoloration of the skin, nausea and vomiting. QTc prolongation and hyperbilirubinemia were the only grade 3 toxicities noted. No confirmed tumor response was observed; however, two patients had prolonged stable disease. Both C_{end} and area under the plasma concentration–time curve increased in a dose related manner. Plasma drug concentrations declined in a biphasic manner with a mean terminal elimination half-life ($t_{1/2}$) of 7.1 h (± 1.3). There was no change in clearance or volume of distribution over the dose range studied. Due to cardiac toxicity occurring with both the parent compound, SR233377, as well as this analog, this series of agents was abandoned from further clinical development.

Keywords

Thioxanthone; SR271425; QTc prolongation

Introduction

SR271425 (*N*-[[1-[[2-(diethylamino) ethyl]amino]-7-methoxy-9-oxo-9H-thioxanthen-4-yl]methyl]-formamide) is a third-generation thioxanthone derived from hycanthone, which shows broad spectrum solid tumor activity both in vitro and in vivo in murine as well as in human xenograft tumor models [1, 2]. Hycanthone, originally used as an anti-schistosomal agent, was found to have cytotoxic anti-tumor activity [3], but with a liability to cause, on rare occasions, a lethal fulminant hepatic necrosis. Hycanthone was poorly tolerated in phase I clinical trials due to hepatic toxicity [4].

Subsequent screening of a thioxanthone compound library identified the second generation thioxanthone, SR233377 [1, 5] and two phase I pharmacokinetic studies with SR233377 were conducted in patients with a range of solid tumors [6, 7]. Both studies demonstrated potential life-threatening cardiac toxicities (asymptomatic prolongation of the QT/QTc interval and Torsade de Pointes), prompting closure of the studies and a halt to further clinical evaluation of this drug. The cause of QT prolongation was thought to be localized to the -SO₂CH₃ group in the 4-position on the molecule [7]. SR271425, which does not contain the 4-methylsulphoxide function, was identified as a third generation anti-tumor agent with superior anti-tumor activity and reduced hepatotoxic and cardiotoxic liabilities.

In the NCI 60 tumor cell line panel, SR 271425 showed a median IC₅₀ of 1.7 μM, with the maximum range being 0.28 μM (MOLT-4 leukemia) to 10 μM (K562 leukemia). Non-small cell lung cancer and colon cancer cell lines displayed the most sensitivity to SR271425, whereas melanoma and central nervous system cancers were predominantly less sensitive [8].

In the Corbett soft agar disk diffusion assay, SR271425 had solid tumor-selective activity in both murine and human solid tumors. In tumor cloning assays, SR271425 at continuous drug concentrations (between 3 and 10 μg/ml) inhibited most of the tumors studied and was thus predicted to have broad human antitumor activity.

In vivo, the antitumor efficacy of SR271425 was evaluated against established murine tumor models [2], demonstrating a wide spectrum of activity and a high degree of efficacy including complete tumor regressions and cures, even in tumors which are largely or completely refractory to standard agents. SR271425 was at least minimally active in eight of 13 xenograft models, with substantial activity against the CFPAC pancreatic tumor xenograft [9]. In the WSU-1 mammary and BG-1 ovarian tumor model, on the contrary, SR271425 showed moderate efficacy at best.

The mechanism of action of SR271425 has not been fully elucidated. SR271425 appears to bind to DNA. Structurally similar cytotoxic agents are inhibitors of topoisomerase-II, but SR271425 does not inhibit topoisomerase-I or topoisomerase-II [10]. Another structurally related agent, CI-934, is reported to inhibit helicase [11]. SR271425 does inhibit helicase, but the IC₅₀ (20 μM) appears to be too high to account for its cytotoxicity. A different mechanism, DNA alkylation, has been proposed for hycanthones [12]. However, these thioxanthones do not have the same substituent, which, in the case of hycanthone, is the proposed leaving group.

Unlike hycanthone and SR233377, SR271425 was not toxic to human hepatocytes and thus was judged to have a low hepatotoxic potential for humans [2].

