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ORIGINAL ARTICLE

Trabectedin has a low cardiac risk profile: a comprehensive cardiac safety analysis

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Abstract
Purpose This analysis provides a cross-study evaluation of the cardiac safety of trabectedin.
Methods Drug-related cardiac adverse events (CAEs) were retrieved from phase I–III clinical trials, pharmacovigilance databases, and spontaneously reported cases. Left ventricular ejection fraction (LVEF) was monitored in combination phase I studies with doxorubicin or pegylated liposomal doxorubicin (PLD) and in a phase III trial (with PLD).
Results CAEs [grade 4 cardiac arrest with severe pancytopenia and sepsis ($n = 1$ patient), grade 4 atrial fibrillation ($n = 2$), and grade 1 tachycardia ($n = 1$)] occurred in 4/283 patients (1.4%) in 6 single-agent phase I trials. CAEs (grade 1 sinus tachycardia in a hypertensive patient and grade 1 ventricular dysfunction) occurred in 2/155 patients (1.3%) in 4 phase I combination trials. Results from 19 single-agent phase II trials showed CAEs in 20/1,132 patients (1.8%): arrhythmias (tachycardia/palpitations; $n = 13$; 1.1%) were the most common. A rather similar rate of symptomatic CAEs was observed in both arms of a phase III trial in recurrent ovarian cancer: 6/330 patients (1.8%; PLD) and 11/333 patients (3.3%; trabectedin/PLD). No clinically relevant LVEF changes occurred in phase I combination trials. In the phase III trial, LVEF decreases from baseline were similar: 9% of patients (PLD) and 7% (trabectedin/PLD), with no relevant symptoms. During postmarketing experience in soft tissue sarcoma (2,046 patients treated), 4 CAEs (2 cardiac arrest, 2 cardiac failure; ~0.2%) occurred in patients with preexisting conditions.
Conclusions Trabectedin has a low incidence of CAEs, consisting mainly of arrhythmias. This extensive data review indicates a low cardiac risk profile for trabectedin.

Keywords Trabectedin · Cardiac events · Safety · Pharmacovigilance

Introduction

Cardiac toxicity is a potential short- or long-term complication of anticancer therapy [1]. Exposure to chemotherapy agents, particularly anthracyclines, can lead to potentially irreversible clinically significant cardiac dysfunction [2–5]. The arrival of novel agents has modified the treatment of several types of malignancies, but although some of these new therapies are considered better tolerated by patients compared with classic chemotherapy agents, rare serious complications have been observed, and longer-term follow-up is needed to determine the exact profile of related cardiac adverse effects [4, 6].

Trabectedin (Yondelis®) is a marine-derived antineoplastic agent, initially isolated from the tunicate *Ecteinascidia*

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turbinata and currently produced synthetically. Trabectedin is a first-in-class antitumor agent with a complex mechanism of action at the level of gene transcription. Trabectedin binds covalently to the minor DNA groove and alkylates the N2 amino group of a guanine residue, which bends toward the major groove [7]. Cytotoxic concentrations of trabectedin delay cell cycle progression through the S phase and produce arrest at G2/M, ultimately resulting in p53-independent apoptosis [8–11]. Trabectedin-induced DNA damage is recognized by the nucleotide excision repair (NER) pathway, resulting in stalled DNA–protein repair complexes [12, 13] and cell death. Therefore, in contrast to what would be expected from a DNA-damaging agent, sensitivity to trabectedin is correlated with a functional NER pathway [14]. In addition, trabectedin induces DNA double-strand breaks, mainly during early S phase, and this damage is repaired by the homologous recombination repair pathway [15].

Preclinical studies showed that, in vitro, trabectedin did not induce toxicity in cultured rat myocytes and had no significant effect on the membrane K^+ current. In vivo, single- and repeated doses of trabectedin in Cynomolgus monkeys did not induce any relevant effects on heart rate, lead II electrocardiogram (ECG) variables, waveform and rhythm, left ventricular cardiac output variables, stroke volume, arterial blood variables, or respiratory variables. No evidence of cardiovascular disorders was found [16–19].

