EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004

Invented name: Yondelis

INN: trabectedin

Procedure number: EMEA/H/A-20/1493/C/0773/0060

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

Yondelis is an anti-cancer medicinal product with two indications:

1. treatment of patients with advanced *soft-tissue sarcoma*, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents;

2. in combination with pegylated liposomal doxorubicin (PLD), Yondelis is indicated for the treatment of patients with relapsed platinum-sensitive *ovarian cancer*.

After the indication in ovarian cancer was authorised in the EU, trial OVC-3006 was started. It was a randomised, open-label, multicentre phase 3 study evaluating the efficacy and safety of trabectedin in combination with PLD in patients with advanced, relapsed ovarian cancer who had received two previous lines of platinum-based chemotherapy, compared to PLD alone and with overall survival (OS) as primary endpoint.

Following a review of results of a second interim analysis for futility, the Independent data Monitoring Committee recommended discontinuation of the study due to lack of survival superiority in the trabectedin in combination with PLD arm over PLD alone arm. The study failed to achieve both the primary endpoint of OS and the secondary endpoint of progression-free survival (PFS).

On 21 February 2020 the European Commission therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and requested the CHMP to assess study 3006 and its impact on the benefit-risk balance of Yondelis and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Yondelis (trabectedin) is a tris tetrahydroisoquinoline alkaloid originally isolated from the marine ascidian Ecteinascidia turbinata. It exerts its action by binding to the N2 position of guanine in the minor groove of deoxyribonucleic acid (DNA), unlike other DNA-binding agents that bind to the major groove. In contrast to other DNA-binding cytotoxic agents, which are either equally or more effective in cells containing defects of the transcription-coupled nucleotide excision repair (NER) pathway, trabectedin is more effective in cells with an intact NER pathway. Additionally, trabectedin has been proposed to have unique modulatory effects on the tumours microenvironment that has been attributed to its effect on tumour-associated macrophages and histiocytes.

The marketing authorisation for Yondelis was first issued on 17 September 2007 for the soft tissue sarcoma indication. The ovarian cancer indication was authorised in 2009 based mainly on study OVA-301, a randomised, open-label, multicentre phase 3 trial to evaluate the efficacy and safety of trabectedin in combination with pegylated liposomal doxorubicin (PLD) in 645 patients with relapsed ovarian cancer. The trial showed superiority of trabectedin with PLD compared to PLD alone in terms of progression-free survival (PFS, primary endpoint): 21% risk reduction for disease progression (HR=0.79, CI: 0.65-0.96, p=0.02)-. Also, overall response rates were higher with trabectedin combined with PLD (27.6% vs. 18.8% with PLD alone). Results for overall survival were compatible with a risk reduction for death with a 95% CI 0.72-1.02, but without significance. On the basis of this study, the following indication was granted: "Yondelis in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer".

No additional studies on the ovarian cancer indication were requested of the MAH.

2.2. Clinical aspects

The full clinical study report for study 2012-004808-34 (OVC-3006), hereafter study 3006, was provided for assessment.

2.2.1. Data on efficacy

Study 3006

This was a Phase 3, randomized, open-label, active-controlled, multicenter study designed to evaluate the efficacy and safety of trabectedin+DOXIL as a third-line chemotherapy in subjects with advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer.

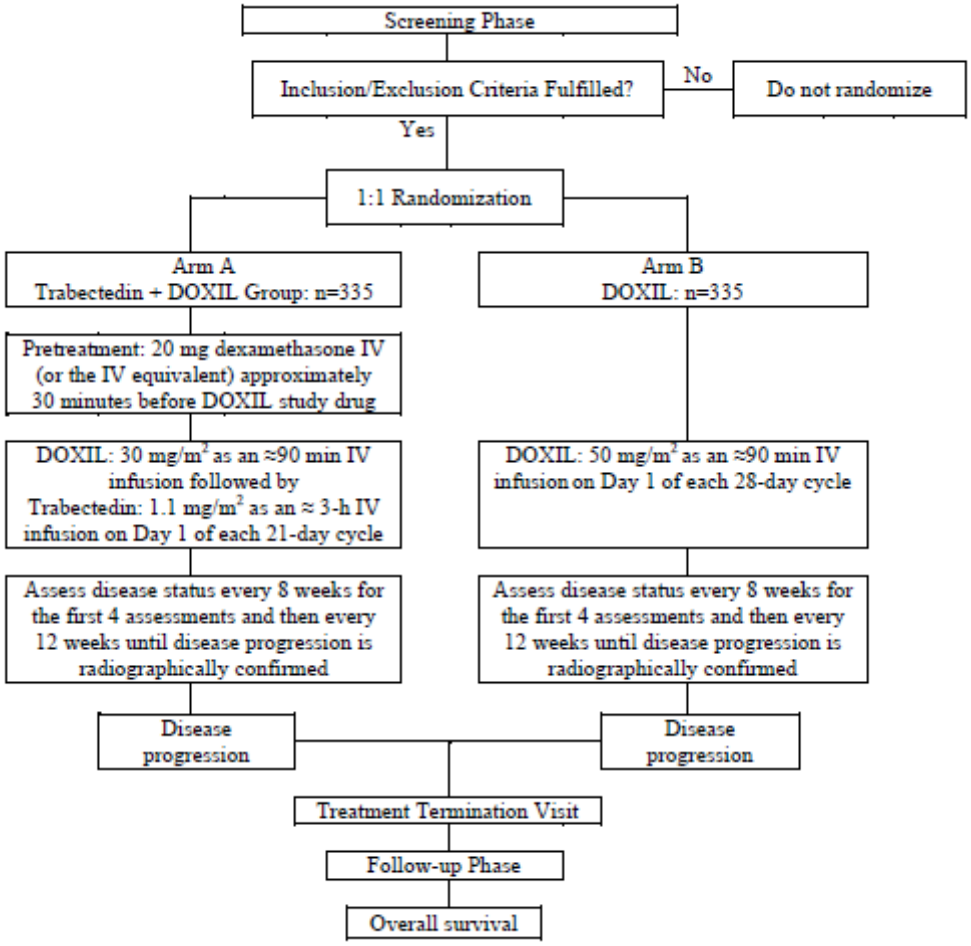

Figure 1 - Study design 3006

2.2.1.1. Methods

- **Study participants**

Inclusion Criteria:

- Histologically proven advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer
- Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or 1

- Received first-line treatment with a platinum-based regimen and had no evidence of disease progression for >= 6 months after the last dose
- Received second-line treatment with a platinum-based regimen, with progression of disease after attaining a response
- Progression of disease based on imaging after the second-line platinum-based regimen (individuals treated with a pegylated liposomal doxorubicin-containing regimen as a second-line therapy are eligible if subsequent disease progression occurs >=9 months from the first dose)
- Evidence of measurable disease at screening as evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) (Version 1.1)
- Participants no longer need to be able to receive intravenous (IV) dexamethasone or an equivalent IV corticosteroid
- Have a known BRCA 1/2 mutation status (for participants who do not have a known BRCA 1/2 status at screening, a blood sample will be collected to determine the status with the results available prior to randomization
- Laboratory values within protocol -defined parameters
- Have left ventricular ejection fraction by multigated acquisition scan (MUGA) scan or 2D-ECHO within normal limits for the institution
- Have side effects (except alopecia) of prior treatment resolved to at least Grade 1 according to the National Cancer Institute - Common Terminology Criteria of Adverse Events (NCICTCAE) (Version 4.0)
- Have a negative urine or serum pregnancy test at screening
- Agrees to protocol-defined use of effective contraception

Exclusion Criteria:

- Diagnosis of ovarian carcinoma with mucinous histology
- Had more than 2 prior lines of systemic therapy. Maintenance therapies and hormonal therapies are not considered additional lines of therapy
- Participants who had a prior exposure to trabectedin or hypersensitivity to any of the excipients will not be excluded from receiving single-agent Doxil
- Prior treatment with doxorubicin or other anthracycline at cumulative doses greater than 300 mg/m2 (calculated using doxorubicin equivalent doses: 1 mg doxorubicin = 1 mg Doxil/Caelyx = 1.8 mg epirubicin = 0.3 mg mitoxantrone = 0.25 mg idarubicin)
- Participants unwilling or unable to have a central venous catheter placed will not be excluded from receiving single-agent Doxil
- Pregnant or breast-feeding
- Would receive study treatment within 3 weeks from radiation therapy, experimental therapy, hormonal therapy, prior chemotherapy, or biological therapy; use an invasive investigational device; or is currently enrolled in an investigational study
- History of another invasive malignancy (except non-metastatic basal cell carcinoma or squamous cell carcinoma of the skin or cervical carcinoma in situ adequately treated) unless in remission for >=5 years, or a non - invasive malignancy requiring ongoing therapy
- Known allergies, hypersensitivity, or intolerance to Doxil, dexamethasone, or their excipients
- Known history of central nervous system metastasis

- Known significant chronic liver disease, such as cirrhosis or active hepatitis (potential participants who test positive for hepatitis B surface antigen or hepatitis C antibodies are allowed provided they do not have active disease requiring antiviral therapy)
- Had a myocardial infarct within 6 months before enrollment, New York Heart Association (NYHA) Class II or greater heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, clinically significant pericardial disease, or electrocardiographic evidence of acute ischemic or active conduction system abnormalities
- Has any of the following medical conditions: uncontrolled diabetes, psychiatric disorder (including dementia) that prevents compliance with protocol, uncontrolled seizures, newly diagnosed deep vein thrombosis, active systemic infection that is likely to interfere with study procedure or results
- Has any condition that, in the opinion of the investigator, would compromise the well-being of the participant or the study or prevent the participant from meeting or performing study requirements

- **Treatments**

During the treatment phase, subjects were to receive study drug by IV infusion on

- **Arm A:** Day 1 of a 21-day cycle (DOXIL 30 mg/m^2 administered over approximately 90 minutes [q3wk; 90-min], followed by **trabectedin** 1.1 mg/m^2 administered over approximately 3h [q3wk; 3-h], via central venous access) Subjects assigned to Arm A were pretreated with 20 mg of dexamethasone IV, or an equivalent IV corticosteroid, approximately 30 minutes prior to initiation of infusion of DOXIL on Day 1 of each treatment cycle, to reduce the incidence of transaminase elevations related to trabectedin

- **Arm B:** Day 1 of a 28-day cycle (DOXIL 50 mg/m^2 over approximately 90 minutes per package insert [q4wk; 90-min]).

Treatment was to be continued until the occurrence of disease progression or unacceptable treatment toxicity, or until 2 cycles after assessment of a complete response (CR).

- **Objectives**

Primary Objective

The primary objective was to compare the OS after treatment with trabectedin+DOXIL combination therapy to that observed after treatment with DOXIL monotherapy for subjects with advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer who had received 2 previous lines of platinum-based chemotherapy.

Secondary Objectives

The secondary objectives were:

- To evaluate PFS.
- To evaluate the objective response rate (ORR).
- To characterize the plasma pharmacokinetics (PK) of trabectedin using a sparse sampling scheme in the trabectedin+DOXIL treatment group.
- To evaluate the safety of the trabectedin+DOXIL combination therapy and DOXIL monotherapy.

Exploratory Objectives

- To conduct pharmacogenomic evaluations of OS, PFS and other endpoints in subjects with and without mutations in BRCA 1 or BRCA 2.
- To evaluate patient-reported outcomes (PROs).

Hypothesis: Trabectedin in combination with DOXIL will improve OS compared with DOXIL monotherapy in the treatment of subjects with platinum-sensitive advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer who received 2 previous lines of platinum-based chemotherapy.

- **Outcomes/endpoints**

Primary endpoint: OS

The primary efficacy endpoint was OS, defined as the time between randomization and death from any cause. Secondary endpoints were PFS (defined as the time between the date of randomization and the date of disease progression or death), and ORR (defined as the proportion of subjects who achieve CR or partial response [PR]). The analysis of the primary endpoint, OS, was to be conducted after at least 514 events (deaths) were observed or up to the clinical cutoff date.

Secondary endpoints:

- PFS
- ORR
- PK
- Safety

Secondary efficacy endpoints of PFS and ORR were to be assessed using the Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.1). Scheduled assessments of disease status were planned to be performed within 30 days before randomization, every 8 weeks (±5 days) after randomization for the first 4 assessments, and then every 12 weeks (±5 days) thereafter. Disease assessments, including assessments for subjects who discontinued treatment for reasons other than disease progression, were to be performed until disease progression was radiographically confirmed, the start of subsequent anticancer therapy, withdrawal of subject consent, or the clinical cutoff date (18 January 2018). For subjects who discontinued study treatment, documentation of all subsequent anticancer therapy, survival status, and safety evaluations as outlined in the Time and Events Schedule of the protocol (Appendix 1) was required. Survival status was recorded at least every 8 weeks for the first 2 years after the treatment termination visit and approximately every 12 weeks thereafter. Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors, central/independent reviews).

- **Sample size**

It was assumed that OS would follow an exponential distribution with a constant hazard rate. Assuming a median OS of 16 months for the active control group (DOXIL monotherapy), a planned sample size of approximately 670 subjects was expected to provide 80% power to detect a HR of 0.78 (16 months vs. 20.5 months, corresponding to a 28% improvement in median OS) at a 2-tailed significance level of 0.05 and an enrollment duration of approximately 52 months (13 subjects/month enrollment) over a total study duration of 64 months to obtain the required 514 events. The OS endpoint incorporated group sequential design by including 1 interim analysis and 1 final analysis using the O'Brien-Fleming boundaries as implemented by Lan-DeMets α-spending method.

- **Randomisation**

At randomization, subjects were stratified by 4 criteria:

1) the time from the last dose of first-line platinum therapy to disease progression (6 months to 12 months vs. >12 months to 24 months vs. >24 months),
2) Eastern Cooperative Oncology Group (ECOG) performance status score (0 vs. 1),
3) BRCA 1/2 status (mutation vs. no mutation), and
4) prior DOXIL therapy (no vs. yes).

Subjects were then randomly assigned in a 1:1 ratio to the trabectedin+DOXIL combination therapy arm (Arm A) or to the DOXIL monotherapy arm (Arm B).

- **Blinding (masking)**

This was an open-label study.

- **Statistical methods**

Statistical Hypotheses for Trial Objectives

Overall survival was compared between treatment arms using an unstratified one-sided log-rank test. The trabectedin+DOXIL combination therapy was to be declared better than DOXIL monotherapy if the OS was better with a p-value less than or equal to the significance level as specified by the α-spending function. The overall 2-tailed significance level of 0.05 was to be spread over 1 interim efficacy and 1 final OS analyses, when approximately 308 and 514 death events were to be seen. Operating characteristics for these boundaries are presented in the following table.

Table 1 Study 3006 - Stopping Boundaries for Overall Survival (Study ET743-OVC-3006)

	Analyses	
Variable	Interim	Final
Projected Observed OS Events	308	514
Anticipated Time to Analysis (months)	43	64
Anticipated Enrollment (n)	563	669
Efficacy Boundary (HR)	0.74	0.84
Boundary Crossing Prob. (H_0)	0.008	0.048
Cumulative α spent	0.008	0.050

HR=Hazard ratio; Ho=0% improvement; H_1=28% improvement; n=number; OS=overall survival

Interim Futility Analysis

A non-binding futility analysis for OS was implemented after observing 33% (170 events) of the total number of required 514 events per request by the IDMC. The study was to be considered futile if the estimated HR from the Cox proportional-hazard model was equal to or greater than 0.95. After the futility analysis at 33% of the total number of OS events, on 26 June 2017, the IDMC requested one more futility analysis at 45% (232 events) of the total number of required 514 death events. The study was to be considered futile if the estimated HR from Cox proportional-hazard model was equal to or greater than 0.93. The second futility analysis was conducted, and the results were reviewed by the IDMC on 15 December 2017, wherein the HR for OS was 0.962, crossing the previously agreed upon threshold for futility of 0.93. The IDMC recommended discontinuing the study due to (1) futility of the primary analysis on OS and (2) excessive risk based on imbalance of adverse events not in favour of Yondelis+PLD.

Interim Efficacy Analysis

The interim efficacy analysis was planned for this study after observing 60% (308 events) of the total number of required (514) events. Following the review of the study data by the IDMC in the second futility analysis, the IDMC recommended discontinuing the study. The planned interim analysis was, therefore, not performed.

Efficacy

Primary Endpoint

OS was defined as the time between the date of randomization and the date of death. Subjects who die, regardless of the cause of death, were to be considered to have had an event. Subjects who were still being treated, who were lost to follow-up prior to the end of the study, or who had withdrawn consent from the study were to be censored at the last available date where the subject was known to be alive.

Overall survival was compared between both treatment arms by the unstratified, 2-sided, log-rank test. The Kaplan-Meier method was used to estimate the distribution of functions of OS for each treatment arm. The number of events, subjects censored, the estimate of medians and 95% CI for the medians were to be presented. Six-month and 1-year survival rates were to be calculated using the Kaplan-Meier method. Unstratified log-rank test was to be used as the primary analysis for treatment comparison Unstratified Cox proportional hazards model was used to obtain the HR and 95% CI. Sensitivity analyses for the primary endpoint using the stratified log-rank test were to be performed.

Secondary Endpoints

Progression-free survival was defined as the time between the date of randomization and the date of disease progression or death. Subjects who progressed or died were to be considered to have had an event, except if the event occurred after the start of subsequent therapy for ovarian cancer, in which case the subject was to be censored at the time of the last tumour assessment (prior to or on the first day of the first subsequent therapy for ovarian cancer). Subjects who did not progress or die (i.e., lost to follow-up, or receiving treatment without documented disease progression, or started subsequent therapy for ovarian cancer and still alive) were to be censored at the date of the last tumour assessment (prior to or on the first day of the first subsequent therapy for ovarian cancer). Progression-free survival was compared between both treatment arms using the unstratified log-rank test. The Kaplan-Meier method was used to estimate the distribution function of PFS for each treatment arm. The number of events, subjects censored, the estimate of medians and 95% CIs were to be presented. Six-month and 1-year progression-free rates were to be calculated using the Kaplan-Meier product limit method. The unstratified Cox proportional hazards model was used to obtain the HR and it's 95% CI. Sensitivity analyses for the primary endpoint using the stratified log-rank test were to be performed.

The best overall response was to be summarized per treatment arm in a frequency table with categories: CR, PR, stable disease, progressive disease (PD), and not evaluable (NE). The response rate was evaluated using the Fisher's exact test.

In case an imbalance in baseline prognostic factors was observed for OS or PFS, especially PFI, a Cox proportional hazards model will also be used to compare the 2 treatment arms. The following baseline information was to include covariates: baseline ECOG (0 vs. 1), PFI (as continuous), BRCA 1/2 status (mutation vs. no mutation), prior DOXIL therapy (no vs. yes), and any imbalanced factors. From the Cox proportional hazards regression, HRs and 95% CIs were to be estimated for treatment and for the prognostic factors.

Subgroup analyses were to be carried out to assess if the treatment effect was consistent across clinically relevant subgroups. The planned subgroup analysis included analysis by age (<65, ≥65), PFI (6 to 12 months vs. >12 to 24 months vs. >24 months), ECOG performance status score (0 vs. 1), BRCA 1/2 status (mutation vs. no mutation) and prior DOXIL therapy (no vs. yes).

Symmetry Analysis of Tumour Assessment Schedules

Tumour assessments were to be performed every 8 weeks. Timing of assessments in both treatment groups was to be presented side by side with boxplots.