Cardiac electrophysiological studies demonstrated that QT interval prolongation was the most sensitive indicator of the potential for disturbing cardiac electrophysiology [13]. SR271425 showed less potential than the previously studied SR233377 for causing conduction disturbances, with a 24-fold higher dose for QT prolongation and an 8-fold higher dose for death [14]. Multiple phase I studies were conducted with different administration schedules in an attempt to avoid the side-effect of QT prolongation that could possibly lead to Torsade de Pointes [15–19], while evaluating the potential anti-tumor activity against a wide range of tumor types. The study reported here involved a single 1 h infusion administered on a 3 week cycle, representing the shortest infusion duration investigated [15–19].

Patient and methods

Patients

Patients who were unresponsive to conventional therapy and who had histologic or cytologic evidence of metastatic or locally advanced solid tumors with measurable or non-measurable disease were eligible for this phase I study if they met the following criteria: age ≥ 18 years; ECOG performance status 0–2 with life expectancy of at least 3 months; adequate bone marrow (platelets 100×10^9 cells/L, absolute neutrophil count $2,000 \times 10^9$ cells/L), hepatic (total bilirubin ≤ 2 mg/dL and AST/ALT $< 2.5 \times$ the upper limit of normal (ULN), or $< 5 \times$ ULN (for patients with known liver metastasis) and renal function (serum creatinine ≤ 1.5 mg/dL and $< 2+$ proteinuria); electrolytes (including Mg^{++}) within normal institutional limits within 24 h of SR271425 administration; a normal baseline 12-lead electrocardiogram (ECG); and a baseline 24-h Holter monitor not diagnostic of repetitive ventricular arrhythmias or significant conduction disturbances. Patients must have recovered from previous surgical procedures. Eligible patients with reproductive potential were required to use adequate birth control. Informed consent was obtained according to federal and participating institutional guidelines. Exclusion criteria included any radiation within 3 weeks of SR271425 administration or radiation therapy to $> 25\%$ of bone marrow, serious infection or intercurrent illness, evidence of NYHA $>$ Class II congestive heart failure, history of arrhythmia or myocardial infarction within 6 months, use of anti-arrhythmic or other cardiac medications that could alter cardiac conduction within 2 months of study entry, use of any medications which may be associated with prolonged QTc intervals or Torsade de Pointes, family history in first degree relatives of unexplained death or prolonged QTc interval, a baseline QTc interval ≥ 430 ms for men or ≥ 450 ms for women based on Bazett's correction, participation in another experimental agent clinical trial within 3 weeks or within five expected half lives of SR271425 (whatever was the longest), and women pregnant or breast-feeding.

Treatment schedule and dose escalation

SR271425 was diluted in 250 mL of normal saline and administered intravenously over 1 h every 3 weeks as a citrate buffered saline solution. The starting dose of 17 mg/m^2 of SR271425 was determined based on the lower limit of the 95% confidence interval (CI) of $1/10$ of the dose that killed 10% of mice (LD_{10}).

Dose escalation was carried out in two successive phases: a 2B accelerated dose escalation followed by standard dose escalation [20]. During the accelerated dose escalation phase, doses were increased by increments of 40% and during the standard dose escalation, doses were increased by 33%. Inpatient dose escalation was allowed after one cycle. If a patient

had no CTC grade 2 or greater toxicities, the dose could be increased for the next course, but only if another patient had already safely received one course (3 weeks of intravenous dosing) at the next dose level.

Dose limiting toxicity

Toxicity was evaluated using the NCI Common Terminology Criteria for Adverse Events Version 2.0 except for QTc, for which version 3.0 (NCI CTCAE) was applied. This updated version was used because it provides numeric values for QTc measurements instead of grading according to symptoms only. DLTs were defined as any of the following events attributed to SR272425 occurring during the first course of administration: grade 4 neutropenia for five or more consecutive days or febrile neutropenia, grade 4 thrombocytopenia or grade 3 thrombocytopenia requiring platelet transfusion, any grade 3 nonhematologic toxicity (except injection site reaction or alopecia), grade 3 QTc prolongation, and/or retreatment delay of more than four weeks due to delayed recovery from a toxicity caused by SR271425.

