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ASSESSMENT REPORT FOR YONDELIS

International non-proprietary name/Common name: trabectedin

Procedure No.EMEA/H/C/000773/II/0008

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

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1. Introduction

Yondelis (trabectedin) is an antineoplastic agent that binds to the minor groove of DNA, bending the helix to the major groove. This binding to DNA triggers a cascade of events affecting several transcription factors, DNA binding proteins, and DNA repair pathways, resulting in perturbation of the cell cycle. Trabectedin has been shown to exert antiproliferative *in vitro* and *in vivo* activity against a range of human tumour cell lines and experimental tumours, including malignancies such as sarcoma, breast, non-small cell lung, ovarian and melanoma.

Yondelis (trabectedin), formerly known as ecteinascidin 743 (ET-743) was granted orphan designation (EU/3/01/039) by the European Commission on 30 May 2001 for the treatment of soft tissue sarcoma. Subsequently, an orphan designation (EU/3/03/171) was granted by the European Commission for trabectedin for the treatment of ovarian cancer.

Yondelis was granted a marketing authorisation in the European Union on 17 September 2007. Yondelis is indicated for the treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.

This type II variation concerns the addition of a new indication of Yondelis in combination with pegylated liposomal doxorubicin (PLD) in the treatment of patients with relapsed platinum-sensitive ovarian cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SPC have been updated. The Package Leaflet has been updated accordingly. Further, annex II has been updated to include the agreed version 6.0 of the RMP.

1.2 Background

Epithelial carcinoma of the ovary is one of the most common gynaecologic malignancies and the fifth most frequent cause of cancer death in women, with 50% of all cases occurring in women older than 65 years. Approximately 5% to 10% of ovarian cancers are familial and three distinct hereditary patterns have been identified: ovarian cancer alone, ovarian and breast cancers, or ovarian and colon cancers. The most important risk factor for ovarian cancer is a family history of a first-degree relative (e.g., mother, daughter, or sister) with the disease.

Prognosis in ovarian cancer is influenced by several factors, but multivariate analyses suggest that the most important favourable factors include:

- Younger age.
- Good performance status.
- Cell type other than mucinous and clear cell.
- Lower stage.
- Well-differentiated tumour.
- Smaller disease volume prior to any surgical procedure.
- Absence of ascites.
- Smaller residual tumour following primary cytoreductive surgery

Management of ovarian carcinoma depends on the extent of disease and prior therapy that the patient has received. The FIGO (Federation Internationale de Gynecologie et d'Obstetrique) staging system is used to classify the extent of disease and provide the basis for treatment considerations. Patients with newly diagnosed Stage I or II disease have limited ovarian carcinoma confined to the ovaries and pelvis. Patients diagnosed with Stage III or IV disease have advanced ovarian carcinoma that is intraperitoneal (IP) or involves distant metastases. Patients whose disease recurs or persists after prior therapy are referred to as having recurrent or persistent disease. Most patients (75%) present with disseminated (Stage III or IV) disease; 17% with Stage III disease, 58% with Stage IV.

The standard of care for advanced disease, set forth at a 2004 Gynecologic Cancer Intergroup (GCIG) consensus conference, consists of maximum attempted surgical cytoreduction, chemotherapy following surgery, and a drug regimen of paclitaxel/carboplatin repeated every 3 weeks for 6 cycles.

Results with this approach depend on the volume of residual disease. Those with large-volume residual disease (nodules >2 cm in diameter remaining after surgery) will achieve a clinical CR in 40 to 50% of cases and will have a median PFS of 17 months and median survival of 30 months. Those with small-volume residual disease (no nodule >2 cm in diameter after surgery) have a 95% probability of ending initial therapy with no clinical evidence of disease and will exhibit median PFS of 25 months and median survival of 60 months.

For Stage I or II, the general practice is to look at tumour features that predict prognosis and divide patients according to low and high risk for recurrence. Low-risk patients are those with low-grade disease whose cancer is intracystic, who have no extraovarian disease, have negative peritoneal cytology, and have no ascites. High-risk patients are those with intermediate- to high-grade disease whose cancer is extracystic and who have extraovarian disease, positive peritoneal cytology, and ascites. Treatment recommendations for limited disease include platinum-based therapy, total abdominal hysterectomy–bilateral salpingo-oophorectomy, and careful surgical exploration. Some patients with low-risk limited disease have no further therapy. Those with high-risk disease receive platinum-based therapy; adjunct platinum-based therapy cuts relapse in half. Patients with advanced disease receive surgical cytoreduction and paclitaxel/carboplatin.

Most patients (62%) will not achieve long-term control of the disease and will develop either recurrent or persistent disease. Management of such patients requires that they first be classified as having either chemosensitive disease (i.e., response to first-line therapy leading to a treatment-free interval of at least 6 months) or chemoresistant disease (i.e., progression during first-line therapy or best response to first-line therapy: stable disease or recurrence within 6 months of completing first-line therapy). Those with chemosensitive disease are retreated with a platinum-based regimen; the expected RR is >60% and median survival is ≥30 months. Those with chemoresistant disease are treated with alternative drug therapy; expected RR is 12 to 32% and median survival is ≥8 months.

Clinical recurrences that take place within 6 months of completion of a platinum-containing regimen are considered platinum-refractory or platinum-resistant recurrences. Anthracyclines (particularly when formulated as PLD), taxanes, topotecan, and gemcitabine are used as single agents for these recurrences based on activity and their favourable therapeutic indices.
Treatment with paclitaxel historically provided the first agent with consistent activity in patients with platinum-refractory or platinum-resistant recurrences (Kohn EC, Sarosy G, Bicher A, et al 1994 and Trimble EL, Adams JD, Vena D, et al. 1993). Subsequently, randomized studies have indicated that the use of topotecan achieved results that were comparable to those achieved with paclitaxel (ten Bokkel Huinink W, Gore M, Carmichael J, et al. 1997). Topotecan was compared with pegylated liposomal doxorubicin in a randomized trial of 474 patients and demonstrated similar response rates, PFS, and OS at the time of the initial report, contributed primarily by the platinum-resistant subsets (Gordon AN, Fleagle JT, Guthrie D, et al. 2001).

PLD is marketed in the European Union under the brand name of Caelyx (it is also known as DOXIL). PLD is a liposomal anthracycline with a broad spectrum of antineoplastic activity including ovarian cancer. Caelyx is indicated for the treatment of advanced ovarian cancer in women after failure of first-line platinum-based chemotherapy.

The application is based primarily on clinical data from one pivotal Phase III study (ET743-OVA301) of Yondelis in combination with Caelyx in patients with advanced ovarian cancer who had failed a first-line platinum-based chemotherapy. In addition results from 3 Phase II trials of trabectedin as single agent in a similar patient population are included as supportive efficacy data.

1.3 Toxico-pharmacological aspects

An environmental risk assessment was submitted in this application in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (CHMP/SWP/4447/00).

The MAH has estimated the partition coefficient log K_{ow} based on theoretical considerations. Although the estimated log K_{ow} is far from the action limit, this approach is not considered acceptable. The MAH should determine the partition coefficient in accordance with the current OECD guidelines, i.e., OECD 107 or 117 (the latter method is only applicable for compounds with a log K_{ow}<4). The MAH should submit the study report when available.

The MAH has calculated the PEC_{SW} based on the maximum dose per patient adjusted for treatment duration. This approach is not acceptable. In the Phase I environment risk assessment, the calculation of the PEC_{SW} is based on a screening model (snapshot model) in which the patient population is treated with the product and the maximum daily dose on a given day. Therefore, the MAH's calculation on an average daily dose for one patient is not acceptable. The MAH has provided justified epidemiological data published by EMEA (EMEA/COMP/96616/2008, EMEA/COMP/48649/2008) on the incidence of the target diseases for Yondelis (soft tissue sarcoma and ovarian cancer) within the EU. Using the maximum daily dose of 2.595 mg/day and 1.903 mg/day for soft tissue sarcoma and ovarian cancer, respectively, and the refined F_{pen} yield a PEC_{SW} of approximately 0.0003 µg/L for both indications. Thus, PEC_{sw} values are well below the threshold for a Phase II environmental risk assessment.

The MAH commits to submit the experimental value of log P according to the relevant OECD methods.

1.4 Clinical aspects

All clinical trials were conducted in accordance with GCP and local requirements of individual countries. All studies were closely monitored by PharmaMar or J&JPRD personnel or a contract research organisation. All protocols and amendments were submitted for approval to the ethics committees and health authorities if required following GCP standards.

The table below summarises the clinical study conducted.

Table 1 –Clinical Studies Included for Evaluation of Efficacy

Study	Design and Study Population	Study Treatment(s), Starting Dose, and Regimen	Subjects Evaluated		
Phase 3					
ET743-OVA-301	Randomized, open-label, pivotal study in subjects with relapsed epithelial ovarian, epithelial fallopian tube, or primary peritoneal cancer	Trabectedin 1.1 mg/m^2 q3wk 3-h + Caelyx 30 mg/m^2 q3wk 1.5-h vs Caelyx 50 mg/m^2 q4wk 1.5-h	672 337 trabectedin + Caelyx 335 Caelyx monotherapy		
Phase 2					
ET-B-026-03	Randomized, open-label, study of 2 dose regimens in subjects with potentially platinum-sensitive, recurrent, advanced epithelial ovarian carcinoma	Trabectedin 1.5 mg/m^2 q3wk 24-h Trabectedin 1.3 mg/m^2 q3wk 3-h	54 53		
ET-B-009-99	Open-label, single arm study in subjects with advanced epithelial ovarian carcinoma	Trabectedin 1.3 mg/m^2 q3wk 3-h Trabectedin 1.5 mg/m^2 q3wk 3-h Trabectedin 1.65 mg/m^2 q3wk 3-h	41/59*		
ET743-INT-11	Open-label, single arm study in subjects with epithelial ovarian, fallopian tube, or primary peritoneal cancer	Trabectedin 0.58 mg/m^2 qwk 3-h	147		
Phase 1			Ovarian	Other	All
ET743-USA-11	Open-label study evaluating 6 dose levels of trabectedin in combination	Trabectedin 0.4 - 1.3 mg/m^2 q3wk 3-h +	4	32	36

	with Caelyx in subjects with a malignancy refractory to standard therapy or for which an anthracycline-based regimen was appropriate	Caelyx 30 mg/m^2 q3wk 1- to 2- h		
Total		971	32	1003

qwk= weekly dosing ; q3wk= every 3 week dosing

*Fifty-nine subjects were enrolled & treated. However, among the 59 subjects, 18 subjects received 1.5 mg/m^2 or 1.65 mg/m^2 as their starting dose and 41 subjects received 1.3 mg/m^2 as the starting dose. Subjects in the 2 highest dose groups (1.5 mg/m^2 or 1.65 mg/m^2) were excluded from the integrated efficacy analysis.

1.4.1 *Clinical Pharmacology*

New pharmacokinetic data have been obtained since the marketing authorisation of Yondelis, mainly in 5 clinical trials (one in monotherapy and four in combination with other drugs). The potential for an interaction between trabectedin and PLD was assessed in patients with ovarian cancer enrolled in the phase I study ET743-USA-11. Additionally, the pharmacokinetics of trabectedin and doxorubicin (non-liposomal) when given as a combination therapy was characterised in the phase I studies ET743-SAR-1001 and ET-A-007-00.

Three phase II studies (ET-B-009-99, ET-B-026-03 and ET743-INT-11) evaluated the pharmacokinetics of trabectedin given as a single agent in patients with advanced ovarian cancer. Data from studies ET-B-009-99 and ET743-INT-11 were already included in the initial marketing authorisation application of Yondelis in soft tissue sarcoma. Finally, a population pharmacokinetic analysis has been performed using data from the phase III study OVA-301. The concentrations of trabectedin and doxorubicin (given as PLD) were analyzed.

In study ET-B-026-03 all patients received 20 mg of dexamethasone at 30 minutes prior to start of the trabectedin infusion. Those who received the 1.3 mg/m^2 dose were also given 4 mg of oral dexamethasone at 24 h and 12 h before the start of the trabectedin infusion and 5 more doses every 12 h beginning 24 h after the start of the 3-h infusion. Full pharmacokinetic profiles (up to 6 to 8 days after the end of the 24-h and 3-h infusions) of trabectedin were collected during Cycle 1.

As expected much higher mean concentrations in plasma were observed just prior the end of the infusion when given over 3 h as compared to 24 h (Table 2). The minor differences observed in the mean CL,Vss, and the terminal half-life values between the regimens were within the degree of interpatient variability and are not likely to be clinically significance.

Table 2 - Plasma Pharmacokinetic Parameters of Trabectedin Following Administration of 1.5 mg/m2 as a 24-Hour and 1.3 mg/m2 as a 3-Hour Intravenous Infusions (Study ET-B-026-03)

Parameter	1.5 mg/m^2; 24-h infusion (n=11)	1.3 mg/m^2; 3-h infusion (n=7)
C_{max} (ng/mL)	1.38 ± 0.73	12.1 ± 6.38
AUC_∞ (ng·h/mL)	60.8 ± 28.2	75.3 ± 42.2
CL (L/h)	46.7 ± 12.1	37.2 ± 15.6
V_{ss} (L)	3718 ± 2301	2565 ± 1382
Terminal $t_{1/2}$ (h)	95.9 ± 46.3	96.1 ± 45.4

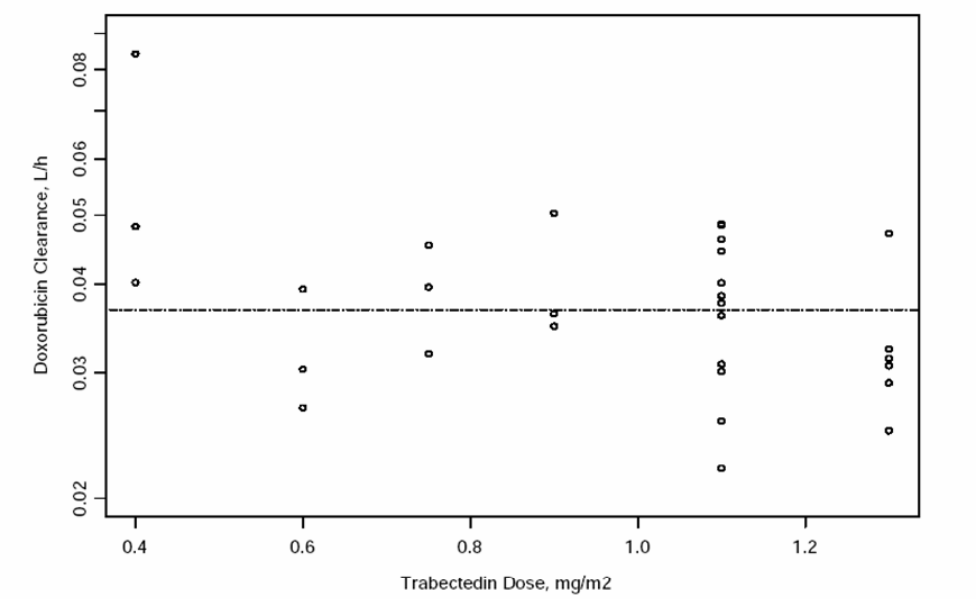
Note: Results presented as mean ± standard deviation

The main objective of Study ET-743-USA-11 was to determine the maximum tolerated dose (MTD) of trabectedin when administered in combination with Caelyx (doxorubicin HCl liposome injection). Secondary objectives were to evaluate the safety profile of this combination of study drugs, to investigate potential pharmacokinetic (PK) interactions between trabectedin and Caelyx. A sparse pharmacokinetic sampling procedure was used during Cycles 1, 2, and 3. Venous blood samples were collected during the three cycles at the following times: before the start of the intravenous infusion, 10 minutes before the end of 1-h intravenous infusion, and 2.83 h and 168 h after the end of the infusion. The concentrations of total (encapsulated plus free) doxorubicin in plasma were measured

using a validated LC-MS/MS method. A population approach (non-linear mixed-effects model software; NONMEM) was used to characterize the pharmacokinetics of total doxorubicin. A total of 234 liposomal doxorubicin plasma concentrations from 30 patients were available for the analysis. An open one-compartment model with linear elimination was used to fit the plasma concentration versus time data of total (liposomal encapsulated and free) doxorubicin. The model was parameterized in terms of systemic clearance (CL) and volume of the central compartment (V). The interindividual (IIV, between patient) and interoccasion (IOV) variability in the pharmacokinetic parameters were assumed to follow the log-normal distribution. Residual variability was evaluated using an additive error model.

Pegylated liposomal doxorubicin showed a long terminal half-life (74 h), a slow clearance (0.037 L/h), and a small volume of distribution (3.9 L) in plasma. No evidence of changes in pegylated liposomal doxorubicin clearance appear to occur within the range of trabectedin doses studied.