2.2.1.2. Results

- **Participant flow**

576 subjects were randomized, 289 subjects in the trabectedin+DOXIL arm and 287 subjects in the DOXIL arm. Eight subjects did not receive study drug (3 subjects in the trabectedin+DOXIL arm and 5 subjects in the DOXIL monotherapy arm) due to worsening of health status (5 subjects) or withdrawal of subject consent (3 subjects). The remaining 568 subjects received at least 1 dose of study medication (286 subjects received trabectedin+DOXIL and 282 received DOXIL alone (Table 2).

Table 2 Subject Disposition; All Randomized Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=289)	DOXIL (N=287)	Total (N=576)
Randomized	289 (100.0%)	287 (100.0%)	576 (100.0%)
Not treated	3 (1.0%)	5 (1.7%)	8 (1.4%)
Treated	286 (99.0%)	282 (98.3%)	568 (98.6%)
Trabectedin/DOXIL	286 (99.0%)	0	286 (49.7%)
DOXIL	0	282 (98.3%)	282 (49.0%)

Note: Percentages calculated with the number of subjects randomized in each treatment group as denominator.
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Disease progression was the most common reason (46.5% of subjects) for the permanent discontinuation of study treatment regardless of treatment arm. Other reasons for the discontinuation of study treatment included AEs (17.4%), withdrawal of consent (15.3%), physician decision (5.8%), CR (2.8%), and death (1.2%). The incidence of discontinuation due to disease progression was lower in the trabectedin+DOXIL arm (39.2%) compared with the DOXIL monotherapy arm (53.9%). Incidences of discontinuation due to AEs and CRs were higher in the in the trabectedin+DOXIL arm (24.1% and 3.8%, respectively) than in the DOXIL monotherapy arm (10.6% and 1.8%, respectively) (Table 3).

27 (9.4%) subjects in the trabectedin+DOXIL combination therapy arm and 35 (12.4%) subjects in the DOXIL monotherapy arm discontinued study treatment due to 'Other'; the predominant reason was study termination.

Table 3 Primary Reason for Treatment Discontinuation; All Treated Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=286)	DOXIL (N=282)	Total (N=568)
Treatment discontinued	286 (100.0%)	282 (100.0%)	568 (100.0%)
Disease progression	112 (39.2%)	152 (53.9%)	264 (46.5%)
Adverse event	69 (24.1%)	30 (10.6%)	99 (17.4%)
Complete response	11 (3.8%)	5 (1.8%)	16 (2.8%)
Death	4 (1.4%)	3 (1.1%)	7 (1.2%)
Lost to follow-up	0	0	0
Physician decision	19 (6.6%)	14 (5.0%)	33 (5.8%)
Completed < 6 cycles	4 (1.4%)	3 (1.1%)	7 (1.2%)
Withdrawal of consent	44 (15.4%)	43 (15.2%)	87 (15.3%)
Completed < 6 cycles	21 (7.3%)	16 (5.7%)	37 (6.5%)
Other	27 (9.4%)	35 (12.4%)	62 (10.9%)

Note: Percentages calculated with the number of subjects treated in each treatment group as denominator.
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- **Recruitment**

Study Period: 04 October 2013 to 18 January 2018

Study Centres: United States (59 sites); Russian Federation (21 sites); Australia (8 sites); Israel (8 sites); United Kingdom (7 sites); China (5 sites); South Africa (4 sites); New Zealand (2 sites); Poland (2 sites); Switzerland (1 sites). Subjects were enrolled at 117 sites.

- **Conduct of the study**

Changes to Planned Analyses

Patient reported outcome analysis were not performed due to the lack of efficacy per the futility.

Changes in Conduct

There were 6 amendments to the original protocol dated 19 December 2012. The following key changes were identified in each amendment:

- The first amendment (25 March 2013) clearly identified the selected subject population. Specifically, progression of disease had to occur ≥9 months from the first dose in subjects treated with DOXIL-containing regimen as a second-line therapy.
- The second amendment (29 August 2013) extended the use of contraceptives from 3 months to 6 months after the last dose of study drug, changed the creatinine clearance rate from ≥40 mL/min/1.73 m^2 to ≥60 mL/min/1.73 m^2 as a part of subject inclusion criteria, and added a prohibition regarding subjects receiving a yellow fever vaccine.
- The third amendment (26 August 2015) added to and revised study inclusion and exclusion criteria to allow greater flexibility in demonstrating eligibility based on response to previous therapy.
- The fourth amendment (17 December 2015) enhanced cardiac-safety monitoring. Additional LVEF evaluations were scheduled at pre-specified times throughout the treatment period.

- The fifth amendment (18 March 2016) was initiated to clarify the timing of LVEF assessments for subjects experiencing a significant decline in LVEF including assessments during the follow-up period.
- The sixth amendment (09 January 2018) was initiated in response to an IDMC recommendation to discontinue the study based on the results of a futility analysis of OS, in which the pre-specified futility threshold was crossed.

Note: Following Protocol Amendment 6, study data collection for adverse events (AEs) (except for serious adverse events [SAEs]), laboratory tests, cardiovascular monitoring, vital signs, and physical examinations were to cease when subjects on study treatment completed the treatment termination visit assessments as specified in the Time and Events Schedule of the protocol or by 18 January 2018, whichever occurred first. For subjects who continued treatment with single-agent DOXIL, as per the local standard of care, only SAEs were reported to the sponsor.

Protocol deviations

Forty (13.8%) subjects in the trabectedin+DOXIL arm and 22 (7.7%) subjects in the DOXIL monotherapy arm had a major protocol deviation. Twelve (2.1%) subjects were not withdrawn from study per protocol specified criteria and 7 (1.2%) subjects each did not meet protocol inclusion or exclusion criteria or received the wrong treatment (including the incorrect rate of infusion or the incorrect dose) (Table 4). Forty-four (7.6%) subjects had "Other" as the reported protocol deviation, and the deviations were largely related to endpoint assessments.

Three (0.5%) subjects met criteria for protocol violations. In the trabectedin+DOXIL arm, 2 (0.7%) subjects had inclusion criteria violations (i.e., did not meet predefined protocol limits for screening hematologic or liver function test results) and 1 of these subjects also had an exclusion criterion violation (i.e., the subject received an excluded therapy within 3 weeks of the first study treatment). In the DOXIL arm, 1 (0.2%) subject had an inclusion criteria violation (i.e., informed consent was not signed prior to the optional pharmacogenomic blood sample collection) (Table 5).

Table 4 Major Protocol Deviations; All Randomised Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=289) n (%)	DOXIL (N=287) n (%)	Total (N=576) n (%)
Total number of subjects with deviation	40 (13.8%)	22 (7.7%)	62 (10.8%)
Subject did not meet inclusion or exclusion criteria	4 (1.4%)	3 (1.0%)	7 (1.2%)
Subject received wrong treatment, incorrect rate of infusion or incorrect dose	6 (2.1%)	1 (0.3%)	7 (1.2%)
Subject was not withdrawn as per protocol	8 (2.8%)	4 (1.4%)	12 (2.1%)
Other	26 (9.0%)	18 (6.3%)	44 (7.6%)

Note: only sponsor derived major protocol deviations are tabulated.
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Table 5 Inclusion / Exclusion Violations; All Randomised Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=289) n (%)	DOXIL (N=287) n (%)	Total (N=576) n (%)
Total no. subjects with a violation	2 (0.7%)	1 (0.3%)	3 (0.5%)
Exclusion criteria	1 (0.3%)	0	1 (0.2%)
Exclusion criterion 7	1 (0.3%)	0	1 (0.2%)
Inclusion criteria	2 (0.7%)	1 (0.3%)	3 (0.5%)
Inclusion criterion 11	1 (0.3%)	0	1 (0.2%)
Inclusion criterion 14	1 (0.3%)	0	1 (0.2%)
Inclusion criterion 21	0	1 (0.3%)	1 (0.2%)

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- **Baseline data**

Table 6 Demographic Data; All Randomised Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=289)	DOXIL (N=287)	Total (N=576)
Age, years			
N	289	287	576
Category, n (%)			
18 - <65	179 (61.9%)	183 (63.8%)	362 (62.8%)
65 - <75	93 (32.2%)	81 (28.2%)	174 (30.2%)
≥75	17 (5.9%)	23 (8.0%)	40 (6.9%)
Mean (SD)	59.8 (10.16)	59.9 (10.35)	59.9 (10.25)
Median	61.0	60.0	61.0
Range	(31; 83)	(30; 91)	(30; 91)
Race, n (%)			
N	289	287	576
White	261 (90.3%)	251 (87.5%)	512 (88.9%)
Black or African American	3 (1.0%)	4 (1.4%)	7 (1.2%)
Asian	15 (5.2%)	23 (8.0%)	38 (6.6%)
American Indian/Alaska Native	1 (0.3%)	1 (0.3%)	2 (0.3%)
Native Hawaiian or Other Pacific Islander	1 (0.3%)	1 (0.3%)	2 (0.3%)
Other	4 (1.4%)	3 (1.0%)	7 (1.2%)
Unknown	3 (1.0%)	1 (0.3%)	4 (0.7%)
Not Reported	1 (0.3%)	3 (1.0%)	4 (0.7%)
Ethnicity, n (%)			
N	289	287	576
Hispanic or Latino	10 (3.5%)	5 (1.7%)	15 (2.6%)
Not Hispanic or Latino	270 (93.4%)	278 (96.9%)	548 (95.1%)
Unknown	3 (1.0%)	1 (0.3%)	4 (0.7%)
Not Reported	6 (2.1%)	3 (1.0%)	9 (1.6%)
Baseline weight, kg			
N	284	281	565
Mean (SD)	75.65 (16.322)	73.67 (16.252)	74.67 (16.303)
Median	74.00	71.00	72.00
Range	(41.9; 136.0)	(41.0; 181.4)	(41.0; 181.4)
Height, cm			
N	283	281	564
Mean (SD)	161.36 (6.844)	161.96 (6.860)	161.66 (6.852)
Median	161.00	162.00	161.70
Range	(142.0; 179.0)	(134.6; 180.0)	(134.6; 180.0)
Baseline BMI, kg/m²			
N	283	281	564
Category, n (%)			
<20	12 (4.2%)	9 (3.2%)	21 (3.7%)
20 - <25	62 (21.9%)	82 (29.2%)	144 (25.5%)
25 - <30	100 (35.3%)	103 (36.7%)	203 (36.0%)
≥30	109 (38.5%)	87 (31.0%)	196 (34.8%)
Mean (SD)	29.05 (5.969)	28.10 (6.019)	28.57 (6.008)
Median	28.19	27.01	27.64
Range	(16.4; 49.6)	(16.0; 66.5)	(16.0; 66.5)
Baseline BSA, m²			
N	283	281	564
Mean (SD)	1.84 (0.213)	1.81 (0.210)	1.83 (0.211)
Median	1.80	1.80	1.80
Range	(1.4; 2.5)	(1.3; 2.9)	(1.3; 2.9)

Key: BMI=body mass index, BSA=body surface area
Note: Percentages calculated with the number of subjects randomized with in each category as denominator.
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Table 7 Disease Characteristics at Baseline; All Randomised Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=289)	DOXIL (N=287)	Total (N=576)
Histology, n (%)			
N	289	287	576
Mucinous (EXCLUSION)	0	0	0
Endometrioid	15 (5.2%)	21 (7.3%)	36 (6.3%)
Clear Cell Carcinoma	11 (3.8%)	5 (1.7%)	16 (2.8%)
Mixed Epithelial Tumor	3 (1.0%)	0	3 (0.5%)
Papillary/Serous	192 (66.4%)	196 (68.3%)	388 (67.4%)
Peritoneal Carcinoma	10 (3.5%)	8 (2.8%)	18 (3.1%)
Fallopian Tube Carcinoma	7 (2.4%)	13 (4.5%)	20 (3.5%)
Transitional Carcinoma (Brenner)	3 (1.0%)	0	3 (0.5%)
Other	48 (16.6%)	44 (15.3%)	92 (16.0%)
Baseline ECOG performance status score, n (%)			
N	289	287	576
0	149 (51.6%)	141 (49.1%)	290 (50.3%)
1	140 (48.4%)	146 (50.9%)	286 (49.7%)
≥2	0	0	0
Time from initial diagnosis to randomization, months			
N	289	287	576
Mean (SD)	41.56 (18.564)	43.07 (25.323)	42.31 (22.184)
Median	36.67	35.02	36.14
Range	(16.6; 126.8)	(2.5; 230.4)[a]	(2.5; 230.4)[a]
Time from last disease progression to randomization, months			
N	289	287	576
Mean (SD)	2.01 (3.905)	1.97 (3.139)	1.99 (3.541)
Median	1.18	1.22	1.18
Range	(0.1; 39.1)	(0.1; 33.6)	(0.1; 39.1)
Current Extent of Disease, n (%)			
N	289	287	576
Pelvis	54 (18.7%)	62 (21.6%)	116 (20.1%)
Abdomen (including retroperitoneal space)	108 (37.4%)	115 (40.1%)	223 (38.7%)
Liver	23 (8.0%)	35 (12.2%)	58 (10.1%)
Spleen	6 (2.1%)	4 (1.4%)	10 (1.7%)
Lungs	6 (2.1%)	12 (4.2%)	18 (3.1%)
Mediastinum	6 (2.1%)	3 (1.0%)	9 (1.6%)
Other	86 (29.8%)	56 (19.5%)	142 (24.7%)
BRCA 1/2 status, n (%)			
N	289	287	576
Mutation	78 (27.0%)	77 (26.8%)	155 (26.9%)
No Mutation	211 (73.0%)	210 (73.2%)	421 (73.1%)
Prior DOXIL, n (%)			
N	289	287	576
No	270 (93.4%)	267 (93.0%)	537 (93.2%)
Yes	19 (6.6%)	20 (7.0%)	39 (6.8%)
Time from the last dose of first-line platinum therapy to disease progression, n (%)			
N	289	287	576
6 months to 12 months	111 (38.4%)	113 (39.4%)	224 (38.9%)
>12 months to 24 months	107 (37.0%)	103 (35.9%)	210 (36.5%)
>24 months	71 (24.6%)	71 (24.7%)	142 (24.7%)

Note: Percentages calculated with the number of subjects randomized in each treatment group as denominator.

[a] The minimum for time from initial diagnosis to randomization in the DOXIL arm of 2.5 months was due to a data entry error for the initial ovarian cancer diagnosis date for one subject. The correct initial diagnosis date for this subject is 31 August 2012, not 31 AUG 2017 as in the database.

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Table 8 Previous Therapy for Malignancy; All Randomised Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=289) n (%)	DOXIL (N=287) n (%)
Had any previous chemotherapy, n (%)		
N	289	287
Yes	289 (100.0%)	287 (100.0%)
Cumulative prior anthracycline dose mg/m^2		
N	36 (12.5%)	36 (12.5%)
Mean (SD)	191.21 (92.311)	186.49 (81.965)
Median	190.00	182.00
Range	(30.0; 300.0)	(38.0; 300.0)
Had any previous surgery for malignancy, n (%)		
N	289	287
Yes	286 (99.0%)	286 (99.7%)
No	3 (1.0%)	1 (0.3%)
Had any previous radiotherapy for malignancy, n (%)		
N	289	287
Yes	15 (5.2%)	11 (3.8%)
No	274 (94.8%)	276 (96.2%)

Note: Percentages calculated with the number of subjects treated in each column as denominator

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- **Numbers analysed**

All efficacy analyses were based on the All Randomized Analysis set, defined as all subjects who were randomized to study treatment independent of whether they received study drug.

- **Outcomes and estimation**

Primary Efficacy Analysis – Overall Survival

Unstratified Analysis

The unstratified final analysis of OS was conducted at the 18 January 2018 cut-off. At that time, there were 266 deaths in the study; 134 (46.4%) subjects in the trabectedin+DOXIL arm and 132 (46.0%) subjects in the DOXIL monotherapy arm. The median OS for the trabectedin+DOXIL arm was 23.82 months and 22.21 months for the DOXIL arm.

The HR was 0.925 (95% CI: 0.727, 1.177; p=0.5236) (Table 9), indicating no significant difference in OS between treatment arms. The Kaplan-Meier curve for OS is presented in Figure 2.

Table 9 Overall Survival - Unstratified Analysis; All Randomized Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=289)	DOXIL (N=287)
N	289	287
Number of censored, n (%)	155 (53.6)	155 (54.0)
Number of died, n (%)	134 (46.4)	132 (46.0)
25 Quantile (95% CI), months	13.27 (9.72, 15.24)	11.37 (10.12, 13.90)
Median (95% CI), months	23.82 (20.30, 26.12)	22.21 (18.10, 24.67)
75 Quantile (95% CI), months	47.77 (34.17, NE)	39.79 (31.57, NE)
3 months event-free rate (95% CI)	0.950 (0.918, 0.970)	0.971 (0.943, 0.985)
6 months event-free rate (95% CI)	0.905 (0.863, 0.934)	0.917 (0.877, 0.945)
9 months event-free rate (95% CI)	0.825 (0.773, 0.866)	0.839 (0.787, 0.879)
12 months event-free rate (95% CI)	0.764 (0.706, 0.812)	0.739 (0.679, 0.790)
15 months event-free rate (95% CI)	0.697 (0.635, 0.752)	0.653 (0.586, 0.712)
18 months event-free rate (95% CI)	0.607 (0.538, 0.668)	0.575 (0.504, 0.640)
21 months event-free rate (95% CI)	0.553 (0.483, 0.618)	0.508 (0.435, 0.577)
24 months event-free rate (95% CI)	0.488 (0.415, 0.557)	0.434 (0.358, 0.507)
27 months event-free rate (95% CI)	0.400 (0.326, 0.473)	0.393 (0.317, 0.468)
30 months event-free rate (95% CI)	0.345 (0.270, 0.421)	0.326 (0.250, 0.404)
33 months event-free rate (95% CI)	0.334 (0.259, 0.410)	0.315 (0.239, 0.393)
36 months event-free rate (95% CI)	0.290 (0.213, 0.373)	0.285 (0.207, 0.367)
39 months event-free rate (95% CI)	0.290 (0.213, 0.373)	0.264 (0.184, 0.351)
42 months event-free rate (95% CI)	0.290 (0.213, 0.373)	0.206 (0.118, 0.311)
45 months event-free rate (95% CI)	0.261 (0.176, 0.355)	0.165 (0.076, 0.284)
48 months event-free rate (95% CI)	0.131 (0.016, 0.365)	0.165 (0.076, 0.284)
Overall p-value		0.5236
Hazard ratio (95% CI)		0.925 (0.727, 1.177)

Note: Quantiles and event-free rates and their 95% CIs are based on Kaplan-Meier product limit estimates.
Note: P- value is based on unstratified log rank test.
Note: Regression analysis of overall survival data based on Cox proportional hazards model with treatment group as the only covariate.
Note: The hazard ratio is calculated as the hazard in the trabectedin/DOXIL treatment group, divided by the hazard in the DOXIL treatment group.

