Cardiac Safety of Trabectedin Monotherapy or in Combination with Pegylated Liposomal Doxorubicin in Patients with Sarcomas and Ovarian Cancer

Short Running Title: Cardiac Safety of Trabectedin

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AUTHOR CONTRIBUTIONS

Robin L. Jones, Shreyaskumar Patel, Spyros Triantos, Bradley Monk and George Demetri: conceptualization, study design, acquisition/collection of data, analysis/interpretation of data, drafted/revised manuscript content; Thomas J Herzog, Robert Coleman and Waleed Shalaby: conceptualization, study design, analysis/interpretation of data, drafted/revised manuscript content; Tracy McGowan: conceptualization, study design, drafted/revised manuscript content; Margaret von Mehren, Scott Schuetze and Brian Van Tine: acquisition/collection of data, analysis/interpretation of data, drafted/revised manuscript content; Roland Knoblauch: acquisition/collection of data, drafted/revised manuscript content; Peter Hu: analysis/interpretation of data, drafted/revised manuscript content. All authors approved the final article and agreed to be accountable for all aspects of the work.

DATA SHARING STATEMENT

The data sharing policy of the study sponsor, Janssen Pharmaceutical Companies of Johnson & Johnson, is available at https://www.janssen.com/clinical-trials/transparency. As noted on

this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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ABSTRACT

Background: As with other alkylating agents, cardiac dysfunction can occur with trabectedin therapy for advanced soft tissue sarcomas (STS) or recurrent ovarian cancer (ROC) where treatment options for advanced disease are still limited. Cardiac safety for trabectedin monotherapy (T) for STS or in combination with pegylated liposomal doxorubicin (T+PLD) for ROC was evaluated in this retrospective postmarketing regulatory commitment.

Methods: Patient data for multiple cardiac-related treatment-emergent adverse events (cTEAEs) were evaluated in pooled analyses of ten phase 2 trials, one phase 3 trial in STS (n=982), and two phase 3 trials in ROC (n=1231).

Results: Multivariate analyses on pooled trabectedin data revealed that cardiovascular medical history (risk ratio [RR (95% CI)]: 1.90 [1.24-2.91]; P=0.003) and age ≥65 years (RR [95% CI]: 1.78 [1.12-2.83]; P=0.014) were associated with increased risk for cTEAEs. Multivariate analyses showed increased risk of experiencing cTEAEs with T+PLD compared to PLD monotherapy (RR [95% CI]: 2.70 [1.75-4.17]; P<0.0001) and with history of prior cardiac medication (RR [95% CI]: 1.88 [1.16-3.05]; P=0.010).

Conclusions: For patients with STS or ROC who still have limited treatment options, trabectedin may be initiated after carefully considering benefit versus risk.

Trial Registration (ClinicalTrials.gov)**:** NCT01343277; NCT00113607; NCT01846611

Key words: soft tissue sarcomas, cardiac toxicity, anthracycline, chemotherapy, patient outcomes

INTRODUCTION

Trabectedin is a DNA-binding agent with a unique antitumor mechanism of action (MOA) targeting the transcription-coupled nucleotide excision repair (NER) system. Trabectedin was

developed for treatment of soft tissue sarcomas (STS) and epithelial ovarian cancer based on its novel cytotoxic activity. These cancers still have limited treatment options, particularly where advanced disease has progressed with other therapies.[1]

Preclinical studies with trabectedin showed no toxicity in cultured rat myocytes in vitro, while single and repeated doses in Cynomolgus monkeys did not induce any relevant cardiac, vascular, or respiratory effects.[2] Further, a low incidence of cardiac-related treatment-emergent adverse events (cTEAE) was reported in previous analyses from earlier phase 1–2 clinical trials and one phase 3 (OVA-301), pharmacovigilance databases, and spontaneously reported cases; tachycardia or palpitations were the most common cTEAEs reported.[2] No clinically relevant left ventricular ejection fraction (LVEF) changes occurred in phase 1 combination trials while LVEF decreases from baseline were similar [9% of patients (pegylated liposomal doxorubicin [PLD]) and 7% (trabectedin+PLD)] with no relevant symptoms in one phase 3 trial.[2]

Trabectedin is now approved for STS in 80 countries and for ovarian cancer in combination with PLD in 71 countries. European Union (EU) approval for trabectedin+PLD for relapsed platinum-sensitive ovarian cancer was granted in October 2009. In the United States (US), trabectedin was approved for STS treatment following failure of anthracycline-based chemotherapy in October 2015. Approval in the US was contingent upon undertaking post-marketing requirements to characterize risk of cardiotoxicity and its sequelae with trabectedin to identify risk factors including previous treatments known to be cardiotoxic (e.g., anthracyclines).