Figure 1 – Plasma Clearance of Pegylated Liposomol Doxorubicin versus the Administered Dose of Trabectedin (Study ET743-USA-11: Pharmacokinetic Analysis Set)



The results on Trabectedin pharmacokinetics are presented in the following figures and tables:

Figure 2 – Mean Plasma Concentrations of Trabectedin Given as a 3-hour Intravenous Infusion to Subjects Coadministered Caelyx (Study ET743-USA-11: Pharmacokinetic Analysis Set)

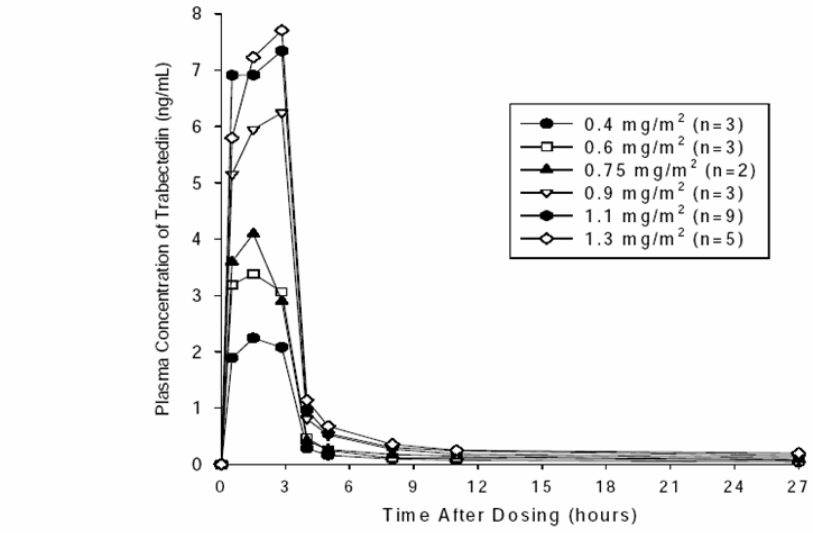


Table 3 – Mean (SD) Pharmacokinetic Parameters of Trabectedin Given as a 3-hour Intravenous Infusion to Subjects Coadministered Caelyx

Parameter	Trabectedin Dose-Level Cohort					
	0.4 mg/m2 (N=3)	0.6 mg/m2 (N=3)	0.75 mg/m2[a] (N=2)	0.9 mg/m2 (N=3)	1.1 mg/m2 (N=9)	1.3 mg/m2 (N=5)
T_{max} (h)	2.40 (0.77)	1.93 (0.78)	1.50, 1.50	2.83 (0.0)	1.71 (0.93)	2.60 (0.62)
C_{max} (ng/mL)	2.30 (0.46)	3.47 (0.51)	4.76, 3.43	6.24 (0.69)	7.87 (2.04)	7.71 (1.66)
AUC_{∞} (ng*h/mL)	9.86 (1.57)	19.2 (8.34)	28.6, 13.1	37.6 (2.08)	53.5 (22.2)[b]	53.2 (10.8)
CL (L/h)	74.5 (8.88)	70.9 (29.4)	51.2 78.2	45.5 (6.49)	40.8 (14.8)[b]	48.4 (10.7)
V_{ss} (L)	744 (453)	1595 (1075)	1915, 1141	2395 (1103)	2643 (1219)[b]	3093 (411)
$t_{½term}$ (h)	19.6 (5.43)	43.1 (37.4)	54.4, 27.0	75.6 (15.7)	93.0 (36.2)[b]	83.2 (8.25)

Note: AUC_{∞} = area under plasma concentration-time curve from 0 to infinity; C_{max} = peak plasma concentration; CL = clearance; $t_{½term}$ = terminal half-life; T_{max} = time to peak plasma concentration; V_{ss} = volume of distribution at steady state.

[a] Individual parameter values provided.

[b] N=8.

The primary objective of Study ET743-SAR-1001 was to determine the regimen of the combination of trabectedin and (non-liposomal) doxorubicin for which neutropenia was manageable in patients with soft tissue sarcoma. Evaluation of the pharmacokinetics of both drugs was a secondary objective.

The following regimens, each administered every 3 weeks, were evaluated in separate cohorts: (i) trabectedin 0.9 mg/m^2 and doxorubicin 60 mg/m2, (ii) trabectedin 1.1 mg/m2 and doxorubicin 60 mg/m2, and (iii) trabectedin 1.3 mg/m2 and doxorubicin 60 mg/m2. For all treatments, doxorubicin was administered as a 10- to 15-minute infusion and immediately followed by trabectedin as a 3-h infusion. Both drugs were administered via a central venous catheter. All patients received 20 mg intravenous dexamethasone within 1 h before the start of doxorubicin.

Regarding the trabectedin data, the relatively small sample sizes and between-subject variability precluded comparison of the pharmacokinetic parameters between the treatment groups. The data are shown below

Table 4 – Mean (SD) Trabectedin Pharmacokinetic Parameter Values Following Single-Dose Administration of Trabectedin in Subjects Coadministered Doxorubicin

PK Parameters		Cohort 2: Trabectedin 0.9 mg/m^2, Doxorubicin 60 mg/m^2 (n=3)	Cohort 3: Trabectedin 1.1 mg/m^2, Doxorubicin 60 mg/m^2 (n=5)	Cohort 4: Trabectedin 1.3 mg/m^2, Doxorubicin 60 mg/m^2 (n=5)
C_{max}	(ng/mL)	5.97 (0.92)	8.44 (2.74)	8.91 (3.38)
t_{max}[a]	(h)	2.75 (2.72-2.83)	1.00 (0.92-2.87)	2.83 (0.92-2.97)
AUC_{last}	(ng.h/mL)	32.7 (3.63)	51.4 (14.5)	59.9 (26.9)
AUC_{∞}	(ng.h/mL)	36.3 (3.89)	57.3 (12.5)	72.2 (28.2)[b]
$t_{1/2}$	(h)	69.5 (17.7)	85.4 (24.88)	90.9 (17.8)[b]
λ_z	(h^{-1})	0.0105 (0.00286)	0.00880 (0.00305)	0.00786 (0.00158)[b]
CL	(L/h)	42.0 (7.69)	37.2 (9.10)	37.4 (17.4)[b]
V_{ss}	(L)	2163 (197)	2574 (1193)	3028 (1811)[b]

[a] Median (range).

[b] n=4

With respect to the doxorubicin data, maximum plasma concentrations of doxorubicin were generally observed 15 to 20 minutes after the start of the infusion. The concentrations then declined in a multiexponential manner. An increase in the mean plasma C_{max} and AUC_{∞} values of doxorubicin was observed with increasing coadministered doses of trabectedin despite administration of the same dose of doxorubicin to all patients. However, minimal differences and no clear trend are observed when comparing the mean plasma concentrations at each time point between 1.25 h and 51 h (inclusive) after the start of the infusions. Thus, the concentration of the first pharmacokinetic sample (0.25 h) for each profile accounted for the differences in the plasma C_{max} and AUC values observed across the dose groups. Minimal differences in the mean $t_{1/2}$ values were observed substantiating the absence of an effect of trabectedin on doxorubicin elimination.

Table 5 – Mean (SD) Doxorubicin Pharmacokinetic Parameter Values Following Single-Dose Administration of Doxorubicin in Subjects Coadministered Trabectedin

PK Parameters		Cohort 2: Trabectedin 0.9 mg/m^2, Doxorubicin 60 mg/m^2 (n=3)	Cohort 3: Trabectedin 1.1 mg/m^2, Doxorubicin 60 mg/m^2 (n=5)	Cohort 4: Trabectedin 1.3 mg/m^2, Doxorubicin 60 mg/m^2 (n=5)
C_{max}	(ng/mL)	1750 (453)[b]	2452 (286)	3596 (1972)
t_{max}[a]	(h)	0.25 (0.25-0.25)[b]	0.25 (0.20-0.30)	0.25 (0.17-0.33)
AUC_{last}	(ng.h/mL)	2000 (187)[b]	2505 (88)	3187 (1273)
AUC_{∞}	(ng.h/mL)	2406 (55.5)[b]	2781 (111)	3499 (1206)
$t_{1/2}$	(h)	29.2 (3.62)	24.1 (2.30)	27.2 (8.66)
λ_z	(h^{-1})	0.0239 (0.00295)	0.0290 (0.00293)	0.0279 (0.00969)
CL	(L/h)	42.5 (6.86)[b]	40.1 (5.12)	33.5 (7.79)
V_{ss}	(L)	956 (474)[b]	561 (124)	495 (318)

[a] Median (range).

[b] n=2

The between subject variability in the pharmacokinetic parameters of doxorubicin is relatively high (37% to 93%). For this reason, and due to the relatively small number of subjects evaluated, a strict assessment of the impact of trabectedin on the pharmacokinetics of doxorubicin (and doxorubicinol) is not possible.

ET-A-007-00 was conducted to establish the maximum tolerated dose and least toxic sequence of trabectedin and doxorubicin in combinations to patients with advanced soft tissue sarcoma and breast

cancer. In addition, the potential for a pharmacokinetic interaction between these drugs was assessed as secondary endpoint.

During the Part 1 of the study, patients were randomized to receive doxorubicin (60 mg/m^2, 5-minute intravenous infusion) either before or after escalating doses of trabectedin (starting dose 0.6 mg/m^2, as a 3-h infusion) in Cycles 1 and 2. For either sequence, the second drug was started at 1 h after the end of the administration of the first drug. Part 2 of the study was designed to optimize the dose regimens by evaluating the tolerability of a fixed dose of doxorubicin (50 mg/m^2 or 60 mg/m^2) and various doses levels of trabectedin. Oral dexamethasone (4 mg) was given to all patients at 24 h before doxorubicin/trabectedin dosing on Day 1 and again 15 minutes before and 7 h after the start of administration of the combination. Dexamethasone continued to be given twice daily on Days 2 and 3.

Table 6 –Plasma Pharmacokinetic Parameters of Doxorubicin Following Administration of 60 mg/m2 as 5-Minute Intravenous Infusion To Patients Coadministered Trabectedin (Study ET743-A-007-00)

Dose of Trabectedin (mg/m^2)	Sequence	C_{max} [a] (ng/mL)	AUC_∞ [b] (ng·h/mL)	CL [c] (L/h/m²)	Terminal $t_{1/2}$ (h)
0.6	A (n=4)	3033 ± 1522	1163 ± 109	84.1 ± 7.8	36.2 ± 9.5
	B (n=6)	2979 ± 544	989 ± 217	not reported	29.4 ± 6.1
0.7	A (n=1)	1087 [d]	984 [d]	99.0 [d]	39.2 [d]
	B (n=2)	723, 544 [d]	1027, 587 [d]	94.5, 165.4 [d]	57.6, 23.1 [d]
0.8	A (n=6)	2087 ± 1141	995 ± 163	100 ± 16.6	34.6 ± 6.0
	B (n=3)	3446 ± 815	1076 ± 163	91.7 ± 13.5	35.8 ± 4.0

Table 7 –Plasma Pharmacokinetic Parameters of Doxorubicinol Following Administration of 60 mg/m2 of Doxorubicin as a 5-Minute Intravenous Infusion To Patients Coadministered Trabectedin (Study ET743-A-007-00)

Dose of Trabectedin (mg/m^2)	Sequence	C_{max} [a] (ng/mL)	AUC_∞ [b] (ng·h/mL)	Terminal $t_{1/2}$ (h)
0.6	A (n=4)	10.3 ± 1.09	452 ± 163	40.0 ± 8.4
	B (n=6)	12.0 ± 5.44	414 ± 109	38.2 ± 7.2
0.7	A (n=1)	10.3 [c]	441 [c]	42.2 [c]
	B (n=2)	10.3, 6.53 [c]	457, 272[c]	55.2, 25.7 [c]
0.8	A (n=6)	9.26 ± 2.72	457 ± 109	36.4 ± 9.5
	B (n=3)	7.62 ± 1.63	506 ± 109	38.0 ± 1.4

Sequence A, doxorubicin followed by trabectedin; Sequence B, trabectedin followed by doxorubicin

Regarding the trabectedin PK data, full pharmacokinetic profiles (up to 71 h after the start of the 3-h infusion) of trabectedin were to be collected during Cycles 1 and 2. Again, samples were collected from most patients during only one cycle.

Table 8 –Plasma Pharmacokinetic Parameters of Trabectedin Following Administration as a 3-Hour Intravenous Infusion To Patients Coadministered Doxorubicin (Study ET743-A-007-00)

Dose (mg/m^2)	Sequence	C_{max} (ng/mL)	AUC_∞ (ng·h/mL)	CL (L/h)	Terminal $t_{1/2}$ (h)
0.6	A (n=4)	3.6 ± 1.0	20.1 ± 3.9[a]	30.7 ± 5.7[a]	40.9 ± 11.6[a]
	B (n=6)	3.3 ± 1.2	17.1 ± 0.4	38.1 ± 12.9	38.6 ± 8.5
0.7	A (n=1)	1.3 [b]	5.9 [b]	119 [b]	14.5 [b]
	B (n=2)	2.4 ± 0.4	13.0 ± 0.15	53.9 ± 0.64	35.0 ± 7.6
0.8	A (n=6)	3.9 ± 2.4	14.4 ± 6.7	72.8 ± 51.0	27.3 ± 12.6
	B (n=3)	3.6 ± 0.8	17.7 ± 5.2	48.6 ± 17.1	39.3 ± 16.0

Finally, the pivotal study included a Population Pharmacokinetic Analysis of Trabectedin in Patients With Ovarian Cancer. Plasma samples for pharmacokinetic assessment were collected from patients who enrolled in the study ET743-OVA-301 at select sites during Cycles 1 and 2. The population analysis included 2074 samples that were collected from 166 patients and analyzed for total (liposomal encapsulated and free) doxorubicin concentrations and 963 samples collected from 86 patients that were analyzed for trabectedin concentrations. An additional 361 trabectedin concentrations collected from 142 patients enrolled in ET743-INT-11 were included in this population analysis.

Structural Model Parameter Estimates: An open 4-compartment model with linear elimination from the central compartment adequately characterized the time course of trabectedin plasma concentrations. Population pharmacokinetic parameters estimates of trabectedin in patients with cancer are presented in Table 11. Population values for clearance, central volume of distribution and K_{12} obtained during the analysis of data from ET743-OVA-301 were significantly lower relative to previous values.

Table 9 –Basic Population Plasma Pharmacokinetic Parameters of Trabectedin in Patients With Ovarian Cancer Received Trabectedin and PLD (Population Pharmacokinetics Report)

Parameter[a]	Typical Value (Male / Female)	Interpatient Variability (%CV)	Interoccasion Variability %CV)
CL (L/h)	30.9 / 30.9	49.5	27.5
V_c (L)	16.5 / 13.9	33.9	24.2

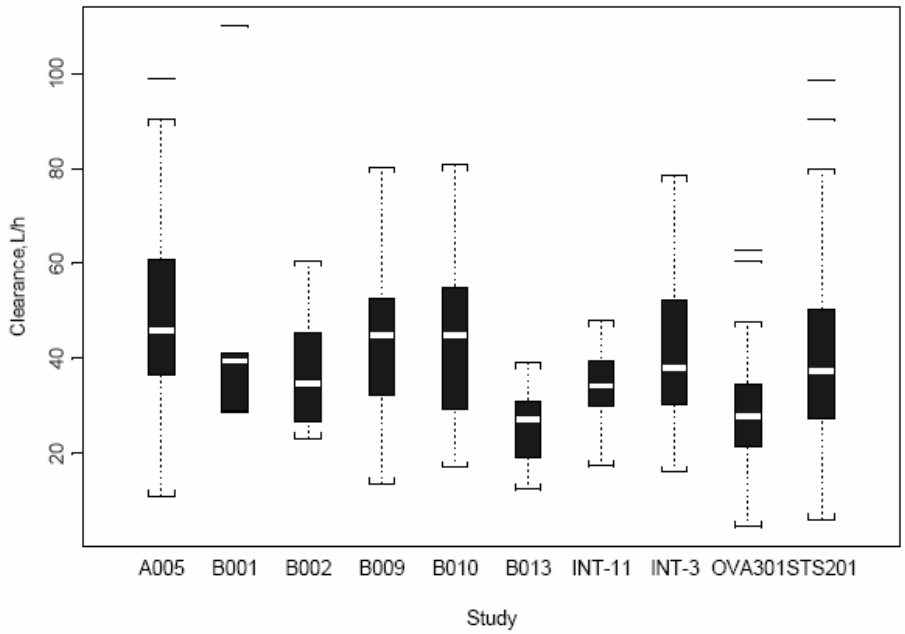
[a] Single-agent trabectedin (no concomitant dexamethasone)

Notably, these results are not consistent with those obtained during Phase 1 study ET743-USA-11, which suggested that the pharmacokinetics of trabectedin are not influenced by the concomitant administration of PLD.

The effect of dexamethasone on the plasma clearance of trabectedin was reassessed using data from the present and former population analysis (n=831 patients in total). In agreement with the previous results, the plasma clearance of trabectedin was 19% higher in patients who received any concomitant dexamethasone administration relative to those who did not.

The total plasma doxorubicin concentration-time data were adequately characterized with a one-compartmental model. Patient body surface area was an important covariate that could explain interpatient variability in clearance and distribution volume. Importantly, the estimated values of these pharmacokinetic parameters of doxorubicin were similar when PLD was coadministered with trabectedin and when given as a single agent.

Figure 3 –Boxplot of Trabectedin Clearance Split by Studies Included in the Population PK Analysis



All studies except OVA301 received trabectedin only. Study OVA301 received trabectedin and DOXIL.
All subjects of the studies included in the plot were taking dexamethasone as a comedication.

The MAH conclusions of Population PK Study Report regarding interactions between trabectedin and Caelyx were as follows:
1) The ET743-OVA301 parameter estimates for clearance, central volume of distribution and K12 obtained during the analysis of historical trabectedin data combined with INT11 and OVA301 data were significantly lower relative to previous values. The clearance of trabectedin was on average 31% lower, causing a higher exposure when given with Caelyx, relative to administration as a single agent.
2) The plasma clearance of Caelyx was approximately 7% lower when given with trabectedin, relative to administration as a single agent.

Discussion on Clinical Pharmacology

Regarding the PK in ovarian patients, the MAH has submitted three phase II studies and one phase III trial (pivotal study). The phase II clinical trials evaluated the PK characteristics of trabectedin administered at different regimens in patients with ovarian cancer. In general, the pharmacokinetics of trabectedin in ovarian cancer patients seems to be very similar to that described in previous studies.