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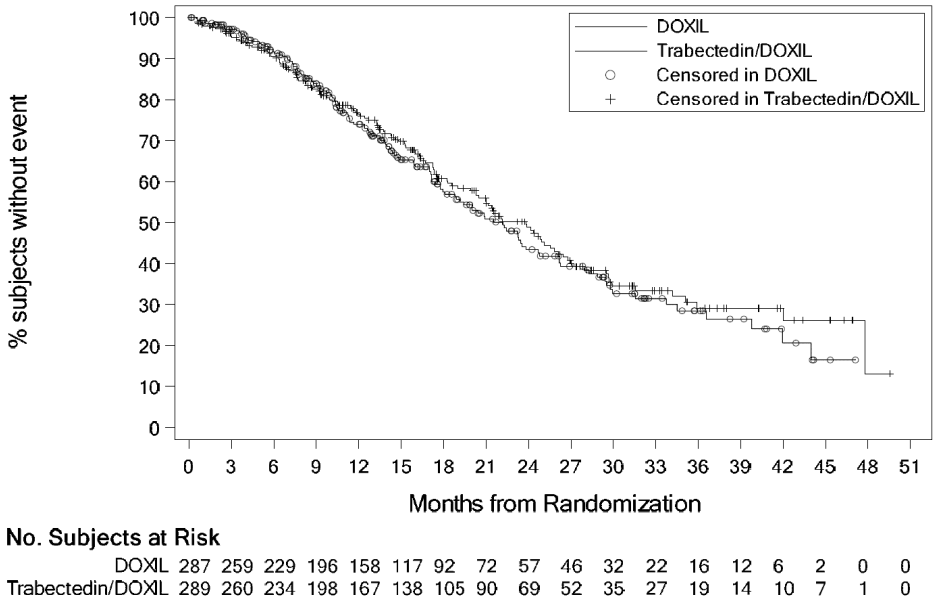
Figure GEFOS01: Kaplan-Meier Plot of Overall Survival;
All Randomized Subjects (Study ET743-OVC-3006)



No. Subjects at Risk

DOXIL	287	259	229	196	158	117	92	72	57	46	32	22	16	12	6	2	0	0
Trabectedin/DOXIL	289	260	234	198	167	138	105	90	69	52	35	27	19	14	10	7	1	0

Figure 2 Kaplan-Meier Plot of Overall Survival; All Randomized Subjects (Study ET743-OVC-3006)

Stratified Analysis

Table 10 presents an analysis of OS stratified by the time from the last dose of first-line platinum therapy to disease progression, ECOG performance status score, BRCA 1/2 mutation status, and prior DOXIL therapy (the pre-specified stratification factors). The stratification analysis is consistent with the unstratified analysis of OS.

Table 10 Overall Survival - Stratified Analysis; All Randomized Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=289)	DOXIL (N=287)
N	289	287
Number of censored, n (%)	155 (53.6)	155 (54.0)
Number of died, n (%)	134 (46.4)	132 (46.0)
25 Quantile (95% CI), months	13.27 (9.72, 15.24)	11.37 (10.12, 13.90)
Median (95% CI), months	23.82 (20.30, 26.12)	22.21 (18.10, 24.67)
75 Quantile (95% CI), months	47.77 (34.17, NE)	39.79 (31.57, NE)
3 months event-free rate (95% CI)	0.950 (0.918, 0.970)	0.971 (0.943, 0.985)
6 months event-free rate (95% CI)	0.905 (0.863, 0.934)	0.917 (0.877, 0.945)
9 months event-free rate (95% CI)	0.825 (0.773, 0.866)	0.839 (0.787, 0.879)
12 months event-free rate (95% CI)	0.764 (0.706, 0.812)	0.739 (0.679, 0.790)
15 months event-free rate (95% CI)	0.697 (0.635, 0.752)	0.653 (0.586, 0.712)
18 months event-free rate (95% CI)	0.607 (0.538, 0.668)	0.575 (0.504, 0.640)
21 months event-free rate (95% CI)	0.553 (0.483, 0.618)	0.508 (0.435, 0.577)
24 months event-free rate (95% CI)	0.488 (0.415, 0.557)	0.434 (0.358, 0.507)
27 months event-free rate (95% CI)	0.400 (0.326, 0.473)	0.393 (0.317, 0.468)
30 months event-free rate (95% CI)	0.345 (0.270, 0.421)	0.326 (0.250, 0.404)
33 months event-free rate (95% CI)	0.334 (0.259, 0.410)	0.315 (0.239, 0.393)
36 months event-free rate (95% CI)	0.290 (0.213, 0.373)	0.285 (0.207, 0.367)
39 months event-free rate (95% CI)	0.290 (0.213, 0.373)	0.264 (0.184, 0.351)
42 months event-free rate (95% CI)	0.290 (0.213, 0.373)	0.206 (0.118, 0.311)
45 months event-free rate (95% CI)	0.261 (0.176, 0.355)	0.165 (0.076, 0.284)
48 months event-free rate (95% CI)	0.131 (0.016, 0.365)	0.165 (0.076, 0.284)
Overall p-value		0.9629
Hazard ratio (95% CI)		0.942 (0.739, 1.202)

Note: Quantiles and event-free rates and their 95% CIs are based on Kaplan-Meier product limit estimates.
Note: P- value is based on Log-rank test stratified by IWRS stratification factors: platinum-free interval; Eastern Cooperative Oncology Group performance status score; mutations in BRCA 1 or BRCA 2; and prior DOXIL therapy.
Note: Regression analysis of progression-Free survival data based on Cox proportional hazards model stratified by IWRS stratification factors.
Note: The hazard ratio is calculated as the hazard in the trabectedin/DOXIL treatment group, divided by the hazard in the DOXIL treatment group.

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Secondary Analyses

Progression-Free Survival

Unstratified Analysis

At the final clinical cutoff (18 January 2018), 371 PFS events had occurred. The Kaplan-Meier curve for PFS is provided in Figure 3.

Table 11 Progression-Free Survival - Unstratified Analysis; All Randomized Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=289)	DOXIL (N=287)
N	289	287
Number of censored, n (%)	104 (36.0)	101 (35.2)
Number of events, n (%)	185 (64.0)	186 (64.8)
25 Quantile (95% CI), months	3.71 (2.96, 4.63)	2.37 (1.91, 3.71)
Median (95% CI), months	7.52 (6.93, 9.43)	7.26 (6.14, 7.59)
75 Quantile (95% CI), months	13.08 (10.35, 15.34)	12.88 (10.15, 15.70)
2 months event-free rate (95% CI)	0.877 (0.831, 0.911)	0.786 (0.732, 0.831)
4 months event-free rate (95% CI)	0.711 (0.650, 0.763)	0.652 (0.590, 0.707)
6 months event-free rate (95% CI)	0.600 (0.533, 0.660)	0.567 (0.502, 0.626)
8 months event-free rate (95% CI)	0.472 (0.403, 0.538)	0.421 (0.356, 0.485)
10 months event-free rate (95% CI)	0.392 (0.324, 0.459)	0.328 (0.265, 0.393)
12 months event-free rate (95% CI)	0.282 (0.219, 0.349)	0.280 (0.220, 0.344)
14 months event-free rate (95% CI)	0.233 (0.173, 0.299)	0.220 (0.163, 0.283)
16 months event-free rate (95% CI)	0.137 (0.088, 0.197)	0.184 (0.128, 0.248)
18 months event-free rate (95% CI)	0.137 (0.088, 0.197)	0.151 (0.098, 0.216)
20 months event-free rate (95% CI)	0.104 (0.061, 0.161)	0.129 (0.078, 0.194)
22 months event-free rate (95% CI)	0.066 (0.032, 0.119)	0.091 (0.046, 0.155)
24 months event-free rate (95% CI)	0.044 (0.016, 0.094)	0.073 (0.031, 0.139)
26 months event-free rate (95% CI)	0.044 (0.016, 0.094)	0.073 (0.031, 0.139)
28 months event-free rate (95% CI)	0.033 (0.010, 0.081)	0.073 (0.031, 0.139)
30 months event-free rate (95% CI)	0.022 (0.005, 0.067)	0.000 (NE, NE)
Overall p-value		0.5174
Hazard ratio (95% CI)		0.935 (0.762, 1.147)

Note: Quantiles and event-free rates and their 95% CIs are based on Kaplan-Meier product limit estimates.
Note: P- value is based on unstratified log rank test.
Note: Hazard ratio is estimated using Cox proportional hazards model with treatment group as the only covariate.
Note: The hazard ratio is calculated as the hazard in the trabectedin/DOXIL treatment group, divided by the hazard in the DOXIL treatment group.

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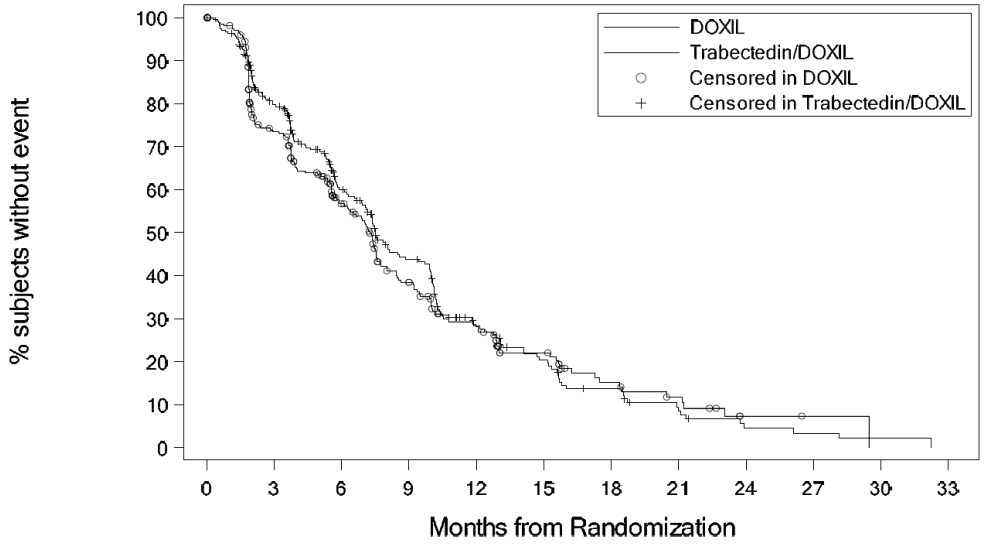
Figure GEFPFS01: Kaplan-Meier Plot of Progression-Free Survival;
All Randomized Subjects (Study ET743-OVC-3006)



No. Subjects at Risk

DOXIL	287	182	118	72	46	26	14	9	2	1	0	0
Trabectedin/DOXIL	289	195	118	77	41	28	17	9	4	3	1	0

Figure 3 Kaplan-Meier Plot of Progression-Free Survival; All Randomized Subjects (Study ET743-OVC-3006)

Stratified Analysis

Table 12 presents an analysis of PFS stratified by the time from the last dose of first-line platinum therapy to first disease progression after first-line therapy, ECOG performance status score, BRCA 1/2 mutation status, and prior DOXIL therapy (the pre-specified stratification factors). The stratification analysis is consistent with the unstratified analysis of PFS.

Table 12 Progression-Free Survival - Stratified Analysis; All Randomized Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=289)	DOXIL (N=287)
N	289	287
Number of censored, n (%)	104 (36.0)	101 (35.2)
Number of event, n (%)	185 (64.0)	186 (64.8)
25 Quantile (95% CI), months	3.71 (2.96, 4.63)	2.37 (1.91, 3.71)
Median (95% CI), months	7.52 (6.93, 9.43)	7.26 (6.14, 7.59)
75 Quantile (95% CI), months	13.08 (10.35, 15.34)	12.88 (10.15, 15.70)
2 months event-free rate (95% CI)	0.877 (0.831, 0.911)	0.786 (0.732, 0.831)
4 months event-free rate (95% CI)	0.711 (0.650, 0.763)	0.652 (0.590, 0.707)
6 months event-free rate (95% CI)	0.600 (0.533, 0.660)	0.567 (0.502, 0.626)
8 months event-free rate (95% CI)	0.472 (0.403, 0.538)	0.421 (0.356, 0.485)
10 months event-free rate (95% CI)	0.392 (0.324, 0.459)	0.328 (0.265, 0.393)
12 months event-free rate (95% CI)	0.282 (0.219, 0.349)	0.280 (0.220, 0.344)
14 months event-free rate (95% CI)	0.233 (0.173, 0.299)	0.220 (0.163, 0.283)
16 months event-free rate (95% CI)	0.137 (0.088, 0.197)	0.184 (0.128, 0.248)
18 months event-free rate (95% CI)	0.137 (0.088, 0.197)	0.151 (0.098, 0.216)
20 months event-free rate (95% CI)	0.104 (0.061, 0.161)	0.129 (0.078, 0.194)
22 months event-free rate (95% CI)	0.066 (0.032, 0.119)	0.091 (0.046, 0.155)
24 months event-free rate (95% CI)	0.044 (0.016, 0.094)	0.073 (0.031, 0.139)
26 months event-free rate (95% CI)	0.044 (0.016, 0.094)	0.073 (0.031, 0.139)
28 months event-free rate (95% CI)	0.033 (0.010, 0.081)	0.073 (0.031, 0.139)
30 months event-free rate (95% CI)	0.022 (0.005, 0.067)	0.000 (NE, NE)
Overall p-value		0.3545
Hazard ratio (95% CI)		0.934 (0.760, 1.146)

Note: Quantiles and event-free rates and their 95% CIs are based on Kaplan-Meier product limit estimates.
Note: P- value is based on Log-rank test stratified by IWRS stratification factors: platinum-free interval; Eastern Cooperative Oncology Group performance status score; mutations in BRCA 1 or BRCA 2; and prior DOXIL therapy.
Note: Regression analysis of progression-Free survival data based on Cox proportional hazards model stratified by IWRS stratification factors.
Note: The hazard ratio is calculated as the hazard in the trabectedin/DOXIL treatment group, divided by the hazard in the DOXIL treatment group.

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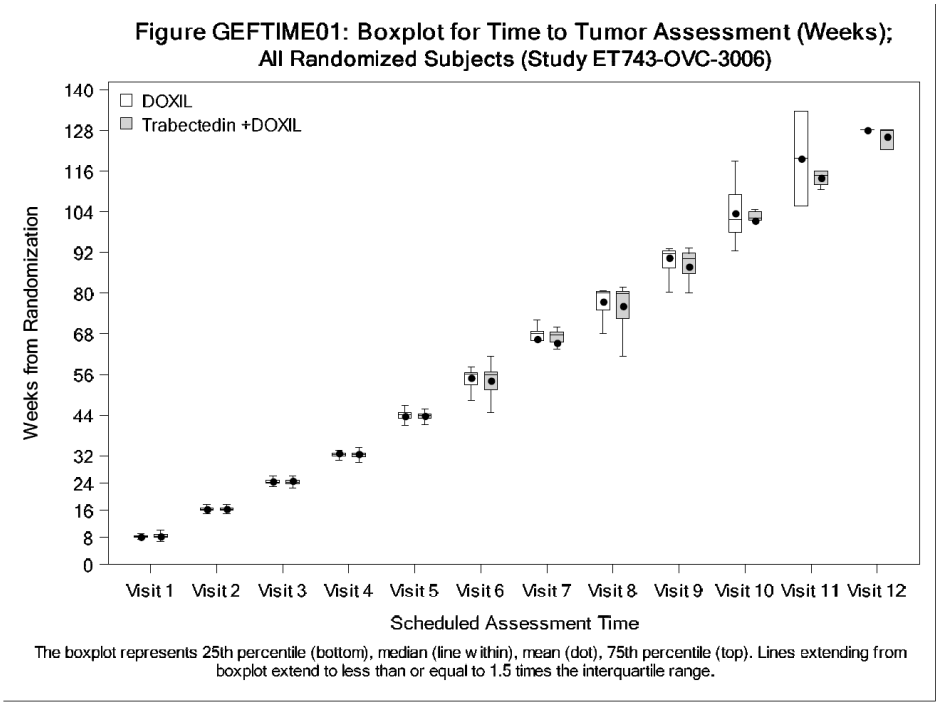
Symmetry of Tumour Assessments

Tumour assessments for the first 4 evaluations were conducted every 8 weeks after randomization and then every 12 weeks until disease progression, the start of subsequent anticancer therapy, withdrawal of subject consent, or the clinical cut-off date. Figure 14 shows the first 12 tumour assessments. The timing of assessments for both treatment groups was consistent with the schedule specified in the protocol.



Cross reference: Attachment TEFTIME01

Figure 4 Boxplot of Time to Tumour Assessment (Weeks); All Randomized Subjects (Study ET743-OVC-3006)

Objective Response Rate

The objective response rate (CR or PR as best responses) was 46.0% for the trabectedin+DOXIL arm and 35.9% for the DOXIL arm. The odds ratio was 1.523 (95% CI: 1.075; 2.158; p= 0.0142) favouring the trabectedin+DOXIL treatment arm (Table 13).

Table 13 Objective Response Rate; All Randomized Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=289)	DOXIL (N=287)
ORR, n (%)	133 (46.0)	103 (35.9)
ORR 95% CI	(40.2; 52.0)	(30.3; 41.7)
P-value		0.0142
Odds ratio (95% CI)		1.523 (1.075; 2.158)

Note: ORR 95% CI is based on Fisher's exact CI.
Note: P-value and Odds ratio(95% CI) is based on Fisher's exact test.
Key: CI=confidence interval, ORR=objective response rate.
[TEFORR01A.RTF] [JNJ-17027907\OVC3006\DBR_CSR\RE_CSR\PROD\TEFORR01A.SAS] 26AUG2018, 08:34

Best Overall Response

CR and PR rates were higher in the trabectedin+DOXIL arm as compared with the DOXIL monotherapy arm. Stable disease and progressive disease occurred at slightly higher rates in the DOXIL arm (36.2% and 19.5%, respectively) compared with the trabectedin+DOXIL arm (30.4% and 13.1%, respectively) (Table 14).

Table 14 Best Overall Response; All Randomized Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=289)	DOXIL (N=287)
Complete Response	22 (7.6%)	8 (2.8%)
Partial Response	111 (38.4%)	95 (33.1%)
Stable Disease	88 (30.4%)	104 (36.2%)
Progressive Disease	38 (13.1%)	56 (19.5%)
Not Evaluable	0	2 (0.7%)
Not Done	30 (10.4%)	22 (7.7%)

Note: Percentages calculated with the number of subjects randomized in each treatment group as denominator.
[TEFOR02A.RTF] [JNJ-17027907\OVC3006\DBR_CSR\RE_CSR\PROD\TEFOR02A.SAS] 12SEP2018, 12:58

- **Ancillary analyses**

OS - Subgroup Analyses

Table 15 provides a summary of OS analysed by stratification factors and combinations of stratification factors. A forest plot is also provided in Figure 5. A summary of findings is provided below.

- Subjects with a BRCA 1/2 mutation who received trabectedin+DOXIL had a 45.8% reduction in the risk of death as compared with subjects who received DOXIL monotherapy (HR=0.542; 95% CI: 0.327, 0.901). The median OS was 34.2 months in the trabectedin+DOXIL arm and 20.9 months in the DOXIL arm.
- Subjects with a PFI of 6 months to 12 months who received trabectedin+DOXIL exhibited a trend towards a reduced risk of death as compared with the DOXIL monotherapy arm (30.6% reduction in the risk of death [HR=0.694; 95% CI: 0.476, 1.012]). The median OS was 24.8 months for the trabectedin+DOXIL arm and 17.4 months for the DOXIL arm.
- Subjects with a BRCA 1/2 mutation and a PFI of 6 months to 12 months who received trabectedin+DOXIL had a 62.6% reduction in the risk of death as compared with subjects who received DOXIL monotherapy (HR=0.374; 95% CI: 0.171, 0.819). The median OS was 31.5 months in the trabectedin+DOXIL arm and 14.9 months in the DOXIL arm.
- Subjects with a BRCA 1/2 mutation or a PFI of 6 months to 12 months who received trabectedin+DOXIL had a 30.0% reduction in the risk of death as compared with subjects who received DOXIL monotherapy (HR=0.700; 95% CI: 0.504, 0.972). The median OS was 27.0 months in the trabectedin+DOXIL arm and 19.4 months in the DOXIL arm.