As an extension to the cTEAE analysis reported in 2011[2], we now report the findings of this retrospective pooled analysis of key cTEAEs for all patients enrolled in ten phase 2 trials and one phase 3 trial involving trabectedin monotherapy (T) for STS and other solid tumors and two phase 3 trials in combination with PLD for recurrent ovarian cancer (ROC).

METHODS

Overall Safety Evaluation Plan and Description of Safety Studies

Safety analysis sets incorporated two pooled analyses: Cardiac safety with T was evaluated using data from ten phase 2 and one phase 3 trial (SAR-3007 [NCT01343277]) in STS and other solid tumors at a dose and regimen of 1.5 mg/m^2 every 3 weeks (q3wk), 24 h. Cardiac

safety with combination trabectedin+PLD was derived from two phase 3 ovarian cancer trials (OVA-301 [NCT00113607] and OVC-3006 [NCT01846611]) where trabectedin (1.1 mg/m^2 q3wk; 3 h) was co-administered with PLD (30 mg/m^2 q3wk; 90 min). Phase 3 trial designs are described in Table 1. Key inclusion/exclusion criteria for enrollment are presented for each phase 3 trial (eTable 1), cardiac safety evaluations by individual trial (eTable 2), and exposure and cancer diagnoses for pooled data from phase 2 and 3 studies (eTable 3). Study protocols and amendments were reviewed by an Independent Ethics Committee or an Institutional Review Board.

Statistical Methodology

Definition of Subgroups and General Analysis Methods

Continuous variables were summarized using descriptive statistics (i.e., mean, standard deviation [SD], median, and range) and categorical variables by frequency counts and percentages. Time-to-event variable data were summarized by Kaplan-Meier methods for 25th, 50th, and 75th percentiles with 95% confidence intervals (CIs). Treatment group comparisons are presented by hazard ratios and 95% CI from Cox proportional hazards models. Anthracycline exposure data are summarized for subjects who received anthracyclines prior to study (i.e., prior anthracycline) and for subjects who received anthracyclines prior to and during the study (i.e., cumulative anthracycline).

Cardiac-Related Adverse Events

cTEAEs are summarized from time of first administration to 30 days after last dose and graded using Common Terminology Criteria for Adverse Events (CTCAE; version 4.0). Incidences of cTEAEs are defined by eight Medical Dictionary for Regulatory Activities (MedDRA) high-level group terms (HLGTs) and associated preferred terms (PTs) and two Standardized MedDRA Queries (narrow SMQ) (Table 2). HLGTs included cardiac and vascular investigations (excluding enzyme tests), cardiac arrhythmias, cardiac disorder signs and symptoms, coronary artery disorders, endocardial disorders, heart failures, myocardial disorders, and pericardial disorders. TEAEs were coded to MedDRA version 16.0 for OVA-301, SAR-3007, and pooled safety analysis for T. TEAEs in OVA-301 were aligned to MedDRA version 19.0 to match the MedDRA version of OVC-3006 and cTEAEs presented by HLGTs and SMQs and related PTs.

Left Ventricular Ejection Fraction

Two parameters were used: LVEF significant decline where available and cardiac-related AEs of special interest (cardiac-related AEs). Cross tabulation of electrocardiogram (ECG) data were included when available. LVEF significant decline was defined as absolute decrease ≥15%, or <lower limit of normal and absolute decrease ≥5%. LVEF recovery for subjects with significant LVEF decline was defined as either return to baseline values or <Grade 2 ejection fraction decreased toxicity (CTCAE v4.0). In all three phase 3 studies (SAR-3007, OVA-301, and OVC-3006), LVEF assessments were performed at baseline and end of treatment. Additionally, OVC-3006 was amended to provide comprehensive cardiac evaluations of patients while on treatment. Collection time points for LVEF in each study are described in eTable 2.

RESULTS

Overall Exposure

Table 3 shows number of patients exposed to study drug by individual trial and by pooled safety analysis sets for T and trabectedin+PLD. 982 patients were exposed to T, and 619 patients were treated with trabectedin+PLD.

