

Effect of trabectedin on the QT interval in patients with advanced solid tumor malignancies

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Abstract

Purpose The primary objective of this study was to access the potential effects of trabectedin on the QT/QTc interval in patients with locally advanced or metastatic solid tumors.

Methods Patients ($n = 75$) who had received ≤ 3 previous lines of chemotherapy and had either relapsed or had progressive disease were enrolled. Patients were administered 3-h intravenous infusions of placebo (saline) on day 1 and trabectedin (1.3 mg/m^2) on day 2. Time-matched serial triplicate ECG recordings and pharmacokinetic blood samples were collected over 24 h on both days. Heart rate corrected

mean QT intervals and changes from predose baseline in QTc (ΔQTc) were assessed. The difference in ΔQTc between trabectedin and placebo was calculated at each time point ($\Delta\Delta\text{QTc}$).

Results The upper limits of the 90% confidence interval for $\Delta\Delta\text{QTcF}$ and $\Delta\Delta\text{QTcB}$ at all time points were less than the prespecified noninferiority margin of 10 ms (≤ 6.65 ms). No patient had a QTc > 500 ms or a time-matched increase from baseline in QTc > 60 ms at any time point. Regression analyses indicated $\Delta\Delta\text{QTc}$ was poorly correlated with trabectedin concentration. No adverse events suggestive of proarrhythmic potential were reported.

Conclusion Trabectedin did not prolong the QTc interval. Safety and pharmacokinetic profiles of trabectedin were similar to that observed in other ovarian and breast cancer studies.

Registration: The study is registered at Clinicaltrials.gov (NCT00786838).

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Introduction

Trabectedin is a tris, tetrahydroisoquinoline alkaloid originally isolated from the marine ascidian, *Ecteinascidia turbinate*, and now produced synthetically. It binds to the minor groove of DNA and interacts with proteins of the DNA-repair machinery [1], disrupting the cell cycle and inhibiting cell proliferation [2]. Trabectedin is approved in several countries including the European Union (not approved in the United States) for patients with advanced soft tissue sarcoma after treatment failure with anthracycline and ifosfamide. It is also approved in the European Union in combination with pegylated liposomal doxorubicin for the treatment of patients with relapsed, platinum-sensitive ovarian cancer [3].

In a population pharmacokinetic (PK) analysis, trabectedin as a single intravenous (i.v.) infusion for periods of 1, 3, and 24 h showed time-independent and linear PK [4]. Trabectedin is highly bound (94.2%) to plasma proteins [5] and undergoes extensive metabolism via the cytochrome P450 system, mainly by the CYP3A4 isoenzyme [6]. The extensive tissue distribution of trabectedin (distribution volume of >5,000 L) accounts for the multi-exponential decline in concentrations in plasma and relatively long terminal half-life of approximately 180 h [4].

The present study was conducted primarily to assess the potential effects of therapeutic doses of trabectedin on the QT/QTc interval duration in patients with advanced solid tumor malignancies, as recommended in the International Conference of Harmonization (ICH) E14 guidelines. The secondary objectives of this study were to assess the safety and PK of trabectedin and its effect on patient survival.

Patients and methods

Patients

Seventy-five male and female patients (age, 18–65 years, inclusive) with locally advanced or metastatic solid tumors who had received not more than 3 lines of systemic chemotherapy or were intolerant to standard chemotherapy were enrolled in the study. Additional inclusion criteria were left ventricular ejection fraction within normal limit in patients previously treated with a cumulative anthracycline dose over 260 mg/m²; supine blood pressure between 90 and 140 mmHg systolic and not more than 90 mmHg diastolic; a 12-lead electrocardiogram (ECG) consistent with normal cardiac conduction and function; Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; and clinical laboratory values within acceptable limits as predefined in the protocol. Patients had to be non-smokers (for at least 6 months before study drug administration) and be able to receive dexamethasone.

Patients treated with more than 3 prior chemotherapy regimens and those with previous exposure to trabectedin, known hypersensitivity to any of the components of the trabectedin (i.v.) formulation or dexamethasone, heart rhythm disturbances, unusual T- and U-wave (if present) morphology, CNS metastasis, cardiac failure, myocardial infarction or cardiomyopathy, additional risk factors for torsade de pointes (e.g., heart failure, electrolyte abnormalities, family history of long QT syndrome) and with any condition likely to interfere with placement of the ECG electrode and electrical conduction were excluded from the study. Furthermore, patients at screening receiving medication that prolonged QT interval or who were on CYP3A4 inhibitors or inducers and with current clinically significant other medical illness were excluded. Women who were breastfeeding and those planning to become pregnant during the study were also excluded.