Table 15 Overall Survival Analysis by Subgroups; All Randomized Subjects (Study ET743- OVC-3006)

		N	Median in months (Trabectedin + DOXIL/ DOXIL)	Hazard Ratio	95% CI of Hazard Ratio	p-value (log-rank test)
BRCA mutation	Yes	155	34.2/20.9	0.542	(0.327, 0.901)	0.0165
	No	421	21.5/22.2	1.127	(0.856, 1.485)	0.3933
PFI	6 to 12 months	224	24.8/17.4	0.694	(0.476, 1.012)	0.0565
	>12 to <24 months	210	21.6/20.4	1.027	(0.685, 1.539)	0.8975
	>=24 months	142	23.9/27.9	1.263	(0.763, 2.090)	0.3630
BRCA mutation and PFI=6 to 12 months		60	31.5/14.9	0.374	(0.171, 0.819)	0.0108
BRCA mutation or PFI=6 to 12 months		319	27.0/19.4	0.700	(0.504, 0.972)	0.0323
ECOG status score	0	290	25.9/23.5	0.817	(0.574, 1.162)	0.2592
	1	286	19.0/20.0	1.061	(0.762, 1.477)	0.7250
Prior DOXIL therapy	Yes	39	34.2/28.9	0.933	(0.335, 2.596)	0.8938
	No	537	22.1/20.9	0.917	(0.716, 1.175)	0.4947

Key: PFI= platinum-free interval, ECOG=Eastern Cooperative Oncology Group
Note: Hazard ratio is estimated using Cox proportional hazards model with treatment group as the only covariate for each subgroup.
Note: Hazard ratio is calculated as the hazard in Trabectedin +DOXIL treatment group divided by the hazard in DOXIL treatment group.
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Figure GEFOS02: Hazard Ratio and Its 95% Confidence Intervals Between Treatment Groups for All Subjects and Subgroups - Overall Survival; All Randomized Subjects (Study ET743-OVC-3006)

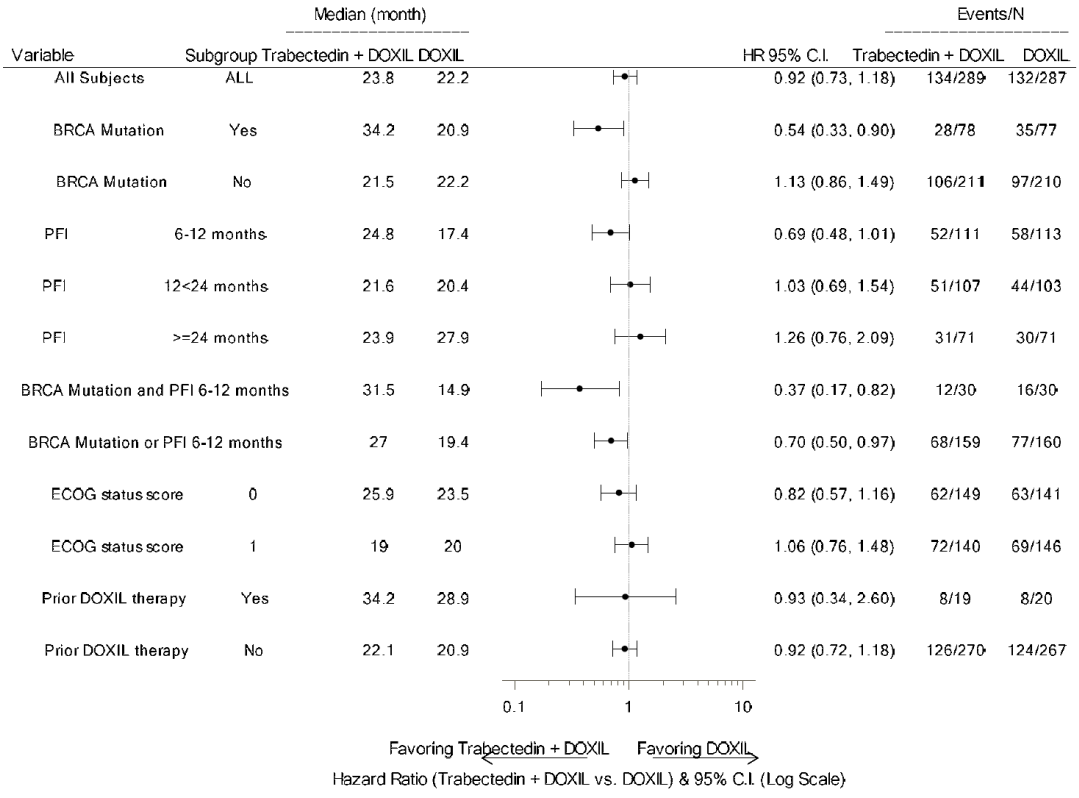

Figure 5 Forest Plot of Overall Survival by Subgroup; All Randomized Subjects (Study ET743-OVC-3006)

Table 16 provides a summary of the multivariate analysis of OS by randomization stratification factors to assess potential prognostic effects. The HR for the treatment effect after adjustment for pre-specified potential prognostic factors was 0.949 (95% CI: 0.744, 1.210). Prognostic factors that influenced OS independent of treatment effect were BRCA 1/2 mutation status, ECOG performance status score, and PFI. Survival outcomes showed improvement for subjects with a BRCA 1/2 mutation (versus no mutation), ECOG performance status score of 0 (versus 1), and PFI >12 months (versus 6 to 12 months).

Table 16 Overall Survival Multivariate Analysis; All Randomized Subjects (Study ET743- OVC-3006)

	Parameter Estimate	Standard Error	Hazard Ratio	95% CI for Hazard Ratio	p-value
Treatment group: trabectedin +DOXIL vs. DOXIL	-0.052	0.124	0.949	(0.744; 1.210)	0.6741
BRCA mutation: Yes vs. No	-0.348	0.146	0.706	(0.530; 0.940)	0.0172
PFI: (6 to 12) months vs. (>12 months)	0.238	0.125	1.269	(0.993; 1.622)	0.0568
ECOG status score: 1 vs. 0	0.445	0.127	1.560	(1.216; 2.002)	0.0005
Prior DOXIL therapy: Yes vs. No	-0.138	0.263	0.871	(0.520; 1.460)	0.6004

Key: PFI=platinum-free interval, ECOG=Eastern Cooperative Oncology Group
Note: Multivariate analysis is based on Cox model with treatment group, platinum-free interval; Eastern Cooperative Oncology Group performance status score; mutations in BRCA 1 or BRCA 2; and prior DOXIL therapy as covariates.

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PFS - Subgroup Analyses

Table 17 provides a summary of PFS analysed by stratification factors and combinations of stratification factors. A forest plot is also provided in Figure 6. A summary of findings is provided below.

- Subjects with a BRCA 1/2 mutation who received trabectedin+DOXIL had a 27.8% reduction in the risk of disease progression or death as compared with subjects who received DOXIL monotherapy (HR=0.722; 95% CI: 0.484, 1.078). The median PFS was 10.1 months in the trabectedin+DOXIL arm and 7.6 months in the DOXIL arm.
- Subjects with a PFI of 6 months to 12 months who received trabectedin+DOXIL had a 28.5% reduction in the risk of disease progression or death as compared with the DOXIL monotherapy arm (HR=0.715; 95% CI: 0.519, 0.986). The median PFS was 7.5 months for the trabectedin+DOXIL arm and 5.5 months for the DOXIL arm.
- Subjects with a BRCA 1/2 mutation and a PFI of 6 months to 12 months who received trabectedin+DOXIL had a 52.8% reduction in the risk of disease progression or death as compared with subjects who received DOXIL monotherapy (HR=0.472; 95% CI: 0.255, 0.875). The median PFS was 10.1 months in the trabectedin+DOXIL arm and 6.1 months in the DOXIL arm.
- Subjects with a BRCA 1/2 mutation or a PFI of 6 months to 12 months who received trabectedin+DOXIL had a 22.6% reduction in the risk of disease progression or death as compared with subjects who received DOXIL monotherapy (HR=0.774; 95% CI: 0.588, 1.018). The median PFS was 8.8 months in the trabectedin+DOXIL arm and 7.1 months in the DOXIL arm.

Table 17 Progression-Free Survival Analysis by Subgroups; All Randomized Subjects (Study ET743-OVC-3006)

		N	Median in months (Trabectedin + DOXIL/ DOXIL)	Hazard Ratio	95% CI of Hazard Ratio	p-value (log-rank test)
BRCA mutation	Yes	155	10.1/7.6	0.722	(0.484, 1.078)	0.1080
	No	421	7.1/7.1	1.014	(0.799, 1.287)	0.9081
PFI	6 to 12 months	224	7.5/5.5	0.715	(0.519, 0.986)	0.0388
	>12 to <24 months	210	7.4/7.6	1.172	(0.822, 1.670)	0.3794
	>=24 months	142	9.9/8.0	0.964	(0.640, 1.451)	0.8598
BRCA mutation and PFI=6 to 12 months		60	10.1/6.1	0.472	(0.255, 0.875)	0.0143
BRCA mutation or PFI=6 to 12 months		319	8.8/7.1	0.774	(0.588, 1.018)	0.0652
ECOG status score	0	290	7.5/7.4	1.021	(0.763, 1.368)	0.8874
	1	286	7.5/7.1	0.854	(0.640, 1.140)	0.2829
Prior DOXIL therapy	Yes	39	7.1/5.6	0.626	(0.265, 1.478)	0.2812
	No	537	7.5/7.4	0.951	(0.770, 1.174)	0.6390

Key: PFI= platinum-free interval, ECOG=Eastern Cooperative Oncology Group
Note: Hazard ratio is estimated using Cox proportional hazards model with treatment group as the only covariate for each subgroup.
Note: Hazard ratio is calculated as the hazard in Trabectedin +DOXIL treatment group divided by the hazard in DOXIL treatment group.
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Figure GEFPFS02: Hazard Ratio and Its 95% Confidence Intervals Between Treatment Groups for All Subjects and Subgroups - Progression-free Survival; All Randomized Subjects (Study ET743-OVC-3006)

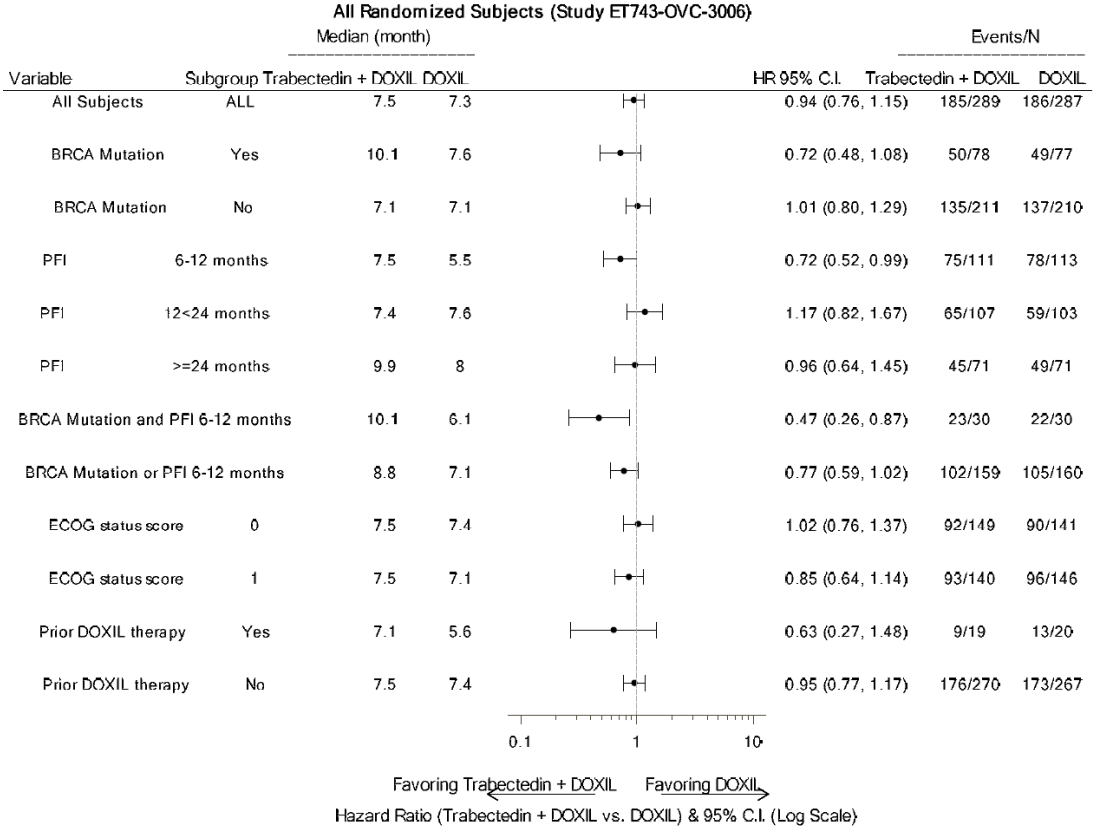

Figure 6 Forest Plot of Progression-Free Survival by Subgroup; All Randomized Subjects (Study ET743-OVC-3006)

Table 18 provides a summary of the multivariate analysis of PFS by randomization stratification factors to assess potential prognostic effects. The HR for the treatment effect after adjustment for pre-specified potential prognostic factors was 0.927 (95% CI: 0.755, 1.139). Prognostic factors that influenced PFS independent of treatment effect were BRCA 1/2 mutation status and PFI.

Progression-free survival showed improvement for subjects with a BRCA 1/2 mutation (versus no mutation) and PFI >12 months (versus 6 to 12 months).

Table 18 Progression-Free Survival Multivariate Analysis; All Randomized Subjects (Study ET743-OVC-3006)

	Parameter Estimate	Standard Error	Hazard Ratio	95% CI for Hazard Ratio	p-value
Treatment group: trabectedin +DOXIL vs. DOXIL	-0.075	0.105	0.927	(0.755; 1.139)	0.4728
BRCA mutation: Yes vs. No	-0.234	0.120	0.791	(0.626; 1.000)	0.0503
PFI: (6 to 12) months vs. (>12 months)	0.265	0.107	1.303	(1.058; 1.606)	0.0129
ECOG status score: 1 vs. 0	0.052	0.109	1.054	(0.852; 1.303)	0.6296
Prior DOXIL therapy: Yes vs. No	0.035	0.227	1.036	(0.664; 1.616)	0.8758

Key: PFI= platinum-free interval, ECOG=Eastern Cooperative Oncology Group
Note: Multivariate analysis is based on Cox model with treatment group, platinum-free interval; Eastern Cooperative Oncology Group performance status score; mutations in BRCA 1 or BRCA 2; and prior DOXIL therapy as covariates.
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ORR - Subgroup Analyses

Table 19 provides a summary of ORR analysed by stratification factors and combinations of stratification factors. Subject and baseline disease characteristics with odds ratios favouring trabectedin+DOXIL treatment as compared with DOXIL monotherapy include BRCA 1/2 mutation (odds ratio 2.143; 95% CI:1.072-4.297), PFI ≥24 months (odds ratio: 2.099; 95% CI: 1.020, 4.332), and no prior DOXIL therapy (odds ratio: 1.490; 95% CI: 1.039, 2.139).

Table 19 Subgroup Analysis of Objective Response Rate; Randomized Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=289)	DOXIL (N=287)	Odds ratio (95% CI)	P-value
BRCA mutation				
Yes	N=78 50 (64.1%)	N=77 35 (45.5%)	2.143 (1.072 - 4.297)	0.0241
No	N=211 83 (39.3%)	N=210 68 (32.4%)	1.354 (0.890 - 2.061)	0.1550
PFI				
6 to 12 months	N=111 48 (43.2%)	N=113 40 (35.4%)	1.391 (0.784 - 2.469)	0.2739
>12 to <24 months	N=107 44 (41.1%)	N=103 35 (34.0%)	1.357 (0.746 - 2.474)	0.3199
>= 24 months	N=71 41 (57.7%)	N=71 28 (39.4%)	2.099 (1.020 - 4.332)	0.0435
BRCA mutation and PFI= 6 to 12 months	N=30 19 (63.3%)	N=30 12 (40.0%)	2.591 (0.813 - 8.366)	0.1205
BRCA mutation or PFI= 6 to 12 months	N=159 79 (49.7%)	N=160 63 (39.4%)	1.520 (0.952 - 2.430)	0.0718
ECOG status score				
0	N=149 71 (47.7%)	N=141 56 (39.7%)	1.382 (0.844 - 2.262)	0.1935
1	N=140 62 (44.3%)	N=146 47 (32.2%)	1.674 (1.006 - 2.790)	0.0389
Prior DOXIL therapy				
Yes	N=19 10 (52.6%)	N=20 7 (35.0%)	2.064 (0.479 - 9.073)	0.3406
No	N=270 123 (45.6%)	N=267 96 (36.0%)	1.490 (1.039 - 2.139)	0.0281

Key: CI=confidence interval, PFI= platinum-free interval
Note: P-value and Odds ratio (95% CI) is based on Fisher's exact test.
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- **Analysis performed across trials**

The MAH provided a comparison of key baseline characteristics between Study 3006 and Study 301 (Table 20).