Baseline Characteristics: Trabectedin Monotherapy (T)

Demographic Characteristics

Patients treated with trabectedin (N=982) had a median (range) age of 54 (12-81) years (eTable 4). Most patients were female (61.6%), white (50.6%), from North America (58.2%) or Western Europe (36.7%), had an Eastern Cooperative Oncology Group performance score of 0 or 1 (99.8%), and a diagnosis of STS (88.0%). Prior anthracycline use was reported for 71.3% (Table 4). Prior anthracycline dose was only captured in the phase 3 SAR-3007 study. A cumulative dose of prior anthracycline was reported for 337/378 subjects in the trabectedin treatment group and 162/172 subjects in the dacarbazine group. Median cumulative prior anthracycline dose was 270.00 mg/m^2 in the trabectedin group and 240.75 mg/m^2 in the dacarbazine group.

Cardiovascular Medical History

Pooled analyses of T, cardiovascular medical history categorized under the vascular disorder and/or cardiac disorder system organ class (SOC) was reported for 355 (36.2%) of 982 trabectedin-treated patients. The most commonly reported cardiovascular medical history for patients treated with trabectedin were hypertension (24.8% [244/982]), followed by deep vein

thrombosis (2.9% [28/982]), hot flush (2.2% [22/982]), and coronary artery disease (2.1% [21/982]).

Baseline Characteristics: Trabectedin in Combination With PLD

Demographic Characteristics

In the pooled analysis of trabectedin+PLD, patient demographic characteristics were consistent in the all-female study populations across the trabectedin+PLD (N=619) and PLD monotherapy (N=612) groups, with median (range) ages of 58 (26-83) and 59 (27-91) years, respectively. Most patients were white (84% and 82%, respectively) (eTable 5), and baseline disease characteristics were consistent across both treatment groups (Table 5).

Cardiovascular Medical History

In pooled analysis of trabectedin+PLD, 45.6% and 51.5% of patients in the trabectedin+PLD and PLD monotherapy groups, respectively, had prior cardiovascular medical history reported for vascular and/or cardiac disorders SOC. These included: hypertension (30.5% [189/619] in the trabectedin+PLD group and 34.6% [212/612] in the PLD monotherapy group), followed by myocardial ischemia (6.0% [37/619] and 6.7% [41/612], respectively), varicose vein (3.9% [24/619] and 3.8% [23/612], respectively), deep vein thrombosis (2.7% [17/619] and 2.5% [15/612], respectively), and hot flush (1.8% [11/619] and 2.9% [18/612], respectively).

Cardiac Safety Results

Trabectedin Monotherapy (T)

In the pooled analysis of T, 110 (11.2%) patients who received ≥1 trabectedin dose experienced a cTEAE (eTable 6). cTEAEs reported for ≥1% of trabectedin-treated patients included tachycardia (3.1%), palpitations (1.5%), LVEF decrease (1.3%), sinus tachycardia (1.0%), and congestive cardiac failure (1.0%). Median time from first dose of study drug to onset of first occurrence of a cTEAE for trabectedin-treated patients was 40 days. For 65% of patients with cTEAE, the event was reported as resolved, with median time to resolution of 8 days. Thirty-seven (3.8%) trabectedin-treated patients experienced a Grade 3 or 4 cTEAE (eTable 7). Cardiac-related serious TEAEs (SAEs) were reported in 36 (3.7%) trabectedin-treated patients (eTable 8); those most frequently-reported (≥5 patients) included: congestive cardiac failure (0.8%), pulmonary edema (0.6%), ejection fraction decreased (0.5%), cardiac failure (0.5%), and atrial fibrillation (0.5%). Six (0.6%) trabectedin-treated patients experienced a cTEAE leading to death (eTable 9).