Study design

This was a single-blind (patients blinded to treatment), multicenter, placebo-controlled, sequential design study. It included a screening period of up to 21 days during which patient eligibility was assessed, followed by a treatment phase of 2 single-dose treatments. On day 1 of the treatment phase, the patients were administered placebo (normal saline, 3-h i.v. infusion), and on day 2, the patients received trabectedin (1.3 mg/m², 3-h i.v. infusion). Dexamethasone (20 mg or equivalent, i.v.) was administered 30 min before the i.v. infusions on day 1 and day 2. Granisetron or ondansetron was also administered 30 min before the i.v. infusions if additional antiemetic therapy was considered necessary. Twelve-lead ECGs were obtained by a GE MAC[®] 1200 resting 12-lead ECG device (General Electric Healthcare) with the capacity for digital signal processing and were extracted by a core ECG laboratory (MDS Pharma Services, Ontario, Canada). Blood samples were collected at prespecified times for the determination of trabectedin concentrations in plasma.

This study was conducted in accordance with the ethical principles originating in the provisions of the World Medical Association Declaration of Helsinki and its amendments concerning medical research in humans and in conformance with all local laws and regulations. Documentation procedures complied with ICH guidelines. Study procedures were designed to ensure adherence to Good Clinical Practices and the Code of Federal Regulations 21 and in compliance with the respective protocols. Written consent was obtained from all patients before performance of any study-related activity. Approval for the study was obtained from an Independent Ethics Committee or Institutional Review Board at each participating investigative site.

Evaluations

ECG acquisition

On days 1 and 2, serial ECGs (10-s digital ECGs) were recorded in triplicate (maximum of 2 min between each of the triplicate) at each of the following time points: predose and at 1, 2, 2.75, 4, 6 and 8 h after the start of the infusion. Electrocardiograms were also collected 24 h after trabectedin administration on day 2. The predose (baseline) ECG assessments were recorded within 30 min before the dose of placebo and trabectedin. Patients remained in the comfortable supine position for at least 10 min preceding and following the ECG tracings. Physical activity, position, external stimulation, and meal ingestion were closely regulated to keep physical activity and emotional excitement to a minimum. Patients were allowed to be ambulatory between ECG assessments.

ECG analysis and interpretation

The ECG tracings were evaluated by the third-party central ECG laboratory, which was blinded to treatment (i.e., study day) and time. All ECGs were read by a certified cardiologist. The ECGs were measured by digital on-screen calipers, using a semi-automated method (prepositioning of the cursors by the automatic analysis followed by an over-read of each ECG by a cardiologist). To correct for possible effects of heart rate, Fridericia ($QTcF = QT/RR^{1/3}$) and Bazetts ($QTcB = QT/RR^{1/2}$) corrections were used as the primary and secondary methods, respectively. The final value for each QTc was the average of three complexes. All recordings, including the waveforms with interval measurements, were digitally stored.

Pharmacokinetic evaluations

Peripheral venous blood samples for the determination of trabectedin plasma concentrations were collected predose and following placebo (day 1) and trabectedin (day 2) administration. The blood samples were time-matched to the ECG measurements and collected within 5 min after the last ECG tracing of the triplicate ECGs was recorded. Blood samples were collected at 2 h 45 min after dosing with placebo on day 1 to verify the absence of trabectedin (as time required to reach the maximum concentration [t_{max}] of trabectedin was observed to be 2–3 h in previous studies). The concentrations of trabectedin in plasma were determined by a validated liquid chromatography–mass spectrometry/mass spectrometry (LC–MS/MS) method at the Slotervaart Hospital in Amsterdam, The Netherlands.

Safety evaluations

Safety evaluations included assessment of treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs measurements, and physical examination. All TEAEs were evaluated in terms of intensity, duration, seriousness, and outcome.

Statistical analysis

Sample size determination

The intrasubject standard deviation for $\Delta QTcF$ was assumed to be 10 ms. For a sample size of 52 patients (completers) and assuming the true difference in means equals 5 ms, the probability that the upper limit of the two-sided 90% confidence interval (CI) for the $\Delta\Delta QTc$ at each time point would fall below 10 ms was estimated to be 80%. Approximately 60 patients were to be enrolled to ensure that at least 52 evaluable patients completed all required assessments.

Statistical methods

ECG-related variables were calculated for all patients who received treatment on both days, had predose baseline values for placebo and trabectedin, and had at least one paired postdose value (evaluable analysis set). The primary pharmacodynamic parameter was the difference in the change from predose (ΔQTc) at each scheduled time point between trabectedin (day 2) and placebo (day 1). The predose time point on day 2 was also the 24-h time point for day 1. For each patient, the difference in ΔQTc between trabectedin and placebo was calculated at each time point ($\Delta\Delta QTc = \Delta QTc$ for trabectedin minus ΔQTc for placebo for the patient at the same time point). Mean $\Delta\Delta QTc$ and the 90% CI for $\Delta\Delta QTc$ were calculated at each time point.