Baseline QTc was defined as the average of three QTc readings from ECGs done prior to treatment. QTc measurements were performed manually by trained personnel at the central reading facility. The rate correction was done by several methods including Bazett and Fridericia methods [21]. During treatment, if a QTc value occurred which met the definition of QTc prolongation, two additional ECGs were performed at 25 and 50 mm/s. The average of the three consecutive QTc values was the value used to determine if a DLT was reached. All ECGs were sent for central review (eResearch Technology, Inc., 30 South 17th Street, Philadelphia, PA 19193-4001 and Covance, Inc., 210 Carnegie Center, Princeton, NJ 08540, USA) in addition to investigator evaluation.

The maximum administered dose (MAD) was defined as that dose at which a DLT was observed in at least two out of six treated patients. If Torsade de Pointes or any other life-threatening arrhythmias were noted in any patient, there was to be no further dose escalation. The dose just below the MAD was considered to be the maximum tolerated dose (MTD), provided a DLT was observed in less than two out of six treated patients (or fewer than one third if more than six patients) at that dose level.

Pretreatment and follow-up studies

Complete patient histories, physical examinations, complete blood counts, serum electrolytes, chemistries, coagulation profile, troponin, urinalysis, and ECGs were obtained at baseline and before each course of treatment. Adverse events (AEs) were collected up to 30 days after the last administered dose of the study drug. ECGs were also obtained every 15 min during infusion and at specific time points after infusion: 15 min, 3 h after expected maximum plasma concentration (C_{max}), at 11 and 23 h after infusion, and as needed to follow any abnormalities. The infusion was stopped for QTc >500 ms or if arrhythmias occurred. Blood pressure and heart rate were measured prior to and every 15 min during infusion. Holter monitoring was performed pretreatment and for 24 h after the first cycle. If the ECGs by automated reading showed a prolonged QTc, the cardiologist was called. If no significant cardiac effects were seen, Holter could be stopped after 12 h (approximately four half lives of the drug). If significant arrhythmias occurred, monitoring continued until the arrhythmias resolved to the satisfaction of the cardiologist. If QTc became prolonged (defined as an absolute value of greater than 450 for men or 470 for women), then Holter monitoring continued until the QTc had returned to within 10% of baseline. In case a significant ECG abnormality was detected, ECG recordings at 25 and 50 mm/s were also performed.

Hematology and blood chemistries were performed weekly for the first cycle and following any dosage increase, thereafter every 2 weeks. Radiological studies were performed at baseline and at the end of every second cycle to assess tumor response. A complete response was defined as disappearance of all disease based on two assessments performed 28 days apart. A partial response required 50% reduction in the sum of the products of the bidimensional measurements of all lesions, documented by two measurements 28 days apart. Disease progression required 25% increase in the size of any lesion or the appearance of a new lesion. Stable disease was achieved if patients were on study for 84 days (3 months) or longer.

QT interval measurement

The QT interval has an inverse relationship to heart rate; the measured QT intervals are generally corrected for heart rate in order to determine whether they are prolonged relative to baseline. QTc also can vary between healthy subjects and cancer patients, as well as present with daily variations [22]. Various correction formulae have been suggested, of which Bazett's and Fridericia's corrections are the most widely used [21]. In this study, both correction methods were used as follows: (1) Fridericia's correction: $QTc = QT / RR^{0.33}$ and (2) Bazett's correction: $QTc = QT / RR^{0.5}$, in order to minimize variability.