Unique Study Features

In the phase 3 study comparing trabectedin vs dacarbazine (SAR-3007), cTEAEs were reported for 58 (15.3%) trabectedin patients and 25 (14.5%) dacarbazine patients; however, cardiac failure (5.0% vs 2.3%), cardiomyopathy (3.7% vs 2.3%), and heart failure (2.9% vs 0.6%) were higher with trabectedin. Furthermore, median cumulative prior anthracycline dose was greater in the trabectedin group (329.75 mg/m^2) compared to the dacarbazine group (180.00 mg/m^2), which should also be taken into consideration. Among patients with a cTEAE, more patients in the trabectedin group (39 [67.2%] of 58) received a prior cumulative anthracycline dose ≥300 mg/m^2 compared with the dacarbazine group (10 [40.0%] of 25). Median time from first dose of study drug to onset of first occurrence of a cTEAE was twice as long in the trabectedin group compared with the dacarbazine group (46 days vs 23 days); however, median time to resolution was twice as long in the trabectedin group (8 days vs 4 days). In terms of prior anthracycline exposure among patients with a significant decrease in LVEF from baseline and for whom dose information was reported, prior cumulative anthracycline dose of ≥300 mg/m^2 was reported in 22/34 (64.7%) in the trabectedin group compared with 7/11 (63.6%) patients in the dacarbazine group.

Trabectedin in Combination With PLD

cTEAEs were reported for 78 (12.6%) patients in the trabectedin+PLD group and 34 (5.6%) patients in the PLD monotherapy group; most commonly reported cTEAE was LVEF decrease (7.8% vs 4.2%, respectively). Within these SMQ/HLGTs, palpitation was the only cTEAE reported with at least a 2% greater incidence in the trabectedin+PLD group compared with the PLD monotherapy group (3.2% vs 1.0%) (eTable 10).

Kaplan-Meier analyses showed increased risk of cTEAEs with trabectedin+PLD compared with PLD monotherapy (Figure 1). Cumulative incident rate curves separated early and remained separated throughout treatment. Median time from first study dose to onset of first occurrence of cTEAE was shorter with trabectedin+PLD (57 days) compared with PLD monotherapy (98 days), while most patients in both groups had similar resolutions of cTEAEs (57.1% and 55.9%) and time to resolution (8 days). However, while Grade 3 or 4 cardiac-related events were reported more frequently with trabectedin+PLD vs PLD monotherapy (14 [2.3%] vs 4 [0.7%] patients; eTable 11); no cTEAEs were reported with an incidence of ≥1% in either group. Lastly, cardiac-related SAEs were reported more frequently

with trabectedin+PLD (11 [1.8%]) vs PLD monotherapy (3 [0.5%]) (eTable 12). Congestive heart failure was quite low in both the combination (3 [0.5%]) and monotherapy groups (1 [0.2%]).

Unique Study Features

In OVA-301, fewer patients with significant decrease from baseline in LVEF in trabectedin+PLD group had a cardiovascular medical history compared with the PLD monotherapy group (23.8% vs 52.6%). In OVC-3006, median cumulative PLD dose for patients with a cTEAE was lower with trabectedin+PLD treatment compared with PLD monotherapy (180.78 vs 329.67 mg/m^2). Median cumulative anthracycline dose of ≥300 mg/m^2 was reported in 11/43 (25.6%) in trabectedin+PLD patients with a cTEAE compared to 17/23 (73.9%) PLD monotherapy patients.

In OVC-3006, median time from first dose of drug to onset of first occurrence of a cTEAE was shorter with trabectedin+PLD compared with PLD monotherapy (68 days vs 169 days); however, median time to resolution was longer with PLD monotherapy group compared with trabectedin+PLD (29 days vs 16 days). Median cumulative PLD dose for patients having significant decreases from baseline in LVEF was lower in the trabectedin+PLD group compared with the PLD monotherapy group (149.39 vs 251.25 mg/m^2). In addition, median cumulative anthracycline doses of ≥300 mg/m^2 were associated with a significant decrease from baseline in LVEF; this was reported in 3/19 (15.8%) trabectedin+PLD and 5/10 (50.0%) PLD monotherapy patients.

Multivariate Analyses

Trabectedin Monotherapy

Trabectedin-treated patients who experienced a cTEAE were generally older (18.4% aged ≥65 years vs 9.6% aged <65 years). Results from multivariate analyses of cTEAEs when controlling for potential risk factors are presented in Figure 2. These showed that patients aged ≥65 years and those with cardiovascular medical history had an increased risk of cTEAEs. The effect of cumulative anthracycline dose of ≥300 vs <300 mg/m^2 and baseline LVEF <lower limit of normal (LLN) vs ≥LLN, however, could not be evaluated in the ten phase 2 studies due to differences in study designs.