Concerning the possible interaction between doxorubicin (pegylated and non-pegylated form) and trabectedin, several studies have been carried out. The phase I study ET743-USA-11 showed that the concentrations of liposomal doxorubicin and trabectedin in plasma were not substantially altered when given in combination. Pharmacokinetic parameter values of each compound were similar to those reported previously when each was given as a single agent. Similar conclusions were drawn from studies ET-A-007-00 and ET743-SAR-1001 with non-liposomal doxorubicin. However, the conclusions regarding the absence of a PK drug-drug interaction cannot be extrapolated from studies with doxorubicin non pegylated to the combination of trabectedin with PLD.

The PK results of the pivotal study OVA-301 and specifically the population PK study, with data from the OVA-301 pivotal, showed a significant discrepancy between these ones data and those from study ET743-USA-11. Study OVA-301 only included population PK data. However, it cannot be excluded that the PK profile of trabectedin is changed with co-administration of pegylated liposomal doxorubicin. The trabectedin clearance was on average 31% lower, causing a higher exposure when given with PLD, relative to its administration as a single agent. The pivotal study represents the target population of this indication. Therefore the results on these patients could be considered as the most predictable information of the “real” characteristics in whole population. A decrease in the Cl of

trabectedin could be expected when it will be co-administered with PLD. The clinical meaning of this fact is for the time being, unknown. Information on PK profile, specifically the interaction between Trabectedin and PLD, is therefore reflected in the section 5.2 of the SPC.

1.4.2 Clinical efficacy

The schedule used for trabectedin in the pivotal phase III trial (q3wk 3-h) was supported by results of a phase II randomised trial (ET-B-026-03), which showed that two every-3-week regimens (1.5 mg/m^2, 24-hour i.v. infusion, and 1.3 mg/m^2, 3-hour i.v. infusion) were similarly active in patients with relapsed, platinum-sensitive ovarian cancer; however, a slightly better safety profile was found for the 3-hour schedule with respect to myelosuppression (neutropenia) and fatigue, together with a more convenient administration schedule. Subsequently, a phase I trial (ET743-USA-11) evaluated the q3wk 3-h regimen of trabectedin in combination with PLD. The recommended doses based on this phase I trial were trabectedin 1.1 mg/m^2 and PLD 30 mg/m^2. These were the doses used in the randomised study OVA-301 for the investigational combination arm.

1.4.2.1 Pivotal study

In August 2004, the applicant requested the European Medicines Agency (EMEA) to provide with CHMP Protocol Assistance for the pivotal study OVA-301. The CHMP feedback was received in December 2004 and March 2005 for the initial and follow-up requests, respectively. In words of the company, the protocol incorporated recommendations received from both the EMEA and the United States Food and Drug Administration (FDA).

Methods

OVA-301 was a phase III, open-label, multicentre, randomised clinical trial designed to investigate the efficacy and safety of the combination of pegylated liposomal doxorubicin (PLD, Caelyx) 30 mg/m^2 followed by trabectedin 1.1 mg/m^2 every 3 weeks compared with the approved standard single-agent PLD 50 mg/m^2 every 4 weeks.

Subjects enrolled were 18 years of age or older with histologically proven epithelial ovarian, epithelial fallopian tube, or primary peritoneal cancer previously treated with 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 initial line of platinum-based chemotherapy for ovarian cancer to include subjects with platinum-resistant disease (platinum-free interval from the end of first-line treatment less than 6 months) and subjects with platinum-sensitive disease (platinum-free interval from the end of first-line treatment ≥6 months) who are not expected to benefit from or who were ineligible for or who were not willing to receive retreatment with platinum-based chemotherapy.

The *primary objective* of this study was as follows:
– compare the PFS of the combination of trabectedin + Caelyx with Caelyx monotherapy in patients with ovarian cancer.

Secondary objectives were as follows:
– compare overall survival (OS) between the 2 treatment arms;
– compare the overall objective response rate (ORR) between the 2 treatment arms;
– compare the safety profiles between the 2 treatment arms; and
– characterize the PK of trabectedin and Caelyx in each treatment arm.

Tertiary objectives included:
– evaluation of quality of life (QOL) and pharmacoeconomics; and
– exploratory evaluation of pharmacogenomic profiles and hypothesis-generating evaluation of the relationship between circulating tumor cells (CTCs), and the response to therapy, disease progression, and OS.

Progression free survival (PFS) is defined as the time between the randomization and disease progression or death. Subjects who progressed or died will be considered to have had an event, except if this event occurs after the start of subsequent therapy for ovarian cancer, in which case the subject is censored at the time of last tumor assessment (prior to or on the first day of the first subsequent therapy for ovarian cancer). Subjects who did not progress nor died (lost to follow-up, or still being treated without documented disease progression, or started subsequent therapy for ovarian cancer and still alive) will be censored at the date of the last tumor assessment (prior to or on the first day of the first subsequent therapy for ovarian cancer). The primary efficacy analysis set is based on the "All Measurable Subjects". "All Measurable Subjects" analysis set is defined as all randomized subjects who have measurable disease at baseline as assessed by the independent review (any of the independent radiologist reviewers).

Sample size: Approximately 650 subjects were randomized over 2 years. The primary analysis (PFS) was conducted after at least 415 events (progression or death) were observed. Assuming that Caelyx has a median PFS of 16 weeks and that the combination of trabectedin + Caelyx has a targeted median PFS of 22 weeks, this design would allow the demonstration of a statistically significant difference in PFS at a one-sided 2.5% significance level with at least 90% power. An interim OS analysis was performed in conjunction with this PFS analysis. The final OS analysis will be conducted when there are 520 observed deaths. Assuming that Caelyx has a median OS of 62.7 weeks and that the combination of trabectedin + Caelyx has a targeted median OS of 83.4 weeks, this design would allow for the demonstration of the statistically significant difference in OS at a 1-sided 2.5% significance level with at least 90% power. It was anticipated that the final OS analysis would be performed at approximately 4.5 years from the start of randomization.

Results

- **Participant flow and Recruitment**

Nine subjects did not receive study drug (6 subjects in the Caelyx monotherapy arm and 3 in the trabectedin + Caelyx arm) as shown in the table below. The remaining 663 randomized subjects received at least 1 dose of study medication (trabectedin + Caelyx, 334; Caelyx alone, 329) and comprise the All-Treated Subjects safety analysis population. One subject was randomly assigned to trabectedin + Caelyx but received only 1 dose of Caelyx, she opted to discontinue treatment without receiving trabectedin. This subject is included in the Caelyx monotherapy arm only for safety analysis.

The first subject was randomly assigned on 20 April 2005. The last subject was randomly assigned on 29 May 2007.

Table 10 –Subject Disposition
(Study ET743-OVA-301: All Randomized Subjects Analysis Set)

Population	DOXIL (N=335) n (%)	Trabectedin+DOXIL (N=337) n (%)	Total (N=672) n (%)
Randomized	335 (100)	337 (100)	672 (100)
Not Treated	6 (2)	3 (1)	9 (1)
Treated[a]	329 (98)	334 (99)	663 (99)
Trabectedin+DOXIL	0	333 (99)	333 (50)
DOXIL	329 (98)	1 (<1)	330 (49)
Measurable[b]	317 (95)	328 (97)	645 (96)
Evaluable[c]	291 (87)	308 (91)	599 (89)

Note: Percentages calculated with the number of subjects in each group as denominator.
[a] Subject 220079 was randomized to the trabectedin+DOXIL but received only one dose of DOXIL, had adverse event and discontinued due to 'SUBJECT CHOICE' without receiving any Trabectedin.
[b] Measurable is defined as subjects having measurable disease at baseline assessed by the independent radiologist reviewer.
[c] Evaluable is defined as All-Measurable Subjects who received at least 1 dose of trabectedin or DOXIL, and for whom at least 1 post baseline response evaluation was available before the start of subsequent therapy for ovarian cancer, as assessed by the independent radiological review.
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Demographic and baseline disease characteristics for patients were similar between the two treatment arms and consistent with those of the planned study population described in the study protocol. The median age of the study population was 57 years (range, 26-87 years), 78% were white and 63% had a baseline performance status of 0. Serous histology (68%) was the most prevalent subtype and 52% had grade 3 tumours. Sites of involvement at baseline (median of 2 lesions) included abdomen (74%), pelvis (69%), liver (29%) and lungs (18%). The vast majority (99%) had previously undergone surgery for their cancer and 2% had received prior radiotherapy.

Consistent with the eligibility requirements, all patients had previously received at least one course of platinum-based chemotherapy, with 64% having platinum-sensitive disease (i.e., with PFI $\geq$ 6 months). The median number of agents used for prior chemotherapy was 2 (range, 1 to 7), including taxanes in approximately 80% of patients.

Table 11 –Demographics Data
(Study ET743-OVA-301: All Randomized Subjects Analysis Set)

(Study ET743-OVA-301: All Randomized Subjects Analysis Set)

	DOXIL (N=335)	Trabectedin/DOXIL (N=337)	Total (N=672)
Race, n (%)			
N	335	337	672
White	259 (77)	265 (79)	524 (78)
Asian	71 (21)	66 (20)	137 (20)
Black	3 (1)	2 (1)	5 (1)
Other	2 (1)	4 (1)	6 (1)
Age, Years			
N	335	337	672
Category, n (%)			
< 65	229 (68)	257 (76)	486 (72)
≥ 65	106 (32)	80 (24)	186 (28)
Mean (SD)	58.2 (10.75)	56.8 (10.48)	57.5 (10.63)
Median	58.0	56.0	57.0
Range	(27; 87)	(26; 82)	(26; 87)
Age ≥ 75, Years			
N	16	20	36
Mean (SD)	79.1 (3.48)	77.8 (2.27)	78.4 (2.91)
Median	78.5	77.5	78.0
Range	(75; 87)	(75; 82)	(75; 87)
Baseline Weight, kg			
N	335	337	672
Mean (SD)	68.9 (14.29)	69.5 (16.64)	69.2 (15.51)
Median	68.0	65.9	66.1
Range	(42; 111)	(36; 140)	(36; 140)
Height , (cm)			
N	330	334	664
Mean (SD)	159.9 (7.01)	160.3 (6.53)	160.1 (6.77)
Median	160.0	160.0	160.0
Range	(140; 188)	(144; 175)	(140; 188)
Baseline ECOG Performance Status, n (%)			
N	335	337	672
0	192 (57)	230 (68)	422 (63)
1	132 (39)	98 (29)	230 (34)
2	11 (3)	9 (3)	20 (3)
Platinum Sensitivity, n (%)			
N	335	337	672
Platinum Sensitive	212 (63)	218 (65)	430 (64)
Platinum Resistant	123 (37)	119 (35)	242 (36)
Baseline BMI, kg/m2			
N	330	334	664
Category, n (%)			
< 20	16 (5)	21 (6)	37 (6)
20 - < 25	118 (36)	129 (39)	247 (37)
25 - < 30	110 (33)	98 (29)	208 (31)
≥ 30	86 (26)	86 (26)	172 (26)
Mean (SD)	26.9 (5.23)	26.9 (5.83)	26.9 (5.54)
Median	26.2	25.5	25.9
Range	(16; 43)	(14; 47)	(14; 47)
Baseline BSA, m2			
N	335	336	671
Mean (SD)	1.719 (0.1834)	1.725 (0.1936)	1.722 (0.1885)
Median	1.700	1.700	1.700
Range	(1.29; 2.23)	(1.30; 2.42)	(1.29; 2.42)
Investigator Measurability, n (%)			
N	335	337	672
Measurable	305 (91)	317 (94)	622 (93)
Unmeasurable	30 (9)	20 (6)	50 (7)

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- **Efficacy results**

Primary endpoint: Progression Free Survival

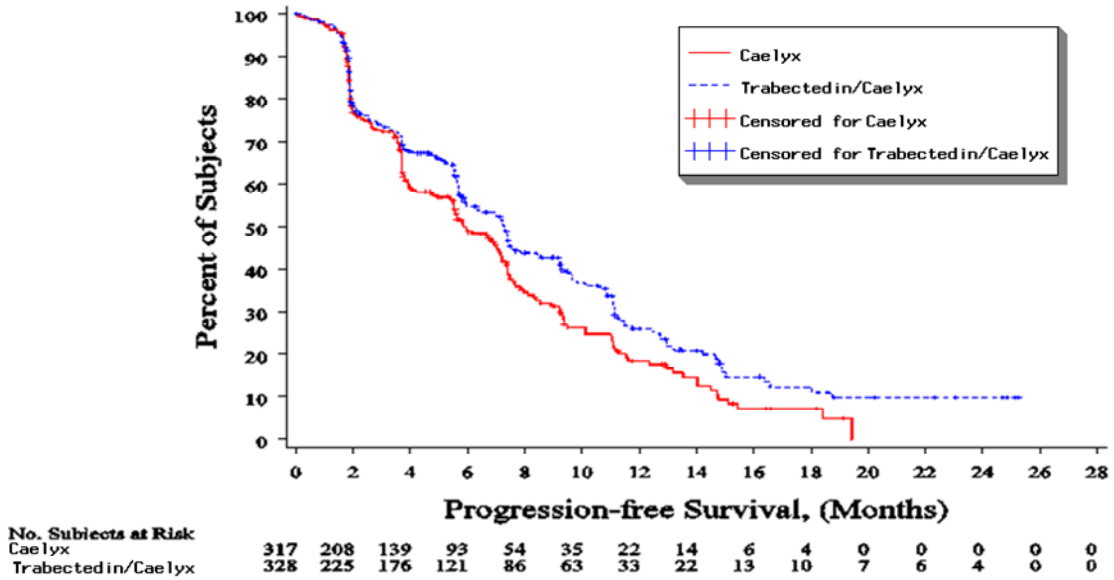
Regarding the analysis from independent radiologist, the results on PFS are described as follows:

Table 12 – Progression-Free Survival: Independent Radiologist Review Data (Study ET743-OVA-301: All-Measurable Subjects Analysis Set) Primary endpoint.

Descriptive[a]	Caelyx	Trabectedin + Caelyx
Progression free survival (months)		
Number of Assessed	317	328
Number Censored (%)	123 (38.8)	133 (40.5)
Number Failed (%)	194 (61.2)	195 (59.5)
25% Quantile (95% CI)	2.4 (1.9; 3.6)	2.6 (1.9; 3.7)
Median (95% CI)	5.8 (5.5; 7.1)	7.3 (5.9; 7.9)
75% Quantile (95% CI)	10.1 (8.9; 11.6)	12.7 (11.1; 14.8)
4 Months PFS Rate % (95% CI)	58.9 (52.7; 64.5)	67.6 (61.9; 72.6)
6 Months PFS Rate % (95% CI)	48.9 (42.5; 55.0)	54.6 (48.5; 60.4)
12 Months PFS Rate % (95% CI)	18.5 (12.9; 24.9)	25.8 (19.7; 32.3)
Overall p value[b]	0.0190	
Hazard Ratio (95% CI)(over Caelyx)		0.79 (0.65; 0.96)

PFS= progression-free survival
[a] Based on Kaplan-Meier product limit estimates.
[b] Log-rank test.
The Hazard Ratio is calculated as the hazard in the Trabectedin + Caelyx dosage group, divided by the hazard in the Caelyx dosage group.

Figure 4 –Kaplan-Meier Plot for Progression Free Survival: Independent Radiologist Review (Study: ET743-OVA-301: All-Measurable Subjects Analysis Set)



Regarding the analysis from oncologist and investigators, the results are described as follows:

Table 13 – Progression-free survival (OVA-301 study)

	Trabectedin + PLD	PLD	Hazard ratio[a]	p-value[b]
PFS – Independent oncology review in all randomised patients (sensitivity analysis)				
n	336	335		
Censored, n (%)	129 (38.4)	110 (32.8)		
Median PFS (95% CI) (months)	7.4 (6.4-9.2)	5.6 (4.2-6.8)	0.72 (0.60-0.88)	0.0008[c]
6 months PFS rate (95% CI) (%)	57.3 (51.3-62.8)	46.2 (40.2-52.0)		
12 months PFS rate (95% CI) (%)	26.0 (20.2-32.1)	16.2 (11.3-21.9)		
PFS – Per investigator in all randomised patients (sensitivity analysis)				
n	337	335		
Censored, n (%)	89 (26.4)	63 (18.8)	0.72 (0.61-0.86)	0.0002 [c]
Median PFS (95% CI) (months)	7.4 (6.2-8.3)	5.6 (5.1-5.8)		
6 months PFS rate (95% CI) (%)	55.8 (49.9-61.2)	43.7 (38.0-49.2)		
12 months PFS rate (95% CI) (%)	24.2 (19.2-29.5)	15.1 (11.1-19.7)		

Based on Kaplan-Meier product limit estimates.
[a]Over PLD alone. [b]Unstratified log-rank test. [c] Statistically significant at the 5% significance level.
PFS, progression-free survival.

Secondary analyses

Overall survival
In the initial variation application, the MAH submitted an analysis of OS data with the clinical cut-off date of 15 May 2008 established to achieve a pre-specified (415) number of PFS events. A total of 300 deaths (145 in the combination arm and 155 in the PLD alone arm) had occurred at cut-off date (55% censored data). Median OS was 20.5 months (95% CI, 18.7-24.2) in the combination arm and 19.4 months (95% CI, 17.3-21.7) in the PLD alone arm.
Further to the request of the CHMP to further justify the efficacy of the combination, on the basis of the magnitude of PFS gain of 6-8 weeks, the MAH conducted an *ad hoc* interim analysis of the secondary endpoint OS with a prospectively established cut-off date of 31 May 2009.