Pharmacokinetic evaluation

Blood samples were obtained for the determination of plasma concentrations of SR271425 for every patient during cycle 1 and repeated only during cycle 1 if inpatient dose escalation occurred. A 5 mL blood sample was drawn into a polypropylene tube with lithium heparin anticoagulant at pretreatment and following the start of infusion at the following times: 15, 30, 45, 60 (end of infusion) 65, 75, and 90 min, and 2, 3, 4, 5, 6, 8, 10, 12, 24, 32, and 48 h on day 1 of cycle 1. Within 30 min of collection, plasma was separated by centrifugation of the blood sample at $1,500 \times g$ for 10 min at 4°C, and transferred into a 5 mL screw-capped polypropylene tube. All samples were kept on ice (~4°C) during processing. Plasma samples were stored at -20°C until analysis. The concentrations of SR271425 in plasma samples were determined using a validated high performance liquid chromatographic method with tandem mass spectrometric detection (LC-MS/MS) at the Department of Clinical Metabolism and Pharmacokinetics, Sanofi-Synthelabo. SR271425 pharmacokinetic parameters for individual patients were estimated using noncompartmental analysis with the computer software program WinNonlin version 4.0 (Pharsight Corporation, Mountain View, CA, USA). The C_{max} was obtained by visual inspection of the plasma concentration–time curves. The total area under the plasma concentration–time curve from time zero to the last measurable time point (AUC_{0-t}) was calculated using the linear and logarithmic trapezoidal method for ascending and descending plasma concentrations, respectively. The total area under the plasma concentration–time curve from time zero to infinity ($AUC_{0-\infty}$) was calculated as the sum of AUC_{0-t} and the extrapolated area, which was calculated by the last observed plasma concentration divided by the terminal rate constant (λ_z), where λ_z was estimated by the terminal log-linear phase of the plasma concentration–time curve. The terminal plasma half-life ($t_{1/2,z}$) was calculated as $0.693 / \lambda_z$. Systemic clearance was calculated as $Dose / AUC_{0-\infty}$. The apparent volume of distribution (V_{ss}) was estimated as $Dose \times AUMC / AUC^2$, where AUMC is the area under the first-moment concentration–time curve.

Results

Patients demographics and disposition

A total of 64 patients were screened and 38 were enrolled, treated and included in the safety analysis. Five patients were not eligible due to a baseline prolonged QTc value; other

reasons for screen failure included decreasing performance status, progression of disease and withdrawal of consent. Twenty-four patients were male and 14 female; ages ranged from 35 to 78 years. All but one patient had a baseline ECOG performance status of 0 (27%) or 1 (71%). Thirty-five patients had less than or equal to two prior chemotherapy regimens. The most frequent tumor types included colon (24%), lung (10.5%) and pancreas (10.5%). Disease progression or lack of efficacy was observed in 22/38 patients (57.9%) and was the main cause of treatment discontinuation. Only one patient (2.6%) discontinued due to an AE: grade 2 pruritus. The MAD was 1,320 mg/m². Patients were distributed among 16 cohorts (Table 1). The total number of cycles given at any dose level varied from one to 18 and the maximum number of cycles that any patient received was 11 cycles (at dose level 942 mg/m²). Five patients had their dose level changed after the first cycle. Two patients were excluded from the pharmacokinetics analysis as outliers due to poor venous access.

Tolerance

Overall, 37 patients experienced at least one grade 1 AE and 28 experienced at least one grade 2 AE. Grade 3 AEs were experienced by 15 patients and grade 4 AEs by five patients. The wide distribution of the number of cycles by dose level (from 2 to 18) does not allow any conclusion on a dose-related frequency of grade 1 or grade 2 AEs. However, grade 3 AEs were more frequent beginning at dose level 226 mg/m². The following AEs (>1%) were considered to be drug-related (Table 2): nausea (7.5%), vomiting (3.7%), skin discoloration (6.6%), ocular icterus (3.7%), fatigue (4.7%), QTc prolongation (5.6%), pruritus (2.8%), and flushing (1.8%). Most AEs showed no apparent dose-related pattern with the exception of QTc prolongations and skin discolorations which were reported only at dose levels $\geq$ 532 mg/m². Except for grade 3 QTc prolongations in three patients and hyperbilirubinemia in one patient, all other drug-related AEs did not exceed grade 2 severity. One patient at the 942 mg/m² dose level (11 cycles) discontinued the drug due to grade 2 pruritus.

One patient with metastatic rectal cancer experienced blood alkaline phosphatase and aspartate aminotransferase (AST) increase, hyperbilirubinemia, and hyperkalemia at the 400 mg/m² dose level. The grade 3 bilirubin increase was considered drug-related. Grade 3 drug-related QTc prolongation was observed in one patient at 942 mg/m² and in two patients at 1,320 mg/m². According to Bazett's correction, two patients, both at the 1,320 mg/m² dose level, had grade 3 QTc prolongation (Table 3). According to Fridericia's formula, only one of these two patients had a grade 3 QTc prolongation.