Trabectedin in Combination With PLD

In the multivariate analyses, when controlling for potential risk factors, results showed that patients receiving trabectedin+PLD were at increased risk for experiencing a cTEAE compared with PLD monotherapy (risk ratio [RR] 2.70; 95% CI: 1.75-4.17; P<0.0001). Furthermore, patients with a history of prior cardiac medication use who received trabectedin+PLD vs. PLD were also at increased risk of experiencing a cTEAEs (RR 1.88; 95% CI: 1.16-3.05; P=0.010). Patients with a cumulative anthracycline dose of ≥300 mg/m^2 who received trabectedin+PLD in the OVC-3006 and OVA-301 trials were at increased risk for significant decrease in LVEF compared with patients who received PLD monotherapy (RR 0.54; 95% CI: 0.30-0.99; P=0.046) (Figure 3).

DISCUSSION

Trabectedin was developed based on its novel chemical structure and promising preclinical activity in several types of human tumors. The development program focused on STS[3] and ROC[4,5] in which trabectedin was active at very low concentrations in both preclinical models and clinical trials.[1] Trabectedin binds to the N2 position of guanine in the minor groove of DNA and bends the helix toward the major groove, a unique property in the class of DNA-binding agents; it triggers a cascade of events affecting several transcription factors, DNA-binding proteins, and DNA-repair pathways (e.g., transcription-coupled NER), resulting in slowed progression through S and G2/M phases and p53-independent apoptosis. Trabectedin also prevents binding of translocation-related oncogenic fusion proteins to DNA promoter regions, thereby interfering with the function of proteins that contribute to the malignant phenotype and tumor progression.[6-9]

PLD is doxorubicin hydrochloride encapsulated in STEALTH® liposomes for intravenous administration. PLD was granted approvals for advanced ovarian cancer in June 1999 and October 2000 in the US and EU, respectively. As with any anthracycline, PLD can cause myocardial damage, including congestive heart failure, as the total cumulative dose of doxorubicin hydrochloride approaches 550 mg/m^2. In a clinical study of 250 patients with advanced cancer who were treated with PLD, the risk of cardiotoxicity was 11% when the cumulative anthracycline dose was 450 to 550 mg/m^2.[10]

This is the most comprehensive analysis of cardiac safety in the setting of trabectedin administration from clinical trial data including more than 1600 patients. Strengths include pooled analyses of one phase 3 trial and ten phase 2 trials of T in STS and two phase 3 trials

of trabectedin in combination with PLD for ROC. Limitations include patient heterogeneity and varying dosing, scheduling, and infusion times for T (1.5 mg/m^2 q3wk; 24 h) compared with PLD combination therapy (trabectedin 1.1 mg/m^2 q3wk; 3 h). The authors recognize that cardiac adverse events with diverse etiologies makes it difficult to ascribe the outcomes to trabectedin alone or identify specific causal mechanisms. Cardiotoxicity may be mediated by multiple mechanisms including damage from prior cardiotoxic therapies (anthracyclines), preexisting cardiovascular comorbidities, and the alkylating MOA among others. Lastly, the retrospective nature of data collection and other events, such as sepsis (that could contribute to cardiac events) are additional limitations.

In the phase 3 SAR-3007 study[3], no difference in overall incidence rate of any-grade cTEAEs was observed between trabectedin- and dacarbazine-treated patients. Multivariate analysis of safety data (data not shown) indicated that cumulative anthracycline dose of ≥300 mg/m^2 and baseline LVEF <LLN were risk factors for development of cTEAEs in STS. In pooled analyses, only age ≥65 years and cardiovascular medical history were associated with an increased risk of cTEAEs. This difference could be attributed to variability in patient populations, pretreatment history, and consistent baseline LVEF testing in the ten phase 2 studies compared with SAR-3007. In summation, cardiac safety signals observed with T may be, in part, due to history of prior or concurrent therapy with an anthracycline, known for potential short- and long-term cardiotoxicity, and longer median duration of treatment for patients receiving trabectedin.

In OVA-301 and OVC-3006, patients in the trabectedin+PLD groups experienced cTEAEs at a higher incidence, regardless of toxicity grade, compared with PLD monotherapy patients. In OVA-301, multivariate analyses indicated increased risk of cTEAEs among patients in the trabectedin+PLD group compared with PLD monotherapy (data not shown). In OVC-3006, however, a cumulative anthracycline dose of ≥300 mg/m^2 and prior cardiac medication use were also identified as independently associated with increased risk of cTEAEs (data not shown). Differences between the two studies may be attributed to enrollment criteria for each study. Inclusion criteria for OVC-3006 differed from OVA-301 in that patients were allowed to have received two prior lines vs one line of chemotherapy for ROC, and prior PLD combination therapy was also allowed.