A mixed effect analysis of variance (ANOVA) model was fitted with the ΔQTc data as the dependent variable and treatment (trabectedin, placebo), scheduled time point of measurement, and treatment by scheduled time point of measurement interaction as fixed effects and patients as a random effect. Using the estimated least square means and intrasubject variance obtained from this model, 2-sided 90% CI was calculated for $\Delta\Delta QTc$ at each scheduled time point. Non-inferiority, defined as the absence of QTc prolongation when compared with placebo, was concluded if at each scheduled time point the upper limit of the two-sided 90% CI fell below 10 ms. Mean QTc, ΔQTc , and $\Delta\Delta QTc$ were summarized by using descriptive statistics at each time point and by treatment.

Incidence count and percentage of patients with QTc values above the following limits were summarized: QTc

interval >450 ms, QTc interval >480 ms, and QTc interval >500 ms. Incidence count and percentage of patients with QTc increase from predose (Δ QTc) for each treatment and time point were summarized for the following categories: QTc interval increase from baseline >30 ms and QTc interval increase from baseline >60 ms. Additional analyses were performed after the QTc results became available to summarize the incidence count and percentage of patients whose QTc values were reduced from baseline by >30 ms, >60 ms, and absolute QTc intervals that were <360 and <320 ms.

The intervals RR, PR, and QRS were listed over time for each patient and treatment. For each treatment group and time point of measurement, the data were summarized using descriptive statistics. The number and percentage of patients who experienced PR or QRS interval abnormalities based on the following criteria were summarized by treatment: PR interval >200 ms and QRS interval >120 ms.

Relationship between plasma trabectedin and QT/QTc interval changes

Analysis using a linear mixed effects model was performed with Δ QTc as dependent variable and trabectedin concentration as a predictor and patients as random effect. The random intercept model was selected as the best fit model, and the predicted value of Δ QTc (along with 90% CI) was estimated at the mean C_{\max} values of trabectedin based on this model.

Morphological analyses of heart rate ECG waveforms

Mean heart rate (HR) and corresponding changes from baseline were summarized using descriptive statistics by treatment group and time point. T-wave morphology and abnormal U-waves were summarized by treatment group.

Safety evaluations

Safety analyses were summarized with descriptive statistics, for the treated analysis set that was composed of all patients who received at least 1 dose of study drug or placebo and provided at least one postdose measurement.

Results

Patient enrollment, demographics, and baseline characteristics

This single-blind study enrolled 75 patients at 20 sites in 7 countries from October 14, 2008 to April 16, 2009. Of the enrolled patients, 72 completed the study, and 3 patients

Table 1 Demographic and baseline characteristics

	Total (N = 75)
Age (years), Mean (SD)	50.1 (11.03)
Sex, n (%)	
Female	51 (68)
Male	24 (32)
Race, n (%)	
White	51 (68)
Asian	23 (31)
Other	1 (1)
BMI (kg/m ²), mean (SD)	25.6 (5.45)
BSA (m ²), mean (SD)	1.8 (0.22)
Baseline ECOG performance status, n (%)	
0	31 (41)
1	44 (59)
Tumor type, n (%)	
Sarcoma	25 (33)
Breast	11 (15)
Ovarian	23 (31)
Other	16 (21)
Stage of disease, n (%)	
II	8 (11)
III	15 (20)
IV	51 (68)
NA	1 (1)
Number of site involvement at baseline, mean (SD)	1.8 (1.37)
Total no. of patients with previous chemotherapy, n (%)	74 (99)
Antineoplastic agents	74 (99)
All other therapeutic products, n (%)	4 (5)
Endocrine therapy	4 (5)
Antipsoriatics	3 (4)
Cough and cold preparations	3 (4)
Antianemic preparation	2 (3)
Sex hormones and modulators of the genital system	1 (1)

BMI body mass index, BSA body surface area, ECOG Eastern Cooperative Oncology Group

died within 30 days after study treatment. All 75 patients were included in the treated analysis set, and 74 patients were included in the evaluable analysis set (one patient who received trabectedin and placebo in the reverse order was not included).

The demographic and baseline characteristics of the enrolled population are given in Table 1. The most common tumor types were sarcoma (33%) and ovarian cancer (31%). Most patients (99%) had received prior cancer therapy.