Grade 4 AEs were reported in five patients all at dose levels $\geq$ 301 mg/m² and included nephrolithiasis, increased AST, disease progression and respiratory arrest. None of these were drug-related. There were no grade 5 treatment-related adverse events.

Ten patients (26.3%) experienced a total of 19 serious adverse events (SAEs). All SAEs were Grade 3 or 4 events. Except for Grade 3 hyperbilirubinemia and QTc prolongation, the SAEs were not considered to be drug-related.

Maximum tolerated dose

After the occurrence of drug-related grade 3 QTc prolongation in two out of the three patients at 1,320 mg/m², along with prior ECG toxicities demonstrated by the precursor drug SR233377 (WIN33377), further development of this class of drugs was abandoned. This dose level, 1,320 mg/m² was considered to be the MAD. The cohort at the MTD level was not expanded as required per protocol, and therefore, was not confirmed as the MTD.

Pharmacokinetics

Table 4 summarizes the pharmacokinetic parameters of SR271425 in cancer patients receiving SR271425 as a 1-h intravenous infusion. The C_{max} of SR271425 was generally observed at the end of the 1 h infusion, with mean values ranging from 251 to 12,700 ng/ml when the SR271425 dose was escalated from 17 to 1,320 mg/m² (Table 4). SR271425 had a systemic clearance ranging from 2.0 to 86.0 L/h (mean, 16.1 L/h) and a terminal elimination half-life ($t_{1/2}$) ranging from 3.1 to 20.8 h (mean, 7.6 h), and showed a distribution in excess of blood volume with a V_{ss} ranging from 11.4 to 421.0 L (mean, 128.6 L; Table 4). The drug systemic exposure (C_{max} , AUC_{0-t} , AUC_{∞}) was increased in a dose-proportional manner over the studied dose range from 17 to 1,320 mg/m² (Fig. 1), and there was no evidence for any systematic change in clearance, $t_{1/2}$ and V_{ss} with dose, indicating a linear pharmacokinetic profile of SR271425.

Anti-tumor activity

No confirmed tumor response was seen. Three patients with colon cancer (one at 65 increased to 170 mg/m², one at 17 increased to 24 mg/m² and the third at the 942 mg/m² dose level) remained on study for 11, 6 and 11 cycles, respectively. One patient with liver cancer (1,320 mg/m² dose level) had stable disease for 7 cycles. Two patients with lung cancer (301 mg/m² dose level and 91 increased to 128 mg/m²) and 1 with kidney cancer (532 mg/m²) continued on study for 4 cycles. One patient with prostate cancer (1,320 decreased to 942 mg/m² due to QTc prolongation) had a short-lived (2 cycles) decrease in PSA value.

Discussion

SR271425 is a novel cytotoxic agent, a third generation thioxanthone, the mechanism of action of which is still unknown and does not appear to be related to topoisomerase II inhibition as seen in structurally similar compounds. Preclinically, the acute toxicities in animal models (mice, rabbit and dogs) were mainly of a cardiovascular nature, including vasovagal syncope, development of PVCs and QTc prolongation.

As previously noted, efficacy was observed in the mouse at 110 mg/m², while QT prolongation occurred in the rabbit at 660 mg/m². Thus, SR271425 was efficacious using mouse models at doses six-fold below those causing cardiac conduction abnormalities in rabbit models. Therefore, there was reason to believe that one could achieve potentially efficacious doses before finding cardiotoxic effects with SR271425.

