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CLINICAL TRIAL REPORT

Phase I dose-escalation study of a novel antitumor agent, SR271425, administered intravenously in split doses (d1–d2–d3) in patients with refractory solid tumors

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Abstract
Background SR271425 is a novel DNA-binding cytotoxic agent with a broad spectrum of antitumor activity in preclinical models,across a variety of the schedule of administration. In toxicological studies, it has been reported to prolong QTc proportionally to C_{max}. In order to circumvent this C_{max}-related QTc prolongation, 5 phase I studies were initiated to investigate 1-h, 24-h, weekly, and split iv infusions. This phase I study assessed a split-dose regimen (a 1-h infusion on each of Days 1 to 3, repeated every 3 weeks) to establish the dose limiting toxicities (DLT), to recommended a phase II dose, and to characterize PK/PD.
Methods Patient with advanced solid tumors, adequate bone marrow, hepatic, renal function and on specific cardiac criteria were eligible and "3 + 3" design was used for dose escalation. That dose escalation was guided by PK data, toxicities observed and information from other ongoing phase I studies with SR271425. SR271425 plasma levels (PK samples) were measured using a validated LC-MS/MS method. Careful monitoring of ECGs was done, and ECGs were read centrally.
Results Three centers enrolled 19 heavily pretreated patients to six dose levels, from 75 to 450 mg/m²/day (i.e., 225–1,350 mg/m²/cycle): 12 males and 7 females. Median age 56. Median ECOG, PS = 1. Main tumor types were brain, breast, gynecological, and urological. Patients received a median of 2 cycles (range: 1–6). NCI-CTC Grade 1-2 toxicities included nausea, vomiting, asthenia, rash, and yellow skin discoloration. No DLTs were reported, and there were no dose-limiting prolongations of QTc. Both C_{end} and AUC increased in a dose-related manner, with no evidence of accumulation between Day 1 and Day 3, consistent with the mean (±SD) terminal elimination half-life of 5.11 ± 1.21 h. Stable disease was observed in five cases.
Conclusion Split doses allow high cumulative exposure to SR271425 without significant toxicity, especially without QTc prolongation. MTD was not reached due to the early termination of the SR271425 program by the sponsor.

Keywords Thioxanthone · Phase I · Cytotoxics · SR271425

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Introduction

SR271425 is the third generation of a novel class of cytotoxic agents, the thioxanthone derivatives. These compounds were originally synthetized as candidate anti-parasitic agents. The first-generation compound, hycanthone (a potent anti-schistosomal agent), showed cytotoxic antitumor activity, but was discontinued due to hepatotoxicity and non-proportional pharmacokinetic parameters [1–3]. A second-generation compound, SR233377, was found to cause cardiac

arrhythmias and torsades de pointe, and was therefore discontinued [4, 5]. SSR271425, a third-generation compound, was advanced into clinical trials based on an acceptable toxicity profile and on robuste of in vivo antitumor activity in a broad range of transplanted tumor models [6]. The exact mechanism of action of this compound is unknown, but it seems to act as a non-alkylating DNA binder. This compound is metabolized primarily by CYP3A4, is largely distributed throughout the body (including the brain in rats), is highly bound to plasma proteins (>90%), and is eliminated primarily in feces (96% in rats). PK values in animals were proportional to the dose administered.

Preclinical studies identified lymphematopoetic effects as dose-limiting toxicities in rats, dogs, mice, and rabbits. The highest non-lethal doses administered ranged from 200 mg/m² (1-h infusion in female dogs) to 5,280 mg/m² (24-h infusion in female rabbits). Hepatic toxicity was reported at higher doses, ranging from 500 mg/m² (24-h infusion in female dogs) to 5,280 mg/m² (24-h infusion in female rabbits).

Due to cardiac toxicity with SR233377, specific toxicology studies were performed to assess QTc prolongation or other cardiac toxicities. Cardiac toxicity, mainly QTc prolongation, was observed in only one species, rabbit. In other species tested, the onset of other toxicities (hematopoetic and hepatic) did not allow dose escalation. This QTc prolongation was correlated with C_{max} and not with AUC.