Table 20 Summary of Key Baseline Characteristics for Study 301 and Study 3006

Key Baseline Characteristic	Study 301			Study 3006		
	Yondelis + PLD N=337	PLD N=335	Total N=672	Yondelis + PLD N=289	PLD N=287	Total N=576
Prior Treatment for Advanced Disease						
Lines of chemotherapy, n (%)						
1	337 (100)	335 (100)	672 (100)	0	0	0 (0)
2	0	0	0 (0)	289 (100)	287 (100)	576 (100)
PFI following first line platinum, n (%)						
< 6 months	119 (35.3)	123 (36.7)	242 (36.0)	0	0	0
≥ 6 months	218 (64.7)	212 (63.3)	430 (64.0)	289 (100)	287 (100)	576 (100)
PFI following last line platinum*, n (%)						
< 6 months	119 (35.3)	123 (36.7)	242 (36.0)	117 (40.5)	126 (43.9)	243 (42.2)
≥ 6 months	218 (64.7)	212 (63.3)	430 (64.0)	172 (59.5)	161 (56.1)	333 (57.8)
Prior chemotherapy, n (%)						
Platinum	337 (100)	335 (100)	672 (100)	289 (100)	287 (100)	576 (100)
Taxane	269 (79.8)	271 (80.9)	540 (80.4)	277 (95.8)	273 (95.1)	550 (95.5)
Anthracycline	29 (8.6)	26 (7.8)	55 (8.2)	36 (12.5)	36 (12.5)	72 (12.5)
Potential Prognostic Factors						
Age, n (%)						
< 65 years	257 (76.3)	229 (68.4)	486 (72.3)	179 (61.9)	183 (63.8)	362 (62.8)
≥ 65 years	80 (23.7)	106 (31.6)	186 (27.7)	110 (38.3)	104 (35.9)	214 (37.2)
ECOG PS, n (%)						
0	230 (68.2)	192 (57.3)	422 (62.8)	149 (51.6)	141 (49.1)	290 (50.3)
1	98 (29.1)	132 (39.4)	230 (34.2)	140 (48.4)	146 (50.9)	286 (49.7)
2	9 (2.7)	11 (3.3)	20 (3.0)	0	0	0
Tumour histology, n (%)						
Papillary/serous	225 (66.8)	230 (68.7)	455 (67.7)	192 (66.4)	196 (68.3)	388 (67.4)
Endometroid	23 (6.8)	17 (5.1)	40 (6.0)	15 (5.2)	21 (7.3)	36 (6.3)
Clear cell carcinoma	13 (3.9)	16 (4.8)	29 (4.3)	11 (3.8)	5 (1.7)	16 (2.8)
Peritoneal carcinoma	11 (3.3)	9 (2.7)	20 (3.0)	10 (3.5)	8 (2.8)	18 (3.1)
Mucinous	5 (1.5)	4 (1.2)	9 (1.3)	0	0	0
Mixed epithelial tumour	4 (1.2)	5 (1.5)	9 (1.3)	3 (1.0)	0	3 (0.5)
Fallopian tube carcinoma	3 (0.9)	3 (0.9)	6 (0.9)	7 (2.4)	13 (4.5)	20 (3.5)
Transitional cell carcinoma	2 (0.6)	2 (0.6)	4 (0.6)	3 (1.0)	0	3 (0.5)
Other	50 (14.8)	49 (14.6)	99 (14.7)	48 (16.6)	44 (15.3)	92 (16.0)
unknown	1 (0.3)	0	1 (0.1)	0	0	0
Histology grade, n (%)						
Grade 1	18 (5.3)	10 (3.0)	28 (4.2)	Not reported in Study 3006		
Grade 2	58 (17.2)	59 (17.6)	117 (17.4)			
Grade 3	175 (51.9)	174 (51.9)	349 (51.9)			
unknown	86 (25.5)	92 (27.5)	178 (26.5)			
Liver metastases	100 (30)	92 (27)	192 (29)	33 (11.4)	48 (16.7)	81 (14.1)
Lung metastases	69 (20)	50 (15)	119 (18)	10 (3.5)	15 (5.2)	25 (4.3)
BRCA1/2 status, n (%)	n=135	n=129	n=264			
Mutation	24 (17.8)	17 (13.2)	41 (15.5)	78 (27.0)	77 (26.8)	155 (26.9)
No mutation	111 (82.2)	112 (86.8)	223 (84.5)	211 (73.0)	210 (73.2)	421 (73.1)
CA-125 > 100 IU/mL, n (%)	216 (64.1)	221 (66.0)	437 (65.0)	176 (60.9)	171 (59.6)	347 (60.2)
WBC $\leq 6x10^9/L$	158 (46.9)	132 (39.4)	290 (43.1)	142 (49.1)	144 (50.1)	286 (49.7)

BMI: body mass index, PFI: platinum-free interval, PS: performance status
*PharmaMar post-hoc analysis for Study 3006

2.2.2. Discussion on efficacy

Study 3006 was a phase 3, randomized, open-label, multicenter study that compared the efficacy and safety of trabectedin+DOXIL in women with recurrent ovarian cancer after failure of second-line platinum-based chemotherapy.

The study included women with advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer, ECOG 0-1. The primary objective of the study was to compare the OS after treatment with trabectedin+doxorubicin vs doxorubicin monotherapy. Secondary objectives were PFS, ORR, PK and safety.

The study sponsor assumed that 670 patients would be needed to provide 80% power to show a HR = 0.78 at alpha =5%. Patients were randomized 1:1 using four clinically meaningful stratification factors: 1) the time from the last dose of first-line platinum therapy to disease progression (6 months to 12 months vs. >12 months to 24 months vs. >24 months), 2) Eastern Cooperative Oncology Group (ECOG) performance status grade (0 vs. 1), 3) BRCA 1/2 status (mutation vs. no mutation), and 4) prior DOXIL therapy (no vs. yes).

Overall, the baseline demographic and disease characteristics are well-balanced. The majority of the patients were white, relatively young women (<65 years), mean age of 60-61. The majority had papillary/serous histology, and locally advanced disease (pelvis and abdomen), and had prior surgery. About 27% of the patients had BRAC 1/2 mutated disease. Only a minority had received prior doxorubicin.

It should be noted that study participants were required to be platinum sensitive (PFI ≥ 6 months) following their first platinum-containing regimen and have a complete or partial response to a second line platinum-based chemotherapy (without PFI restrictions), meaning that these patients could be either platinum-sensitive (PFI ≥ 6 months) or platinum-resistant (PFI < 6 months) following their second platinum-containing regimen. A post hoc analysis determined that 42% of enrolled subjects were platinum-resistant (PFI < 6 months) following their last platinum-containing regimen.

The study sponsor conducted, at the request of the IDMC, one non-binding unplanned interim futility analyses for OS after 170 events corresponding to 33% of event. The IDMC requested an additional futility analysis at 45% of events. This analysis showed a HR=0.962, which crossed the pre-specified boundary for futility of 0.93. The study was subsequently discontinued. The stratified analysis of OS of all randomized patients showed a HR=0.942 (0.739, 1.202), p=0.9629. PFS showed a HR=0.934 (0.760, 1.146), p=0.3545.

The study had an exploratory endpoint; OS as function of BRCA 1/2 mutation. The results of this analysis showed that OS was statistically significantly prolonged, HR=0.542 (0.327, 0.901), p=0.0165. Furthermore, subgroup analyses showed that patients who had a platinum-free interval (PFI) of 6-12 months from last dose of first-line therapy had a HR=0.69 (0.48, 1.01). However, considering that the study failed to achieve its primary endpoint and that these were exploratory endpoints not adjusted for multiplicity, no conclusions can be drawn from these findings.

Overall the observed data cannot be used for testing the statistical hypothesis related to the hypothesis in the study protocol (i.e. Yondelis + PLD will improve OS compared with PLD monotherapy in the treatment of subjects with platinum-sensitive advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer who received 2 previous lines of platinum-based chemotherapy). Furthermore, the data are deemed to lack the strength and level of evidence that would have been obtained had the study been completed as planned.

In light of the above, data from Study 3006 do not permit to conclude on the effects of Yondelis + PLD in third line platinum-sensitive ovarian cancer.

2.2.3. Data on safety

Summaries of TEAEs and other safety data are based on 576 subjects (289 in the trabectedin+DOXIL arm and 287 in the DOXIL arm) who received at least 1 dose of study drug (i.e., the all-treated population).

2.2.3.1. Patient exposure

Table 21 Study Medication Administration; All Treated Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=286)		DOXIL (N=282)
	Trabectedin	DOXIL	DOXIL
Cumulative dose [a]			
N	286	286	282
Mean (SD)	6.83 (5.164)	193.95 (142.671)	297.94 (233.778)
Median	5.61	164.07	248.26
Range	(0.1; 32.6)	(29.3; 888.0)	(49.7; 1250.0)
Dose intensity [b]			
N	286	286	282
Mean (SD)	0.92 (0.138)	23.73 (3.068)	44.70 (4.970)
Median	0.93	24.02	46.67
Range	(0.1; 1.1)	(13.4; 32.1)	(29.3; 50.6)
Relative dose intensity, %			
N	286	286	282
Mean (SD)	0.84 (0.126)	0.79 (0.102)	0.89 (0.099)
Median	0.85	0.80	0.93
Range	(0.1; 1.0)	(0.4; 1.1)	(0.6; 1.0)

Note: [a] Cumulative dose unit is mg/m^2.
Note: [b] Dose intensity unit is mg/m^2 per cycle.
Note: Percentages calculated with the number of subjects treated in each treatment group as denominator.
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Table 22 Treatment Duration; All Treated Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=286)	DOXIL (N=282)
Total treatment duration, weeks		
N	286	282
Mean (SD)	24.05 (19.000)	27.41 (21.793)
Median	19.50	24.14
Range	(1.6; 105.4)	(2.1; 115.1)
Total treatment cycles		
N	286	282
Category, n(%)		
1 cycle	24 (8.4%)	16 (5.7%)
2 cycles	33 (11.5%)	69 (24.5%)
3 cycles	31 (10.8%)	13 (4.6%)
4 cycles	21 (7.3%)	31 (11.0%)
5 cycles	24 (8.4%)	10 (3.5%)
6 cycles	24 (8.4%)	34 (12.1%)
7 cycles	21 (7.3%)	13 (4.6%)
8 cycles	25 (8.7%)	30 (10.6%)
9 cycles	11 (3.8%)	12 (4.3%)
10 cycles	18 (6.3%)	7 (2.5%)
11 cycles	7 (2.4%)	6 (2.1%)
12 cycles	9 (3.1%)	4 (1.4%)
≥13 cycles	38 (13.3%)	37 (13.1%)
Mean (SD)	7.0 (5.36)	6.5 (5.18)
Median	6.0	6.0
Range	(1; 30)	(1; 27)

Note: Percentages calculated with the number of subjects treated in each treatment group as denominator.
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Table 23 Treatment Cycle Delays and Dose Reductions; Treated Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=286)		DOXIL (N=282)
	Trabectedin	DOXIL	DOXIL
Total no. of subjects with at least 2 cycles	261 (91.3%)	262 (91.6%)	266 (94.3%)
Cycle Delay			
Yes	198 (69.2%)	197 (68.9%)	165 (58.5%)
No	63 (22.0%)	65 (22.7%)	101 (35.8%)
Number of cycle delays			
1	66 (23.1%)	62 (21.7%)	84 (29.8%)
2	51 (17.8%)	51 (17.8%)	45 (16.0%)
3	28 (9.8%)	29 (10.1%)	15 (5.3%)
4	13 (4.5%)	14 (4.9%)	11 (3.9%)
>=5	40 (14.0%)	41 (14.3%)	10 (3.5%)
Dose Reduction			
Yes	141 (49.3%)	120 (42.0%)	104 (36.9%)
No	120 (42.0%)	142 (49.7%)	162 (57.4%)
Number of Dose Reductions			
1	89 (31.1%)	93 (32.5%)	87 (30.9%)
2	52 (18.2%)	27 (9.4%)	17 (6.0%)

Note: LVEF decline=a significant decline in left ventricular ejection fraction.
Note: Percentages calculated with the number of subjects treated in each treatment group as denominator.
Note: Delay/Reduction only tabulated for subjects with at least 2 cycles.
[TSIEXP02.RTF] [JNJ-17027907\OVC3006\DBR_CSR\RE_CSR\PROD\TSIEXP02.SAS] 12SEP2018, 13:04

2.2.3.2. Adverse events

Common AEs

Table 24 Treatment-Emergent Adverse Events, by System organ Class and Preferred Term in at Least 2% of Subjects in Any Treatment Group; All Treated Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=286)	DOXIL (N=282)
Total number of subjects with TEAEs	283 (99.0%)	277 (98.2%)
System organ class		
Preferred term		
Gastrointestinal disorders	252 (88.1%)	206 (73.0%)
Nausea	214 (74.8%)	114 (40.4%)
Vomiting	147 (51.4%)	55 (19.5%)
Constipation	87 (30.4%)	61 (21.6%)
Diarrhoea	61 (21.3%)	47 (16.7%)
Abdominal pain	57 (19.9%)	47 (16.7%)
Stomatitis	52 (18.2%)	91 (32.3%)
Dyspepsia	23 (8.0%)	18 (6.4%)
Abdominal distension	20 (7.0%)	15 (5.3%)
Ascites	13 (4.5%)	21 (7.4%)
Abdominal pain upper	12 (4.2%)	8 (2.8%)
Gastrooesophageal reflux disease	12 (4.2%)	16 (5.7%)
Flatulence	7 (2.4%)	8 (2.8%)
Abdominal pain lower	6 (2.1%)	8 (2.8%)
Mouth ulceration	6 (2.1%)	14 (5.0%)
Dry mouth	5 (1.7%)	10 (3.5%)
Oral pain	5 (1.7%)	10 (3.5%)
Small intestinal obstruction	5 (1.7%)	14 (5.0%)
Dysphagia	1 (0.3%)	8 (2.8%)
General disorders and administration site conditions	231 (80.8%)	169 (59.9%)
Fatigue	172 (60.1%)	113 (40.1%)
Pyrexia	41 (14.3%)	26 (9.2%)
Asthenia	39 (13.6%)	17 (6.0%)
Oedema peripheral	32 (11.2%)	22 (7.8%)
Mucosal inflammation	22 (7.7%)	33 (11.7%)
Non-cardiac chest pain	11 (3.8%)	8 (2.8%)
Pain	11 (3.8%)	6 (2.1%)
Peripheral swelling	9 (3.1%)	6 (2.1%)
Chills	8 (2.8%)	5 (1.8%)
Malaise	7 (2.4%)	5 (1.8%)
Influenza like illness	6 (2.1%)	5 (1.8%)
Blood and lymphatic system disorders	216 (75.5%)	147 (52.1%)
Neutropenia	151 (52.8%)	105 (37.2%)
Anaemia	137 (47.9%)	70 (24.8%)
Thrombocytopenia	69 (24.1%)	18 (6.4%)
Leukopenia	54 (18.9%)	38 (13.5%)
Febrile neutropenia	22 (7.7%)	3 (1.1%)
Investigations	216 (75.5%)	116 (41.1%)
Alanine aminotransferase increased	155 (54.2%)	12 (4.3%)
Aspartate aminotransferase increased	104 (36.4%)	11 (3.9%)
Blood alkaline phosphatase increased	73 (25.5%)	16 (5.7%)
Platelet count decreased	53 (18.5%)	16 (5.7%)
Neutrophil count decreased	52 (18.2%)	37 (13.1%)
White blood cell count decreased	33 (11.5%)	29 (10.3%)
Bilirubin conjugated increased	24 (8.4%)	2 (0.7%)
Blood bilirubin increased	24 (8.4%)	3 (1.1%)
Ejection fraction decreased	22 (7.7%)	11 (3.9%)
Blood creatinine increased	21 (7.3%)	21 (7.4%)
Gamma-glutamyltransferase increased	14 (4.9%)	5 (1.8%)
Blood creatine phosphokinase increased	13 (4.5%)	9 (3.2%)
Weight decreased	13 (4.5%)	16 (5.7%)
Lymphocyte count decreased	8 (2.8%)	4 (1.4%)
Blood urea increased	6 (2.1%)	4 (1.4%)
Haemoglobin decreased	6 (2.1%)	1 (0.4%)

Skin and subcutaneous tissue disorders	131 (45.8%)	169 (59.9%)
Palmar-plantar erythrodysaesthesia syndrome	58 (20.3%)	117 (41.5%)
Alopecia	32 (11.2%)	22 (7.8%)
Dry skin	22 (7.7%)	21 (7.4%)
Rash	22 (7.7%)	26 (9.2%)
Pruritus	11 (3.8%)	14 (5.0%)
Skin hyperpigmentation	10 (3.5%)	12 (4.3%)
Rash maculo-papular	8 (2.8%)	24 (8.5%)
Night sweats	5 (1.7%)	6 (2.1%)
Pigmentation disorder	5 (1.7%)	6 (2.1%)
Erythema	3 (1.0%)	7 (2.5%)
Skin toxicity	3 (1.0%)	6 (2.1%)
Skin ulcer	0	6 (2.1%)
Metabolism and nutrition disorders	129 (45.1%)	84 (29.8%)
Decreased appetite	83 (29.0%)	52 (18.4%)
Dehydration	24 (8.4%)	9 (3.2%)
Hypokalaemia	22 (7.7%)	13 (4.6%)
Hypoalbuminaemia	21 (7.3%)	8 (2.8%)
Hypomagnesaemia	19 (6.6%)	6 (2.1%)
Hyponatraemia	14 (4.9%)	6 (2.1%)
Hyperglycaemia	10 (3.5%)	6 (2.1%)
Hypophosphataemia	6 (2.1%)	2 (0.7%)
Respiratory, thoracic and mediastinal disorders	106 (37.1%)	88 (31.2%)
Dyspnoea	44 (15.4%)	28 (9.9%)
Cough	41 (14.3%)	34 (12.1%)
Oropharyngeal pain	16 (5.6%)	17 (6.0%)
Epistaxis	12 (4.2%)	5 (1.8%)
Dyspnoea exertional	10 (3.5%)	3 (1.1%)
Nasal congestion	10 (3.5%)	14 (5.0%)
Pleural effusion	9 (3.1%)	5 (1.8%)
Pulmonary embolism	8 (2.8%)	3 (1.1%)
Productive cough	7 (2.4%)	5 (1.8%)
Respiratory disorder	6 (2.1%)	8 (2.8%)
Rhinitis allergic	6 (2.1%)	5 (1.8%)
Rhinorrhoea	6 (2.1%)	4 (1.4%)
Musculoskeletal and connective tissue disorders	89 (31.1%)	60 (21.3%)
Arthralgia	25 (8.7%)	12 (4.3%)
Back pain	24 (8.4%)	15 (5.3%)
Muscular weakness	16 (5.6%)	9 (3.2%)
Myalgia	16 (5.6%)	6 (2.1%)
Bone pain	11 (3.8%)	4 (1.4%)
Flank pain	8 (2.8%)	2 (0.7%)
Pain in extremity	8 (2.8%)	16 (5.7%)
Joint swelling	6 (2.1%)	2 (0.7%)
Musculoskeletal chest pain	4 (1.4%)	7 (2.5%)
Nervous system disorders	89 (31.1%)	76 (27.0%)
Headache	38 (13.3%)	29 (10.3%)
Dysgeusia	35 (12.2%)	20 (7.1%)
Neuropathy peripheral	11 (3.8%)	13 (4.6%)
Dizziness postural	10 (3.5%)	3 (1.1%)
Dizziness	7 (2.4%)	6 (2.1%)
Peripheral sensory neuropathy	7 (2.4%)	7 (2.5%)
Infections and infestations	87 (30.4%)	80 (28.4%)
Urinary tract infection	16 (5.6%)	15 (5.3%)
Upper respiratory tract infection	15 (5.2%)	6 (2.1%)
Pneumonia	7 (2.4%)	8 (2.8%)
Viral upper respiratory tract infection	7 (2.4%)	11 (3.9%)
Sinusitis	5 (1.7%)	7 (2.5%)

Vascular disorders	54 (18.9%)	30 (10.6%)
Hypertension	22 (7.7%)	7 (2.5%)
Hypotension	11 (3.8%)	4 (1.4%)
Hot flush	7 (2.4%)	8 (2.8%)
Psychiatric disorders	41 (14.3%)	33 (11.7%)
Insomnia	19 (6.6%)	16 (5.7%)
Anxiety	18 (6.3%)	8 (2.8%)
Depression	8 (2.8%)	14 (5.0%)
Cardiac disorders	28 (9.8%)	11 (3.9%)
Tachycardia	10 (3.5%)	2 (0.7%)
Palpitations	7 (2.4%)	6 (2.1%)
Injury, poisoning and procedural complications	24 (8.4%)	23 (8.2%)
Contusion	8 (2.8%)	3 (1.1%)
Renal and urinary disorders	23 (8.0%)	24 (8.5%)
Pollakiuria	3 (1.0%)	7 (2.5%)
Ear and labyrinth disorders	15 (5.2%)	13 (4.6%)
Vertigo	6 (2.1%)	6 (2.1%)
Reproductive system and breast disorders	9 (3.1%)	20 (7.1%)
Vulvovaginal dryness	1 (0.3%)	6 (2.1%)