At the 31 May 2009 cut-off, a total of 419 death events (215 in the PLD monotherapy arm and 204 in the trabectedin + PLD combination arm) had occurred. This represents 81% of the 520 death events required for the final OS analysis, or 62% of the 672 randomised population. Current follow-up ranges from April 2005 to May 2009.

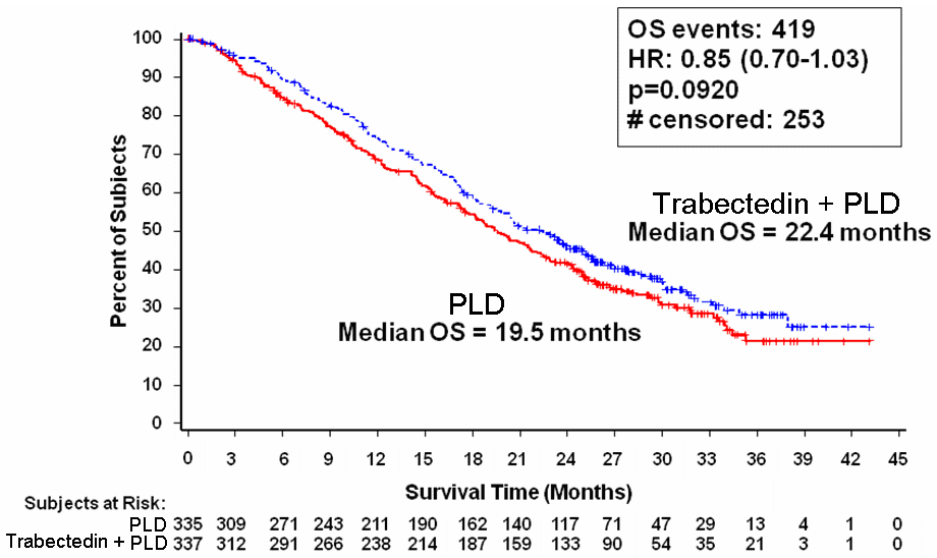
The trabectedin + PLD combination resulted in a 15% decrease in the risk of death compared with PLD alone [HR=0.85 (95% CI, 0.70-1.03); p=0.0920]. The median OS was 19.5 months (95% CI, 17.4-22.1) in the PLD monotherapy arm and 22.4 months (95% CI, 19.4-25.1) in the combination arm (Table 14 and Figure 5).

Table 14 –Unstratified analysis of overall survival in all randomised patients (study OVA-301).

	Trabectedin + PLD (n=337)	**PLD** (n=335)
Number of assessed	337	335
Number censored (%)	133 (39.5)	120 (35.8)
Number failed (%)	204 (60.5)	215 (64.2)
25% quartile (95% CI)	11.6 (10.5-14.0)	9.9 (8.3-11.7)
Median (95% CI)	22.4 (19.4-25.1)	19.5 (17.4- 22.1)
75% quartile (95% CI)	> 43.0 (33.1- --)	34.0 (30.8- --)
6-month survival rate % (95% CI)	89.6 (85.8-92.5)	84.7 (80.3- 88.2)
12-month survival rate % (95% CI)	74.4 (69.3-78.8)	68.4 (63.0-73.2)
18-month survival rate % (95% CI)	59.3 (53.8- 64.5)	54.3 (48.6-59.6)
24-month survival rate % (95% CI)	46.1 (40.5-51.5)	41.5 (36.0-47.0)
30-month survival rate % (95% CI)	36.9 (31.2-42.6)	30.8 (25.3-36.5)
36-month survival rate % (95% CI)	28.2 (21.9-34.9)	21.4 (15.2-28.4)
Overall p-value*		0.0920
Hazard ratio (95% CI) (over PLD)	0.85 (0.70-1.03)	

Based on Kaplan-Meier product limit estimates.
*Log rank test.
The hazard ratio is calculated as the hazard in the trabectedin + PLD treatment arm, divided by the hazard in the PLD treatment arm.
CI, confidence interval.

Figure 5 –Kaplan-Meier plot of overall survival (all randomised patients)



As shown above, with 419 death events (38% censored data) and an additional year of follow-up, the observed favourable trend for the trabectedin + PLD combination arm was maintained, with an identical HR=0.85 and a narrower 95% CI. Due to the larger number of events, the p value is now

0.0920. Median OS was identical at 19.5 months in PLD monotherapy arm, but is now 22.4 months, i.e., a 3-month difference with the combination arm.

Objective Response Rate

Table 15 –Objective response rate: independent radiology review in all randomised patients (OVA-301 study).

	Trabectedin + PLD	PLD	Odds ratio [a]	p-value [b]
N	337	335		
All responders (n)	93	63		
ORR (95% CI) (%)	27.6 (22.9-32.7)	18.8 (14.8-23.4)	1.646 (1.144-2.367)	0.0080
Best overall response, n (%)				
CR	2 (1)	4 (1)		
PR	91 (27)	59 (18)		
SD	146 (43)	164 (49)		
PD	74 (22)	72 (21)		
NE	24 (7)	36 (11)		

[a]Odds ratio for (trabectedin/PLD *vs.* PLD alone) calculated with the Cochran-Mantel-Haenszel test. [b] Fisher's exact test.
CR complete response; NE; non evaluable; PD, progressive disease; PR, partial response; ORR, objective response rate; SD, stable disease.

Others secondary endpoints
The median duration of response for the independent radiologist review in the Caelyx monotherapy arm was 7.7 months (range; 6.5 to 9.0 months) compared with the trabectedin + Caelyx arm which was 7.9 months (range; 7.4 to 9.2 months). The hazard ratio was 0.95 (95% CI: 0.62;1.46)

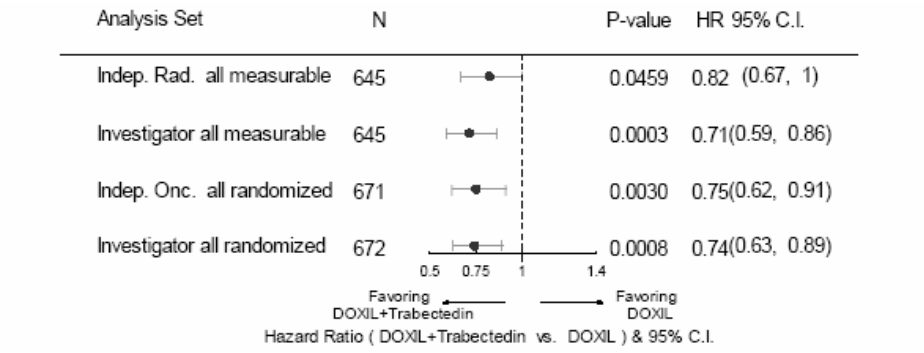
The Caelyx monotherapy arm showed a lower CA-125 CR rate than in the trabectedin + Caelyx arm (20% CR versus 30% CR). The Caelyx monotherapy arm showed a lower CA-125 PR rate than in the trabectedin + Caelyx arm (13% PR compared with 18% PR)

No statistically significant differences were found between treatment arms in global measures of QoL. Only minor, sporadic differences in the fatigue symptom scale were found in cycles 3 and 9, with some worsening of fatigue for subjects in the combination arm. Mixed-effects models predicting the score at baseline and follow-up scores as a function of treatment, days after baseline, and interaction between treatment and days after baseline showed no significant differences between arms for any QoL measure.

Supportive analyses

Progression-free survival analyses were repeated using platinum sensitivity as a stratification factor. Using the stratified log-rank test, a statistically significant treatment effect was observed in all analyses. Due to the low number of subjects with an ECOG performance status score of 2, these analyses were not carried out using ECOG performance status score as a stratification factor.

Figure 6 –Progression-Free Survival for Independent Reviewers and Investigator by Platinum Sensitivity (Study ET743-OVA-301, by Analysis Set).



Based on the Investigator's assignment of platinum sensitivity, a subgroup analysis was conducted using the updated survival data. The effect of trabectedin + PLD combination was more pronounced in platinum-sensitive patients (Figure 7) than in those with platinum-resistant disease (Figure 8), although in the resistant stratum both the HR=0.90 and median values (14.2 *vs.* 12.4 months) still favour the combination arm.

Figure 7 - Kaplan-Meier plot of overall survival in the platinum-sensitive stratum (PFI ≥ 6 months, study OVA-301).

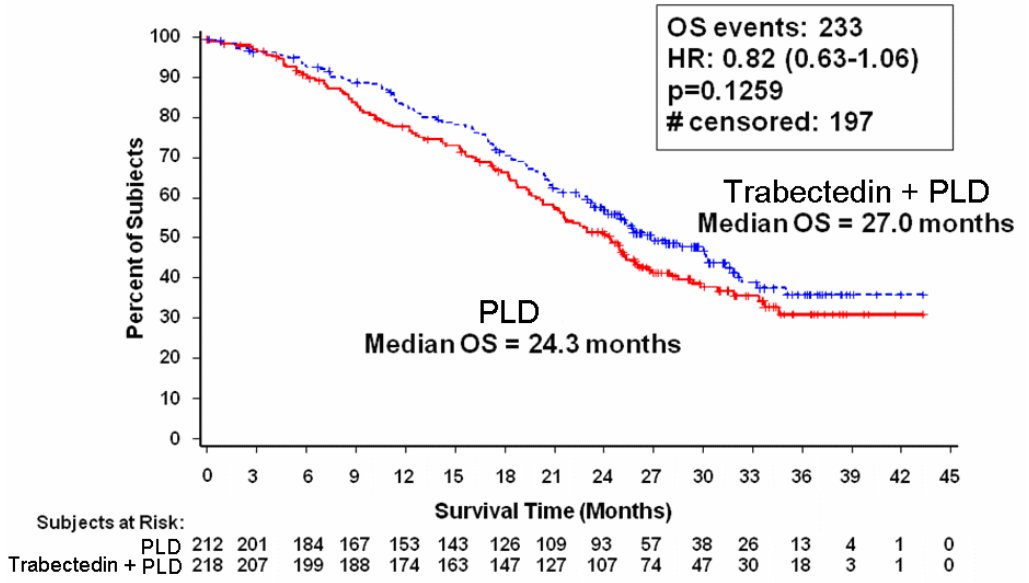
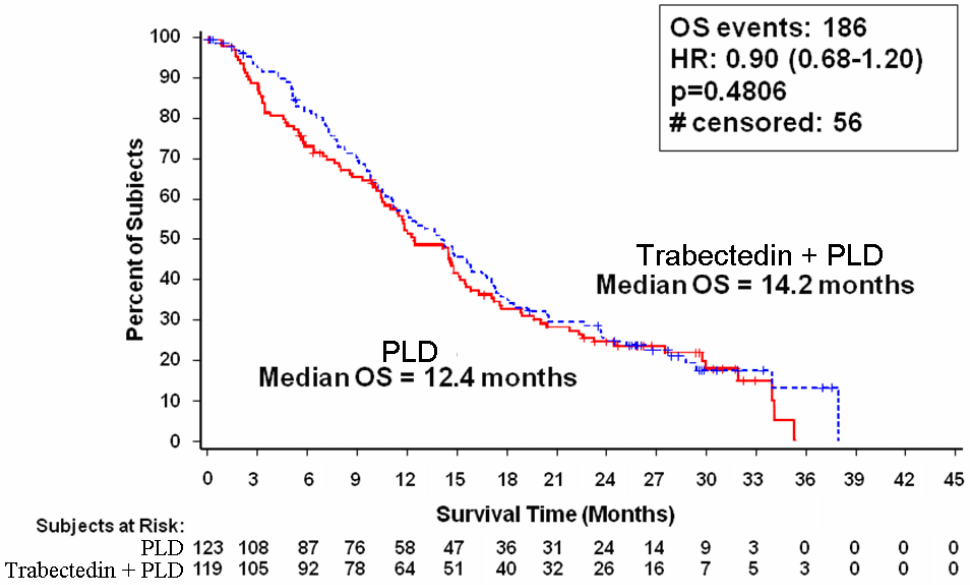


Figure 8 - Kaplan-Meier plot of overall survival in the platinum-resistant stratum (PFI < 6 months, study OVA-301).



As an exploratory analysis, the therapeutic effects of the trabectedin + PLD combination *vs.* PLD alone have been compared in the subset of patients with intermediate platinum-sensitivity, i.e., those with platinum-free interval (PFI) 6-12 months. The OS of this subset is shown in Figure 9. This is a subpopulation where there is a high medical need for new agents, and where single agent PLD is most often recommended, as indicated by the National Institute for Clinical Excellence (NICE) and the National Comprehensive Cancer Network (NCCN) guidelines.
In this subpopulation with intermediate platinum sensitivity (PFI 6-12 month) of OVA-301, with relatively mature data (~70% events), trabectedin + PLD induced a highly significant 41% reduction in the risk of death (HR=0.59; p=0.0015), with a 6-months advantage in median survival relative to single-agent PLD.

Figure 9. Kaplan-Meier plot of overall survival in intermediate platinum-sensitive (PFI 6-12 months) patients (study OVA-301).

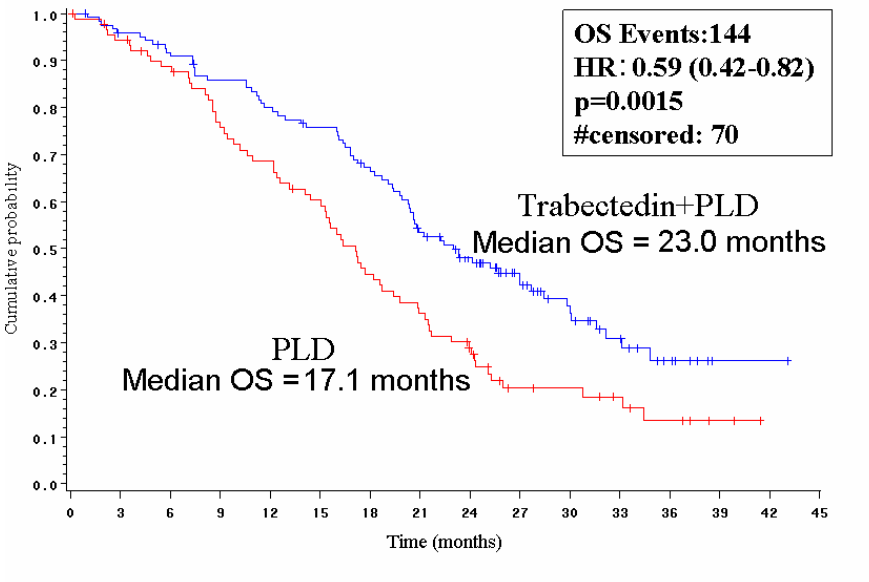
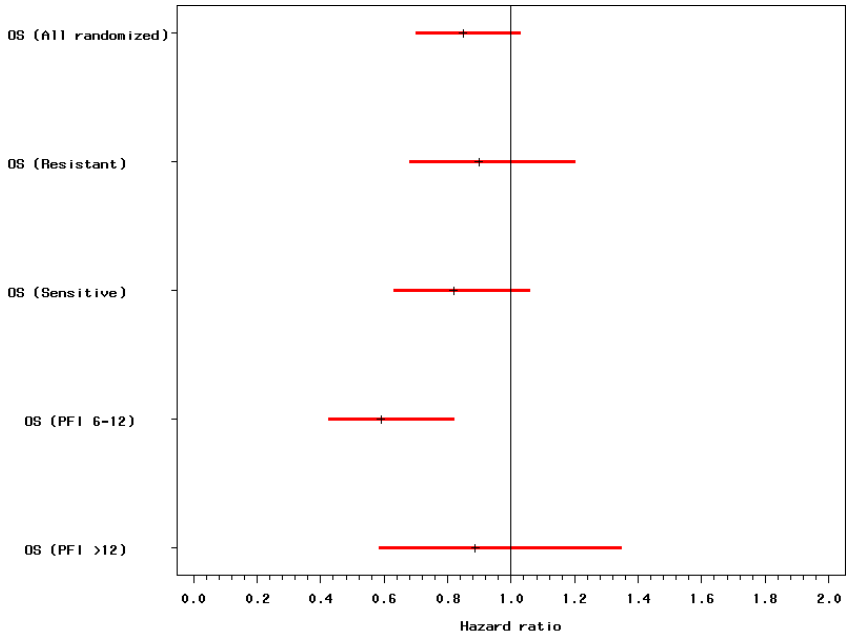


Figure 10 outlines a summary of the main and sensitivity analyses for the updated OS data. This figure illustrates again the consistency of the survival benefit obtained with the trabectedin + PLD combination. The favourable and consistent OS findings in this study strongly support the role of PFS as an appropriate surrogate for survival in this patient population.

Figure 10. Forest plot. Summary of main and sensitivity analyses for OS (study OVA-301).



Multivariate analyses

Cox proportional hazard models were used to compare the 2 treatment arms and included the following baseline covariates: ECOG performance status score (0 or >0), platinum sensitivity (platinum sensitive or platinum resistant), race (white or non–white), CA-125 (<2 times ULN or ≥2 times ULN), age (<65 years or ≥65 years of age), liver or lung involvement (yes or no), and prior taxane use (yes or no). Race, age, and prior taxane use were not considered in the reduced model, which excluded variables at a 0.15 significance level (p values for these covariates are 0.30, 0.42, and 0.86, respectively). Age <65 years and ≥65 years did not have a statistically significant effect on the outcome. The remainder of the covariates were included in the final mode. The interaction between treatment arms and platinum sensitivity was not statistically significant. Subjects with an ECOG performance status score of 0 or who were platinum-sensitive were at a lower risk of disease progression. The hazard ratio for the treatment effect is 0.763 (95% CI: 0.59;0.99), which represents a 24% reduction in risk of disease progression or death after adjustment for potential confounding factors. Similar results were obtained from oncologist and investigators reviews.