In rabbits, the highest non-lethal dose (cardiac electrophysiological disturbances were observed) was 1,980 mg/m² administered at a 2-h infusion, and 5,280 mg/m² administered as a 24-h infusion. It was therefore anticipated that myelotoxicity would be dose-limiting in humans, and a first-in-man study was initiated in 2002 using a 1-h infusion administered on Day 1 every 3 weeks with very close cardiac monitoring. Preliminary data from this study showed a linear pharmacokinetic profile. There was a correlation between C_{max} and QTc prolongation, although QTc remained within the normal range [7]. For this reason, studies testing different schedules of administration were inititated with split doses or prolonged administration, in order to provide higher dose exposure without increasing C_{max}.

Four such studies were initiated in 2003 to assess different regimens: a 24-h infusion on Day 1 every 3 weeks, a 1-h infusion on each of Days 1 and 8 every 3 weeks, a 2-h infusion weekly, and a 1-h infusion on each of Days 1, 2, and 3 every 3 weeks. The results of the last study (1-h infusion on each of Days 1, 2, and 3 every 3 weeks) are presented here.

Patients and methods

Patient population

Patients with histological or cytological diagnosis of advanced solid tumors, refractory to standard forms of therapy or for which no standard therapy of proven benefit exists, were candidates for entry into the study. Eligibility criteria included: males or females between 18 and 70 years of age; life expectancy of at least 3 months; ECOG performance status ≤2; no chemotherapy, immunotherapy, or radiotherapy for at least 4 weeks prior to treatment initiation (6 weeks in case of treatment with mitomycin C or nitrosoureas agents) and recovery from all toxic effects of previous treatments; prior cumulative dose of doxorubicin ≤400 mg/m² and epirubicin ≤750 mg/m²; normal liver function (serum bilirubin ≤1.5 × UNL; ϒGT, SGOT, SGPT, and alkaline phosphatase ≤2.5 × UNL); normal renal function (serum creatinine ≤1.5 × UNL); serum calcium, potassium, and magnesium within normal values within 24-h prior to SR271425 administration; adequate bone marrow (absolute neutrophil count ≥1,000/mm^3, platelet count ≥100,000/mm^3, absolute hemoglobin ≥10 g/dl); adequate birth control; not pregnant or breast-feeding; no serious infection (e.g., tuberculosis, HIV, hepatitis C and B) or other intercurrent illness; no participation in another experimental agent clinical trial within 4 weeks prior to study entry; and no symptomatic untreated brain or leptomeningeal metastases. Specific cardiac requirements included: Patients were to have at least 3 baseline 12-lead ECGs within a 10-min period, all demonstrating a normal sinus rhythm with no significant conduction defects and no sequelae of myocardial infarction; median baseline QTc interval calculated on these 3 baseline ECGs had to be strictly ≤450 ms (NCI-CTCAE v.3.0 [8] <Grade 1); a baseline 24-h Holter monitor showing no significant ventricular arrhythmias or conduction disturbances; and a LVEF within normal limits. Patients with any of the following were not to be included: ≥Class II NYHA congestive heart failure, use within 2 months of study entry of antiarrhythmic therapy or other cardiac medication that could alter cardiac conduction, a history of any type of arrhythmia of NCI-CTCAE v. 2.0 Grade >1, myocardial infarction within 6 months of study entry, a family history of unexplained sudden death or prolonged QTc. Adequate overall patient status was evaluated by a cardiologist. Informed consent was to be signed by the patients following institutional guidelines. Patients were informed of known potential toxicities.

Dose-limiting toxicities (DLT)/maximum administered dose (MAD)/maximum tolerated dose (MTD)

The MAD and MTD are defined according to the onset of dose-limiting toxicities (DLT). Dose-limiting toxicities were pre-defined in the protocol as followed:

Toxicity was evaluated using the NCI Common Toxicity Criteria Version 2.0, with the exception of the adverse event "Prolonged QTc interval," which was graded according to Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

Dose-limiting toxicity was defined as any of the following events attributed to SR271425 and occurring during the first treatment cycle (normally within 3 weeks or a maximum of 4 weeks administration):

1. Grade 4 neutropenia for 5 or more consecutive days.
2. Febrile neutropenia or neutropenic infection.
3. Thrombocytopenia (<25,000/mm^3) or Grade 3 thrombocytopenia with bleeding requiring platelet transfusion.
4. Any Grade 3 or greater non-hematological toxicity occurring despite optimal symptomatic treatment (except for alopecia, anorexia, fatigue, and injection site reaction).
5. Any QTc prolongation of Grade 3 or greater.
6. Retreatment delay of more than 2 weeks from date of planned retreatment, due to delayed recovery from a toxicity related to SR271425.
7. Torsades de pointes or any life-threatening arrhythmia.
8. A 25% or more prolongation of QRS duration when compared to baseline QRS duration.