Trabectedin has shown antitumor activity in different neoplastic diseases: soft tissue sarcoma (STS) [20–22], advanced ovarian cancer relapsing after platinum- and taxane-based chemotherapy [23–26], metastatic hormone-refractory prostate cancer [27], or pretreated advanced breast cancer [28, 29]. The antitumor activity of trabectedin 1.5 mg/m^2 24-h i.v. infusion once every 3 weeks (q3wk 24-h) was evaluated in single-arm phase II trials in STS patients previously treated with anthracyclines and/or ifosfamide [20–22]. Based on promising results, a phase II randomized trial was subsequently conducted and the q3wk 24-h regimen was found to provide clinical benefit to patients with leiomyosarcomas and liposarcomas, following failure of standard-of-care treatment including at least an anthracycline and ifosfamide. These results formed the basis for the approval in 2007 as a single agent in the European Union for treatment of STS after failure of standard-of-care chemotherapy (doxorubicin and/or ifosfamide) or for patients unsuited to receive it [30], Furthermore, 3 phase II trials showed encouraging activity for trabectedin as a single agent in relapsed ovarian cancer [23, 25, 26]. A subsequent randomized phase III trial confirmed that trabectedin 1.1 mg/m^2 3-h i.v. infusion plus pegylated liposomal doxorubicin (PLD; Doxil®/Caelyx®) 30 mg/m^2 90 min i.v. infusion every 3 weeks improved progression-free survival over PLD alone (50 mg/m^2, 90 min i.v. infusion every 4 weeks) [31]. The trabectedin plus PLD combination received approval in 2009 in Europe for treatment of patients with relapsed, platinum-sensitive ovarian cancer [31]. The two pivotal randomized trials with trabectedin in STS and ovarian cancer had antitumor response evaluated by an independent review. In the trials with trabectedin alone, nausea, fatigue, and vomiting were common trabectedin-related adverse events, reported in ≥20% of patients. Reversible myelosuppression (mainly neutropenia) and transient reversible transaminase increases were the most common laboratory abnormalities seen with trabectedin, with a very low incidence of relevant clinical consequences [32]. The safety profile of the trabectedin plus PLD combination was consistent with the known toxicities characteristic of each agent alone, and no new or unexpected toxicity was observed [31].

This review provides a comprehensive summary of the clinical cardiac tolerability of trabectedin. The aim of this analysis is to summarize information on cardiac adverse events (CAEs) occurred in clinical trials evaluating trabectedin as monotherapy or in combination with doxorubicin or PLD in adult patients with advanced solid tumors during the clinical development of this antitumor agent. The information on spontaneously reported CAEs retrieved during postmarketing experience with trabectedin is also provided.

Materials and methods

CAEs related to trabectedin administration were retrieved from phases I, II, and III clinical trials, pharmacovigilance databases, and spontaneous cases reported during the postmarketing experience. The reviewed sources of information were case report forms (CRFs), serious adverse events (SAEs) reports, follow-up reports, and their supplementary reports.

A search for all CAEs reported in the CRFs with preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA) that could potentially be classified as cardiac were evaluated. The following group categories were included as follows: arrhythmias or rhythm abnormalities; myocardial ischemia; myocardial dysfunction; and other [e.g., blood pressure increase/decrease, cardiac arrest]. With respect to SAEs, an analysis of reports with at least one term within the system organ class (SOC) "Cardiac Disorders" or related terms within the "Investigations", SOC was performed on the trabectedin Pharmacovigilance Database.

Left ventricular ejection fraction (LVEF) was monitored in combination phase I studies with anthracyclines (doxorubicin or PLD) and in the pivotal phase III randomized study OVA-301 evaluating trabectedin/PLD versus PLD alone.

Spontaneous cases from non-clinical trial reports reported during the postmarketing experience of trabectedin were also analyzed with the aforementioned search criteria.