Table 16 – Progression-Free Survival: Multivariate Prognostic Factor Analysis-Reduced Model Independent Radiologist Review Data, All Measurable Subjects (Study ET743-OVA-301)

(Study ET743-OVA-301)

Factor	Parameter Estimate	Standard Error	Hazard Ratio	95% CI for Hazard Ratio	P-value
Number of Observations (N= 645)					
Treatment Arm: Trabectedin/DOXIL versus DOXIL	-0.270	0.135	0.763	(0.59;0.99)	0.0457
ECOG: 1 and 2 versus 0	0.234	0.106	1.263	(1.03;1.56)	0.0276
Platinum-Sensitivity: Resistant versus Sensitive	0.704	0.147	2.022	(1.52;2.70)	<.0001
Baseline CA-125: ≥2x ULN versus <2x ULN	0.185	0.133	1.203	(0.93;1.56)	0.1638
Baseline Liver/Lungs Involvement: Yes versus No	0.187	0.105	1.206	(0.98;1.48)	0.0737
Interaction[a]	0.276	0.207	1.318	(0.88;1.98)	0.1818

[a] Treatment x Platinum Sensitivity Interaction

Subjects having missing Baseline CA-125 are tabulated in <2x ULN.

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The subgroup analyses of PFS using the independent radiologists review of data from All-Measurable Subjects are presented in next figure. Progression-free survival was analyzed for each category of the following variables: baseline ECOG performance status score, platinum sensitive or platinum resistant, age group (<65 years or ≥65 years), baseline CA-125 (≥2 times the ULN or <2 times the ULN), prior taxanes use (yes or no), baseline liver/lung (yes or no), race (white or non-white), and histology grade (Grades 1, 2, 3, or unknown).

Figure 11 –PFS, Independent Radiologist Review for All Measurable Subjects Hazard Ratio and 95% Confidence Interval (Study ET743-OVA-301, PFS Independent Radiologist Review, All Measurable Subjects).

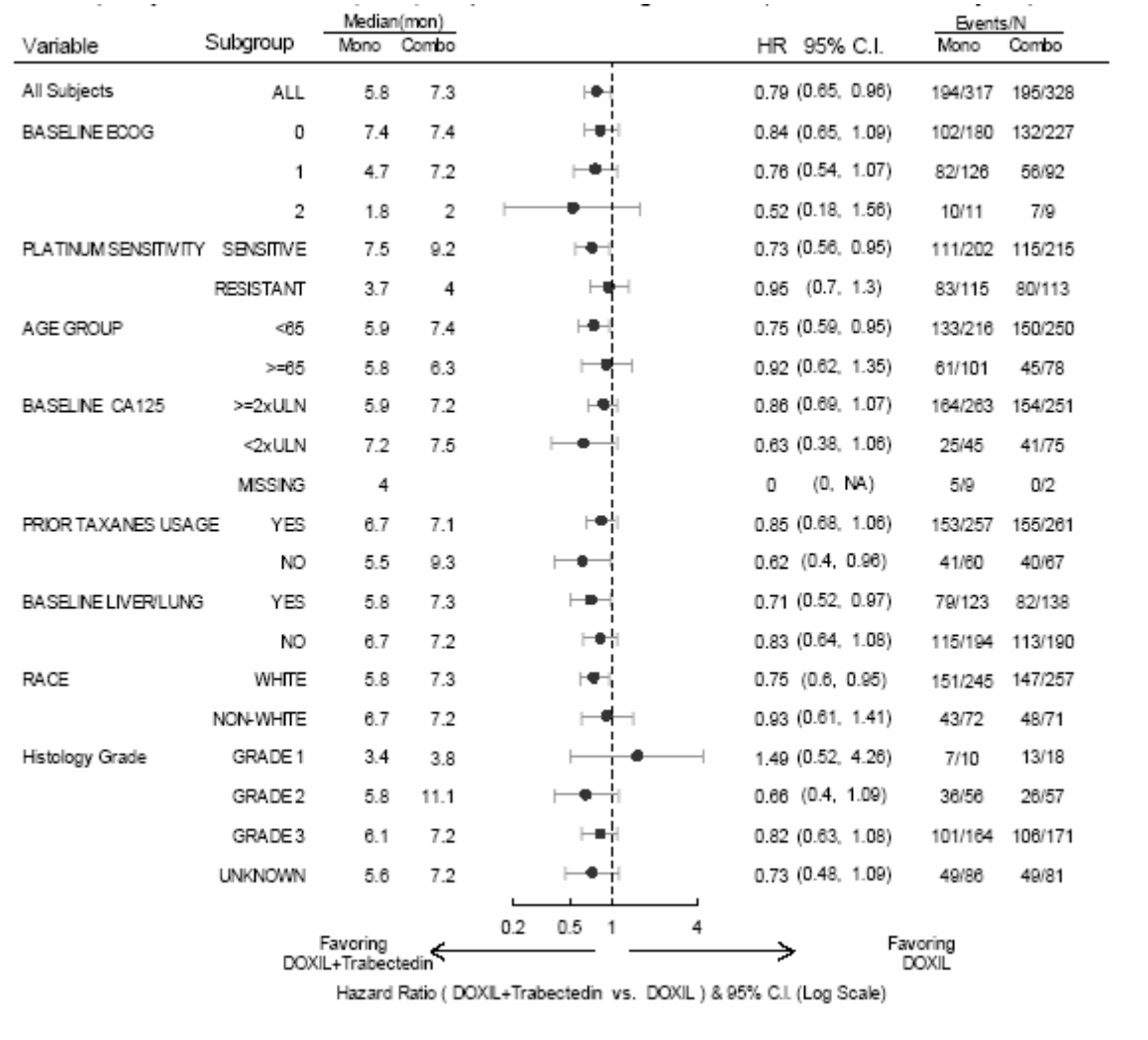
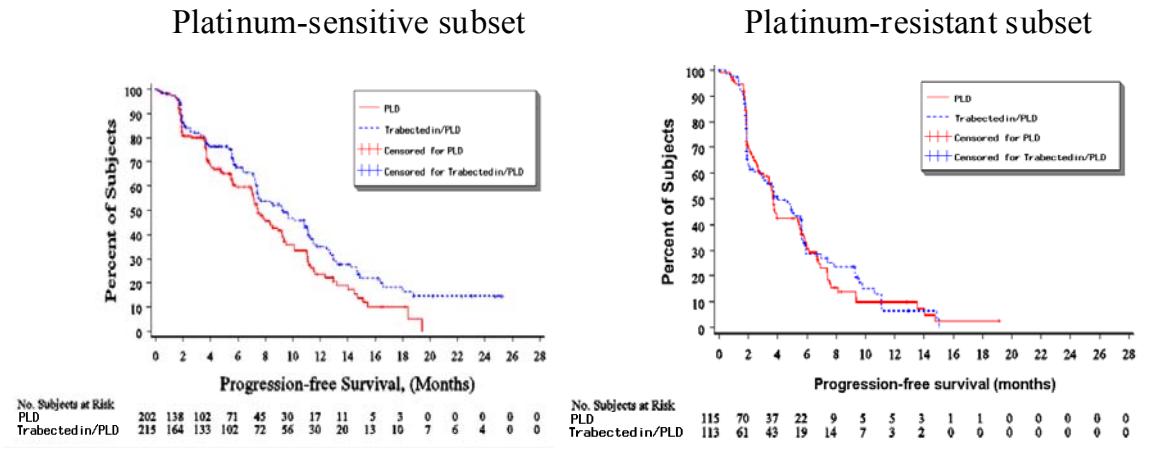
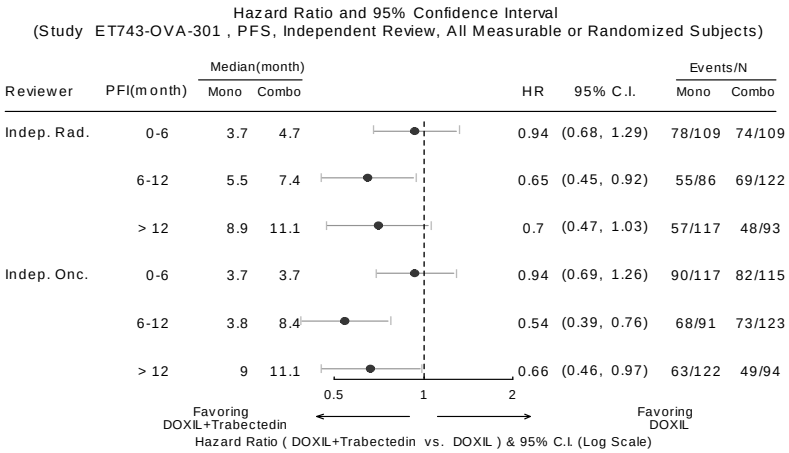


Figure 12 –Kaplan-Meier plot of progression-free survival: subset analysis per platinum-free interval (left graph: platinum-sensitive subset; right graph, platinum-resistant disease) (OVA-301 study).



In addition, the MAH has submitted an analysis of Progression-Free Survival by Sponsor's Assignment of Platinum-Free Interval. The subgroup analysis of PFS by platinum sensitivity based on

Sponsor's assignment of PFI was conducted using both independent radiologist review and independent oncologist review.



The importance of the imbalanced prognostic factors observed (Age, ECOG and ascites) on the PFS and OS was uncertain. In order to correctly show the effect of the imbalanced prognostic factors, the MAH was requested to submit further analyses of univariate results for treatment effect, multivariate approach for main effects and multivariate approach for evaluation of interaction effects. Each analysis included at least the variable (treatment group, ECOG PS, Platinum sensitivity, Ascite and Bulky disease), hazard ratio, 95% CI & p-value. These data reinforced the overall conclusion that the combination trabectedin + PLD arm has a significant effect independent from the effect of the covariates and, in consequence, the results have not been influenced by the imbalances observed in some baseline patient characteristics. Moreover, the results of the additional analyses on the impact of ascites (yes vs. no), together with an exploratory multivariate analysis addressing the combined potential influence of baseline ascites and platinum-free interval, do not suggest a negative impact of these prognostic factors on the treatment effects favouring the trabectedin + PLD combination in OVA-301.

1.4.2.2. Supportive studies

OVA-301 results are supported by data from trabectedin administered as a single-agent using three different regimens (two every-3-week schedules, q3wk 3-h and q3wk 24-h, and one weekly schedule, qwk 3-h) in three phase II clinical trials: ET-B-026-03, ET-B-009-99 and ET743-INT-11. The efficacy results for these three phase II trials are summarised in next table.

Table 17 –Overview of efficacy results for phase II studies with trabectedin as single-agent administered to patients with relapsed, advanced ovarian cancer.

	ET-B-026-03*		ET-B-009-09** (q3wk 3-h 1.3 mg/m²)§	ET743-INT-11*** (qwk 3-h 0.58 mg/m²)
	Arm A (q3wk 24-h 1.5 mg/m²)	Arm B (q3wk 3-h 1.3 mg/m²)		
n	54	53	29	51
ORR (%)	38.9 (25.9-53.1)	35.8 (23.1-50.2)	43.5 (23.3-65.5)	29.4 (17.5-43.8)
TTP				
Median (months)	6.2 (5.3-8.6)	6.8 (4.6-7.4)	6.7 (5.0-7.9)	5.3 (3.1-6.5)
PFS				
Median (months)	6.0 (4.6-8.6)	6.8 (4.1-7.4)	6.7 (5.1-7.9)§§	5.3 (3.1-6.4)
OS[a]				
Median (months)	-	-	-	17.1 (14.3-nr)

In brackets, 95% confidence intervals (CI). [a]Follow-up for survival was no planned in most of these phase II studies. The primary efficacy outcome was ORR.
* Platinum-sensitive disease. Data shown are per investigator assessment of tumour response in all randomised patients (primary analysis of efficacy, including seven patients with platinum-resistant disease).
**Data shown are per peer review of tumour response in the relapsed patients group.
***Data shown are for patients with platinum-sensitive disease.
§Starting dose 1.5 mg/m^2 in eight patients.
§§Data from Summary of Clinical Efficacy
nr, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q3wk 3-h, every 3 weeks (Day 1 of 21-day cycle) 3-hour intravenous infusion; q3wk 24-h, every 3 weeks (Day 1 of 21-day cycle) 24-hour intravenous infusion; qwk 3-h, weekly (Days 1, 8, and 15 of a 28-day cycle) 3-hour intravenous infusion; TTP, time to progression.

Study ET-B-026-03 was a multicentre, two-arm, randomised, controlled, phase II clinical trial evaluating two schedules of trabectedin administered to a relapsed, platinum-sensitive, advanced ovarian cancer population. The primary objective was to determine the optimal regimen of trabectedin when infused over a 24-hour or 3-hour infusion in an every-3-weeks schedule by evaluating objective response rate. As of February 2007, 107 (100 evaluable patients planned) were treated and randomly assigned to either a q3wk 24-h regimen at 1.5 mg/m2 (Arm A, n=54) or a q3wk 3-h regimen at 1.3 mg/m2 (Arm B, n=53).
In the ITT primary analysis, which included all randomised patients, the ORR was 38.9% (95% CI, 25.9-53.1%) in Arm A and 35.8% (95% CI, 23.1-50.2%) in Arm B. Whilst not powered statistically in its design to compare efficacy outcomes in either arm, an exploratory analysis revealed no statistically significant differences between treatment arms with respect to ORR (p=0.8422). Twelve patients (6 in each treatment arm) achieved complete response and 28 patients (15 patients in Arm A and 13 patients in Arm B) achieved partial response.

In an exploratory analysis, no statistically significant differences were seen between treatment arms for any of the secondary time-to-event endpoints, which included duration of response, TTP and PFS. Observed toxicities were similar as well, with the 3-hour infusion having a slightly lower rate of myelosuppression (55 vs. 37% of grade 3/4 neutropenia) and less fatigue, thus resulting the 3-hour infusion schedule more convenient for patients.

Based on these results, no additional comparisons between these two trabectedin every-3-week schedules were deemed warranted. Trabectedin infusion every three weeks had promising activity in advanced ovarian cancer patients previously treated with a platinum-based chemotherapeutic regimen.

Study ET-B-009-99 was a multicentre, single-arm, open-label, two-step phase II trial. The primary objective was to determine the antitumour activity (in terms of ORR) of trabectedin administered as a 3-hour i.v. infusion (q3wk 3-h regimen) as a salvage therapy in ovarian cancer patients failing one platinum-taxane containing regimen. Patients with persistent or recurrent ovarian cancer were eligible. As required by the protocol, all patients had received therapy with platinum- and taxane-containing regimens. Refractory patients were defined in this study as those with progression on chemotherapy or within 6 months from the discontinuation of previous chemotherapy. Relapsed patients were defined as those having relapsed following an objective response to platinum-taxane chemotherapy, with an

interval ≥ 6 months between the last dose received and the documentation of relapse. Fifty-nine patients were enrolled overall: 29 patients in the relapsing group and 30 in the refractory group, of whom 51 were evaluable for efficacy. The first six patients received a higher initial dose (1.65 mg/m2). Due to the poor tolerance of this dose, the study was amended to include a lower starting dose. The remaining patients received trabectedin 1.3 mg/m2 every 3 weeks, which was well tolerated. However, 12 patients received an initial dose of 1.5 mg/m2.

ORR (per RECIST and peer-review evaluated) was 43.5% (95% CI, 23.3-65.5%) for the relapsing patient group (with one complete response and nine partial responses) and 7.1% (95% CI, 0.9-23.5%) for the refractory patient group, TTP for relapsed patient group was 6.7 months (95% CI, 5.0-7.9 months).

Study ET743-INT-11 was a multicentre, single-arm, open-label phase II trial. Trabectedin 0.58 mg/m2 was administered as a 3-hour infusion weekly (qwk 3-h) for the first 3 weeks of a 4-week cycle. A total of 147 patients were accrued and treated, including 51 patients with platinum-sensitive disease and 62 patients with platinum-resistant disease in the primary efficacy analysis.

The primary objective of this study was to determine the ORR in patients with platinum-sensitive and platinum-resistant advanced ovarian cancer after treatment with trabectedin, administered as a 3-hour infusion at the starting dose of 0.58 mg/m2 every week for 3 weeks of a 4-week cycle. Patients with platinum-sensitive ovarian carcinoma had disease progression > 6 months after cessation of platinum-based chemotherapy, whereas patients with platinum-resistant ovarian carcinoma were defined in this study as those with disease progression during treatment or disease relapse at ≤ 6 months after cessation of platinum-based chemotherapy.

The ORR was 29.4% (95% CI, 17.5-43.8%) for the platinum-sensitive cohort and 4.8% (95% CI, 1.0-13.5%) for the platinum-resistant cohort. Median PFS and OS for the platinum-sensitive cohort were 5.3 months (95% CI, 3.1-6.4 months) and 17.1 months (95% CI; 14.3 months-upper level not reached), respectively.

1.4.2.3. Analysis performed across trials (pooled analyses and meta-analysis)

Integrated analysis of PFS data from all three phase II trials evaluating trabectedin as single-agent treatment in patients with relapsed ovarian cancer is shown in next table. Median PFS of the integrated q3wk regimens for the 3-hour or the 24-hour i.v. infusions were very similar: 5.5 months (range, 4.6-6.9) for the 3-hour infusion and 6.0 months (range, 4.6-8.6) for the 24-hour infusion. In contrast, PFS for the qwk 3-hour treatment regimen was shorter, with a median of 2.8 months (range, 2.0-3.8).