Table 2 Estimated means and confidence intervals of the effect of placebo and trabectedin on the QTcF interval (ms) in patients with advanced solid tumor malignancies treated with a single dose of 1.3 mg/m² trabectedin (3-h infusion) (evaluable analysis set)

<i>N</i>	Scheduled time	Arithmetic mean trabectedin concentration (ng/ml)	Arithmetic mean (ms) (95% CI)	Arithmetic mean (ms) CFB (95% CI)	Placebo-adjusted LS mean CFB (ms) (90% CI)
Placebo (Day 1)					
<i>n</i> = 74	Predose	–	406.2 (402.0;410.5)	–	–
<i>n</i> = 74	1 h	–	408.0 (403.6;412.3)	1.7 (0.1;3.4)	–
<i>n</i> = 74	2 h	–	411.4 (406.9;415.9)	5.2 (3.2;7.1)	–
<i>n</i> = 74	2 h 45 min	–	413.4 (409.0;417.9)	7.2 (5.3;9.1)	–
<i>n</i> = 74	4 h	–	415.9 (411.5;420.3)	9.7 (7.3;12.0)	–
<i>n</i> = 74	6 h	–	411.5 (407.1;416.0)	5.3 (3.1;7.4)	–
<i>n</i> = 73	8 h	–	408.9 (404.8;413.1)	2.5 (0.3;4.8)	–
<i>n</i> = 74	24 h	–	409.8 (405.8;413.8)	3.6 (1.2;5.9)	–
Trabectedin 1.3 mg/m ² (Day 2)					
<i>n</i> = 74	Predose	–	409.8 (405.8;413.8)	–	–
<i>n</i> = 74	1 h	7.15	410.1 (405.8;414.5)	0.3 (–1.7;2.4)	–1.4 (–3.35;0.51)
<i>n</i> = 74	2 h	8.07	411.3 (406.9;415.8)	1.5 (–0.8;3.8)	–3.7 (–5.68;–1.63)
<i>n</i> = 72	2 h 45 min	6.98	413.1 (408.5;417.7)	2.7 (0.6;4.8)	–4.5 (–6.55;–2.40)
<i>n</i> = 72	4 h	1.70	413.8 (409.7;417.9)	3.8 (1.5;6.1)	–5.8 (–8.19;–3.45)
<i>n</i> = 73	6 h	0.909	411.0 (407.1;414.9)	1.0 (–1.3;3.4)	–4.2 (–6.26;–2.22)
<i>n</i> = 73	8 h	0.690	410.2 (406.1;414.4)	0.3 (–2.3;2.8)	–2.3 (–4.82;0.26)
<i>n</i> = 73	24 h	0.443	403.7 (399.4;408.0)	–6.2 (–8.7;–3.8)	–9.8 (–12.65;–6.99)

Sample sizes provided in the table refer to the QTcF results. The descriptive statistical analyses of the trabectedin concentrations included 67–73 patients at each time point

CFB change from base line, CI confidence interval, ms milliseconds

ECG analysis

QTcF and QTcB

As mentioned earlier, for QT interval assessment, Fridericia and Bazetts methods were used to correct for heart rate. The appropriateness of the correction factors was assessed by simple linear regression of QTc versus the RR interval. The results indicate that both correction methods were adequate. The analyses resulted in slopes of 0.101 ($R^2 = 0.12$) and -0.065 ($R^2 = 0.05$) for Fridericia and Bazetts methods,

respectively. The regression analysis of uncorrected QT versus RR resulted in a slope of 0.435 ($R^2 = 0.72$).

The mean baseline (predose) QTcF and QTcB intervals were similar before placebo and trabectedin administration (Tables 2 and 3). The mean QTcF intervals increased during the first 4 h after the start of either placebo or trabectedin (Table 2). Thereafter, the QTcF intervals declined gradually to approximate predose values at the time of the 8-h ECG assessments. Small changes were also observed in the mean QTcB intervals during 24 h after the start of the placebo or infusions (Table 3).