Results

Phase I clinical trials evaluating trabectedin as a single agent

Results from 6 single-agent phase I trials evaluating trabectedin at doses from 0.006 to 1.9 mg/m^2 given as a 1-, 3-, 24- or 72-h intravenous (i.v.) infusions administered every 3 weeks (q3wk) or 4 weeks (q4wk) showed CAEs related to trabectedin in 4 of 283 treated patients (1.4%). These CAEs consisted of grade 4 cardiac arrest in one patient with severe pancytopenia and sepsis treated at the trabectedin dose of 1.9 mg/m^2 1-h day 1–5 q3wk; grade 4 atrial fibrillation in 2 patients treated with trabectedin 72-h q3wk at 1.2 mg/m^2, and grade 1 tachycardia in one patient treated with trabectedin 3-h q3wk at 1.8 mg/m^2.

Phase I clinical trials evaluating trabectedin in combination with doxorubicin or PLD

Results from 4 phase I combination trials of trabectedin with doxorubicin or PLD showed CAEs of mild severity related to treatment in 2 of 155 patients (1.3%): grade 1 sinus tachycardia in a hypertensive patient treated with trabectedin plus doxorubicin, and grade 1 ventricular dysfunction (consisting of a decrease in ejection fraction greater than 20% from baseline; i.e., from 75 to 50%) in a patient treated with trabectedin plus PLD after having received 24 combination cycles (PLD was discontinued, and the patient continued trabectedin alone treatment for 12 further cycles until discontinuation due to disease progression; last LVEF value of 64%).

Phase II clinical trials evaluating trabectedin as a single agent

Overall, 1,132 patients were treated in 19 completed single-agent phase II clinical trials with three different dose schedules: 3-h infusion q3wk at a starting dose of 1.3 mg/m^2 (q3wk 3-h), 24-h infusion q3wk at a starting dose of 1.5 mg/m^2 (q3wk 24-h) or 3-h weekly infusion at a starting dose of 0.58 mg/m^2 (qwk 3-h). Most patients had good performance status (ECOG of 0 in 53.2% and 1 in 46.5%). The most frequent tumor types at diagnosis were sarcoma [56%, L-type (liposarcoma or leiomyosarcoma; 34%) and non-L-type (22%) that included rhabdomyosarcoma, osteosarcoma, and gastrointestinal stromal tumor], ovarian (26%) and breast (7%) cancer. As expected for this clinical setting, most patients (90.2%) had received previous systemic anticancer therapy, with 49.2% of patients having previously received anthracyclines. In addition, 96.0% had undergone surgery and 37.5% had had radiotherapy.

The CAEs reported in phase II trials as related to trabectedin treatment are shown in Table 1. As expected from phase I data, the most frequent CAEs were arrhythmias ($n = 13$; 1.1%), usually consisting of grade 1/2 tachycardia ($n = 6$) and grade 1 palpitations ($n = 4$), with a borderline clinical significance. Only one of these 13 arrhythmia events was severe (grade 3 atrial fibrillation) and occurred in a patient treated with trabectedin 1.5 mg/m^2 q3wk 24-h and with previous cardiac medical history, including atrial fibrillation, irregular heart rate for 5 years, and a pacemaker. The patient was treated with intravenous fluids and diltiazem hydrochloride, which resolved the event. Other types of CAEs were infrequent and usually occurred in one patient each (<1%).

One of 1,132 patients (0.1%) who were treated with trabectedin and had a treatment-related CAE (grade 3 cardiac failure) died. This was a 58-year-old female patient with platinum-sensitive, advanced ovarian cancer treated with trabectedin 0.58 mg/m^2 qwk 3-h. The patient had been previously treated with paclitaxel and carboplatin. After 7 cycles of treatment, the patient was hospitalized for grade 3 left ventricular failure, chest pain, dyspnea, cardiac murmur, pleural effusion, and pulmonary edema. She was treated with heparin, furosemide, and prednisolone. On Day 4, a grade 2 pulmonary hypertension occurred that was treated with ramipril; this resolved in 27 days and was considered possibly related to trabectedin. The patient was withdrawn from the study, and the patients' death due to disease progression was reported about 1 month after starting the events.

In these phase II trials, pharmacokinetic data were available for 482 patients overall and for 60 patients with CAEs regardless of relationship (i.e., including trabectedin-unrelated cases). Drug exposure (as reflected by the area under the curve data) was similar in patients with CAEs [mean (SD) of 79.5 (33.6) h ng/ml] and in those without cardiac AEs [78.8 (48.8) h ng/ml].