Table 18 –Integrated analysis of progression-free survival in phase II studies with trabectedin as single-agent in patients with relapsed ovarian cancer

	q3wk 24-h (1.5 mg/m^2)	**q3wk 3-h (1.3 mg/m^2)**	**qwk 3-h (0.58 mg/m^2)**	**Total**
n	54	94	147	295
Censored, n (%)	19 (35.2)	22 (23.4)	24 (16.3)	65 (22.0)
Median (95% CI)	6.0 (4.6-8.6)	5.5 (4.6-6.9)	2.8 (2.0-3.8)	4.6 (3.6-5.3)
6 Month PFS Rate (95% CI)	52.2 (36.1-66.0)	45.4 (34.4-55.7)	24.5 (17.6-32.0)	35.8 (30.0-41.7)
12 Month PFS Rate (95% CI)	14.3 (4.8-28.7)	10.8 (4.5-20.1)	5.9 (1.9-13.2)	8.9 (5.2-13.7)

Based on Kaplan-Meier product limit estimates. All treated patients (includes patients with both platinum-sensitive and platinum-resistant disease).

1.4.2.4. Discussion on clinical efficacy

ET743-OVA-301 was a well-conducted phase III trial comparing Caelyx with Caelyx/trabectedin in 663 patients with relapsed ovarian cancer. The primary endpoint PFS showed a clear advantage for the combination therapy whichever dataset was used. With the most conservative assessment a 21% risk

reduction for the PFS endpoint could be considered evidence of activity of trabectedin (this is also supported by phase II data). However, the absolute magnitude of PFS prolongation (about 1.5 months) is not impressive considering that there is no clear support of overall survival prolongation. Final overall survival analysis is pending, since it only will performed when 520 deaths are observed. Whereas PFS may be a valid surrogate for the OS endpoint in first-line treatment (chemo-naïve patients) this correlation may not be well substantiated in later-line therapy situations and that is the main weakness of the application dossier.

The magnitude of PFS gain (6-8 weeks) and the HR (0.72-0.79) in favour of the combination of trabectedin + PLD observed in the OVA-301 trial do not differ from efficacy results of other randomised trials in comparable populations of women with ovarian carcinoma. A number of sensitivity analyses support the robustness of the PFS endpoint. At the request of the CHMP, the importance of the imbalanced prognostic factors observed (Age, ECOG and ascites) on the PFS and OS has been further analysed. In summary, these data reinforce the overall conclusion that the combination trabectedin + PLD arm has a significant effect independent from the effect of the covariates and, in consequence, the results have not been influenced by the imbalances observed in some baseline patient characteristics. Moreover, the results of the additional analyses on the impact of ascites (yes vs. no), together with an exploratory multivariate analysis addressing the combined potential influence of baseline ascites and platinum-free interval, do not suggest a negative impact of these prognostic factors on the treatment effects favouring the trabectedin + PLD combination in OVA-301.

Moreover, the difference in PLD dosing schedule was of concern. In the combination arm, PLD is given every three weeks, compared to every four weeks in the monotherapy arm, raising doubts on whether the effect seen in the combination arm is actually an effect of treating with PLD more frequently. Thus, the actual benefit of adding Yondelis to PLD could be less than 1.5 months PFS gain. The two parameters better correlated with the efficacy of PLD are dose intensity and C_{max}. Both were substantially greater in the control arm than in the combination arm, favouring an enhanced efficacy of PLD in the control arm. Thus, the more frequent administration of PLD at lower doses in the combination arm is an unlikely explanation for the improved outcomes demonstrated with trabectedin + PLD in OVA-301. Therefore, such superior outcomes with the combination support the contribution of trabectedin, an agent with proven single agent activity in advanced relapsed ovarian cancer.

As previously stated there is clear evidence of antitumour activity of the combination of PLD and trabectedin and provided that a significant improvement in overall survival support the PFS endpoint this would be considered sufficient evidence of benefit in terms of efficacy.

Further reassurance on the maturity of the OS data was needed. The protocol-specified interim analysis of overall survival (OS) was carried out with 300 events, and even though the data are clearly immature, a favourable trend appears for the combination (HR=0.85) and survival curves remain separated throughout the entire observation period. The MAH conducted an *ad hoc* interim analysis with approximately 80% death events (416 of the required 520 deaths at the cut-off date of 31 May 2009 when a total of 419 death events (215 in the PLD monotherapy arm and 204 in the trabectedin + PLD combination arm) had occurred). This represents 81% of the 520 death events required for the final OS analysis, or 62% of the 672 randomised population. Due to the larger number of events, the p value is now 0.0920. Median OS was identical at 19.5 months in PLD monotherapy arm, but is now 22.4 months, i.e., a 3-month difference with the combination arm.

The benefit in terms of PFS prolongation appeared more evident in the subset of patients with platinum-sensitive disease as compared to patients with platinum-resistant disease. This finding does not in itself have a negative impact of the overall conclusion on clinical efficacy but the population with platinum-resistant disease has the highest medical need whereas patients with platinum-sensitive disease may have a second treatment cycle with tumour response. However, Study OVA 301 was not powered to detect differences in outcome according to platinum-resistance status. The result of a multivariate analysis indicates that treatment effect and platinum sensitivity acted as independent factors with influence on PFS. Although a long platinum-free interval points to a better outcome in

terms of PFS as compared to a short interval (platinum-resistance), the CHMP agree that the benefit in the platinum-resistant subset cannot be ruled out.

The fact that patients with platinum sensitive disease (as measured by a long platinum-free interval) still have the option to be retreated with a platinum-containing regimen should not per se be an obstacle for approving the combination of PLD and trabectedin. PLD was approved for "*treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen*". The registration study for PLD with topotecan as comparator also included patients with both platinum-sensitive and platinum-refractory disease. However, it is unfortunate that the performance of trabectedin + PLD against common practice (retreatment with platinum) is unknown. Superiority against the approved PLD has been demonstrated. Based on the Investigator's assignment of platinum sensitivity, a subgroup analysis was conducted using the updated survival data. The effect of trabectedin + PLD combination was more pronounced in platinum-sensitive patients than in those with platinum-resistant disease, although in the resistant stratum both the HR=0.90 and median values (14.2 *vs.* 12.4 months) still favour the combination arm.

1.4.3. Clinical Safety

1.4.3.1. Patient exposure

Safety data from Study ET743-OVA-301 comprise the principal information supporting the safety of trabectedin in combination with Caelyx for the treatment of relapsed ovarian cancer. Safety information from the 3 Phase 2 studies in subjects with relapsed ovarian cancer with trabectedin as a single agent provide the primary supporting data for the safety of trabectedin in this population.

Thus, the main analyses of safety in this document are based on the following 3 safety analysis sets, which are derived from data from completed Phase 3 and Phase 2 studies:

- Study ET743-OVA-301 safety analysis set (N=663)
- Integrated Phase 2 ovarian safety analysis set (N=295): Pooled data from the Phase 2 Studies ET743-INT-11, ET-B-026-03, and ET-B-009-99 of trabectedin as a single agent in women with relapsed ovarian cancer. Data are categorized according to the trabectedin dosing schedule and starting dosage: 1.3 mg/m2 q3wk 3-h, 1.5 mg/m2 q3wk 24-h, and 0.58 mg/m2 qwk 3-h.
- Integrated Phase 2 safety analysis set (N=1,132): Pooled data from the 19 Phase 2 studies of trabectedin as a single agent in various tumour types, including 3 Phase 2 studies in relapsed ovarian cancer analysed separately in group 2, and 16 Phase 2 studies in non-ovarian solid tumours. Data are categorized according to the trabectedin dosing schedule and starting dosage: 1.3 mg/m2 q3wk 3-h, 1.5 mg/m2 q3wk 24-h, and 0.58 mg/m2 qwk 3-h.

The integrated safety analysis was based on data from 19 Phase 2 studies completed up to April 2008, and is presented as a full revised analysis.

Table 19 – Completed Phase 2/3 Clinical Studies in Ovarian Cancer

Study Phase/ Study Number	Study Design (Diagnosis)	Study Treatment(s), Starting Dose, and Regimen(s)	No. Subjects Evaluable for Safety[a]	No. Subjects Included in Integrated Safety Analysis Sets
Phase 3				
ET743-OVA-301[e]	Randomized, open-label, comparison Advanced ovarian cancer failing platinum regimen	Trabectedin 1.1 mg/m^2 (q3wk 3-h) + Caelyx 30 mg/m^2 (q3wk 1.5-h)	333[b]	N/A
		Caelyx 50 mg/m^2 (q4wk 1.5 h)	330[b]	N/A
Phase 2				
ET-B-009-99*[f]	Open-label Advanced ovarian cancer failing platinum + taxane regimen	Trabectedin 1.3 mg/m^2 q3wk 3-h	59	41[c]
ET-B-026-03[f]	Randomized, open-label	Trabectedin 1.3 mg/m^2 q3wk 3-h	53	53
	Advanced, recurrent, platinum-sensitive ovarian cancer	Trabectedin 1.5 mg/m^2 q3wk 24-h	54	54[d]
ET743-INT-11*[f]	Open-label Advanced ovarian cancer	Trabectedin 0.58 mg/m^2 qwk 3-h	147	147
Grand Total Receiving Trabectedin			***646***	***295***

KEY: q3wk 3-h: 3-h infusion on Day 1 of 3-week cycle.
q3wk 1.5-h: 90 minute infusion on Day 1 of 3-week cycle.
q4wk 1.5-h: 90-minute infusion on Day 1 of 4-week cycle.
q3wk 24-h: 24-h infusion on Day 1 of 3-week cycle.
qwk 3-h: 3-h infusion on Days 1, 8, and 15 of 4-week cycle.

N/A = not applicable; No. = number

[a] Any subject who received at least 1 dose of study treatment.

[b] One subject randomized to the trabectedin + Caelyx arm received the initial infusion of Caelyx and was discontinued before receiving any exposure to trabectedin. Safety data for this subject were analyzed under the treatment that was actually received (Caelyx) and not the treatment group to which she had been randomized.

[c] Eighteen subjects received trabectedin starting doses of 1.5 mg/m^2 (n=12) or 1.65 mg/m^2 (n=6) and were not included in the integrated safety analyses. Safety information for these subjects are included in the clinical study report for Study ET-B-009-99

[d] Subject No. 127 was assigned to receive 1.2 mg/m^2 as a starting dose (actual dose received was 1.3 mg/m^2 based on body surface area calculation), instead of recommended 1.5 mg/m^2. This subject was included in the integrated safety analyses.

[e] CSR

[f] CSR

* **Phase 2 studies included in the Integrated Analysis of the STS MAA Clinical Safety Summary.**

1.4.3.2. Adverse events

In general, the incidence rates for Grade 3 or 4 adverse events, serious adverse events, and adverse events leading to discontinuation were higher for trabectedin administered in combination with Caelyx (Study ET743-OVA-301) compared with trabectedin as a single agent in the target indication at the proposed regimen (q3wk 3-h) for the integrated Phase 2 ovarian safety analysis set.

Table 20 – Safety Profile
(Study ET743-OVA-301: All-Treated Subjects Analysis Set)

	Caelyx (N=330) n (%)	Trabectedin + Caelyx (N=333) n (%)
Treatment-emergent adverse events (TEAEs)	326 (99)	333 (100)
Drug-related	312 (95)	332 (>99)
Grade 3-4 TEAEs	237 (72)	304 (91)
Drug-related	193 (58)	295 (89)
Serious TEAEs	101 (31)	130 (39)
Drug-related	44 (13)	90 (27)
Grade 3-4	77 (23)	112 (34)
TEAE leading to treatment termination[a]	50 (15)	78 (23)
Drug-related	31 (9)	57 (17)
All deaths within 30 days of last dose	8 (2)	11 (3)
Deaths due to TEAE	1 (<1)	5 (2)
Progressive disease	6 (2)	6 (2)
Other	1 (<1)	0

TEAE = treatment-emergent adverse event

[a] The information regarding TEAE leading to treatment termination in this table is based on data collected on the Adverse Event page of the CRF.

Table 21 - Safety Profile
(Trabectedin - Integrated Phase 2 Ovarian Studies: All-Treated Subjects Analysis Set)

	q 3 wk; 24-h (1.5 mg/m^2) (N=54) n (%)	q wk; 3-h (0.58 mg/m^2) (N=147) n (%)	q 3 wk; 3-h (1.3 mg/m^2) (N=94) n (%)	Total (N=295) n (%)
Treatment-emergent adverse events (TEAEs)	52 (96)	146 (99)	92 (98)	290 (98)
Drug-related	50 (93)	141 (96)	87 (93)	278 (94)
Grade 3-4 TEAEs	39 (72)	91 (62)	43 (46)	173 (59)
Drug-related	38 (70)	58 (39)	32 (34)	128 (43)
Serious TEAEs	13 (24)	48 (33)	24 (26)	85 (29)
Drug-related	8 (15)	22 (15)	14 (15)	44 (15)
Grade 3-4	13 (24)	40 (27)	21 (22)	74 (25)
Drug-related Grade 3-4	8 (15)	14 (10)	14 (15)	36 (12)
TEAE leading to discontinuation	13 (24)	18 (12)	11 (12)	42 (14)
Death due to TEAE	0	3 (2)	3 (3)	6 (2)
Within 30 days of last dose	0	3 (2)	1 (1)	4 (1)
Within 60 days of first dose	0	2 (1)	3 (3)	5 (2)
Drug-related TEAE leading to death	0	1 (1)	1 (1)	2 (1)

qwk = once weekly; q3wk = once every 3 weeks; TEAE = treatment-emergent adverse event
Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events.
Note: All adverse events with toxicity Grade 1-5 and unknown toxicity grades are included in the analysis.

Gastrointestinal disorders were the most common adverse events in Study ET743-OVA-301. While the overall incidence of these disorders were similar for the Caelyx monotherapy (83%) and trabectedin + Caelyx (89%) arms, the frequencies for certain of these events differed by ≥10% between the 2 treatment arms. Specifically, nausea (42% for Caelyx monotherapy versus 74% for trabectedin + Caelyx) and vomiting (30% for Caelyx monotherapy versus 56% for trabectedin + Caelyx) were reported more frequently in the trabectedin + Caelyx arm, while stomatitis (33% for Caelyx monotherapy versus 20% for trabectedin + Caelyx) was more frequent in the Caelyx monotherapy arm.

Blood and lymphatic system disorders were reported less frequently in the Caelyx monotherapy arm (55%) than in the trabectedin + Caelyx arm (88%). This was mainly due to a higher incidence for the trabectedin + Caelyx arm for neutropenia (38% for Caelyx monotherapy versus 77% for trabectedin + Caelyx), leukopenia (26% for Caelyx monotherapy versus 48% for trabectedin + Caelyx), anaemia (25% for Caelyx monotherapy versus 48% for trabectedin + Caelyx), and thrombocytopenia (8% for Caelyx monotherapy versus 36% for trabectedin + Caelyx).

Compared with the Caelyx monotherapy arm, the trabectedin + Caelyx arm had higher rates for ALT increased (9% for Caelyx monotherapy versus 55% for trabectedin + Caelyx), AST increased (10% for Caelyx monotherapy versus 40% for trabectedin + Caelyx), blood alkaline phosphatase increased (8% for Caelyx monotherapy versus 23% for trabectedin + Caelyx), and hyperbilirubinemia (7% for Caelyx monotherapy versus 16% for trabectedin + Caelyx).

Hand-foot syndrome, was reported by more than one-half (54%) of subjects in the Caelyx monotherapy arm but occurred at a lower rate (24%) in the trabectedin + Caelyx arm.