Table 3 Estimated means and confidence intervals of the effect of placebo and trabectedin on the QTcB interval (ms) in patients with advanced solid tumor malignancies treated with a single dose of 1.3 mg/m² trabectedin (3-h infusion) (evaluable analysis set)

<i>N</i>	Scheduled time	Arithmetic mean trabectedin concentration (ng/ml)	Arithmetic mean (ms) (95% CI)	Arithmetic Mean CFB (ms) (95% CI)	Placebo-adjusted LS mean CFB (ms) (90% CI)
Placebo (Day 1)					
<i>n</i> = 74	Predose	–	426.3 (422.3;430.3)	–	–
<i>n</i> = 74	1 h	–	425.1 (420.9;429.3)	–1.2 (–3.4;1.0)	–
<i>n</i> = 74	2 h	–	428.0 (423.4;432.5)	1.7 (–0.7;4.0)	–
<i>n</i> = 74	2 h 45 min	–	430.4 (426.1;434.7)	4.1 (1.7;6.4)	–
<i>n</i> = 74	4 h	–	435.4 (431.3;439.5)	9.1 (6.4;11.8)	–
<i>n</i> = 74	6 h	–	435.5 (431.0;440.0)	9.2 (6.6;11.7)	–
<i>n</i> = 73	8 h	–	433.3 (429.0;437.6)	6.7 (4.1;9.4)	–
<i>n</i> = 74	24 h	–	426.4 (422.3;430.4)	0.1 (–2.3;2.4)	–
Trabectedin 1.3 mg/m ² (Day 2)					
<i>n</i> = 74	Predose	–	426.4 (422.3;430.4)	–	–
<i>n</i> = 74	1 h	7.15	423.7 (419.6;427.9)	–2.6 (–5.4;0.1)	–1.4 (–4.04;1.23)
<i>n</i> = 74	2 h	8.07	426.0 (421.7;430.3)	–0.3 (–3.1;2.4)	–2.0 (–4.65;0.65)
<i>n</i> = 72	2 h 45 min	6.98	430.8 (426.4;435.1)	4.0 (1.3;6.6)	–0.1 (–2.66;2.50)
<i>n</i> = 72	4 h	1.70	439.1 (435.4;442.7)	12.5 (9.6;15.4)	3.4 (0.07;6.65)
<i>n</i> = 73	6 h	0.909	439.0 (435.3;442.7)	12.4 (9.8;15.0)	3.2 (0.56;5.92)
<i>n</i> = 73	8 h	0.690	435.9 (432.0;439.8)	9.3 (6.7;11.9)	2.6 (–0.38;5.63)
<i>n</i> = 73	24 h	0.443	425.1 (420.8;429.4)	–1.5 (–4.7;1.7)	–1.6 (–4.83;1.72)

Sample sizes provided in the table refer to the QTcB results. The descriptive statistical analyses of the trabectedin concentrations included 67–73 patients at each time point

CFB change from base line, CI confidence interval, ms milliseconds

Smaller Δ QTcF and comparable Δ QTcB values were observed following trabectedin administration, relative to placebo, at the majority of the corresponding time points after dosing (Tables 2, 3). The mean Δ QTcF ranged from 1.7 ms to 9.7 ms after placebo administration on day 1 and from –6.2 ms to 3.8 ms after trabectedin administration on day 2 (Table 2). The mean Δ QTcB ranged from –1.2 ms to 9.2 ms after placebo administration on day 1 and from –2.6 ms to 12.5 ms after trabectedin administration on day 2 (Table 3).

The QTcF and QTcB interval placebo-adjusted changes from baseline in least square means and the corresponding

90% CIs are summarized in Tables 2, 3, and Fig. 1. The upper limits of the 90% CI for all mean Δ QTcF and Δ QTcB values were \leq 6.65 ms at all time points, indicating non-inferiority of trabectedin to placebo with respect to QTc prolongation.

Categorical analyses revealed no patient with an absolute postdose QTcF or QTcB value $>$ 500 ms after treatment with trabectedin or placebo. No patient and 2 patients (3%) exhibited a QTcF and QTcB $>$ 480 ms, respectively, following treatment with trabectedin. No patient and 1 patient (1%) had a QTcF and QTcB $>$ 480 ms, respectively, after placebo. Four patients (5%) and 23 patients (31%) exhibited

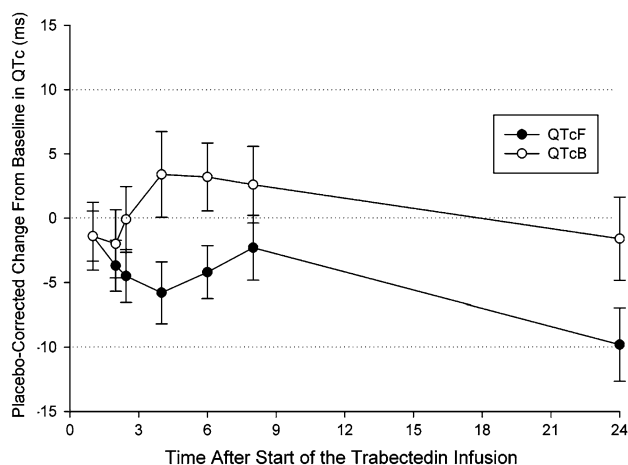


Fig. 1 Placebo-adjusted least square mean ($\pm 90\%$ confidence interval) change from baseline in QTc ($\Delta\Delta$ QTc) intervals following treatment with a single dose of trabectedin 1.3 mg/m^2 (3-h infusion) in patients with advanced solid tumor malignancies