This phase I study evaluated escalating doses of SR271425 from 17 to 1,320 mg/m². Thirty-seven of the 38 included patients (94.7%) experienced at least one AE. Nineteen percent of the AEs were drug-related. Based on descriptive evaluation, there was no apparent dose-related pattern of AEs, except for QTc prolongation, which appeared at doses $\geq$ 532 mg/m². Grade 3 QTc prolongations were observed in 1 patient at 942 mg/m² and 2 patients at 1,320 mg/m². The 1,320 mg/m² dose level was considered to be the MAD. The occurrence of QTc prolongation and the concern of its development into Torsade de Pointes or other clinically fatal arrhythmias led to the discontinuation of the study and halted the progression of this drug's clinical development. The cohort at the MTD level was thus not expanded as required per protocol, and, therefore, was not confirmed as the MTD. SR271425 given as a 1 h infusion had QTc prolongation as the dose limiting toxicity.

Following a single 1-h infusion of SR271425, peak plasma concentrations were generally observed at the infusion end and then declined with a terminal half-life of approximately 8 h. Exposure to SR271425 increased in a dose proportional manner, with no effect on CI or V_{ss} .

These data suggested that QTc prolongation may have reached a maximal effect ($E_{\max}$) with little evidence for any systematic change in the QTc interval at plasma concentrations in excess of approximately 2,000 ng/mL. Due to the potential of development of life-threatening cardiac arrhythmias already exhibited by precursor thioxanthenes, SR271425 development was not moved forward into phase II trials and clinical responses were not further explored.

Acknowledgments

We would like to thank Dr. Scott Walder (*in memoriam*), S. Halloway and N. Matthews, from the Weill Medical College of Cornell University, New York, NY, US for their contributions to the study.

Grant support Sanofi-Synthelabo

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Table 1

Patients and dose escalation

Cohort number	Dose given (mg/m ²)	Total number of cycles given at dose level	Total number of patients enrolled at dose level ^a
1	17	4	1
3	33	3	1
4	47	2	1
5	65	3	1
6	91	4	2
7	128	11	5
8	170	9	4
9	226	5	3
10	301	10	4
11	400	10	6
12	532	11	4
13	708	3	2
14	942	18	4
15	1130	6	1
16	1320	3	3

^aTotal number of patients exceeds 38 due to inpatient dose escalation

Table 2

Summary of all drug-related adverse events by onset of dose level and cycle

Drug-related toxicities	SR271425 (# of cycles)									
	All dose levels (N=106; %)		17-170 mg/m ² (N=40; %)		226-532 mg/m ² (N=36; %)		708-1320 mg/m ² (N=30; %)			
	All grades	Grade 3, 4	All grades	Grade 3, 4	All grades	Grade 3, 4	All grades	Grade 3, 4	All grades	Grade 3, 4
Nausea	8 (7.5%)	0	0	0	4 (11.1%)	0	4 (13.3%)	0	0	0
Vomiting	4 (3.7%)	0	0	0	3 (8.3%)	0	2 (6.6%)	0	0	0
Diarrhea	1 (1.0%)	0	0	0	1 (2.7%)	0	0	0	0	0
Pruritus	3 (2.8%)	0	0	0	2 (5.5%)	0	1 (3.3%)	0	0	0
Weight loss	1 (1.0%)	0	0	0	1 (2.7%)	0	0	0	0	0
Dysgeusia	1 (1.0%)	0	0	0	0	0	1 (3.3%)	0	0	0
Ocular icterus	4 (3.7%)	0	0	0	0	0	4 (13.3%)	0	0	0
QTc prolongation	6 (5.6%)	3 (2.8%)	0	0	2 (5.5%)	0	4 (13.3%)	3 (10%)	0	0
Skin discoloration	7 (6.6%)	0	0	0	2 (5.5%)	0	5 (16.6%)	0	0	0
Hyperhidrosis	1 (1.0%)	0	0	0	0	0	1 (3.3%)	0	0	0
Rash	1 (1.0%)	0	1	0	0	0	0	0	0	0
Papular rash	1 (1.0%)	0	0	0	0	0	1 (3.3%)	0	0	0
Fatigue	5 (4.7%)	0	0	0	3 (8.3%)	0	2 (6.6%)	0	0	0
Flushing	2 (1.8%)	0	0	0	1 (2.7%)	0	1 (3.3%)	0	0	0
Pyrexia	1 (1.0%)	0	0	0	0	0	1 (3.3%)	0	0	0
Infusion site phlebitis	2 (1.8%)	0	0	0	0	0	2 (6.6%)	0	0	0
Infusion site pain	1 (1.0%)	0	0	0	1 (2.7%)	0	0	0	0	0
Infusion site pruritus	1 (1.0%)	0	0	0	0	0	1 (3.3%)	0	0	0
Injection site discomfort	1 (1.0%)	0	0	0	0	0	1 (3.3%)	0	0	0
Injection site pain	1 (1.0%)	0	0	0	0	0	1 (3.3%)	0	0	0
Injection site phlebitis	1 (1.0%)	0	0	0	0	0	1 (3.3%)	0	0	0
Phlebitis	1 (1.0%)	0	0	0	0	0	1 (3.3%)	0	0	0
Hyperbilirubinemia	1 (1.0%)	1 (1.0%)	0	0	1 (2.7%)	1 (2.7%)	0	0	0	0
Cough	1 (1.0%)	0	0	0	0	0	1 (3.3%)	0	0	0