TEAE=treatment-emergent adverse event
Note: Adverse events reported any time from the first treatment dose to within 30 days after last treatment dose are included.
Note: Incidence is based on the number of subjects, not the number of events.
Note: Adverse events are coded using MedDRA version 19.0.
[TSFAE02A2.RTF] [JNJ-17027907\OVC3006\DBR_CSR\RE_CSR\PROD\TSFAE02A2.SAS] 12SEP2018, 12:59

Grade 3-4 AEs

Table 25 Treatment-Emergent Grade 3-4 Adverse Events, by Organ Class and Preferred Term; All Treated Subjects (Study ET743-OVC-3006)

	Trabectedin/DOXIL n (N=286)			DOXIL n (N=282)		
	Grade 3/4	Toxicity Grade *		Grade 3/4	Toxicity Grade *	
	n (%)	3	4	n (%)	3	4
Total Number of Subjects With Treatment-Emergent Grade 3-4 Adverse Events	243 (85.0%)	117 (40.9%)	126 (44.1%)	180 (63.8%)	151 (53.5%)	29 (10.3%)
System organ class Preferred term						
Blood and lymphatic system disorders	162 (56.6%)	71 (24.8%)	91 (31.8%)	78 (27.7%)	59 (20.9%)	19 (6.7%)
Neutropenia	124 (43.4%)	47 (16.4%)	77 (26.9%)	59 (20.9%)	43 (15.2%)	16 (5.7%)
Anaemia	61 (21.3%)	61 (21.3%)	0	20 (7.1%)	19 (6.7%)	1 (0.4%)
Leukopenia	41 (14.3%)	32 (11.2%)	9 (3.1%)	20 (7.1%)	15 (5.3%)	5 (1.8%)
Febrile neutropenia	22 (7.7%)	11 (3.8%)	11 (3.8%)	3 (1.1%)	2 (0.7%)	1 (0.4%)
Thrombocytopenia	43 (15.0%)	22 (7.7%)	21 (7.3%)	3 (1.1%)	3 (1.1%)	0
Iron deficiency anaemia	1 (0.3%)	1 (0.3%)	0	0	0	0
Gastrointestinal disorders	55 (19.2%)	54 (18.9%)	1 (0.3%)	55 (19.5%)	53 (18.8%)	2 (0.7%)
Stomatitis	5 (1.7%)	5 (1.7%)	0	23 (8.2%)	22 (7.8%)	1 (0.4%)
Ascites	9 (3.1%)	9 (3.1%)	0	12 (4.3%)	12 (4.3%)	0
Small intestinal obstruction	2 (0.7%)	2 (0.7%)	0	12 (4.3%)	11 (3.9%)	1 (0.4%)
Abdominal pain	6 (2.1%)	6 (2.1%)	0	10 (3.5%)	10 (3.5%)	0
Vomiting	18 (6.3%)	18 (6.3%)	0	5 (1.8%)	5 (1.8%)	0
Nausea	21 (7.3%)	21 (7.3%)	0	4 (1.4%)	4 (1.4%)	0
Abdominal distension	1 (0.3%)	1 (0.3%)	0	2 (0.7%)	2 (0.7%)	0
Constipation	5 (1.7%)	5 (1.7%)	0	2 (0.7%)	2 (0.7%)	0
Ileus	0	0	0	2 (0.7%)	2 (0.7%)	0
Abdominal discomfort	0	0	0	1 (0.4%)	1 (0.4%)	0
Abdominal pain lower	1 (0.3%)	1 (0.3%)	0	1 (0.4%)	1 (0.4%)	0
Abdominal pain upper	2 (0.7%)	2 (0.7%)	0	1 (0.4%)	1 (0.4%)	0
Dental caries	0	0	0	1 (0.4%)	1 (0.4%)	0
Intestinal obstruction	2 (0.7%)	1 (0.3%)	1 (0.3%)	1 (0.4%)	1 (0.4%)	0
Neutropenic colitis	0	0	0	1 (0.4%)	1 (0.4%)	0
Odynophagia	0	0	0	1 (0.4%)	1 (0.4%)	0
Diarrhoea	5 (1.7%)	5 (1.7%)	0	0	0	0
Enteritis	1 (0.3%)	1 (0.3%)	0	0	0	0
Gastrointestinal haemorrhage	1 (0.3%)	1 (0.3%)	0	0	0	0
Gastrointestinal obstruction	1 (0.3%)	1 (0.3%)	0	0	0	0
Pancreatitis	1 (0.3%)	1 (0.3%)	0	0	0	0
Rectal haemorrhage	1 (0.3%)	1 (0.3%)	0	0	0	0
Upper gastrointestinal haemorrhage	1 (0.3%)	1 (0.3%)	0	0	0	0
Skin and subcutaneous tissue disorders	11 (3.8%)	11 (3.8%)	0	41 (14.5%)	40 (14.2%)	1 (0.4%)
Palmar-plantar erythrodysaesthesia syndrome	10 (3.5%)	10 (3.5%)	0	33 (11.7%)	33 (11.7%)	0
Rash	1 (0.3%)	1 (0.3%)	0	3 (1.1%)	3 (1.1%)	0
Rash maculo-papular	0	0	0	2 (0.7%)	2 (0.7%)	0

Rash papular	0	0	0	2 (0.7%)	2 (0.7%)	0
Skin ulcer	0	0	0	2 (0.7%)	1 (0.4%)	1 (0.4%)
Dermatitis	0	0	0	1 (0.4%)	1 (0.4%)	0
Pruritus	0	0	0	1 (0.4%)	1 (0.4%)	0
Dermatitis bullous	1 (0.3%)	1 (0.3%)	0	0	0	0
Investigations	148 (51.7%)	106 (37.1%)	42 (14.7%)	30 (10.6%)	24 (8.5%)	6 (2.1%)
Neutrophil count decreased	40 (14.0%)	18 (6.3%)	22 (7.7%)	13 (4.6%)	9 (3.2%)	4 (1.4%)
White blood cell count decreased	24 (8.4%)	14 (4.9%)	10 (3.5%)	12 (4.3%)	12 (4.3%)	0
Alanine aminotransferase increased	106 (37.1%)	94 (32.9%)	12 (4.2%)	3 (1.1%)	3 (1.1%)	0
Blood alkaline phosphatase increased	2 (0.7%)	2 (0.7%)	0	3 (1.1%)	3 (1.1%)	0
Platelet count decreased	30 (10.5%)	17 (5.9%)	13 (4.5%)	3 (1.1%)	2 (0.7%)	1 (0.4%)
Aspartate aminotransferase increased	28 (9.8%)	23 (8.0%)	5 (1.7%)	2 (0.7%)	1 (0.4%)	1 (0.4%)
Blood creatinine increased	2 (0.7%)	2 (0.7%)	0	1 (0.4%)	1 (0.4%)	0
Blood potassium decreased	0	0	0	1 (0.4%)	1 (0.4%)	0
Ejection fraction decreased	5 (1.7%)	5 (1.7%)	0	1 (0.4%)	1 (0.4%)	0
Gamma-glutamyltransferase increased	7 (2.4%)	7 (2.4%)	0	1 (0.4%)	1 (0.4%)	0
Activated partial thromboplastin time prolonged	1 (0.3%)	1 (0.3%)	0	0	0	0
Blood creatine phosphokinase increased	5 (1.7%)	2 (0.7%)	3 (1.0%)	0	0	0
Carbohydrate antigen 125 increased	2 (0.7%)	2 (0.7%)	0	0	0	0
Haemoglobin decreased	3 (1.0%)	3 (1.0%)	0	0	0	0
Lymphocyte count decreased	2 (0.7%)	2 (0.7%)	0	0	0	0
Transaminases increased	1 (0.3%)	0	1 (0.3%)	0	0	0
Weight decreased	1 (0.3%)	1 (0.3%)	0	0	0	0
Weight increased	1 (0.3%)	1 (0.3%)	0	0	0	0
General disorders and administration site conditions	37 (12.9%)	37 (12.9%)	0	24 (8.5%)	24 (8.5%)	0
Mucosal inflammation	0	0	0	10 (3.5%)	10 (3.5%)	0
Fatigue	31 (10.8%)	31 (10.8%)	0	7 (2.5%)	7 (2.5%)	0
Asthenia	3 (1.0%)	3 (1.0%)	0	3 (1.1%)	3 (1.1%)	0
Non-cardiac chest pain	0	0	0	2 (0.7%)	2 (0.7%)	0
Performance status decreased	0	0	0	1 (0.4%)	1 (0.4%)	0
Pyrexia	1 (0.3%)	1 (0.3%)	0	1 (0.4%)	1 (0.4%)	0
Catheter site inflammation	1 (0.3%)	1 (0.3%)	0	0	0	0
Influenza like illness	1 (0.3%)	1 (0.3%)	0	0	0	0
Multiple organ dysfunction syndrome	1 (0.3%)	1 (0.3%)	0	0	0	0
Soft tissue inflammation	1 (0.3%)	1 (0.3%)	0	0	0	0
Infections and infestations	21 (7.3%)	16 (5.6%)	5 (1.7%)	11 (3.9%)	10 (3.5%)	1 (0.4%)
Device related infection	2 (0.7%)	2 (0.7%)	0	2 (0.7%)	2 (0.7%)	0
Sepsis	4 (1.4%)	2 (0.7%)	2 (0.7%)	2 (0.7%)	1 (0.4%)	1 (0.4%)
Catheter site infection	0	0	0	1 (0.4%)	1 (0.4%)	0
Cellulitis	1 (0.3%)	1 (0.3%)	0	1 (0.4%)	1 (0.4%)	0
Gastroenteritis	0	0	0	1 (0.4%)	1 (0.4%)	0
Herpes virus infection	0	0	0	1 (0.4%)	1 (0.4%)	0
Neutropenic sepsis	2 (0.7%)	1 (0.3%)	1 (0.3%)	1 (0.4%)	1 (0.4%)	0
Peritonitis	1 (0.3%)	1 (0.3%)	0	1 (0.4%)	1 (0.4%)	0
Pyelonephritis acute	0	0	0	1 (0.4%)	1 (0.4%)	0
Urinary tract infection	3 (1.0%)	3 (1.0%)	0	1 (0.4%)	1 (0.4%)	0
Bacteraemia	1 (0.3%)	1 (0.3%)	0	0	0	0
Device related sepsis	1 (0.3%)	1 (0.3%)	0	0	0	0
Enterobacter bacteraemia	1 (0.3%)	1 (0.3%)	0	0	0	0
Escherichia urinary tract infection	1 (0.3%)	1 (0.3%)	0	0	0	0
Fungal skin infection	1 (0.3%)	1 (0.3%)	0	0	0	0
Nasopharyngitis	1 (0.3%)	1 (0.3%)	0	0	0	0
Peritonitis bacterial	1 (0.3%)	1 (0.3%)	0	0	0	0
Pneumocystis jirovecii pneumonia	2 (0.7%)	1 (0.3%)	1 (0.3%)	0	0	0
Pneumonia	1 (0.3%)	1 (0.3%)	0	0	0	0
Pseudomonal sepsis	1 (0.3%)	0	1 (0.3%)	0	0	0
Septic shock	1 (0.3%)	0	1 (0.3%)	0	0	0
Tracheobronchitis	1 (0.3%)	1 (0.3%)	0	0	0	0
Upper respiratory tract infection	1 (0.3%)	1 (0.3%)	0	0	0	0
Metabolism and nutrition disorders	23 (8.0%)	20 (7.0%)	3 (1.0%)	11 (3.9%)	9 (3.2%)	2 (0.7%)
Hyponatraemia	9 (3.1%)	7 (2.4%)	2 (0.7%)	3 (1.1%)	3 (1.1%)	0
Hypernatraemia	1 (0.3%)	1 (0.3%)	0	2 (0.7%)	2 (0.7%)	0
Hypokalaemia	5 (1.7%)	5 (1.7%)	0	2 (0.7%)	2 (0.7%)	0
Hyperglycaemia	2 (0.7%)	2 (0.7%)	0	1 (0.4%)	0	1 (0.4%)
Hypoalbuminaemia	2 (0.7%)	2 (0.7%)	0	1 (0.4%)	1 (0.4%)	0
Hypocalcaemia	2 (0.7%)	2 (0.7%)	0	1 (0.4%)	0	1 (0.4%)
Hypophosphataemia	1 (0.3%)	1 (0.3%)	0	1 (0.4%)	1 (0.4%)	0
Decreased appetite	1 (0.3%)	1 (0.3%)	0	0	0	0
Dehydration	6 (2.1%)	6 (2.1%)	0	0	0	0
Fluid overload	1 (0.3%)	0	1 (0.3%)	0	0	0
Hyperkalaemia	1 (0.3%)	1 (0.3%)	0	0	0	0
Hypomagnesaemia	2 (0.7%)	1 (0.3%)	1 (0.3%)	0	0	0
Respiratory, thoracic and mediastinal disorders	24 (8.4%)	19 (6.6%)	5 (1.7%)	10 (3.5%)	10 (3.5%)	0
Dyspnoea	5 (1.7%)	4 (1.4%)	1 (0.3%)	2 (0.7%)	2 (0.7%)	0
Pleural effusion	2 (0.7%)	2 (0.7%)	0	2 (0.7%)	2 (0.7%)	0
Pleurisy	2 (0.7%)	2 (0.7%)	0	2 (0.7%)	2 (0.7%)	0
Pulmonary embolism	8 (2.8%)	5 (1.7%)	3 (1.0%)	2 (0.7%)	2 (0.7%)	0
Hypoxia	4 (1.4%)	4 (1.4%)	0	1 (0.4%)	1 (0.4%)	0
Interstitial lung disease	0	0	0	1 (0.4%)	1 (0.4%)	0
Laryngeal inflammation	0	0	0	1 (0.4%)	1 (0.4%)	0
Acute respiratory failure	1 (0.3%)	0	1 (0.3%)	0	0	0
Cough	1 (0.3%)	1 (0.3%)	0	0	0	0

Epistaxis	1 (0.3%)	1 (0.3%)	0	0	0	0
Pneumonitis	1 (0.3%)	1 (0.3%)	0	0	0	0
Pulmonary oedema	1 (0.3%)	1 (0.3%)	0	0	0	0
Vascular disorders	16 (5.6%)	14 (4.9%)	2 (0.7%)	6 (2.1%)	6 (2.1%)	0
Hypertension	10 (3.5%)	10 (3.5%)	0	3 (1.1%)	3 (1.1%)	0
Embolism	1 (0.3%)	0	1 (0.3%)	1 (0.4%)	1 (0.4%)	0
Hypertensive crisis	1 (0.3%)	1 (0.3%)	0	1 (0.4%)	1 (0.4%)	0
Hypotension	1 (0.3%)	0	1 (0.3%)	1 (0.4%)	1 (0.4%)	0
Deep vein thrombosis	2 (0.7%)	2 (0.7%)	0	0	0	0
Pelvic venous thrombosis	1 (0.3%)	1 (0.3%)	0	0	0	0
Injury, poisoning and procedural complications	1 (0.3%)	1 (0.3%)	0	5 (1.8%)	5 (1.8%)	0
Fall	0	0	0	1 (0.4%)	1 (0.4%)	0
Head injury	0	0	0	1 (0.4%)	1 (0.4%)	0
Infusion related reaction	0	0	0	1 (0.4%)	1 (0.4%)	0
Joint dislocation	0	0	0	1 (0.4%)	1 (0.4%)	0
Procedural pain	0	0	0	1 (0.4%)	1 (0.4%)	0
Hip fracture	1 (0.3%)	1 (0.3%)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.0%)	2 (0.7%)	1 (0.3%)	5 (1.8%)	5 (1.8%)	0
Breast cancer	0	0	0	1 (0.4%)	1 (0.4%)	0
Malignant pleural effusion	0	0	0	1 (0.4%)	1 (0.4%)	0
Metastases to abdominal wall	0	0	0	1 (0.4%)	1 (0.4%)	0
Metastases to central nervous system	0	0	0	1 (0.4%)	1 (0.4%)	0
Renal cell carcinoma	0	0	0	1 (0.4%)	1 (0.4%)	0
Basal cell carcinoma	1 (0.3%)	1 (0.3%)	0	0	0	0
Lymphangiosis carcinomatosa	1 (0.3%)	0	1 (0.3%)	0	0	0
Myelodysplastic syndrome	1 (0.3%)	1 (0.3%)	0	0	0	0
Squamous cell carcinoma	1 (0.3%)	1 (0.3%)	0	0	0	0
Nervous system disorders	1 (0.3%)	1 (0.3%)	0	3 (1.1%)	3 (1.1%)	0
Headache	0	0	0	2 (0.7%)	2 (0.7%)	0
Hypoaesthesia	0	0	0	1 (0.4%)	1 (0.4%)	0
Lethargy	1 (0.3%)	1 (0.3%)	0	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.3%)	1 (0.3%)	0	2 (0.7%)	2 (0.7%)	0
Arthralgia	0	0	0	1 (0.4%)	1 (0.4%)	0
Muscular weakness	0	0	0	1 (0.4%)	1 (0.4%)	0
Spinal pain	1 (0.3%)	1 (0.3%)	0	0	0	0
Renal and urinary disorders	2 (0.7%)	1 (0.3%)	1 (0.3%)	2 (0.7%)	1 (0.4%)	1 (0.4%)
Acute kidney injury	2 (0.7%)	2 (0.7%)	0	1 (0.4%)	1 (0.4%)	0
Renal failure	0	0	0	1 (0.4%)	0	1 (0.4%)
Anuria	1 (0.3%)	0	1 (0.3%)	0	0	0
Reproductive system and breast disorders	1 (0.3%)	1 (0.3%)	0	2 (0.7%)	2 (0.7%)	0
Atrophic vulvovaginitis	0	0	0	1 (0.4%)	1 (0.4%)	0
Pelvic fluid collection	0	0	0	1 (0.4%)	1 (0.4%)	0
Vulvovaginal rash	1 (0.3%)	1 (0.3%)	0	0	0	0
Cardiac disorders	3 (1.0%)	3 (1.0%)	0	1 (0.4%)	1 (0.4%)	0
Atrial fibrillation	1 (0.3%)	1 (0.3%)	0	1 (0.4%)	1 (0.4%)	0
Cardiac failure congestive	1 (0.3%)	1 (0.3%)	0	0	0	0
Tachycardia	1 (0.3%)	1 (0.3%)	0	0	0	0
Eye disorders	0	0	0	1 (0.4%)	1 (0.4%)	0
Vision blurred	0	0	0	1 (0.4%)	1 (0.4%)	0
Immune system disorders	0	0	0	1 (0.4%)	1 (0.4%)	0
Hypersensitivity	0	0	0	1 (0.4%)	1 (0.4%)	0
Psychiatric disorders	1 (0.3%)	1 (0.3%)	0	1 (0.4%)	1 (0.4%)	0
Insomnia	0	0	0	1 (0.4%)	1 (0.4%)	0
Depression	1 (0.3%)	1 (0.3%)	0	0	0	0
Endocrine disorders	1 (0.3%)	1 (0.3%)	0	0	0	0
Inappropriate antidiuretic hormone secretion	1 (0.3%)	1 (0.3%)	0	0	0	0
Hepatobiliary disorders	4 (1.4%)	1 (0.3%)	3 (1.0%)	0	0	0
Drug-induced liver injury	1 (0.3%)	0	1 (0.3%)	0	0	0
Hepatitis toxic	2 (0.7%)	1 (0.3%)	1 (0.3%)	0	0	0
Hyperbilirubinaemia	1 (0.3%)	0	1 (0.3%)	0	0	0

[a]Based on NCI common toxicity criteria, version 4.0

Note: Adverse events reported any time from the first treatment dose to within 30 days of last treatment dose are included.