Table 22 - Treatment -Emergent Adverse Events - by Body System and Preferred Term in at Least 5% of Subjects (Study ET743-OVA-301: All-Treated Subjects Analysis Set)

MedDRA SOC Term MedDRA Preferred Term	Caelyx (N=330) n (%)	Trabectedin + Caelyx (N=333) n (%)
Gastrointestinal disorders	273 (83)	297 (89)
Nausea	140 (42)	246 (74)
Vomiting	98 (30)	185 (56)
Constipation	92 (28)	107 (32)
Diarrhoea	63 (19)	86 (26)
Abdominal pain	79 (24)	70 (21)
Stomatitis	108 (33)	68 (20)
Dyspepsia	35 (11)	43 (13)
Abdominal distension	24 (7)	19 (6)
Abdominal pain upper	23 (7)	19 (6)
Ascites	20 (6)	17 (5)
Mouth ulceration	23 (7)	11 (3)
Blood and lymphatic system disorders	180 (55)	293 (88)
Neutropenia	126 (38)	258 (77)
Leukopenia	87 (26)	161 (48)
Anaemia	84 (25)	160 (48)
Thrombocytopenia	27 (8)	121 (36)
Febrile neutropenia	7 (2)	27 (8)
General disorders and administration site conditions	204 (62)	238 (71)
Fatigue	120 (36)	154 (46)
Pyrexia	44 (13)	65 (20)
Asthenia	39 (12)	55 (17)
Mucosal inflammation	64 (19)	41 (12)
Oedema peripheral	27 (8)	30 (9)
Pain	13 (4)	18 (5)
Non-cardiac chest pain	11 (3)	16 (5)
Investigations	92 (28)	223 (67)
Alanine aminotransferase increased	31 (9)	182 (55)
Aspartate aminotransferase increased	34 (10)	134 (40)
Blood alkaline phosphatase increased	28 (8)	76 (23)
Blood creatine phosphokinase increased	10 (3)	24 (7)
Blood creatinine increased	19 (6)	21 (6)
Weight decreased	15 (5)	15 (5)
Skin and subcutaneous tissue disorders	223 (68)	171 (51)
Palmar-plantar erythrodysaesthesia syndrome	177 (54)	81 (24)
Alopecia	45 (14)	40 (12)
Rash	57 (17)	36 (11)
Skin hyperpigmentation	23 (7)	21 (6)
Dry skin	10 (3)	18 (5)
Erythema	19 (6)	18 (5)
Pruritus	19 (6)	12 (4)
Metabolism and nutrition disorders	135 (41)	160 (48)

Anorexia	86 (26)	105 (32)
Hypokalaemia	25 (8)	37 (11)
Hypoalbuminaemia	20 (6)	21 (6)
Hyponatraemia	11 (3)	19 (6)
Dehydration	18 (5)	17 (5)
Infections and infestations	103 (31)	136 (41)
Urinary tract infection	19 (6)	17 (5)
Catheter site infection	5 (2)	15 (5)
Nasopharyngitis	16 (5)	15 (5)
Respiratory, thoracic and mediastinal disorders	99 (30)	115 (35)
Dyspnoea	32 (10)	51 (15)
Cough	38 (12)	39 (12)
Pulmonary embolism	8 (2)	17 (5)
Pharyngolaryngeal pain	24 (7)	16 (5)
Nervous system disorders	76 (23)	110 (33)
Headache	25 (8)	53 (16)
Dizziness	22 (7)	31 (9)
Dysgeusia	10 (3)	18 (5)
Peripheral sensory neuropathy	9 (3)	16 (5)
Musculoskeletal and connective tissue disorders	72 (22)	91 (27)
Back pain	31 (9)	29 (9)
Arthralgia	15 (5)	21 (6)
Pain in extremity	17 (5)	20 (6)
Myalgia	11 (3)	18 (5)
Psychiatric disorders	43 (13)	63 (19)
Insomnia	15 (5)	32 (10)
Anxiety	11 (3)	23 (7)
Hepatobiliary disorders	28 (8)	62 (19)
Hyperbilirubinaemia	24 (7)	52 (16)

SOC = system organ class; MedDRA = Medical Dictionary for Regulatory Activities
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: Percentages calculated with the number of subjects in each group as denominator.

Table 23 - Treatment-Emergent Grade 3 or 4 Adverse Events in at Least 5% of Subjects (Study ET743-OVA-301: All-Treated Subjects Analysis Set)

	Caelyx (N=330)			Trabectedin + Caelyx (N=333)		
MedDRA SOC Term	Total	Toxicity Grade[a]		Total	Toxicity Grade[a]	
MedDRA Preferred Term	n (%)	3	4	n (%)	3	4
Total no. subjects with grade 3-4 TEAE	237 (72)			304 (91)		
Blood and lymphatic system disorders	96 (29)	60 (18)	36 (11)	232 (70)	106 (32)	126 (38)
Neutropenia	74 (22)	46 (14)	28 (8)	210 (63)	97 (29)	113 (34)
Leukopenia	32 (10)	23 (7)	9 (3)	111 (33)	83 (25)	28 (8)
Thrombocytopenia	8 (2)	6 (2)	2 (1)	61 (18)	33 (10)	28 (8)
Anaemia	20 (6)	18 (5)	2 (1)	45 (14)	34 (10)	11 (3)
Febrile neutropenia	7 (2)	6 (2)	1 (<1)	27 (8)	19 (6)	8 (2)
Investigations	11 (3)	10 (3)	1 (<1)	124 (37)	111 (33)	13 (4)
Alanine aminotransferase increased	3 (1)	3 (1)	0	103 (31)	95 (29)	8 (2)
Aspartate aminotransferase increased	3 (1)	2 (1)	1 (<1)	24 (7)	21 (6)	3 (1)
Gastrointestinal disorders	75 (23)	67 (20)	8 (2)	79 (24)	73 (22)	6 (2)
Vomiting	14 (4)	14 (4)	0	40 (12)	39 (12)	1 (<1)
Nausea	12 (4)	12 (4)	0	33 (10)	33 (10)	0
Abdominal pain	18 (5)	17 (5)	1 (<1)	4 (1)	4 (1)	0
Stomatitis	17 (5)	16 (5)	1 (<1)	3 (1)	3 (1)	0
General disorders and administration site conditions	45 (14)	42 (13)	3 (1)	52 (16)	49 (15)	3 (1)
Fatigue	18 (5)	17 (5)	1 (<1)	28 (8)	27 (8)	1 (<1)
Mucosal inflammation	19 (6)	19 (6)	0	7 (2)	7 (2)	0
Skin and subcutaneous tissue disorders	71 (22)	67 (20)	4 (1)	15 (5)	15 (5)	0
Palmar-plantar erythrodysaesthesia syndrome	65 (20)	61 (18)	4 (1)	13 (4)	13 (4)	0

MedDRA = Medical Dictionary for Regulatory Activities; no. = number; SOC = system organ class;
TEAE = treatment-emergent adverse event

[a] Toxicity Grade: NCI common toxicity criteria, version 3.0 (CTC, v3.0).

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

Regarding the discontinuations due to the adverse events in the pivotal study, the percentage of subjects experiencing an adverse event that resulted in discontinuation of study treatment was 15% in the Caelyx monotherapy arm and 23% in the trabectedin + Caelyx arm. Drug-related adverse events that led to treatment discontinuation were reported for 9% and 17% of subjects in the Caelyx monotherapy and trabectedin + Caelyx arms, respectively.

Table 24 - Treatment-Emergent Adverse Events Leading to Treatment Termination in >= 2% of Subjects in Either Treatment Group (Study ET743-OVA-301: All-Treated Subjects Analysis Set)

MedDRA SOC Term MedDRA Preferred Term	Caelyx (N=330) n (%)	Trabectedin + Caelyx (N=333) n (%)
Total no. subjects with TEAE leading to treatment termination	50 (15)	78 (23)
Blood and lymphatic system disorders	5 (2)	25 (8)
Neutropenia	5 (2)	16 (5)
Thrombocytopenia	0	11 (3)
Leukopenia	0	7 (2)
Anaemia	1 (<1)	5 (2)
Investigations	3 (1)	12 (4)
Blood alkaline phosphatase increased	0	8 (2)
Hepatobiliary disorders	1 (<1)	7 (2)
Hyperbilirubinaemia	0	6 (2)
Skin and subcutaneous tissue disorders	16 (5)	7 (2)
Palmar-plantar erythrodysaesthesia syndrome	14 (4)	2 (1)

MedDRA = Medical Dictionary for Regulatory Activities; no. = number; SOC = system organ class; TEAE = treatment-emergent adverse event
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: Percentages calculated with the number of subjects in each group as denominator.

Serious adverse events and deaths

A total of 19 subjects died during treatment or within 30 days of the last dose of study medication, including 8 (2%) subjects in the Caelyx monotherapy arm and 11 (3%) subjects in the trabectedin + Caelyx arm. Twelve (63%) of these deaths (6 in each treatment arm) were the result of disease progression. Deaths associated with adverse events occurred in 1 subject in the Caelyx monotherapy arm (drug-related) and 5 subjects in the trabectedin + Caelyx arm (3 drug related). In the Caelyx monotherapy arm, the adverse event resulting in death was sepsis. The adverse events resulting in the death in the trabectedin + Caelyx arm were acute renal failure and neutropenic sepsis; pancytopenia and sepsis; thrombocytopenia and febrile neutropenia; pulmonary embolism; and general health deterioration.

Table 25 - Deaths During Study (Study ET743-OVA-301: All-Treated Subjects Analysis Set)

Cause of Death	Caelyx (N=330) n (%)	Trabectedin + Caelyx (N=333) n (%)
Total no. subjects who died during treatment	8 (2)	11 (3)
Progressive disease	6 (2)	6 (2)
Consequence of adverse events	1 (<1)	5 (2)
Adverse event	1 (<1)	5 (2)
Drug-related	1 (<1)	3 (1)
Not drug-related	0	2 (1)
Other	1 (<1)	0

no. = number
Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Death during treatment, within 30 days after last dose or before subsequent therapy whichever is earlier.

Table 26 - Deaths During Treatment or Within 30 Days After Last Dose (Any Cause)
(Trabectedin - Integrated Phase 2 Ovarian Studies: All-Treated Subjects Analysis Set)

Primary Cause of Death[a]	q 3 wk; 24-h (1.5 mg/m^2) (N=54) n (%)	q wk; 3-h (0.58 mg/m^2) (N=147) n (%)	q 3 wk; 3-h (1.3 mg/m^2) (N=94) n (%)	Total (N=295) n (%)
Total no. subjects died during treatment or within 30 days after last dose	3 (6)	5 (3)	1 (1)	9 (3)
Progressive disease	2 (4)	2 (1)	0	4 (1)
Consequence of adverse events	0	3 (2)	1 (1)	4 (1)
Non-hematological toxicity	0	3 (2)	1 (1)	4 (1)
Other	1 (2)	0	0	1 (<1)
Total deaths[b]	**15 (28)**	**61 (41)**	**15 (16)**	**91 (31)**

no. = number; qwk = once weekly; q3wk = once every 3 weeks
[a] As stated on the Survival page of the CRF.
[b] At any time during study treatment or follow-up.
Note: Percentages calculated with the number of subjects in each group as denominator.

In Study ET743-OVA-301, 31% of subjects in the Caelyx monotherapy arm and 39% in the trabectedin + Caelyx arm experienced at least 1 serious adverse event from the time of the first dose of study medication through 30 days after the last dose of study drug. Treatment with trabectedin + Caelyx was associated with higher frequencies of serious blood and lymphatic disorders, vomiting, nausea, ALT increased, and AST increased compared with treatment with Caelyx monotherapy. Neutropenia and thrombocytopenia were the most frequently reported serious adverse events with trabectedin + Caelyx, reported by 8% and 6%, respectively. In the Caelyx monotherapy arm, intestinal obstruction and abdominal pain were the most frequent serious adverse events, each reported in 3% of subjects.

Grade 4 serious adverse events reported for ≥1% of subjects in the trabectedin + Caelyx arm included neutropenia (n=22, 7%), thrombocytopenia (n=14, 4%), leukopenia (n=10, 3%), pulmonary embolism (n=7, 2%), febrile neutropenia (n=3, 1%), and anaemia (n=3, 1%). In the Caelyx monotherapy arm, Grade 4 serious adverse events reported for 1% or more of subjects were neutropenia (n=4, 1%), intestinal obstruction (n=3, 1%), leukopenia (n=3, 1%), and pulmonary embolism (n=2, 1%).

Table 27 - Treatment-Emergent Serious Adverse Events by Toxicity Grade in at Least 2% of Subjects (Study ET743-OVA-301: All-Treated Subjects Analysis Set)

	DOXIL (N=330)						Trabectedin/DOXIL (N=333)					
MedDRA SOC Term	Total	Toxicity Grade[a]					Total	Toxicity Grade[a]				
MedDRA Preferred Term	n (%)	Ns	1	2	3	4	n (%)	Ns	1	2	3	4
Total no. subjects with TESAE	101 (31)						131 (39)					
Blood and lymphatic system disorders	18 (5)	0	0	3	7	8	59 (18)	0	1	2	19	37
Neutropenia	7 (2)	0	0	0	3	4	26 (8)	0	0	1	3	22
Thrombocytopenia	1 (<1)	0	0	0	1	0	21 (6)	0	1	1	5	14
Febrile neutropenia	5 (2)	0	0	0	4	1	18 (5)	0	0	0	15	3
Anaemia	7 (2)	0	0	3	4	0	17 (5)	0	0	4	10	3
Leukopenia	3 (1)	0	0	0	0	3	16 (5)	0	1	0	5	10
Pancytopenia	0	0	0	0	0	0	6 (2)	0	0	0	4	2
Gastrointestinal disorders	54 (16)	0	2	15	30	7	45 (14)	0	1	13	26	5
Vomiting	8 (2)	0	0	2	6	0	15 (5)	0	1	5	9	0
Nausea	8 (2)	0	0	5	3	0	14 (4)	0	2	5	7	0
Intestinal obstruction	11 (3)	0	0	2	6	3	7 (2)	0	0	4	2	1
Small intestinal obstruction	3 (1)	0	0	2	1	0	7 (2)	0	0	1	4	2
Ascites	7 (2)	0	0	0	7	0	6 (2)	0	0	0	6	0
Diarrhoea	3 (1)	0	0	3	0	0	6 (2)	0	2	0	4	0
Abdominal pain	9 (3)	0	0	2	6	1	5 (2)	0	1	3	1	0
General disorders and administration site conditions	15 (5)	0	4	4	6	1	31 (9)	0	7	12	9	3
Pyrexia	3 (1)	0	2	1	0	0	10 (3)	0	6	4	0	0
Fatigue	1 (<1)	0	0	0	1	0	8 (2)	0	1	2	4	1
Respiratory, thoracic and mediastinal disorders	11 (3)	0	0	3	6	2	18 (5)	0	0	3	7	8
Pulmonary embolism	6 (2)	0	0	2	2	2	13 (4)	0	0	3	3	7
Metabolism and nutrition disorders	12 (4)	0	3	1	7	1	13 (4)	0	0	4	6	3
Dehydration	4 (1)	0	0	1	3	0	7 (2)	0	0	1	4	2
Anorexia	6 (2)	0	0	1	4	1	3 (1)	0	0	2	1	0
Investigations	0	0	0	0	0	0	10 (3)	0	0	1	5	4
Alanine aminotransferase increased	0	0	0	0	0	0	5 (2)	0	0	1	3	1
Aspartate aminotransferase increased	0	0	0	0	0	0	5 (2)	0	0	0	4	1

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: Percentages calculated with the number of subjects in each group as denominator.
[a] Toxicity Grade: NCI common toxicity criteria, version 3.0 (CTC, v3.0). NS=not specified

The MAH has identified the following safety topics for special consideration concerning the treatment with the trabectedin + Caelyx combination because of their potential for clinical importance: hepatic toxicity, haematologic toxicity neutropenia and infection, thrombocytopenia and bleeding events, abdominal pain, CPK elevations and rhabdomyolysis, cardiac safety, renal and urinary disorders, myelodysplasia and acute myeloid leukaemia, extravasation, respiratory disorders, other events - ototoxicity, neuropathy, and hypersensitivity.

Hepatic toxicity

Trabectedin therapy frequently causes liver function test abnormalities, mainly in the form of elevated serum transaminases. Transaminase elevations of any grade were experienced by >80% of subjects receiving trabectedin in clinical studies (alone or in combination with Caelyx). The MAH states that transaminase elevations in subjects receiving trabectedin + Caelyx followed a predictable pattern of rapid onset and reversibility and decreasing severity with succeeding cycles. There was no indication of cumulative toxicity. Transaminase elevations with trabectedin were managed with dose delays or reductions, using guidelines outlined in the study protocols. In the pivotal study, no subject was withdrawn from treatment with the trabectedin + Caelyx combination due to increased ALT or AST,

reported as an adverse event, and ≤5% subjects receiving the combination treatment had a dose reduction or cycle delay as a result of increased ALT or AST.

In the main study most subjects in the trabectedin + Caelyx arm had an elevation (Grade 1 to 4) in ALT (96%) or AST (89%) at some point during the study, although only 5% and 2% of subjects receiving trabectedin + Caelyx had Grade 4 ALT or AST elevation, respectively. Elevations in ALT and AST were seen in 36% and 43% of subjects in the Caelyx monotherapy arm. Additionally, in this study, Hy's Law criteria were used to predict hepatotoxicity.

Table 28 – Summary Hy's Law Cases – by Treatment Group (Study ET743-OVA-301: All-Treated Subjects Analysis Set)

Treatment Group	Subjects Meeting First Condition *	Subjects Meeting First and Second Condition
DOXIL	18	0
Trabectedin/DOXIL	244	3

First condition: any elevated (ALT/AST) of >3xULN and ALP <2xULN; Second condition: an increase in bilirubin ≥2xULN.

As seem in the above table, in the trabectedin +Caelyx arm, 3 subjects met the criteria. Two hundred forty-four subjects in the trabectedin + Caelyx arm had an elevated ALT or AST level that was ≥3 times ULN and had an ALP value ≤2 times ULN. Three (1%) of these subjects had an increased bilirubin that was ≥2 times ULN. Of the 3 subjects who met the criteria for Hy's law, none developed serious hepatotoxicity. Two had subsequent therapy and died from disease progression, and 1 subject is still in the follow-up phase of the study.