Phase III clinical trial OVA-301

No relevant signs or symptoms associated with cardiac failure were found during treatment in the two treatment arms evaluated in the phase III randomized clinical trial OVA-301. Results from this pivotal trial evaluating trabectedin combined with PLD versus PLD alone in patients with advanced ovarian cancer showed a slightly higher rate of drug-related CAEs in the combination treatment arm compared with the PLD alone arm (Table 2). This small

Table 1 Trabectedin-related cardiac adverse events (CAEs) occurred in phase II single-agent clinical trials (data per patient)

	Schedule and dose															
	q3wk 24-hour 1.5 mg/m^2 (n = 570)				q3wk 3-hour 1.3 mg/m^2 (n = 258)				qwk 3-hour 0.58 mg/m^2 (n = 304)				Total (n = 1,132)			
	Grade, n (%)				Grade, n (%)				Grade, n (%)				Grade, n (%)			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Total of patients with CAEs[a]	6 (1.1)	3 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	–	–	4 (1.3)	2 (<1)	1 (<1)	–	11 (<1)	6 (<1)	2 (<1)	1 (<1)
Arrhythmias or rhythm abnormalities	4 (<1)	1 (<1)	1 (<1)	–	1 (<1)	1 (<1)	–	–	4 (1.3)	1 (<1)	–	–	9 (<1)	3 (<1)	1 (<1)	–
Atrial fibrillation	1 (<1)	–	1 (<1)	–	–	–	–	–	–	–	–	–	1 (<1)	–	1 (<1)	–
Heart rate increased	–	–	–	–	–	–	–	–	–	1 (<1)	–	–	–	1 (<1)	–	–
Palpitations	1 (<1)[b]	–	–	–	1 (<1)	–	–	–	2 (<1)	–	–	–	4 (<1)	–	–	–
Tachycardia	2 (<1)	–	–	–	–	1 (<1)	–	–	2 (<1)	1 (<1)	–	–	4 (<1)	2 (<1)	–	–
Ventricular arrhythmia	–	1 (<1)	–	–	–	–	–	–	–	–	–	–	–	1 (<1)	–	–
Myocardial dysfunction	–	1 (<1)	–	1 (<1)	–	–	–	–	–	1 (<1)	1 (<1)	–	–	2 (<1)	1 (<1)	1 (<1)
Cardiac failure	–	–	–	1 (<1)	–	–	–	–	–	1 (<1)	1 (<1)[c]	–	–	1 (<1)	1 (<1)	1 (<1)
Right ventricular failure	–	1 (<1)	–	–	–	–	–	–	–	–	–	–	–	1 (<1)	–	–
Other	2 (<1)	1 (<1)	–	–	–	–	–	–	1 (<1)	–	–	–	3 (<1)	1 (<1)	–	–
Hypertension/blood pressure increased	2 (<1)	1 (<1)	–	–	–	–	–	–	1 (<1)	–	–	–	3 (<1)	1 (<1)	–	–

Data shown are n (%) of patients

CAE cardiac adverse event, *q3wk* every 3 weeks, *q4wk* every 4 weeks, *qwk* every week

[a] No trabectedin-related events due to myocardial ischemia occurred

[b] One case of grade 1 palpitation with unknown relationship was also reported

[c] This patient had also cardiac murmur reported as concomitant event

difference was due to the occurrence of grade 1 palpitations (n = 4 events) in the combination arm. In fact, the most frequent CAEs related to treatment in both study arms were arrhythmias. The results were also consistent between both arms when only clinically significant symptomatic CAEs (i.e., cardiac events with grade ≥2) were considered (Table 3). No deaths due to CAEs occurred in this study.

LVEF analysis

Phase I combination trials

LVEF changes were observed in combination trials with trabectedin plus doxorubicin or PLD. A total of 5 patients treated with the combinations of trabectedin plus doxorubicin or trabectedin plus PLD had LVEF decrease: three of them discontinued PLD, but continued trabectedin treatment with further increase in LVEF at the end of treatment in 3 patients (no further LVEF assessment was made in the other 2 patients).