Note: Incidence is based on the number of subjects, not the number of events.

Note: Adverse events are coded using MedDRA version 19.0.

2.2.3.3. Serious adverse events and deaths

Death

Table 26 Summary of Deaths; All Treated Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=286)	DOXIL (N=282)
Total number of deaths	132 (46.2%)	131 (46.5%)
Death within 60 days of initiation of study drug	7 (2.4%)	4 (1.4%)
Death within 30 days from last dose	10 (3.5%)	6 (2.1%)
Death due to treatment emergent adverse event	6 (2.1%)	3 (1.1%)
Drug related	0	0
Not Drug related	6 (2.1%)	3 (1.1%)
Death due to progressive disease	116 (40.6%)	119 (42.2%)
Death due to other	10 (3.5%)	9 (3.2%)

Note: Percentages calculated with the number of subjects treated in each treatment group as denominator

[TSFDTH01.RTF] [JNJ-17027907\OVC3006\DBR_CSR\RE_CSR\PROD\TSFDTH01.SAS] 12SEP2018, 13:00

Table 27 Treatment-Emergent Adverse Events Leading to Death, by System Organ Class, Preferred Term; All treated Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=286)	DOXIL (N=282)
Total number of subjects with TEAEs Leading to Death	10 (3.5%)	5 (1.8%)
System organ class Preferred term		
General disorders and administration site conditions	6 (2.1%)	3 (1.1%)
Death	4 (1.4%)	2 (0.7%)
Multiple organ dysfunction syndrome	2 (0.7%)	1 (0.4%)
Cardiac disorders	1 (0.3%)	0
Cardiopulmonary failure	1 (0.3%)	0
Infections and infestations	1 (0.3%)	0
Peritonitis	1 (0.3%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3%)	0
Lymphangiosis carcinomatosa	1 (0.3%)	0
Renal and urinary disorders	1 (0.3%)	1 (0.4%)
Renal failure	1 (0.3%)	0
Acute kidney injury	0	1 (0.4%)
Gastrointestinal disorders	0	1 (0.4%)
Small intestinal obstruction	0	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	0	1 (0.4%)
Pulmonary embolism	0	1 (0.4%)

TEAE=treatment-emergent adverse event
Note: Adverse events reported any time from the first treatment dose to within 30 days after last treatment dose are included.
Note: Incidence is based on the number of subjects, not the number of events.
Note: Adverse events are coded using MedDRA version 19.0.

[TSFAE02F.RTF] [JNJ-17027907\OVC3006\DBR_CSR\RE_CSR\PROD\TSFAE02F.SAS] 12SEP2018, 13:00

Serious Adverse Events

Table 28 Treatment-Emergent Serious Adverse Events, by System Organ Class and Preferred Term; All Treated Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=286)	DOXIL (N=282)
Total number of subjects with Serious TEAEs	118 (41.3%)	58 (20.6%)
System organ class Preferred term		
Blood and lymphatic system disorders	33 (11.5%)	6 (2.1%)
Febrile neutropenia	14 (4.9%)	1 (0.4%)
Neutropenia	12 (4.2%)	4 (1.4%)
Thrombocytopenia	10 (3.5%)	1 (0.4%)
Anaemia	9 (3.1%)	2 (0.7%)
Leukopenia	3 (1.0%)	1 (0.4%)
Gastrointestinal disorders	31 (10.8%)	32 (11.3%)
Vomiting	10 (3.5%)	7 (2.5%)
Nausea	8 (2.8%)	3 (1.1%)
Abdominal pain	6 (2.1%)	3 (1.1%)
Constipation	5 (1.7%)	2 (0.7%)
Small intestinal obstruction	4 (1.4%)	14 (5.0%)
Ascites	3 (1.0%)	8 (2.8%)
Intestinal obstruction	3 (1.0%)	1 (0.4%)
Diarrhoea	2 (0.7%)	0
Abdominal pain upper	1 (0.3%)	0
Dyspepsia	1 (0.3%)	0
Enteritis	1 (0.3%)	0
Gastrointestinal haemorrhage	1 (0.3%)	0
Gastrointestinal obstruction	1 (0.3%)	0
Pancreatitis	1 (0.3%)	0
Rectal haemorrhage	1 (0.3%)	0
Subileus	1 (0.3%)	0
Upper gastrointestinal haemorrhage	1 (0.3%)	0
Abdominal pain lower	0	1 (0.4%)
Gastrooesophageal reflux disease	0	1 (0.4%)
Ileus	0	3 (1.1%)
Neutropenic colitis	0	1 (0.4%)
Oral pain	0	1 (0.4%)
Oral pruritus	0	1 (0.4%)
Stomatitis	0	2 (0.7%)
Infections and infestations	26 (9.1%)	12 (4.3%)
Urinary tract infection	5 (1.7%)	1 (0.4%)
Pneumonia	4 (1.4%)	0
Sepsis	4 (1.4%)	2 (0.7%)
Device related infection	3 (1.0%)	1 (0.4%)
Cellulitis	2 (0.7%)	1 (0.4%)
Neutropenic sepsis	2 (0.7%)	1 (0.4%)
Peritonitis	2 (0.7%)	0
Pneumocystis jirovecii pneumonia	2 (0.7%)	1 (0.4%)
Device related sepsis	1 (0.3%)	0
Enterobacter bacteraemia	1 (0.3%)	0
Infection	1 (0.3%)	0
Peritonitis bacterial	1 (0.3%)	0
Pseudomonal sepsis	1 (0.3%)	0
Septic shock	1 (0.3%)	0
Soft tissue infection	1 (0.3%)	0
Staphylococcal bacteraemia	1 (0.3%)	0

Upper respiratory tract infection	1 (0.3%)	0
Abdominal wall abscess	0	1 (0.4%)
Catheter site infection	0	1 (0.4%)
Gastroenteritis	0	1 (0.4%)
Oral candidiasis	0	1 (0.4%)
Pyelonephritis acute	0	1 (0.4%)
Investigations	24 (8.4%)	1 (0.4%)
Alanine aminotransferase increased	14 (4.9%)	0
Aspartate aminotransferase increased	9 (3.1%)	0
Neutrophil count decreased	5 (1.7%)	0
White blood cell count decreased	4 (1.4%)	0
Platelet count decreased	3 (1.0%)	0
Ejection fraction decreased	2 (0.7%)	1 (0.4%)
Blood creatine phosphokinase increased	1 (0.3%)	0
Blood creatinine increased	1 (0.3%)	0
Gamma-glutamyltransferase increased	1 (0.3%)	0
Transaminases increased	1 (0.3%)	0
Weight decreased	1 (0.3%)	0
General disorders and administration site conditions	22 (7.7%)	11 (3.9%)
Pyrexia	9 (3.1%)	3 (1.1%)
Death	4 (1.4%)	2 (0.7%)
Fatigue	4 (1.4%)	1 (0.4%)
Multiple organ dysfunction syndrome	2 (0.7%)	1 (0.4%)
Catheter site inflammation	1 (0.3%)	0
Influenza like illness	1 (0.3%)	0
Oedema peripheral	1 (0.3%)	0
Asthenia	0	1 (0.4%)
Chest discomfort	0	1 (0.4%)
Chest pain	0	1 (0.4%)
Pain	0	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	17 (5.9%)	7 (2.5%)
Pulmonary embolism	6 (2.1%)	2 (0.7%)
Pleural effusion	4 (1.4%)	2 (0.7%)
Hypoxia	2 (0.7%)	0
Pleurisy	2 (0.7%)	2 (0.7%)
Acute respiratory failure	1 (0.3%)	0
Chronic obstructive pulmonary disease	1 (0.3%)	0
Cough	1 (0.3%)	0
Dyspnoea	1 (0.3%)	1 (0.4%)
Epistaxis	1 (0.3%)	0
Interstitial lung disease	0	1 (0.4%)
Metabolism and nutrition disorders	9 (3.1%)	2 (0.7%)
Dehydration	6 (2.1%)	0
Hyponatraemia	2 (0.7%)	0
Fluid overload	1 (0.3%)	0
Hyperkalaemia	1 (0.3%)	0
Hypokalaemia	1 (0.3%)	1 (0.4%)
Hypophagia	0	1 (0.4%)
Vascular disorders	7 (2.4%)	3 (1.1%)
Deep vein thrombosis	3 (1.0%)	0
Thrombophlebitis	2 (0.7%)	0
Embolism	1 (0.3%)	0
Pelvic venous thrombosis	1 (0.3%)	0

Capillary leak syndrome	0	1 (0.4%)
Flushing	0	1 (0.4%)
Hypertension	0	1 (0.4%)
Renal and urinary disorders	5 (1.7%)	4 (1.4%)
Acute kidney injury	4 (1.4%)	2 (0.7%)
Renal failure	1 (0.3%)	1 (0.4%)
Urinary retention	0	1 (0.4%)
Cardiac disorders	4 (1.4%)	1 (0.4%)
Atrial fibrillation	1 (0.3%)	1 (0.4%)
Cardiac failure congestive	1 (0.3%)	0
Cardiopulmonary failure	1 (0.3%)	0
Tachycardia	1 (0.3%)	0
Hepatobiliary disorders	3 (1.0%)	0
Hepatitis toxic	2 (0.7%)	0
Drug-induced liver injury	1 (0.3%)	0
Injury, poisoning and procedural complications	3 (1.0%)	4 (1.4%)
Anastomotic ulcer	1 (0.3%)	0
Gastrointestinal stoma complication	1 (0.3%)	0
Hip fracture	1 (0.3%)	0
Spinal compression fracture	1 (0.3%)	0
Head injury	0	1 (0.4%)
Infusion related reaction	0	2 (0.7%)
Joint dislocation	0	1 (0.4%)
Nervous system disorders	3 (1.0%)	2 (0.7%)
Lethargy	1 (0.3%)	0
Seizure	1 (0.3%)	1 (0.4%)
Syncope	1 (0.3%)	0
Headache	0	1 (0.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.7%)	4 (1.4%)
Lymphangiosis carcinomatosa	1 (0.3%)	0
Myelodysplastic syndrome	1 (0.3%)	0
Malignant pleural effusion	0	1 (0.4%)
Metastases to abdominal wall	0	1 (0.4%)
Metastases to central nervous system	0	1 (0.4%)
Renal cell carcinoma	0	1 (0.4%)
Endocrine disorders	1 (0.3%)	0
Inappropriate antidiuretic hormone secretion	1 (0.3%)	0
Musculoskeletal and connective tissue disorders	1 (0.3%)	1 (0.4%)
Back pain	1 (0.3%)	1 (0.4%)
Product issues	0	1 (0.4%)
Device malfunction	0	1 (0.4%)
Reproductive system and breast disorders	0	1 (0.4%)
Pelvic fluid collection	0	1 (0.4%)
Skin and subcutaneous tissue disorders	0	1 (0.4%)
Palmar-plantar erythrodysaesthesia syndrome	0	1 (0.4%)

2.2.3.4. Laboratory findings

During the study, 194 (68.3%) subjects in the trabectedin+DOXIL arm and 112 (39.9%) subjects in the DOXIL arm developed Grade 3-4 hematological laboratory values during the study. The most common Grade 3-4 hematological laboratory abnormalities were neutrophil count abnormalities and white blood cell (WBC) count abnormalities. Across all hematologic parameters (hemoglobin levels, neutrophil counts, platelet counts, and WBC counts) Grade 3-4 abnormalities occurred at higher incidences (>5% difference) in the trabectedin+DOXIL arm compared to the DOXIL monotherapy arm.

More subjects in the trabectedin+DOXIL arm (169 subjects [59.5%]) reported with a Grade 3-4 chemistry laboratory abnormality compared with the DOXIL arm (50 subjects [17.8%]). This was primarily due to an increased number of subjects in the trabectedin+DOXIL arm that were reported with Grade 3 laboratory values for ALT (45.1%) and AST (12.3%). Generally, there was a higher frequency grade shifts to Grade 3 or 4 in the trabectedin+DOXIL arm compared with the DOXIL arm. The most common laboratory tests demonstrating this were neutrophil count, platelet count, ALT, and AST.

2.2.3.5. Discontinuation due to AES

Table 29 Treatment-Emergent Adverse Events Leading to Treatment Discontinuation, by System Organ Class, Preferred Term: All Treated Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=286)	DOXIL (N=282)
Total number of subjects with TEAEs Leading to Treatment discontinuation	93 (32.5%)	46 (16.3%)
System organ class Preferred term		
Investigations	26 (9.1%)	11 (3.9%)
Blood creatinine increased	5 (1.7%)	3 (1.1%)
Blood alkaline phosphatase increased	4 (1.4%)	1 (0.4%)
Ejection fraction decreased	4 (1.4%)	4 (1.4%)
Platelet count decreased	4 (1.4%)	0
Blood bilirubin increased	3 (1.0%)	0
Alanine aminotransferase increased	2 (0.7%)	0

Bilirubin conjugated increased	2 (0.7%)	0
Blood creatine phosphokinase increased	2 (0.7%)	0
Carbohydrate antigen 125 increased	2 (0.7%)	3 (1.1%)
Blood potassium decreased	1 (0.3%)	0
Neutrophil count decreased	1 (0.3%)	0
Blood and lymphatic system disorders	19 (6.6%)	2 (0.7%)
Anaemia	7 (2.4%)	1 (0.4%)
Neutropenia	5 (1.7%)	1 (0.4%)
Thrombocytopenia	4 (1.4%)	0
Febrile neutropenia	3 (1.0%)	0
Leukopenia	1 (0.3%)	0
Gastrointestinal disorders	15 (5.2%)	17 (6.0%)
Ascites	3 (1.0%)	8 (2.8%)
Abdominal pain	2 (0.7%)	2 (0.7%)
Intestinal obstruction	2 (0.7%)	1 (0.4%)
Nausea	2 (0.7%)	1 (0.4%)
Vomiting	2 (0.7%)	3 (1.1%)
Gastrointestinal obstruction	1 (0.3%)	0
Haemorrhoids	1 (0.3%)	0
Pancreatitis	1 (0.3%)	0
Small intestinal obstruction	1 (0.3%)	3 (1.1%)
Stomatitis	1 (0.3%)	0
Abdominal discomfort	0	1 (0.4%)
Abdominal distension	0	1 (0.4%)
Duodenal obstruction	0	1 (0.4%)
General disorders and administration site conditions	9 (3.1%)	6 (2.1%)
Fatigue	5 (1.7%)	3 (1.1%)
Pyrexia	3 (1.0%)	1 (0.4%)
Oedema peripheral	1 (0.3%)	0
Performance status decreased	1 (0.3%)	1 (0.4%)
Asthenia	0	1 (0.4%)
Death	0	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	8 (2.8%)	1 (0.4%)
Pulmonary embolism	3 (1.0%)	0
Dyspnoea	2 (0.7%)	0
Pleurisy	2 (0.7%)	0
Acute respiratory failure	1 (0.3%)	0
Pleural effusion	0	1 (0.4%)
Cardiac disorders	4 (1.4%)	0
Cardiac failure congestive	2 (0.7%)	0
Cardiomyopathy	1 (0.3%)	0
Diastolic dysfunction	1 (0.3%)	0
Infections and infestations	4 (1.4%)	3 (1.1%)
Peritonitis	2 (0.7%)	0
Cellulitis	1 (0.3%)	0
Infection	1 (0.3%)	0
Herpes virus infection	0	1 (0.4%)
Pneumonia	0	1 (0.4%)
Pyelonephritis acute	0	1 (0.4%)
Metabolism and nutrition disorders	4 (1.4%)	0
Decreased appetite	2 (0.7%)	0
Dehydration	1 (0.3%)	0
Hypoalbuminaemia	1 (0.3%)	0
Skin and subcutaneous tissue disorders	4 (1.4%)	6 (2.1%)
Rash	3 (1.0%)	0
Dry skin	1 (0.3%)	0
Urticaria	1 (0.3%)	0

Palmar-plantar erythrodysaesthesia syndrome	0	6 (2.1%)
Pruritus	0	1 (0.4%)
Rash papular	0	1 (0.4%)
Vascular disorders	4 (1.4%)	1 (0.4%)
Embolism	1 (0.3%)	0
Hypertension	1 (0.3%)	0
Pelvic venous thrombosis	1 (0.3%)	0
Thrombophlebitis	1 (0.3%)	0
Hypertensive crisis	0	1 (0.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.0%)	1 (0.4%)
Breast cancer	1 (0.3%)	1 (0.4%)
Lymphangiosis carcinomatosa	1 (0.3%)	0
Myelodysplastic syndrome	1 (0.3%)	0
Musculoskeletal and connective tissue disorders	2 (0.7%)	0
Muscular weakness	1 (0.3%)	0
Spinal pain	1 (0.3%)	0
Hepatobiliary disorders	1 (0.3%)	0
Hepatitis toxic	1 (0.3%)	0
Nervous system disorders	1 (0.3%)	2 (0.7%)
Lethargy	1 (0.3%)	0
Aphasia	0	1 (0.4%)
Dizziness postural	0	1 (0.4%)
Facial paresis	0	1 (0.4%)
Renal and urinary disorders	1 (0.3%)	3 (1.1%)
Acute kidney injury	1 (0.3%)	1 (0.4%)
Hydronephrosis	0	2 (0.7%)
Immune system disorders	0	1 (0.4%)
Hypersensitivity	0	1 (0.4%)

TEAE=treatment-emergent adverse event
Note: Adverse events reported any time from the first treatment dose to within 30 days after last treatment dose are included.
Note: Incidence is based on the number of subjects, not the number of events.
Note: Adverse events are coded using MedDRA version 19.0.
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Dose-reduction

Table 30 Treatment-Emergent Adverse Events Leading to Dose Reduction, by System Organ Class, Preferred Term; All Treated Subjects (Study ET743-OVC-3006)

	Trabectedin + DOXIL (N=286)	DOXIL (N=282)
Total number of subjects with TEAEs Leading to Dose reduction	152 (53.1%)	103 (36.5%)
System organ class Preferred term		
Blood and lymphatic system disorders	77 (26.9%)	18 (6.4%)
Neutropenia	47 (16.4%)	13 (4.6%)
Thrombocytopenia	18 (6.3%)	2 (0.7%)