Ultimately, these data suggest that some patients receiving T after prior therapy with anthracyclines are at risk for cTEAEs, which may be serious in a small number. The overall

risk of fatal events is relatively low but appears to be higher for patients with existing myocardial dysfunction (abnormal LVEF) or prior cardiovascular medical history. In the setting of STS, the available data support recommendations to assess LVEF by echocardiogram or multigated acquisition radionuclide scan before initiation of trabectedin and at two- to three-month intervals thereafter until trabectedin is discontinued, particularly for patients with prior cardiovascular disease. Additionally, when using trabectedin in combination with PLD for ROC, cumulative anthracycline dose ≥300 mg/m^2 and prior cardiac medication may increase the risk of cTEAEs if prior lines of therapy involved PLD.

In conclusion, as with any systemic cytotoxic therapy, benefit versus risk should be carefully considered when instituting treatment with trabectedin in patients with few other treatment options and with risk factors for developing cTEAEs. In consultation with a cardiologist or cardio-oncology service, baseline cardiovascular risk should be comprehensively assessed before commencing treatments with cardiotoxic potential as noted above.[11, 12] Cardiotoxicity risk can be minimized by using primary prevention strategies; signs and symptoms of myocardial toxicity including decreases in LVEF should be assessed routinely as described above. Dose reductions or temporary or permanent discontinuation of trabectedin should be considered when serious cTEAEs occur. Once the decision is made that benefits of trabectedin therapy outweigh risk, patients (and caregivers) should be supported throughout treatment with a personalized surveillance program to minimize cTEAE risk and promptly address when cTEAEs do occur.

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TABLES

TABLE 1. Overview of Study Designs for Phase 3 Trials

Protocol	Study Description	Treatment Groups	Patients in Safety Analysis Set, n
Phase 3 Soft Tissue Sarcoma Study – Single Agent Therapy			
SAR-3007 (NCT01343277)	A multicenter, open-label, randomized, active-controlled, parallel-group phase 3 study comparing the safety and efficacy of trabectedin vs dacarbazine among adults with unresectable, locally advanced or metastatic L-sarcoma, previously treated with at least an anthracycline and ifosfamide containing regimen or an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen. A normal LVEF at baseline was not required for enrollment.	Trabectedin Arm: 1.5 mg/m^2 as a 24 h IV infusion q3wk.	378
		Dacarbazine Arm: 1 g/m^2 as a 20- to 120-minute IV infusion q3wk.	172
Phase 3 Ovarian Cancer Studies – Combination Therapy			
OVA-301 (NCT00113607)	A multicenter, open-label, randomized study to assess the safety and efficacy of trabectedin+PLD vs PLD in patients with ROC treated with only 1 platinum-based chemotherapy regimen. Patients with a normal LVEF at baseline were eligible to enroll in the study.	Trabectedin+PLD Arm: PLD, 30 mg/m^2 as a 90-minute infusion immediately followed by a 3 h trabectedin IV infusion 1.1 mg/m^2 q3wk.	333
		PLD Arm: PLD, 50 mg/m^2 as a 90-minute infusion q4wk.	330
OVC-3006 (NCT01846611)	A multicenter, open-label, randomized study to assess the efficacy and safety of trabectedin+PLD as a third line chemotherapy in patients with platinum-sensitive ROC who received 2 previous lines of	Treatment Arm A: PLD 30 mg/m^2 as a 90-minute infusion immediately followed by a 3 h trabectedin infusion	286

Protocol	Study Description	Treatment Groups	Patients in Safety Analysis Set, n
	platinum-based chemotherapy. Patients with a normal LVEF at baseline were eligible to enroll in the study.	1.1 mg/m^2 q3wk.	
		Treatment Arm B: PLD, 50 mg/m^2 as a 90-minute infusion q4wk.	282

IV, intravenous; L-sarcoma, leiomyosarcoma or liposarcoma; LVEF, left ventricular ejection fraction; PLD, pegylated liposomal doxorubicin; q3wk, once every 3 weeks; q4wk, once every 4 weeks; ROC, recurrent ovarian cancer.