a QTcF and QTcB > 450 ms, respectively, following treatment with trabectedin. Six patients (8%) and 21 patients (28%) had a QTcF and QTcB > 450 ms, respectively, after placebo. No patient exhibited an increase in the QTcF or QTcB from baseline > 60 ms. Two patients (3%) and 6 patients (8%) had increase in QTcF and QTcB > 30 ms, respectively, following treatment with trabectedin. Two patients (3%) and 4 patients (5%) exhibited an increase in QTcF and QTcB > 30 ms, respectively, after placebo.

Additional categorical analyses indicated that no patient had a QTcF and QTcB value of < 320 ms. QTcF was < 360 ms in 1 patient in association with trabectedin and 1 patient with placebo. In addition, no patient had a decrease from baseline in QTcF or QTcB > 60 ms. Three patients (4%) and 4 patients (5%) had a decrease in QTcF and QTcB > 30 ms, respectively, following treatment with trabectedin. No patient and 1 patient (1%) exhibited a decrease in QTcF and QTcB > 30 ms, respectively, after placebo.

Heart rate, T- and U-wave morphology, and PR and QRS intervals

The mean (SD) baseline (predose) HR prior to placebo (day 1) and trabectedin (day 2) administration was 81.2 (12.9) bpm and 76.9 (10.5) bpm, respectively. Mean HR values after both i.v. infusions ranged from 76.9–86.0 bpm for placebo and 73.8–90.0 bpm for trabectedin. At 24 h after trabectedin infusion, the mean HR declined to a value similar to baseline value prior to placebo infusion (82.6 [11.1] bpm).

The T-wave morphology was unaltered with trabectedin treatment, and no pathological U-wave morphology was

observed in this study. The PR and QRS intervals were also not affected by trabectedin.

Plasma pharmacokinetics of trabectedin

Plasma samples were available for bioanalysis from a majority of the enrolled patients (Tables 2 and 3). The concentration of trabectedin was below the limit of quantification for all plasma samples collected at 2 h 45 min after start of placebo infusion (day 1). The mean concentrations increased over the course of the i.v. infusion administered on day 2. Maximum concentrations were observed at an average (SD) of 2.22 (0.65) h after the start of the trabectedin infusion. The mean (SD) C_{max} value was 9.24 (3.75) ng/ml. The trabectedin concentrations initially declined rapidly upon completion of the infusion, followed by a protracted decrease in the concentrations, with much lower concentrations observed at the 24-h time point.

Relationship between plasma trabectedin and QT/QTc interval changes

The individual $\Delta\Delta$ QTc intervals and corresponding trabectedin plasma concentrations exhibited a very weak linear relationship (Fig. 2). For both analyses, the range of $\Delta\Delta$ QTc was quite wide as evidenced by the spread of the data around the regression line. At the mean C_{max} of 9.2 ng/ml in plasma, the mean (90% CI) $\Delta\Delta$ QTcF was -2.53 ms ($-4.59, -0.46$ ms) and $\Delta\Delta$ QTcB was -0.68 ms ($-3.26, 1.90$ ms).

Safety

Seventy-one (95%) of the 75 patients in the study experienced TEAEs (Table 4). The most frequent adverse events were nausea ($n = 41$ [55%]), vomiting ($n = 39$ [52%]), abnormal hepatic function ($n = 24$ [32%]), asthenia ($n = 20$ [27%]), anorexia ($n = 15$ [20%]), fatigue ($n = 12$ [16%]), and neutropenia ($n = 12$ [16%]) (Table 4). Three patients died within 30 days after study treatment. One patient with oropharyngeal cancer died 12 days after receiving study drug, due to progressive disease. The second patient experienced serious grade 3 asthenia and grade 3 vomiting, 5 days after receiving study drug, and died the next day. It was unknown whether these events caused the sudden death. The third patient with linitis plastica died due to euthanasia administered 30 days after study drug at the request of the patient, due to progressive disease. There were no clinically noteworthy changes observed in laboratory assessments, vital signs, ECGs, and physical examination in the study. No patient experienced cardiac toxicity in this study.