If a dose limiting toxicity (DLT) was observed in at least 2 of 6 treated patients at a dose level, there was no further dose escalation, and this dose level constituted the maximum administered dose (MAD). If torsades de pointes or any other life-threatening arrhythmia or abnormal conduction of NCI-CTC v.2 Grade 3 or more was noted in any patient, no further dose escalation was planned. All ECGs were transmitted electronically to a central reading system. These ECGs were reviewed by external cardiologists, and the central reading was considered as the only value to be used to evaluate cardiac DLTs.

The dose just below the MAD was considered to be the MTD, if DLT was observed in only 1 of 6 treated patients at that dose level. The MTD was generally the highest dose level at which at most 1 patient experiences DLT.

Baseline/screening procedures (day−14 to day 1)

Pretreatment tests and measurements included detailed medical and surgical history, including age, ethnic origin, cardiac history, family cardiac history, medication list, performance status, height and weight, blood pressure, heart rate, and neurological examination. Laboratory screening included hemoglobin, WBC with differential count, platelets, prothrombin time (INR), and APTT; serology of HBsAg, anti-HCV, anti-HIV1; serum electrolytes, including sodium, potassium, chloride, bicarbonate, calcium, and magnesium; glucose (fasting), urea, creatinine, total protein, albumin, uric acid, AST, ALT, alkaline phosphatase, LDH, GGT, total bilirubin, total cholesterol, triglycerides, CPK, CPK-MB, Troponin I, urinalysis, and pregnancy test for females of child-bearing potential.

Specific cardiac evaluations included: a 24-h Holter monitor, a MUGA or echocardiogram, and three 12-lead ECGs (performed just before vital signs and done within 10 min) with measurement of HR, PR, QRS, QT, and QTc. The median of the 3 QTc values (Bazett's method) was used to determine patient eligibility.

The cardiologist then reviewed the cardiac history of the patient as well as the cardiac studies to ensure compliance with inclusion and exclusion criteria.

Treatment

SR271425 was supplied by Sanofi-Synthelabo Research. Each glass vial of investigational product contained 10 ml of a 10 mg/ml solution in citrate buffered saline at pH 5.2. Investigational product was to be stored at 2–8°C and protected from light. Immediately prior to infusion, the appropriate volume of the concentrate was diluted to a total volume of 250 ml with commercially available 0.9% sodium chloride injection USP. Before and during the 1-h infusion, the solution was protected from direct sunlight and the infusion bag was to be covered with foil. The solution was not to be given as a bolus or more rapidly than within 1 h.

Starting dose

At the time of study initiation, the first clinical trial of SR271425 (administering investigational product as a 1-h infusion on Day 1 of a 3-week cycle) had reached a dose of 225 mg/m^2 [7]. Therefore, the starting dose for the current study was established as 75 mg/m^2 to be administered on each of Days 1, 2, and 3 of a 3-week cycle. This dose was well tolerated in animal studies in which a daily ×5 regimen was administered. Dose was escalated by either 33 or 50% between dose levels, according to PK data, toxicities observed, and

information from other ongoing phase I studies with SR271425. The number of patients to be included at each dose level was to be from 3 to 6 depending on toxicities observed.

Patient monitoring

The investigational product was administered over 1 h during 3 consecutive days every cycle. Plasma values of Mg^{++}, K^{++}, and Ca^{++} were determined before each infusion. Blood pressure, heart rate, and 12-lead ECGs were measured prior to each infusion, every 15 min during infusion, and 15-min, 30-min, 3 h, and 5 h after the end of infusion. Two additional 12-lead ECGs were done at 8 and 24 h after the onset of infusion on Day 3.

On Day 3, patients were on a 24-h Holter monitor until 24 h after the end of infusion. Blood and urine samples for pharmacokinetic analysis were taken as described below.