Febrile neutropenia	14 (4.9%)	2 (0.7%)
Anaemia	8 (2.8%)	1 (0.4%)
Leukopenia	1 (0.3%)	1 (0.4%)
Investigations	73 (25.5%)	5 (1.8%)
Alanine aminotransferase increased	20 (7.0%)	0
Blood alkaline phosphatase increased	20 (7.0%)	0
Bilirubin conjugated increased	16 (5.6%)	0
Blood bilirubin increased	12 (4.2%)	1 (0.4%)
Neutrophil count decreased	12 (4.2%)	3 (1.1%)
Platelet count decreased	8 (2.8%)	0
Aspartate aminotransferase increased	7 (2.4%)	0
White blood cell count decreased	4 (1.4%)	0
Blood creatinine increased	2 (0.7%)	0
Gamma-glutamyltransferase increased	2 (0.7%)	0
Blood creatine phosphokinase increased	1 (0.3%)	0
Haemoglobin decreased	1 (0.3%)	0
Transaminases increased	1 (0.3%)	0
Weight decreased	0	1 (0.4%)
Gastrointestinal disorders	25 (8.7%)	24 (8.5%)
Nausea	16 (5.6%)	0
Vomiting	10 (3.5%)	0
Stomatitis	5 (1.7%)	22 (7.8%)
Diarrhoea	2 (0.7%)	0
Neutropenic colitis	0	1 (0.4%)
Oral pain	0	1 (0.4%)
General disorders and administration site conditions	18 (6.3%)	18 (6.4%)
Fatigue	14 (4.9%)	8 (2.8%)
Asthenia	2 (0.7%)	0
Pyrexia	2 (0.7%)	0
General physical health deterioration	1 (0.3%)	0
Oedema peripheral	1 (0.3%)	0
Mucosal inflammation	0	10 (3.5%)
Performance status decreased	0	1 (0.4%)
Skin and subcutaneous tissue disorders	16 (5.6%)	53 (18.8%)
Palmar-plantar erythrodysaesthesia syndrome	14 (4.9%)	41 (14.5%)
Dry skin	1 (0.3%)	0
Rash	1 (0.3%)	2 (0.7%)
Skin discolouration	1 (0.3%)	0
Urticaria	1 (0.3%)	0
Dermatitis	0	1 (0.4%)
Dermatitis exfoliative	0	1 (0.4%)
Rash maculo-papular	0	8 (2.8%)
Skin ulcer	0	2 (0.7%)
Infections and infestations	6 (2.1%)	2 (0.7%)
Neutropenic sepsis	2 (0.7%)	0
Pneumonia	2 (0.7%)	2 (0.7%)
Device related infection	1 (0.3%)	0
Pneumocystis jirovecii pneumonia	1 (0.3%)	0
Pseudomonal sepsis	1 (0.3%)	0
Septic shock	1 (0.3%)	0
Oral herpes	0	1 (0.4%)
Metabolism and nutrition disorders	2 (0.7%)	0
Decreased appetite	1 (0.3%)	0
Dehydration	1 (0.3%)	0
Nervous system disorders	2 (0.7%)	1 (0.4%)
Ageusia	1 (0.3%)	0
Dizziness exertional	1 (0.3%)	0
Lethargy	1 (0.3%)	0
Hypoaesthesia	0	1 (0.4%)

Vascular disorders	2 (0.7%)	0
Flushing	1 (0.3%)	0
Hypertension	1 (0.3%)	0
Hepatobiliary disorders	1 (0.3%)	0
Hyperbilirubinaemia	1 (0.3%)	0
Psychiatric disorders	1 (0.3%)	1 (0.4%)
Depression	1 (0.3%)	0
Insomnia	0	1 (0.4%)
Reproductive system and breast disorders	1 (0.3%)	0
Vulvovaginal rash	1 (0.3%)	0
Musculoskeletal and connective tissue disorders	0	1 (0.4%)
Muscular weakness	0	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	0	1 (0.4%)
Laryngeal inflammation	0	1 (0.4%)

TEAE=treatment-emergent adverse event
Note: Adverse events reported any time from the first treatment dose to within 30 days after last treatment dose are included.
Note: Incidence is based on the number of subjects, not the number of events.
Note: Adverse events are coded using MedDRA version 19.0.
[TSFAE02E.RTF] [JNJ-17027907\OVC3006\DBR_CSR\RE_CSR\PROD\TSFAE02E.SAS] 12SEP2018, 13:00

2.2.4. Discussion on safety

The combination of trabectidin+doxorubicin is already authorised for the treatment of patients with relapsed platinum-sensitive ovarian cancer. Thus, the safety profile of trabectedin is already well-known, but mainly based on patients in first relapse (study 301). The population studied in study 3006 have 2 relapses and thus is more pre-treated.

Common AEs were related to the GI tract (nausea, vomiting, constipation, diarrhoea, abdominal pain, liver toxicity, etc.), general disorders (fatigue, pyrexia, asthenia, etc.), blood and lymphatic system disorder (neutropenia, anaemia, thrombocytopenia, leukopenia, etc.), skin reactions (palmar-plantar erythrodysaesthesia syndrome, alopecia, etc.), metabolism and nutrition disorder (decreased appetite), respiratory (dyspnoea, cough, oropharyngeal pain, etc), infections, hypertension.

Approximately 85% of patients in the trabectedin+doxorubicin experienced a Grade 3-4 AE compared to 63.8% in the control arm. The greatest difference is seen in terms of Grade 4 AEs, 44.1% vs. 10.3%. Looking at SOCs a clear difference is seen in "blood and lymphatic system disorder", 56.6% vs 27.7%, and "investigations" (neutropenia, leukopenia, thrombocytopenia, etc.) 51.7% vs. 10.6%. Other differences, however, to a lesser extent were also seen in terms of metabolism, respiratory, and vascular Grade 3-4 AEs in favour of the doxorubicin monotherapy arm.

There were significantly fewer Grade 3-4 AEs in terms of skin and subcutaneous tissue disorders in the trabectedin+doxorubicin arm compared to doxorubicin alone, 3.8% vs. 14.5%, which is somewhat puzzling, because trabectedin is add-on to doxorubicin.

With regards to deaths, there was a slight increase in "death within 60 days of initiation of study drug" in the trabectedin+doxorubicin arm, 2.4% vs. 1.4%, and in "death within 30 days from the last dose", 3.5% vs. 2.1%. AEs leading to death was 10 (3.5%) vs. 5 (1.8%) in favour of the doxorubicin monotherapy arm.

A doubling of SAEs is seen in the trabectedin+doxorubicin arm, 41.3% vs 20.6%. A similar pattern as with Grade 3-4 AEs is also observed.

Patients in the trabectedin+doxorubicin arm discontinued to a higher degree compared with the control arm, 93 (32.5%) vs. 46 (16.3%). The main reason being "investigations" (ALT/AST increase, etc.) and "blood and lymphatic disorders" (anaemia, neutropenia, leukopenia).

As expected, dose-reductions had to be made in half of the patients in the trabectedin+doxorubicin arm compared to one third in the control arm, 152 (53.1%) vs. 103 (36.5%). Main reason for dose-reductions

were neutropenia, febrile neutropenia, thrombocytopenia, ALT/AST increase, nausea, vomiting, fatigue, palmar-plantar erythordysaesthesia syndrome, etc.

Overall, the safety profile appears worsened in the third line setting compared to the second line setting based on the observed differences between the combination arm and the control arm in terms of rates of SAEs, Grade 3-4 AEs, AEs leading to dose reductions and AEs leading to discontinuations. This is not unexpected when comparing a combination treatment with monotherapy in more heavily pretreated patients. Overall the safety profile of the combination of trabectedin and PLD in this study appears consistent with the already known safety profile for this combination.

The CHMP noted and endorsed the PRAC request in EMEA/H/C/PSUSA/00003001/201909 for the MAH to submit a variation to update section 4.8 of the SmPC with pooled data from the ovarian cancer phase 3 clinical studies.

3. Benefit-risk balance

Yondelis in combination with pegylated liposomal doxorubicin (Yondelis + PLD) is indicated for the treatment of patient relapsed platinum-sensitive ovarian cancer. Study ET743-OVA-301 (Study 301), a randomised phase 3 study of 672 patients who received either trabectedin (1.1 mg/m^2) and PLD (30 mg/m^2) every 3 weeks or PLD (50 mg/m^2) every 4 weeks, was the basis for this approval. In this study, patients had been previously treated for ovarian carcinoma (80% previously received taxanes) but had only 1 platinum-based chemotherapy regimen and had experienced either recurrence or progression after more than 6 months from the beginning (first dose) of the platinum-based chemotherapy for ovarian cancer. The study included patients with platinum-resistant disease (platinum-free interval from the end of platinum treatment less than 6 months) and patients with platinum-sensitive disease (platinum-free interval from the end of platinum treatment ≥6 months) who were not expected to benefit from or who were ineligible for or who were not willing to receive retreatment with platinum-based chemotherapy. The primary endpoint was PFS and patients were stratified based on platinum sensitive vs. platinum resistant.

Subsequently Janssen conducted study ET743-OVC-3006 (Study 3006). No EU scientific advice had been sought for study 3006. This study was a phase 3, randomized, open-label, multicenter study designed to evaluate the efficacy and safety of trabectedin+PLD as a third-line chemotherapy in subjects with advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer. Study participants were required to be platinum sensitive (PFI ≥ 6 months) following their first platinum-containing regimen and have a complete or partial response to a second line platinum-based chemotherapy (without PFI restrictions) meaning that these patients could be either platinum-sensitive (PFI ≥ 6 months) or platinum-resistant (PFI < 6 months) following their second platinum-containing regimen. Women were allocated randomly 1:1 to Yondelis + PLD or PLD alone with randomization stratified by ECOG PS (0 vs 1), PFI following first-line platinum-based chemotherapy (6 to 12 months, >12 to 24 months, >24 months), BRCA1/2 germline status (mutation vs. no mutation), and use of prior PLD (yes vs. no). The primary objective of the study was to compare OS after treatment with Yondelis + PLD vs. PLD monotherapy. Secondary objectives were PFS, ORR, PK and safety. One non-binding interim futility analysis for OS was conducted after 170 events corresponding to 33% of the pre-specified number of events required for the final analysis (514 events). Following the data review at this first interim analysis, the IDMC requested an additional futility analysis at 45% of events (232 events); this analysis was not planned in the protocol. It showed a HR=0.96 for OS, which crossed the boundary of 0.93 for futility of the study to show that Yondelis + PLD would improve OS compared with PLD monotherapy. The study was subsequently discontinued after the IDMC concluded to recommend discontinuation of the trial for 2 main reasons: a) futility of the primary analysis (OS) and b) excessive risk based on imbalance of AE not in favour of the experimental regimen arm.

The observed data cannot be used for testing the statistical hypothesis related to the hypothesis in the study protocol (i.e. Yondelis + PLD will improve OS compared with PLD monotherapy in the treatment of subjects with platinum-sensitive advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer who received 2 previous lines of platinum-based chemotherapy), and the observed data are deemed to lack the strength and level of evidence that would have been obtained had the study been completed as planned.

Moreover, differences between the two trials (Study 301 and study 3006) hinder an appropriate comparison of populations and outcomes. The main difference is with regards to the number of prior lines of therapy. Study 301 included patients previously treated with one line of platinum-based chemotherapy, while study 3006 included patients failing a second-line platinum-containing chemotherapy). Furthermore, a post hoc analysis determined that 42% of subjects enrolled in study 3006 were platinum-resistant (PFI < 6 months) following their last platinum-containing regimen while Yondelis is only approved in patients with platinum sensitive disease.

With respect to outcomes for primary endpoints, Study 301 found a difference in terms of median PFS of 1.5 months with Yondelis+PLD, whereas Study 3006 was powered to detect a difference in median OS of 4.5 months.

The MAH argued that post-hoc analyses of Study 3006 showed a trend towards improved PFS combined with a significant improvement in ORR among the subset of patients who were platinum-sensitive following their last line of platinum-containing therapy. However, as discussed previously, the study failed to meet its primary objective, to evaluate Yondelis with the assumption that Yondelis + PLD will improve OS compared with PLD monotherapy. Only if study 3006 had been completed as planned and was positive for OS, the submitted ad hoc comparison of study 301 and 3006 (data not shown) might have been considered for the post-hoc defined subgroup of patients in Study 3006 with platinum-sensitive disease after their last line of platinum-containing therapy; however, limitations of comparisons across trials in different patient populations still would have been a high concern.

Even though BRCA and PFI were stratification factors, OS and PFS as a function of BRCA status or of PFI were exploratory endpoints and were not adjusted for multiplicity. As a consequence of the methodological shortcomings, the results for these endpoints and in subgroups defined by these factors are much more likely to be spurious in magnitude and direction and cannot be used for regulatory decision-making.

In light of the above, data from Study 3006 do not permit to conclude on the effects of Yondelis + PLD in third line platinum-sensitive ovarian cancer.

With regards to safety, there was a difference between the two treatment arms in study 3006 in terms of number of AEs, severity and seriousness. Approximately 85% of patients in the Yondelis + PLD experienced a Grade 3-4 AE compared to 63.8% in the control arm. The greatest difference is seen in terms of Grade 4 AEs, 44.1% vs. 10.3%. Looking at SOCs a clear difference is seen in "blood and lymphatic system disorder", 56.6% vs. 27.7%, and "investigations" (neutropenia, leukopenia, thrombocytopenia, etc.) 51.7% vs. 10.6%. However, there were significantly fewer Grade 3-4 AEs in terms of skin and subcutaneous tissue disorders in the Yondelis + PLD arm compared to doxorubicin alone, 3.8% vs. 14.5%, which is somewhat puzzling, because trabectedin is given in study 3006 as add-on treatment to doxorubicin.

There were slightly more deaths in the Yondelis + PLD arm with regards to "death within 60 days of initiation of study drug" in the Yondelis + PLD arm and in "death within 30 days from the last dose". AEs leading to death was 10 (3.5%) vs. 5 (1.8%) in favour of the doxorubicin monotherapy arm.

Patients in the Yondelis + PLD arm discontinued treatment to a much higher degree compared with the control arm and as expected dose-reductions had to be made in half of the patients in the Yondelis + PLD arm compared to one third in the control arm.

Overall, the number of SAEs was considerably higher (41.3% in the combination arm vs 20.6% in PLD arm) and a considerable difference in overall rate of Grade 3-4 AEs was observed (85% in the combination arm vs 63.8% in the control arm). This is not unexpected when comparing a combination treatment with monotherapy in patients who have already received several lines of treatment.

The CHMP noted and endorsed the PRAC request in EMEA/H/C/PSUSA/00003001/201909 for the MAH to submit a variation to update section 4.8 of the SmPC with pooled data from the ovarian cancer phase 3 clinical studies.

Yondelis has been authorised in combination with PLD based on a positive trial rendering a favourable benefit-risk balance in patients with relapsed platinum-sensitive ovarian cancer (study 301). The new study 3006 failed to provide evidence against the statistical hypothesis that OS is the same with Yondelis + PLD and PLD. In addition, results of study 3006 also do not provide a level and strength of clinical evidence that would allow to conclude there are no clinically relevant favourable effects of Yondelis + PLD in terms of OS and PFS in third line platinum-sensitive ovarian cancer.

The positive benefit-risk balance established for the ovarian cancer indication on the basis of the well-conducted phase III trial 301, showing favourable effects of Yondelis + PLD in terms of PFS in patients with a relapsed platinum-sensitive ovarian cancer, therefore remains unchanged.

Furthermore, the CHMP recommended that the marketing authorisation of this product should be varied so that section 5.1 of the SmPC reflects the results from Study 3006.

The CHMP noted from responses submitted by the marketing authorisation during this review that there are two ongoing investigator-sponsored studies (NCT03690739 and NCT03164980), in active recruitment phase, which are investigating the use of trabectedin + doxorubicin in patients with recurrent ovarian cancer. The MAH is requested to submit the final results of these studies when they become available.

4. Amendments to the product information

The CHMP considered that amendments to section 5.1 of the SmPC were necessary to include a summary of the results from study 3006. The agreed amendments are as follows (new text in bold):

The Yondelis+PLD combination in relapsed ovarian cancer also was evaluated in study ET743-OVC-3006, a phase 3 study in which women with ovarian cancer after failure of a second platinum-containing regimen were randomized to Yondelis (1.1 mg/m^2) and PLD (30 mg/m^2) every 3 weeks or PLD (50 mg/m^2) every 4 weeks. Study participants were required to be platinum sensitive (PFI ⩾ 6 months) following their first platinum-containing regimen and have a complete or partial response to a second line platinum-based chemotherapy (without PFI restrictions) meaning that these patients could be either platinum-sensitive (PFI ⩾ 6 months) or platinum-resistant (PFI < 6 months) following their second platinum-containing regimen. A post hoc analysis determined that 42% of enrolled subjects were platinum-resistant (PFI < 6 months) following their last platinum-containing regimen.

The primary endpoint of study ET743-OVC-3006 was OS and secondary endpoints included PFS and ORR. The study was sized to enrol approximately 670 patients in order to observe 514 deaths to detect a HR of 0.78 for OS with 80% power given a two-sided significance level of 0.05 spread across two planned analyses on OS, at interim (60% or 308/514 deaths) and final analysis (514 deaths). Two early unscheduled futility analyses were performed at the request of the Independent Data Monitoring Committee (IDMC). Following the second futility analysis performed at 45% of planned events (232/514 deaths), the

IDMC recommended discontinuing the study due to (1) futility of the primary analysis on OS and (2) excessive risk based on imbalance of adverse events not in favour of Yondelis+PLD. At early termination of the study, 9% (52/572 treated) of subjects stopped treatment, 45% (260/576 randomized) stopped follow-up, and 54% (310/576 randomized) were censored from OS assessment, precluding reliable estimates of PFS and OS endpoints.

5. Grounds for Opinion

Whereas,

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Yondelis;
- The Committee reviewed the clinical study report on study ET743-OVC-3006, a phase 3, randomized, open-label, multicenter study designed to evaluate the efficacy and safety of trabectedin in combination with pegylated liposomal doxorubicin as a third-line chemotherapy in patients with advanced-relapsed epithelial ovarian, primary peritoneal, or Fallopian tube cancer.
- The Committee noted that following a first unplanned interim futility analysis, the Independent Data Monitoring Committee (IDMC) for study 3006 requested an additional futility analysis at 45% of events (232 events). This analysis, which was not planned in the protocol, led to an IDMC recommendation to discontinue the trial for futility of the primary endpoint (OS) and excessive risk based on imbalance of adverse events not in favour of the experimental arm, after which the sponsor prematurely terminated study 3006.
- The Committee further noted that there are differences between study 3006 and study 301 (pivotal study for the authorisation of the ovarian cancer indication) in terms of number of prior lines of therapy, platinum sensitivity status and primary endpoint hampering an appropriate comparison of populations and outcomes. These differences between studies hinder an appropriate comparison of populations and outcomes.
- Overall, the Committee considered that data from the prematurely terminated study 3006 do not provide the level and strength of clinical evidence necessary to conclude on the absence of favourable effects in third line platinum-sensitive ovarian cancer patients.
- The Committee noted that overall, in study 3006, the safety profile of Yondelis +PLD appears consistent with the known safety profile for this combination. While patients in the Yondelis + PLD arm of the study experienced more adverse events than those in the PLD arm, this is not unexpected when comparing a combination treatment with monotherapy.
- The Committee therefore concluded that the positive benefit-risk balance of Yondelis in the ovarian cancer indication, that was established on the basis of the well-conducted phase III trial 301 showing favourable effects of Yondelis in combination with pegylated liposomal doxorubicin in terms of progression-free survival (PFS) in patients with relapsed platinum-sensitive ovarian cancer, remains unchanged.
- The Committee recommended that study 3006 be reflected in section 5.1 of the summary of product characteristics.

In view of the above, the Committee considers that the benefit-risk balance of Yondelis remains favourable subject to the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for Yondelis.