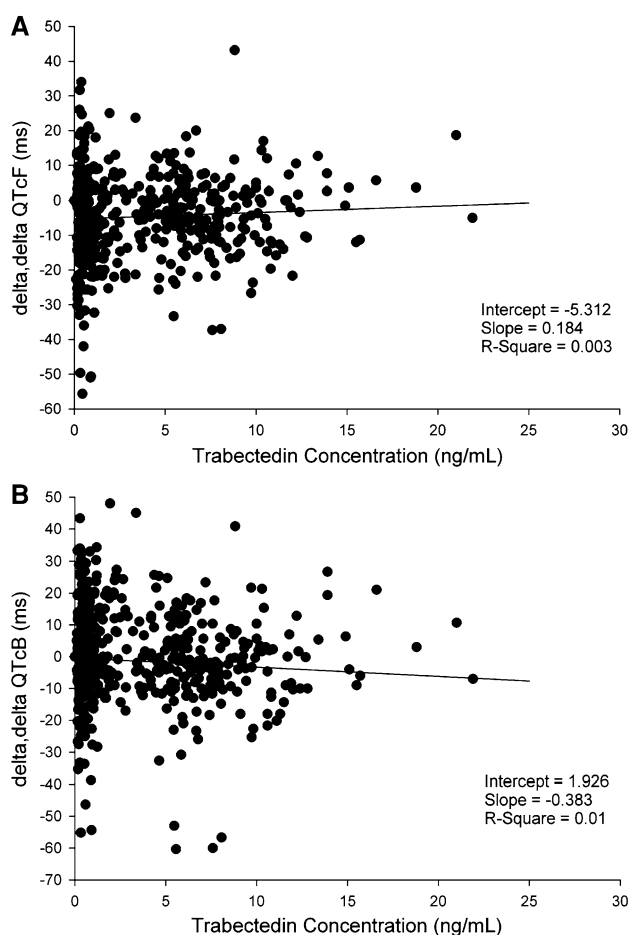


Fig. 2 Correlation between placebo-adjusted change from baseline in QTc ($\Delta\Delta$ QTc) versus concentrations of trabectedin in plasma at corresponding time points following treatment with a single dose of trabectedin 1.3 mg/m^2 (3-h infusion) in patients with advanced solid tumor malignancies

Discussion

Considerable evidence is available demonstrating that some non-cardiac (i.e., non-antiarrhythmic) drugs delay cardiac repolarization. This effect can be measured by ECG and identified by prolongation of the QT/QTc interval [7, 8]. Prolongation of the QT/QTc interval has been associated with the increased susceptibility to arrhythmias, such as the relatively rare event known as torsades de pointes [8]. Thus, premarketing investigation of the safety of a new pharmaceutical agent typically includes rigorous characterization of its effects on the QT/QTc interval [9, 10].

In unpublished nonclinical experiments, trabectedin showed low potential to delay ventricular repolarization. In hERG-transfected HEK293 cells, trabectedin at a concentration of 10^{-8} M to $3 \times 10^{-6} \text{ M}$ (approximately 7.6–2,286 ng/ml) had no significant effect on the membrane K⁺ current (IKr). However, at a high concentration

Table 4 Summary of treatment-emergent adverse events by body system or organ class and dictionary derived term (treated analysis set)

MedDRA preferred term	Total (N = 75) n (%)
Total number of patients with treatment-emergent adverse events	71 (95)
Nausea	41 (55)
Vomiting	39 (52)
Hepatic function abnormal	24 (32)
Asthenia	20 (27)
Anorexia	15 (20)
Neutropenia	12 (16)
Fatigue	12 (16)
Constipation	7 (9)
Anemia	7 (9)
Cough	6 (8)
Enzyme abnormality	5 (7)
Leucopenia	5 (7)
Dizziness	5 (7)
Myalgia	4 (5)
Pyrexia	4 (5)
Pain	4 (5)

The most common (i.e., $\geq 5\%$) treatment-emergent adverse events provided

MedDRA Medical dictionary for regulatory activities

(10^{-5} M or 7,620 ng/ml), only a marginal effect (approximately 10% reduction relative to solvent control) was observed. The effect of a single 1-h i.v. infusion of trabectedin $90 \mu\text{g/kg}$ ($1,080 \mu\text{g/m}^2$) was also investigated in anesthetized cynomolgus monkeys. Relevant effects on heart rate, ECG variables (PR, QT, QTcF and QTcV intervals, and QRS duration), ECG gross morphology and rhythm, left ventricular variables, cardiac output, stroke volume, or respiratory variables were not observed.

In clinical trials, trabectedin was found to be efficacious and well tolerated in the treatment of several tumor types including ovarian cancer (1.3 mg/m^2 , 3-h i.v. infusion every 3 weeks), breast cancer (0.58 mg/m^2 , weekly and 1.3 mg/m^2 every 3 weeks), and soft tissue sarcoma (1.5 mg/m^2 , 24-h i.v. infusion once every 3 week) [11–15]. Although higher doses have been administered to sarcoma cancer patients, the 3-h infusion of 1.3 mg/m^2 used in this study produced concentrations in plasma that are higher than those following infusions of longer duration (e.g., 1.14 ng/ml following 1.5 mg/m^2 given as a 24-h i.v. infusion) [16].