Table 2. MedDRA HLGT and Standardized MedDRA Queries (narrow SMQ)

	cTEAEs
HLGT	Cardiac and vascular investigations (excluding enzyme tests)
	Cardiac arrhythmias
	Cardiac disorder signs and symptoms
	Coronary artery disorders
	Endocardial disorders
	Heart failure
	Myocardial disorders
	Pericardial disorders
SMQ	Cardiac failure
	Cardiomyopathy

cTEAEs, cardiac-related treatment-emergent adverse events; HLGT, high-level group term; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query.

Table 3. Number of Patients Exposed to Study Treatment and Safety Analysis Sets

Study	**No. Patients in Safety Analysis Set**	
Monotherapy	Trabectedin	Dacarbazine
SAR-3007	378	172
10 phase 2 Studies	604	-
Pooled Data (SAR-3007+phase 2 Studies)	982	-
Combination Therapy	Trabectedin+PLD	PLD
OVA-301	333	330
OVC-3006	286	282
Pooled Data (OVA-301+OVC-3006)	619	612

PLD, pegylated liposomal doxorubicin.

Table 4. Disease Characteristics for Patients Treated with Trabectedin 1.5 mg/m^2 q3wk; 24 h (Trabectedin - Pooled Phase 2 and 3 Studies)

Number (%)	**Patients Treated With Trabectedin 1.5 mg/m^2 q3wk; 24 h (N=982)**
Cancer Type	
STS, L-type	661 (67.3)
STS, Non-L-type	203 (20.7)
Ovarian	54 (5.5)
Breast	26 (2.6)
Renal	21 (2.1)
Melanoma	12 (1.2)
Prostate	5 (0.5)
Prior anthracycline treatment	700 (71.3)

Data are presented as No. (%).

L-type, leiomyosarcoma or liposarcoma; STS, soft tissue sarcomas; q3wk, once every 3 weeks.

Table 5. Disease Characteristics at Baseline for Treated Patients (Pooled Studies ET743-OVC-3006 and ET743-OVA-301 Studies)

Number (%)	**Trabectedin+PLD (N=619)**	**PLD (N=612)**
Histology		
Papillary/Serous	412 (66.6)	420 (68.6)
Other	97 (15.7)	92 (15.0)
Endometrioid	38 (6.1)	37 (6.0)
Clear Cell Carcinoma	24 (3.9)	21 (3.4)
Peritoneal Carcinoma	21 (3.4)	17 (2.8)
Fallopian Tube Carcinoma	10 (1.6)	15 (2.5)
Mixed Epithelial Tumor	7 (1.1)	5 (0.8)
Mucinous (exclusion)	5 (0.8)	3 (0.5)
Transitional Carcinoma (Brenner)	5 (0.8)	2 (0.3)
Prior anthracycline treatment	38 (6.1)	36 (5.9)
Time from initial diagnosis to randomization, median (range), months	24.25 (6.6, 169.3)	25.17 (2.5, 230.4)

Data are presented as No. (%) unless otherwise specified.

PLD, pegylated liposomal doxorubicin.

FIGURE LEGENDS

Figure 1. Cumulative Incidence of Cardiac-Related Adverse Events Over Treatment Duration for Treated Patients (Pooled Studies ET743-OVC-3006 and ET743-OVA-301)

PLD, pegylated liposomal doxorubicin.

Figure 2. Multivariate Analysis on Incidence of Cardiac-Related TEAEs (Logistic Regression) for Treated Patients (Trabectedin – Pooled Phase 2 and 3 Studies)