Preliminary QT measurement, PR measurement, and QRS measurement were performed by the automated computerized ECG reader. If the QT was prolonged to the Grade 3 definition (QTc > 500 ms) or the QRS was prolonged ≥25% compared to median baseline QRS, or significant arrhythmias occurred, the attending physician was notified, and ECGs were repeated twice more within the subsequent 10 min. The average of the 3 QTcB (QT corrected by Bazett's method) values or the average of the 3 QRS values was taken as the value to determine whether infusion could be resumed or not. These averages were compared to the median of the 3 QTc calculated from the 3 ECGs done before infusion or compared to the median of the 3 QRS durations calculated from the 3 ECGs done before infusion. If these comparisons met the DLT criteria, then no further treatment was provided in that cycle. Additional ECGs were repeated as clinically indicated.

Collection of pharmacokinetic samples

Blood samples were obtained for the determination of plasma concentrations of SR271425 during the first cycle for every patient. A total of 22 blood samples for pharmacokinetic analysis was drawn at the following times after the start of infusion on Day 1 and on Day 3: 0 (start of infusion), 30, 60, 65, 75, and 90 min; 2, 4, 6, 8, and 24 h. At each sampling time, a 2 ml blood sample was drawn into lithium heparin vacutainers (e.g. 44 ml in total). Within 30-min of collection, samples were centrifuged at 1500×*g* for 10-min at 4°C to yield plasma (1 ml). Plasma was transferred into 5 ml screw-capped polypropylene tubes (Sarstedt 5 ml polypropylene containers, product code 60.558) for shipment. All samples were to be kept on ice (~4°C) during processing. Plasma was to be stored at −20°C prior to shipping to the Sponsor for analysis.

Urine samples

Total urinary output over 24 h was collected into plastic collection vessels on Days 1, 1, and 3. A 45 ml aliquot was removed from 6 specific periods of collection and stored in a clean plastic vessel of appropriate size (Sarstedt 50 ml polypropylene container, product code 62.559) at −20°C prior to shipping to the Sponsor.

Bioanalytical method

The concentration of SR271425 in plasma was determined using a validated LC MS/MS assay in the department of Clinical Metabolism and Pharmacokinetics of Sanofi-Synthelabo, Alnwick, Northumberland, NE66 2JH, UK.

Pharmacokinetic analysis

The following parameters was determined for each patient:

- Concentration of SR271425 in each sample
- C_{end}, AUC_{last}, AUC, $t_{1/2}$, Cl, V_{ss}, R_{ac}, and R_{Cmax}.

For each parameter, mean ± SD (%CV) was determined at each dose level in which more than one patient was dosed. In the event that results from sufficient patients and dose levels were obtained, the relationship between dose and C_{ss}, C_{end}, AUC_{last}, and AUC was statistically assessed for dose proportionality with the log transformed power model.

Results

Between November 2003 and December 2004, 19 patients (12 males and 7 females) were assigned to six dose levels, ranging from 225 mg/m² (75 mg/m²/day) to 1,350 mg/m² (450 mg/m²/day) as shown in Table 1. Median age was 56 years (range: 39–69), and median ECOG performance status was 1 (range: 0–1). Three patients had brain primary tumors, 3 had breast cancer, 3 had gynecologic cancers (2 carcinoma of the cervix and 1 ovarian carcinoma), 3 had urologic carcinomas (2 renal cell and 1 prostate), 2 had non-small cell lung cancer, and 2 had neuroendocrine tumors. The 3 other patients had: 1 head and neck cancer; 1 colorectal cancer, and 1 mesothelium.

Table 1 Summary of the patient's characteristics and clinical evaluation during the study by dose level

Dose (mg/m²)	Histology	Total number of cycles administered	Reason off treatment	Best response	Side effects
I = 75 × 3(225)	Breast*	2	PD	–	
	Uterus*	5	Asthenia	SD	
	Prostate*	3	PD		
	Rectum*	1 (d1 only)	Liver toxicity—PD		Cycle 1, day 2: bilirubin Grade 2
II = 100 × 3 (300)	Glioblastoma	3	PD		–
	Head and neck Squamous	4	PD	SD	
	Ovarian*	2	PD		Cycle 2 : Grade 2 skin rash
III = 135 × 3 (405)	Renal*	2	PD		–
	Renal*	6	PD	SD	
	Lung–Non small cell	4	PD	SD	
IV = 200 × 3(600)	Mesothelioma	2	PD		
	Neuroendocrin	4	PD		
	Glioblastoma	2	PD		
V = 300 × 3(900)	Lung–Non small cell	2	PD		
	Astrocytoma	2	PD		–
	Breast*	5	PD	SD	Cycle 1: cutaneous eruption Grade 1; cycle 2: yellow skin
VI = 450 × 3 (1,350)	Endometrium*	2	PD		Cycle 1, day 2 and day 3: visual disturbance; cycle 1, day 4-day 5: yellow skin and urine discoloration
	Breast*	2	PD		Cycle 1-cycle 2: yellow skin
	Neuro-endocrin	2	PD		Cycle 1-cycle 2: yellow skin