The present study was designed to determine as precisely as possible the effects of trabectedin on QTc. The design included a number of characteristics considered to be important for the systematic evaluation of a drug's effect

on QTc interval prolongation and proarrhythmic potential in humans (i.e., “thorough QT/QTc study”) [17]. It included digital ECG data collection in triplicate with rigorous methodology, ECG review by experts, application of appropriate heart rate corrections of measured QT interval, analysis of central tendency and categorical analysis, and characterization of the concentration–effect relationship by simultaneous measurement of trabectedin concentrations in plasma and QTc intervals. Consistent with guidelines, the criterion for a negative study was determined a priori if the upper bound of the 90% two-sided CI for the largest time-matched mean effect on the QTc excluded 10 ms.

The conventional design of the “thorough QT/QTc” includes administration of substantial multiples of the dose of a test drug to normal healthy volunteers who are not concomitantly taking other medications. These features increase the likelihood of observing QTc prolongation if the test drug exhibits this property. Due to safety and tolerability concerns, patients with advanced malignancies were enrolled in the present study and were administered a therapeutic dose (1.3 mg/m²) of trabectedin. All patients received an i.v. infusion of placebo (i.e., saline) followed by trabectedin in a fixed sequence. The crossover design element allowed patients to be their own control. Random assignment to this sequence versus the reverse order (i.e., trabectedin followed by placebo), as recommended in ICH E14, was neither practical nor ethical since the terminal $t_{1/2}$ of trabectedin is approximately 180 h [4] and would have required a protracted washout between the treatment days. As a consequence, only the patients were blinded to the order of treatments, whereas the investigator and clinical site personnel were unblinded. The consequences of the single-blind nature of the study are likely to be small, since the ECGs were analyzed by independent reviewers who were blinded to treatment (i.e., study day) and time.

The standard “thorough QT/QTc” study includes a positive control, which demonstrates an ability to detect clinically significant prolongation in the QTc interval. It has been customary to administer patients a single 400 mg oral dose of moxifloxacin [18–22]. Due to ethical constraints and practical considerations, the administration of moxifloxacin to the patients enrolled in the present study was not possible. “Thorough QT/QTc” studies also often include a full-day baseline correction method (to account for certain uncontrollable factors such as circadian variation, food effects, etc) where triplicate ECGs at time-matched points are collected on the day before the test drug and placebo are given. However, recent work has provided evidence that this may not be necessary [23]. With the study design utilized in this present study, where each patient was his or her own control, predose baseline is considered to be sufficient,

as the difference in Δ QTc between drug and placebo for each patient effectively accounts for diurnal variation and other factors that are difficult or not possible to control.

Trabectedin did not prolong QT/QTc intervals relative to placebo, in this study. The upper limits of the 90% CI for all mean Δ QTcF and Δ QTcB values were ≤ 6.65 ms at all time points indicating non-inferiority of trabectedin to placebo. Further, no patient had a QTcF or QTcB value that was >500 ms, a time-matched increase in QTc from baseline >60 ms in either treatment at any time point, nor a QTc that was less than 350 ms. Moreover, there were no reports of sudden death or ventricular arrhythmias, including ventricular fibrillation.

There was a modest increase in mean heart rate observed with trabectedin relative to placebo at 4 h after the start of infusion and throughout most of the 24-h observation period. At 24 h after trabectedin infusion, the mean heart rate values were similar to baseline values before placebo infusion. The increase in heart rate with trabectedin was of no clinical significance. Rare and sporadic out of range values were noted for other 12-lead ECG parameters (heart rate, PR interval, QRS interval, T-wave and U-wave morphology). However, no consistent or particular association to any treatment (trabectedin or placebo) was observed.

The safety profile following administration of a single therapeutic dose of trabectedin (1.3 mg/m²) was similar to that reported in previous clinical studies. The most commonly reported adverse events were asthenia, abnormal hepatic function, and vomiting that are consistent with the known safety profile of trabectedin. No adverse events suggestive of proarrhythmic potential were observed.

In conclusion, trabectedin at a therapeutic dose of 1.3 mg/m² administered as a 3-h i.v. infusion did not prolong the QTc interval in patients with advanced solid tumor malignancies in comparison with placebo. Further, the safety profile was consistent with previous studies, indicating trabectedin was well tolerated.

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