Table 3

Number of events with QT c (Bazett's formula) prolongation by onset dose level and number of cycles

Dose level and number of cycles	Grade 1, 2	Grade 3, 4
47 mg/m ² (n=2)	1	0
65 mg/m ² (n=3)	1	0
128 mg/m ² (n=11)	8	0
170 mg/m ² (n=9)	8	0
226 mg/m ² (n=5)	4	0
301 mg/m ² (n=10)	3	0
400 mg/m ² (n=10)	7	0
532 mg/m ² (n=11)	6	0
708 mg/m ² (n=3)	3	0
942 mg/m ² (n=18)	10	0
1,130 mg/m ² (n=6)	1	0
1,320 mg/m ² (n=3)	1	2

Table 4
Pharmacokinetic parameters of SR271425 following 1-h intravenous infusion in cancer patients

Dose (mg/m ²)	Number (n)	C _{max} (ng/ml)	AUC _{last} (h ng/ml)	AUC (h ng/ml)	t _{1/2α} (h)	CI (L/h)	V _{ss} (L)
17	1	251	2320	2360	8.17	7.19	74
24	2	341 (69.7)	2290 (62.8)	2340 (62.5)	9.26 (6.4)	12.8 (62.5)	133 (67.5)
33	1	11200	16400	16500	8.07	2.0	11.4
47	1	667	3720	3740	6.59	12.6	90.5
65	1	577	3560	3840	6.93	16.9	143
91	2	971 (49.5)	4880 (35.2)	4920 (35.2)	7.08 (3.6)	19.7 (35.2)	162 (43.9)
128	5	1380 (8.3)	9470 (51.6)	9650 (52.9)	7.33 (31.2)	17.2 (58.9)	128 (22.9)
170	4	1690 (23.2)	10200 (24.7)	10300 (24.9)	6.91 (14.5)	17.2 (22)	139 (22.4)
226	3	2190 (16.9)	15800 (14)	16000 (14)	7.53 (2.9)	14.3 (14.6)	129 (8.1)
301	4	4540 (65.6)	18800 (72.3)	19200 (73.7)	7.97 (36.4)	32.2 (113)	190 (81.3)
400	6	7320 (23.5)	43700 (48.8)	44200 (49.4)	7.54 (7.1)	10.6 (37.6)	90 (34.8)
532	5	7690 (31.5)	39600 (30.4)	40100 (31)	7.2 (24.7)	14.5 (33.4)	104 (38.7)
708	2	8400 (67.3)	57500 (29.4)	57800 (29)	6.39 (16.6)	12.8 (29.0)	112 (48.8)
942	3	7120 (24.5)	48200 (6.3)	48500 (6.5)	7.06 (2.2)	19.5 (6.5)	171 (8.4)
1320	3	12700 (28.2)	91900 (27.1)	97700 (26)	9.47 (104)	14.2 (29.1)	159 (70.3)
Overall Mean (CV%)					7.6 (34.4)	16.1 (76.6)	128.6 (52.1)
MIN		173.0	1270.0	1300.0	3.1	2.0	11.4
MAX		16800.0	119000.0	120000.0	20.8	86.0	421.0

Values are expressed as mean with CV% in parentheses when possible