PD progressive disease, *SD* stable disease

*Adenocarcinoma

Most patients had received several previous anticancer therapies: 17 had received prior chemotherapy, 7 had received prior hormonal therapy, and 6 had received other specific therapies including targeted therapies.

Toxicity: DLT, MTD, and RD

Due to discontinuation of clinical development of SSR271425, leading to early discontinuation of the present study, no DLT and no MTD have been reported.

Hematologic and biochemical toxicites

Grade 3 hematological and/or biochemical toxicities were observed in 3 patients.

They included anemia (2 patients), acidosis, ALT increased, hyperbilirubinemia, and hypercalcemia (1 patient each). None were considered by investigators to be related to investigational product.

QTc

No QTc prolongation nor QRS prolongation were reported at bedside. However, 3 patients had Grade 2 QTc prolongation reported by e-RT (central reading):

- At dose level II (100 mg/m² × 3), one patient had two QTc prolongations recorded at cycle 2: 18 and 31 min after the start of the infusion on Day 2.
- At dose level VI (450 mg/m² × 3), one patient had 3 QTc prolongations recorded at cycle 1: 44 min after the start of the infusion on Day 1, and 62 and 78 min after the start of the infusion on Day 2. Another patient had 2 QTc prolongations recorded during cycle 1, 4 h and 1 h after the start of infusions on Day 1 and Day 3, respectively, and one QTc prolongation during cycle 2, 90 min after the start of infusion on Day 2.

Grade 2 QTc prolongations were the most severe cardiac abnormalities considered as related to investigational product in this study.

Other non-hematological toxicities

Toxicity was minimal: There was mild to moderate nausea and vomiting and asthenia. One case of Grade 2 alopecia was reported during cycle 5 (dose level I), one Grade 2 visual disturbance was reported during cycle 5 (dose level VI). One Grade 2 skin rash was reported during cycle 2 (dose level II).

Of note, mild skin discoloration was reported in one patient at dose level V beginning at cycle 2, and it was systematically reported for the 3 patients treated at dose level VI, beginning during cycle 1.

Six patients experienced a total of eight serious adverse events and required hospitalization. These events were not considered to be related to investigational product:

- Dose level II (100 mg/m² group): 2 patients (headache, reported in 1 patient; dizziness, back pain reported in 1 patient);
- Dose level II (135 mg/m² group): 2 patients (pathological fracture, hemoptysis);
- Dose level IV (200 mg/m² group): 2 patients (headache, tumor hemorrhage).

Anti-tumor activity

Eight of 19 patients (42%) received 3 or more cycles, with a maximum of 6 cycles at dose level III received by a patient with renal cell carcinoma.

No responses were reported, and only 5 patients experienced stable disease (See Table 1). The reason for going off treatment, as shown in Table 1, was progressive disease, except for 2 patients:

1. One patient with uterus cancer received 5 cycles (dose level I) and left the study for asthenia as per investigator's request.
2. One patient (dose level I) had been treated since 1995 for rectal cancer. He had surgery followed by an adjuvant chemotherapy with LV-5FU. Due to liver relapse in 1998, he had 3 lines of chemotherapy up to October 2003, including CPT11 with and without LV-5FU, then oxaliplatin with LV-5FU, then an investigational drug tested in Phase I.

The patient was initially considered as not eligible due to Grade 2 bilirubin related to post-transfusion hemolysis (free bilirubin = 41 vs. total bilirubin = 47). As soon as bilirubin was normalized and as the other liver parameters were within the inclusion ranges, the patient received treatment on Day 1 (cycle 1). However, liver functions tests done before administration of investigational product on Day 2 (cycle 1) indicated that bilirubin had doubled compared to baseline. Administration of investigational product on Days 2 and 3 were cancelled.

Nine patients died due to progressive disease from 34 to 130 days after the last administration of investigational product. No deaths were related to study drug.