Pivotal phase III trial OVA-301

The percentages of patients with LVEF decline were comparable between the 2 treatment arms in this randomized trial (6.6% in the trabectedin plus PLD arm vs. 8.8% in the PLD arm) (Table 4). The evaluation of LVEF from baseline to treatment termination among patients of OVA-301 trial with paired data also showed no relevant differences between the two treatment arms (Fig. 1).

Analysis of covariance was carried out introducing two variables in the model: treatment arm and LVEF value at baseline (n = 369 patients; PLD = 171 patients and trabectedin plus PLD = 198 patients). This analysis further confirmed a similar LVEF value at the end of treatment in both study arms (P value = 0.8865), despite the trabectedin pus PLD arm had a slightly higher median cumulative PLD dose (232 mg/m^2 vs. 202 mg/m^2 in the PLD alone arm).

Only 2 of 42 patients (5%; one in each treatment arm) with absolute LVEF decrease during treatment discontinued the study drugs. In the case of the patient treated with trabectedin plus PLD, only PLD was discontinued (Table 4).

Postmarketing experience with trabectedin as a single agent in soft tissue sarcoma

During single-agent trabectedin postmarketing experience in EU with 2,046 sarcoma patients treated, only 4 cardiac AEs (2 cardiac arrest, and 2 cardiac failure; ~0.2%)

Table 2 Trabectedin-related cardiac adverse events (CAEs) occurred in the phase III randomized trial OVA-301 (data per patient)

	PLD (n = 330)				Trabectedin + PLD (n = 333)			
	Grade, n (%)				Grade, n (%)			
	1	2	3	4	1	2	3	4
Total of patients with CAEs	4 (1.2)	2 (<1)	1 (<1)	–	9 (2.7)	2 (<1)	3 (<1)	1 (<1)
Arrhythmias or rhythm abnormalities	2 (<1)	1 (<1)	–	–	5 (1.5)	1 (<1)	1 (<1)	1 (<1)
Atrial flutter	1 (<1)	–	–	–	–	–	–	–
Electrocardiogram change	–	–	–	–	–	1 (<1)	–	–
Electromechanical dissociation	–	–	–	–	–	–	–	1 (<1)[a]
Palpitations	–	–	–	–	4 (1.2)	–	1 (<1)	–
Tachycardia	1 (<1)	1 (<1)	–	–	1 (<1)	1 (<1)	–	–
Myocardial ischemia	1 (<1)	–	–	–	–	–	–	–
Angina pectoris	1 (<1)	–	–	–	–	–	–	–
Myocardial dysfunction	1 (<1)	1 (<1)	1 (<1)	–	4 (1.2)	1 (<1)	2 (<1)	–
Cardiac failure	–	–	–	–	–	1 (<1)	1 (<1)	–
Left ventricular dysfunction	1 (<1)	1 (<1)	–	–	4 (1.2)	–	1 (<1)	–
Left ventricular hypertrophy	–	–	1 (<1)	–	–	–	–	–
Other	–	–	–	–	–	–	–	1 (<1)
Cardiac arrest	–	–	–	–	–	–	–	1 (<1)[a]

Data shown are n (%) of patients

Percentages calculated with the number of patients in each group as denominator. The same patient may be reported more than once

CAE cardiac adverse event, *PLD* pegylated liposomal doxorubicin

[a] Grade 4 electromechanical dissociation in one patient with severe pancytopenia, sepsis, and grade 4 cardiac arrest

Table 3 Clinically significant symptomatic cardiac adverse events (CAEs) with grade ≥2 occurred in the phase III randomized trial OVA-301 (all treated patients)

	PLD (n = 330)			Trabectedin + PLD (n = 333)		
	Total	Related[a]		Total	Related[a]	
	n (%)	Yes	No	n (%)	Yes	No
Total no. of patients with CAEs grade ≥2	6 (1.8)			11 (3.3)		
Arrhythmias or rhythm abnormalities	2 (<1)	1	1	5 (1.5)	3	2
Myocardial ischemia	1 (<1)	–	1	1 (<1)	–	1
Myocardial dysfunction	3 (<1)	2	1	6 (1.8)	3	3
Other	–	–	–	1 (<1)	1	–

CAE cardiac adverse event, *PLD* pegylated liposomal doxorubicin

[a] At least possibly related to the study treatment

occurred, all of them in patients with preexisting cardiac conditions, such as cardiomegaly, cardiopathy, or prior chest wall radiotherapy.