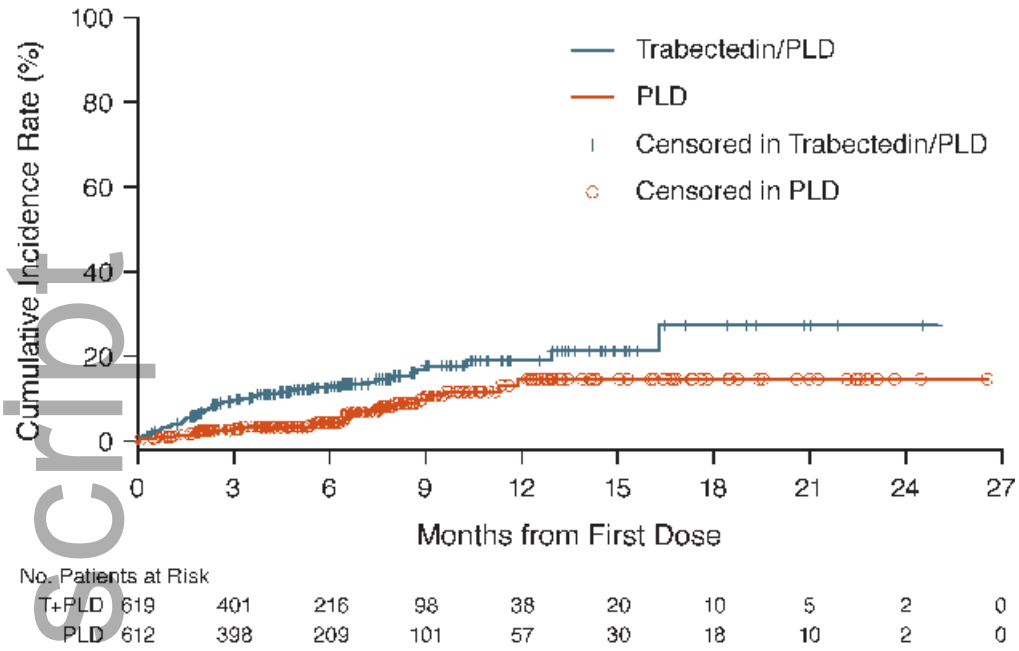
Dependent variable: incidence of cardiac-related TEAEs.

CI, confidence interval; TEAEs, treatment-emergent adverse events.

Figure 3. Multivariate Analysis on Incidence of Significant LVEF Decrease (Logistic Regression) for Treated Patients (Pooled Studies OVC-3006 and OVA-301)

Dependent variable: incidence of significant LVEF decrease.

CI, confidence interval; LVEF, left ventricular ejection fraction; PLD, pegylated liposomal doxorubicin.



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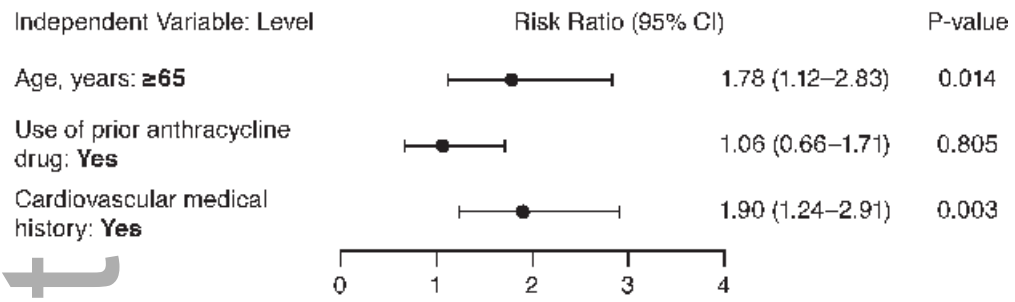

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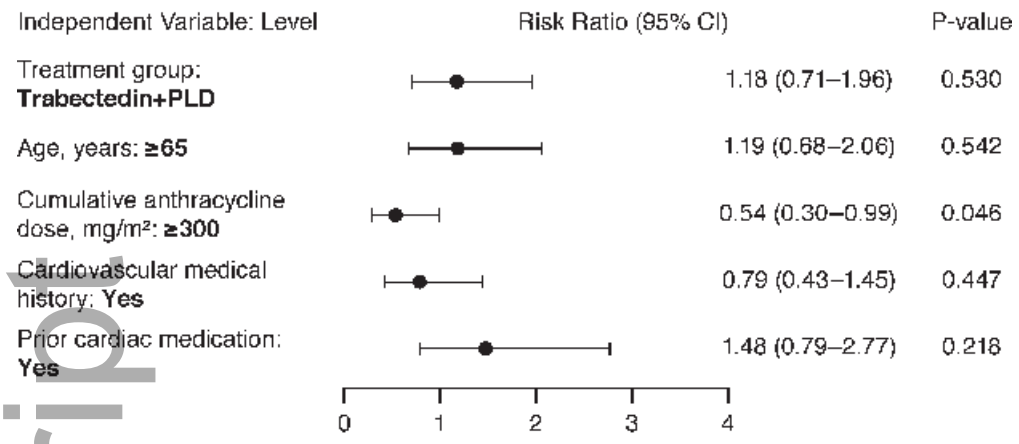

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