PK results

Following single and repeated dosing of SR271425 (75–450 mg/m²) peak plasma concentrations were generally observed at the end of infusion (1-h) and then declined with a terminal half-life of approximately 6-h. Exposure (C_{max}, C_{end} and AUCs) was approximately dose-proportional on Days 1 and 3. There was no evidence of any marked accumulation. Overall, there were no differences observed in pharmacokinetic parameters (Day 3 versus Day 1) following a daily ×3 schedule, as shown in Fig. 1.

At the highest dose level, urine concentrations of SR271425 represented less than 5% of the dose, and therefore no further analysis was conducted on urinary parameters.

Figure 2 presents changes from baseline in QTc plotted against plasma concentration of SR271425. Highest increases (above 30 ms) were observed for plasma concentrations of SR271425 approximately above 1,000 ng/ml.

QTc prolongations were all derived programmatically, and were not associated with any adverse event. However, there is a trend in QTc length increase with dose increase, as shown in Fig. 2.

Conclusion

There were no DLT and no MAD identified in this study due primarily to early termination of the study.

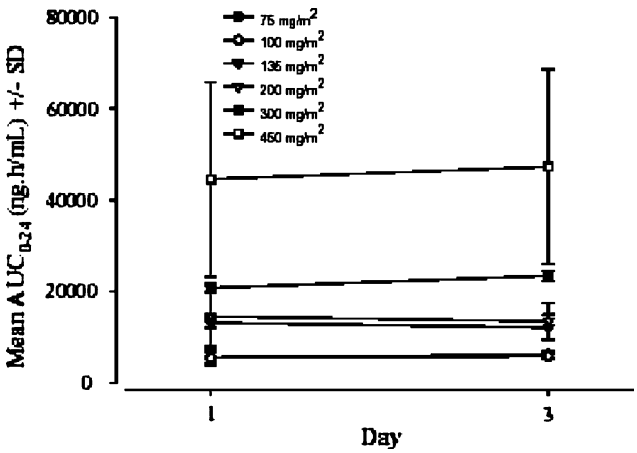

Fig. 1 SR271425 AUC as a function of dose at Days 1 and 3

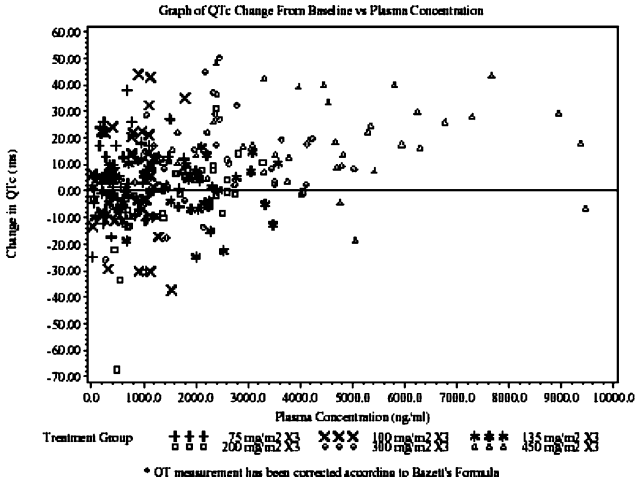

Fig. 2 QTc changes from baseline versus plasma concentrations of SR271425

As these objectives were not reached, no formal conclusion can be drawn.

Peak plasma concentrations were observed at the end of infusion and then declined with a terminal half-life of approximately 6-h. Exposure was approximately dose-proportional on Days 1 and 3. There was no evidence of SR271425 accumulation after 3 daily 1-h infusions (75–450 mg/m²). Overall, there were no differences observed in the pharmacokinetic parameters on Days 1 and 3.

Following administration of SR271425 as a 1-h infusion on Days 1, 2, and 3 of 3-week cycles, at doses levels of 75 × 3, 100 × 3, 135 × 3, 200 × 3, 300 × 3, and 450 × 3 mg/m², in groups of 3 patients (4 at the lowest dose level), no dose-related pattern of AEs was apparent based on descriptive evaluation. Grade ≥3 AEs were observed in 6 patients, and Grade 3 hematological and/or biochemical toxicities were observed in 3 patients. Prolonged QTc was reported at all doses groups, but none of these exceeded Grade 2. QTc prolongations were derived from ECG data and were not reported as AEs by the investigators. Nine deaths occurred during the study, all due to disease progression.

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