Discussion

Cardiac toxicity is a worrisome side effect of anticancer chemotherapy because the gain in life expectancy obtained with treatment might be countered by increased mortality due to CAEs. Furthermore, comorbid medical conditions, such as chronic uncontrolled heart disease, may hamper cancer treatment. Several well-established and widely used anticancer agents have been associated with an increased risk of cardiac toxicity, such as anthracyclines, fluoropyrimidines, etoposide, high-dose alkylating agents, interferon, interleukin-2, taxanes, monoclonal antibodies (trastuzumab, bevacizumab), and tyrosine kinase inhibitors (sunitinib, sorafenib) among others [2, 6, 33]. The most relevant chemotherapy-related cardiac toxicity is myocardial damage, which may lead to impaired cardiac function and overt congestive heart failure. This type of cardiotoxicity has been observed in patients treated with anthracyclines or high doses of alkylating agents and is known as type I chemotherapy-related cardiac dysfunction (i.e., it is present from the earliest administration of the drug) [34].

Table 4 Patients with left ventricular ejection fraction (LVEF) decrease (from baseline to end of treatment) in the phase III randomized trial OVA-301

	PLD (n = 330)	Trabectedin + PLD (n = 333)
	n (%)	n (%)
Patients with baseline and final LVEF measurement[a]	171 (52%)	198 (59%)
No. of patients with LVEF decrease ≥15% and/or 5% less than LLN (absolute value)	15 (8.8%)	13 (6.6%)
Median (range) age, years	53 (42–72)	54 (46–80)
Median (range) number of cycles	5 (1–10)	8 (2–15)
No. of patients with symptoms of cardiac heart failure during treatment	1	2
Median decrease in LVEF (absolute value)	−15%	−16%
Median (range) cumulative PLD dose (mg/m^2)	202 (51–379)	232 (60–438)
Treatment discontinuation due to decrease in LVEF	1	1[b]

LLN lower limit of normal, *LVEF* left ventricular ejection fraction, *MUGA* multiple-gated acquisition scan, *PLD* pegylated liposomal doxorubicin

[a] LVEF measurement at baseline and after the permanent discontinuation of study treatment (MUGA scan or 2D echocardiogram) was added by a protocol amendment once 440 patients were already randomized. Therefore, LVEF follow-up was not available for all patients in this study. For percentages, the denominator was the number of patients with baseline and final LVEF measurement

[b] The patient discontinued PLD but continued trabectedin treatment

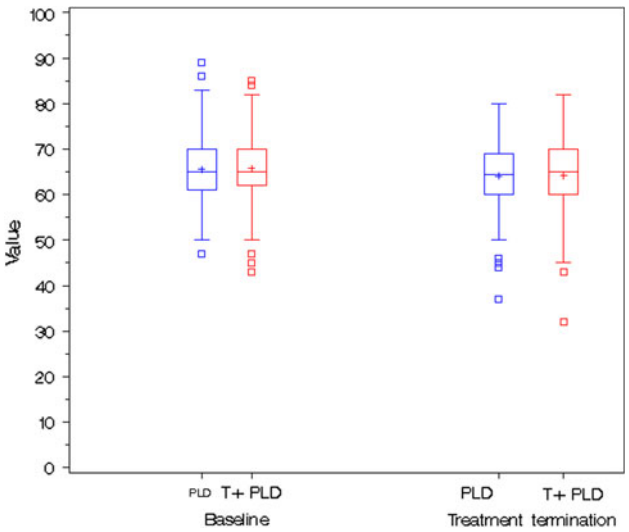

Fig. 1 *Boxplot* for left ventricular ejection fraction (LVEF) in the phase III randomized trial OVA-301 (patients with available paired data: baseline and treatment termination). PLD: baseline (n = 284); treatment termination (n = 184). T + PLD: baseline (n = 296); treatment termination (n = 206). *PLD* pegylated liposomal doxorubicin, *T* trabectedin

Type II chemotherapy-related cardiac dysfunction, characterized by reversibility and lack of dependence on dose or reexposure to the agent, is not associated with myocyte damage and has been observed with the administration of trastuzumab or alemtuzumab [35–37]. In addition, many antineoplastic agents (anthracyclines, 5-fluorouracil, some platinum compounds, multitargeted tyrosine-kinase inhibitors, anti-HER-2, anti-vascular endothelial growth factor (VEGF), vascular disruption agents, and histone deacetylase inhibitors [HDIs]) may affect QT interval duration [38]. This effect is also observed with different non-antineoplastic agents administered to cancer patients as concomitant medications to reduce the side effects of chemotherapy, such as serotonin receptor antagonist antiemetic agents [39].

Given the improvement in survival among cancer patients due to the development of new anticancer therapies, the availability of antitumor agents with a low cardiac toxic effect and the implementation of preventive and protective measures already available in the setting of cardiovascular diseases gain relevance [1, 40]. Cardiac toxicity resulting in myocardial dysfunction can become apparent immediately or long after the end of therapy and is often irreversible. Therefore, early and accurate detection of cardiac injury is crucial because it can lead to early therapeutic measures. Close monitoring is important for early detection of cardiac dysfunction during clinical development of new anticancer therapies, which would lead to well-timed interruption or dose modification of the cardiotoxic drug or the introduction of cardioprotective therapy.

With respect to trabectedin, preclinical studies found no relevant macroscopic, microscopic, or functional cardiac alterations, with no evidence of cardiovascular disorders [16–19]. The current extensive analysis shows that tachycardia or palpitations were the most common CAEs reported. Other types of cardiac events were uncommon (<1%). A limited number of patients had associated LVEF changes with trabectedin in combination with doxorubicin or PLD. This finding may be attributed to the treatment in combination with an anthracycline (given at a higher median cumulative dose, 232 mg/m^2, than in the PLD single-agent arm, 202 mg/m^2) (Table 4). A caveat for the

current safety analysis is that no serial measurements of LVEF were recommended in clinical trials with trabectedin given the relatively low overall incidence of CAEs observed in early phase I and II studies. Nevertheless, no evidence of relevant cardiovascular disorders was found with trabectedin as single-agent therapy. The data shown here agree with a previous analysis conducted on data from phase II trials evaluating single-agent trabectedin, in which nausea, fatigue, vomiting, and transient, reversible laboratory abnormalities (neutropenia and transaminase increases) were the most common side effects, while cardiac toxicity was found not relevant [32]. Indeed, particularly noteworthy for trabectedin treatment is the rarity of many of the unpleasant and/or life-threatening effects typical of commonly used anticancer chemotherapeutic agents, such as cardiac toxicity, but also as alopecia, mucositis, skin/nail toxicities, neurotoxicity, or other major organ-related toxicities.

Relevant predisposing factors for CAEs were retrospectively identified in patient's baseline characteristics, such as age older than 70 years, hypertension, preexisting cardiac disease, female gender, previous cardiac irradiation, or previous anthracycline exposure. In fact, the patient populations evaluated in trabectedin clinical trials were heavily pretreated, with 73 and 49% of patients with CAEs having received previous anthracyclines in phase I and II single-agent trials, respectively.

The incidence of the main cardiac events associated with trabectedin (alone or combined with PLD) is lower than that reported for other anticancer agents. The rate of patients with myocardial dysfunction events found in the current safety analysis for trabectedin alone in phase II trials (0.2% grade 1/2; 0.2% grade 3/4) or combined with PLD in a phase III trial (1.5% grade 1/2; 0.6% grade 3/4) is remarkably lower when compared with the incidence of 3–26% found for anthracyclines like doxorubicin at cumulative doses up to 550 mg/m^2, the 7–28% found for alkylating agents like cyclophosphamide or ifosfamide, or the 2–28% found for monoclonal antibody-based tyrosine kinase inhibitors like trastuzumab.

Chest pain is a common cardiac event experienced by cancer patients, often requiring a workup for myocardial ischemia. Several forms of cancer treatment such as radiation or some agents like capecitabine (incidence of 3–9%), 5-fluorouracil (1–68%), paclitaxel (<1–5%), docetaxel (1.7%), bevacizumab (0.6–1.5%), erlotinib (2.3%), or sorafenib (2.7–3.0%) are associated with an increased risk of coronary artery disease and/or acute coronary syndrome. In contrast, trabectedin alone or combined with PLD did not show any case of treatment-related event associated with myocardial ischemia.

In addition, hypertension has been associated with several anticancer agents: e.g., incidence of 4–35% with bevacizumab, 17–43% with sorafenib, or 5–47% with sunitinib. In clinical trials with trabectedin, only four cases of non-severe hypertension (0.4%) were reported as related to trabectedin treatment (Table 1).

Cancer produces a prothrombotic state, and the risk of thrombosis appears to be highest in cancer patients with metastatic disease and in those with established risk factors (e.g., use of central venous catheters, immobility, and dehydration). Some anticancer agents have been found associated with venous thromboembolism, such as cisplatin (incidence of 8.5%), lenalidomide (3–75%), thalidomide (1–58%), or erlotinib (3.9–11%). No treatment-related thromboembolic events occurred during clinical trials with trabectedin.

Furthermore, and in contrast to the most commonly used agent employed for the treatment of STS, doxorubicin, no cumulative cardiotoxicity was noted with trabectedin despite many patients remaining on active therapy for more than 1 year [30].

Conventional doxorubicin has the concern of toxicities like myelosuppression, alopecia, and especially cardiotoxicity that limit its use in the treatment of cancer [41–43]. Liposomal encapsulation of doxorubicin with pegylation was an interesting approach to reduce cardiotoxicity of anthracycline treatment. The polyethylene glycol-coated liposomes prevent uptake by the reticuloendothelial system and alter the pharmacokinetic and pharmacodynamic profile of doxorubicin, thus ensuring prolonged serum levels of the drug, increasing accumulation in the tumor and reducing cardiac toxicity when compared with conventional doxorubicin [44, 45]. Results of the OVA-301 trial showed that the incidence of cardiotoxicity was not increased by adding trabectedin to PLD. This is supported by the following findings: (1) the vast majority of cardiac events were grade 1 palpitations; (2) treatment-related grade 3 or 4 cardiac events were infrequent in both treatment arms (<1% vs. 1.2%), and (3) similar rates of LVEF decrease were observed (9% for PLD; 7% for trabectedin + PLD).

QT interval prolongation for the ECG is an abnormality of the heart electrical activity that places individuals at risk of ventricular arrhythmias and torsades de pointes. Cancer patients may be particularly prone to QT prolongation, since 16–36% of cancer patients have been shown to have baseline ECG abnormalities [46, 47]. In addition, cancer patients have a high prevalence of comorbidities, including structural heart disease, renal and hepatic dysfunction, as well as the use of concomitant medications, which are known to prolong the QT interval (e.g., antiemetics, antifungals, quinolone antibiotics). Furthermore, cancer patients often experience nausea, vomiting, diarrhea, and decreased oral intake, which may lead to electrolyte disturbances, placing the patient at risk of QT prolongation. Trabectedin did not prolong the QT interval in a clinical trial

designed to evaluate potential trabectedin effect on the QT segment [48]. Of note, neither AEs suggestive of proarrhythmic potential nor cardiac serious adverse events occurred during this study. This finding agrees with the low rate of ventricular arrhythmia events (only one non-severe case; 0.09%) found in clinical trials with trabectedin.

In conclusion, this comprehensive analysis indicates a low cardiac risk profile for trabectedin, with a low incidence of CAEs, which consisted mainly of arrhythmias. Combination of trabectedin plus PLD shows an acceptable cardiac tolerance, which is comparable with that of PLD alone.

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Conflict of interest C. Lebedinsky, J. Gómez, A. Nieto, A. Soto-Matos, V. Alfaro, E.Roy, P.Lardelli and C. Kahatt are employees of PharmaMar and stock ownership. Youn. C. Park and Trilok Parekh are employees of Johnson and Johnson Pharmaceutical Research and Development and stock ownership.

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