Figure 13 –Median Values for ALT - Cycles With a Grade 3 or 4 Event (Study ET743-OVA-301: All-Treated Subjects Analysis Set)

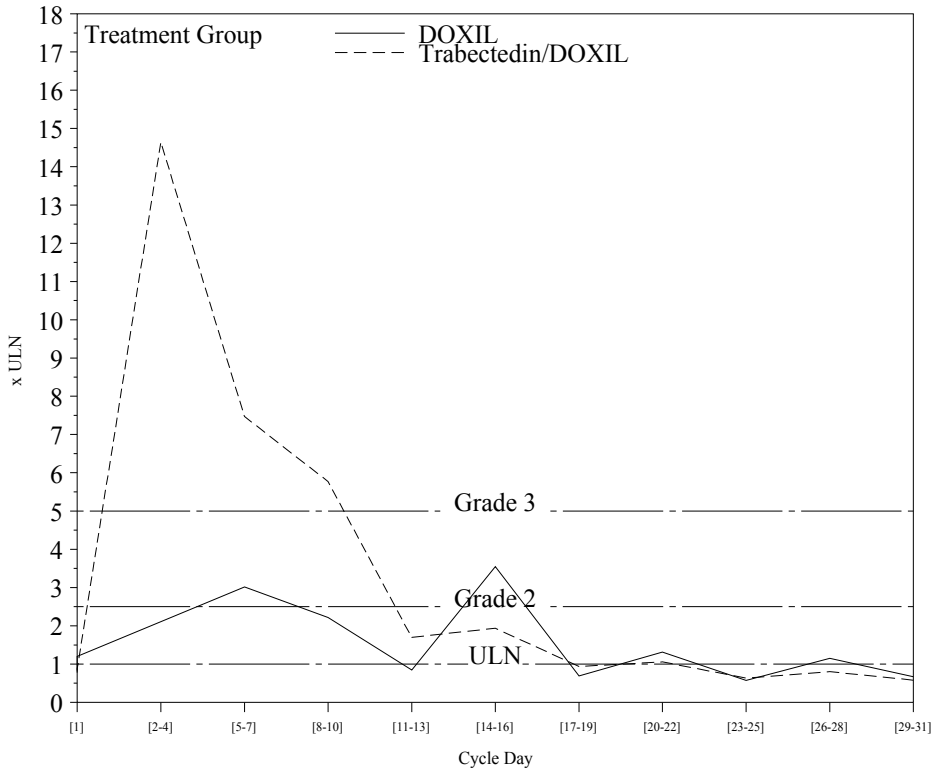
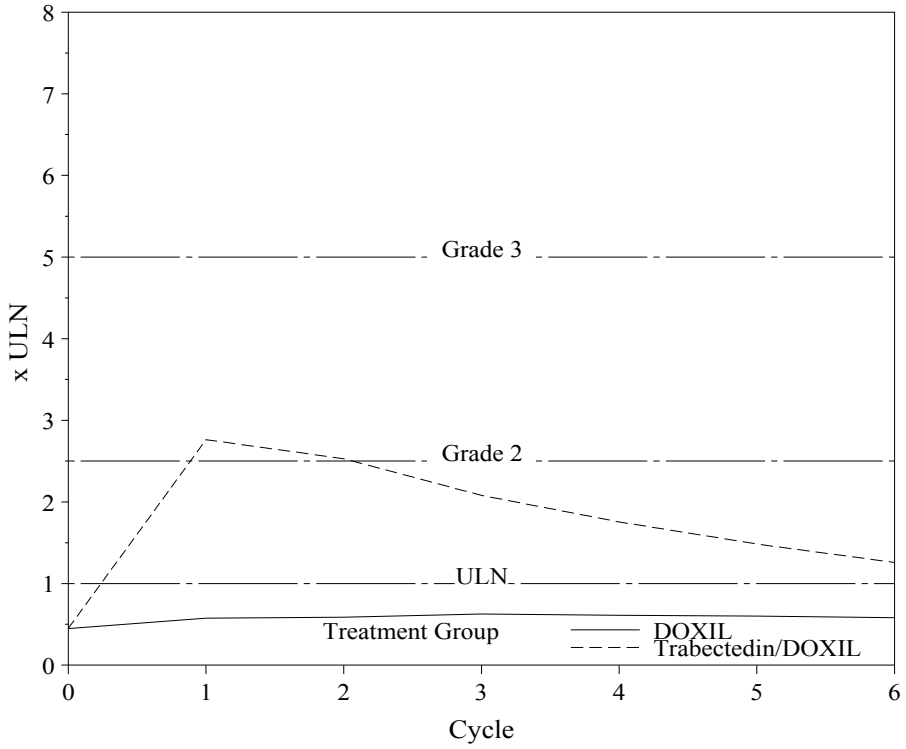


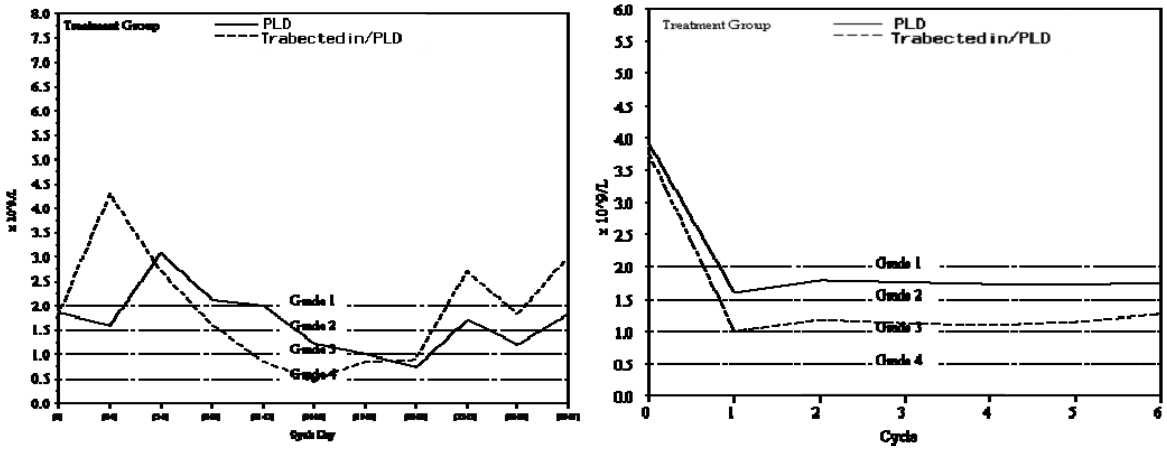
Figure 14 –Median Values for ALT Peak - Subjects Who Received >=6 Cycles of Treatment (Study ET743-OVA-301: All-Treated Subjects Analysis Set)



Haematologic toxicity neutropenia and infection

Neutropenia was the most common haematological laboratory abnormality. The incidence of grade 3/4 neutropenia cases evaluated as drug-related AEs (63%) was higher in the trabectedin plus PLD arm compared with PLD alone (22%). In OVA-301, nadir grade 3 or 4 neutrophil values typically occurred within two weeks of dosing and were resolved among patients receiving trabectedin plus PLD. The MAH states that this pattern was similar regardless of cycle, indicating a lack of cumulative toxicity (see figure below) Compared with PLD alone, grade 3 or 4 neutropenia developed earlier in the combination arm (Day 15 *vs.* Day 22) but could had a similar duration (eight days in both study arms). Neutropenia was managed with dose delays and reductions, using guidelines outlined in the study protocol. Antibiotics were given as concomitant therapy in 20% of patients for both study arms. Growth factors were given in OVA-301 prophylactically according to ASCO guidelines, and they were used more frequently in the combination arm (42% of patients/26% of cycles) than in the PLD alone arm (17% of patients/8% of cycles). The use of growth factors varied substantially according to the geographical area, with the lowest percentage in the European countries (26% of patients/12% of cycles) compared with the United States of America where these factors are more frequently administered in clinical practice (47% of patients/35% of cycles). Drug-related febrile neutropenia was experienced by 7% and 2% of patients in the combination arm and in the PLD alone arm, respectively. Sepsis, septic shock or sepsis syndrome were reported in 2 patients (<1%) in the combination arm and in 4 patients (1%) in the PLD alone arm. 4% of patients with drug-related neutropenia discontinued the study due to this AE.

Figure 15 –Neutropenia during treatment with trabectedin plus PLD. Left graph: intracycle median for grade 3/4 cases; right graph: median nadir values during the first 6 cycles (OVA-301 study).



Thrombocytopenia and Bleeding Events

In the trabectedin + Caelyx arm, the proportion of subjects with Grade 3 or 4 platelet count abnormalities was 4% in Cycle 1 and increased to 7% in Cycle 2 where it remained stable through Cycle 8 (5% to 7%). For Grade 4 platelet counts in the trabectedin + Caelyx arm, the median time to first occurrence was 57 days (range: 11, 294) and the median duration was 7 days (range: 2, 27). Bleeding-related adverse events ere reported in a similar percent of subjects in the Caelyx (8%) and trabectedin + Caelyx (9%) arms of Study ET743-OVA-301. 2 subjects in the trabectedin + Caelyx arm (0.6%; none in Caelyx arm) had a drug-related Grade 3 or 4 bleeding-related adverse event.

In the Caelyx monotherapy arm, the proportion of subjects who had Grade 3 or 4 laboratory abnormalities in Cycles 1 to 6 ranged from 0 to 2% for platelet counts and from 1% to 3% for haemoglobin. Of the 27 subjects in the Caelyx monotherapy arm with Grade 3 or 4 haemoglobin abnormalities, the percentage of subjects who received treatment with blood or blood related products (n=7, 26%), blood transfusions (n=5, 19%), or other antianaemic drugs (n=1, 4%) was lower than in the trabectedin + Caelyx arm. Among subjects receiving the trabectedin + Caelyx combination, cycle delays due to thrombocytopenia reported as an adverse event were more common (13%) than

treatment withdrawals (3%) or dose reductions (5%). One percent or less of subjects in the Caelyx monotherapy arm had a cycle delay, dose reduction, or treatment discontinued due to thrombocytopenia reported as an adverse event.

CPK Elevations/Rhabdomyolysis

In the early phase II studies with single-agent trabectedin treatment, rhabdomyolysis and/or elevations in creatine phosphokinase (CPK) (grade 1-4) were associated with death in three patients (studies ET-B-008-98 and ET-B-005-98, 269 patients treated, 1%), commonly as a component of a syndrome which included neutropenia, sepsis, renal failure and elevated liver enzymes. Thereafter, strict monitoring of liver function tests and CPK levels and dose adjustment guidelines were implemented in all ongoing and subsequently initiated clinical studies, including OVA-301. Rhabdomyolysis is a known risk discussed in several sections of the Summary of Product Characteristics of trabectedin. In OVA-301, grade 3/4 CPK elevations were uncommon: 2% for the trabectedin plus PLD arm of OVA-301 (0% in the PLD arm) and 3% for the integrated phase II ovarian safety analysis set. In the trabectedin + Caelyx arm, 1 subject (<1%) had a dose reduction and 4 subjects (1%) had a cycle delay as a result of increased CPK. Two subjects in the trabectedin + Caelyx arm had treatment discontinued as a result of increased CPK

Cardiac Safety

In Study ET743-OVA-301, MUGA scans or 2-D echocardiograms were performed in 369 subjects at screening and at the end of treatment termination. There was no indication that the addition of trabectedin increased the known cardiac safety profile of Caelyx in the Phase 3 study ET743-OVA-301 or the Phase 1 Study ET743-USA-11.

Extravasation-Related Adverse Events

Extravasation-related adverse events following injection of trabectedin were uncommon in all 3 safety analysis sets, reported for 1% of subjects receiving trabectedin + Caelyx in Study ET743-OVA-301 and 4 to 6% of subjects receiving single-agent trabectedin in the Phase 2 integrated safety analysis sets

Respiratory Disorders

Serious respiratory-related disorders were reported for 5% to 7% of trabectedin-treated subjects in the Study ET743-OVA-301 safety analysis set and the integrated Phase 2 safety analysis set. Most of these serious respiratory-related disorders were assessed by the investigator as not drug related

Myelodysplasia and Acute Myeloid Leukaemia

No subject treated in Study ET743-OVA-301 developed treatment-emergent acute myeloid leukaemia or myelodysplasia within 30 days of the last dose of study medication. Subject 280065 in the trabectedin + Caelyx arm was discontinued due to neutropenia and thrombocytopenia. Approximately 2 weeks later, the subject underwent a bone marrow biopsy due to persistent hematological abnormalities, which revealed acute myeloid leukaemia. The subject died approximately 99 days after the last dose of study drug and the cause of death were pneumonia, neutropenia, and acute myeloid leukaemia. A second subject (140005) who received 13 cycles of Caelyx monotherapy was diagnosed with acute myeloid leukaemia 95 days after the last dose of study drug. The subject died 3 months and 12 days later due to disease progression

Laboratory findings

In Study ET743-OVA-301, compared with the Caelyx monotherapy arm, a higher proportion of subjects in the trabectedin + Caelyx arm had abnormal neutrophil counts (74% versus 92%, respectively), platelet counts (27% versus 64%, respectively), and WBC counts (82% versus 95%, respectively).

White blood cell count abnormalities were frequent in all 3 safety analysis sets. In Study ET743-OVA-301, 62% of subjects in the trabectedin + Caelyx arm had Grade 3 or 4 WBC count abnormalities, compared with 20% of subjects in the Caelyx monotherapy arm. The incidence rate of Grade 3 or 4 WBC count abnormalities was also higher for the trabectedin + Caelyx arm of Study ET743-OVA-301 compared with trabectedin as a single agent in the q3wk 3-h treatment arm of the integrated Phase 2 ovarian safety analysis set (29%) and the integrated Phase 2 safety analysis set (30%). The incidence of

Grade 3 or 4 WBC count abnormalities in the q3wk 24-h arm of the integrated Phase 2 safety analysis set was 49%.

In the pivotal study, the incidence rates of mineral/electrolyte non-haematologic abnormalities were similar in the trabectedin + Caelyx and Caelyx monotherapy arms, with the exception of low potassium, which was higher in the combination arm (42% versus 28%, respectively).
Grade 3 or 4 mineral/electrolyte non-haematologic abnormalities in Study ET743-OVA-301 were equally infrequent in both treatment arms; the most common were low sodium (9%) and low potassium (8%) for the trabectedin + Caelyx arm and low sodium (9%) and elevated potassium (6%) for the Caelyx monotherapy arm.

1.4.3.3. Discussion on clinical safety

Almost all patients experienced drug related AEs. The safety profile of the combination treatment is characterised by the high percentage of adverse events (99%), which includes as more relevant neutropenia, thrombocytopenia, anemia, AST/ALT increases, hyperbilirubinemia, CPK elevations and rhabdomyolysis. The percentages of adverse events observed in the trabectedin group were sometimes as much as 2 times higher than in the trabectedin/Caelyx group. The most common AEs observed in all the patients were the gastrointestinal disorders, with the highest percentage of nausea and vomiting in the trabectedin group.

All the effects mentioned above have been already described in the initial marketing authorisation for soft tissue sarcoma. No new relevant data has been shown. It is acknowledged that the majority of the serious AEs, such as neutropenia, thrombocytopenia, anemia and AST/ALT increases, can be managed with the appropriate dose reduction and/or delays in the cycles. However, the laboratory findings appear to be consistent with relevant clinical implications, such as increased risk of febrile neutropenia.

The rate of drug related AEs, serious adverse events, deaths, AEs leading to the discontinuation, and laboratory values, are without a doubt higher in the trabectedin/Caelyx group.

A higher incidence observed in drug-related grade 3 or 4 AEs, SAEs and drug-related SAEs (especially within the Blood and Lymphatic system) for the non-white population (Asian race) was observed. This is reflected in section 4.8 of the SPC.

The overall clinical safety assessment of the proposed combination of trabectedin + Caelyx does not cause any major concern per se since the toxicity profile is predictable from the known safety profiles for both substances and such toxicity is routine management in oncology centers. The most important additive toxicity is neutropenia and infection-related adverse events due to neutropenia with increasing frequency and severity with the combination as compared to both agents used as monotherapy. Any potential safety concern of the combination should be evaluated in the context of risk/benefit.

1.5. Risk Management Plan

An updated Risk Management Plan (RMP) was submitted in this variation application. The EU-RMP version 6.0 follows the guideline and has included the updated information regarding trabectedin use. The addition of safety data from the use of trabectedin in combination with PLD has revealed a higher risk of bone marrow suppression and a higher need for concomitant anti-emetic treatment. A summary of the RMP is provided in the table below.

Safety concern	**Proposed pharmaco-vigilance (PhV) activities (routine and additional*)**	**Proposed risk minimisation activities (routine and additional*)** **Additional activities common to all risks are indicated at the end of the table to avoid multiple repetitions.*

Hepatic reactions		SPC **Section 4.2: Posology and method of administration** Patients must meet specific criteria on hepatic function parameters to start and continue treatment with Yondelis. Weekly monitoring of LFTs is required during first 2 cycles and at least once between subsequent cycles. There are strict liver function criteria for dose reduction. Patients with elevated bilirubin must not be treated with trabectedin. **Section 4.4: Special warning and precautions for use** Liver Function Test (LFT) abnormalities. Reversible acute increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) have been reported in most patients. Yondelis must not be used in patients with elevated bilirubin. Patients with increases in AST, ALT and alkaline phosphatase between cycles may necessitate dose reduction (see *Section 4.2*). **Section 4.8: Undesirable effects** Hepatic events are labelled.
Neutropenia and infection		SPC **Section 4.2: Posology and method of administration** Patients must meet specific criteria on ANC (≥ 1,500/ mm^3) to start and continue treatment with Yondelis. Weekly haematology monitoring is required during first 2 cycles and at least once between subsequent cycles. There are strict criteria for dose reduction (ANC <500/ mm^3 lasting more than 5 days or associated with fever or infection). **Section 4.3: Contraindications** Concurrent serious or uncontrolled infection. **Section 4.4: Special warning and precautions for use** Neutropenia […] Patients who develop fever should promptly seek medical attention. Yondelis should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/ mm^3 […]. If severe neutropenia (ANC< 500 cells/ mm^3) lasting more than 5 days or associated with fever or infection occurs, dose reduction is recommended (see *Section 4.2*) **Section 4.8: Undesirable effects** Neutropenia related events are labelled and incidences given for monotherapy and combination with PLD, including differences between white and non-white populations.
Thrombocytopenia/ bleeding		SPC **Section 4.2: Posology and method of administration** Patients must meet specific criteria on platelet counts (≥ 100,000/mm^3) to start and continue treatment with Yondelis. Weekly haematology monitoring is required during first 2 cycles and at least once between subsequent cycles. There are strict criteria for dose reduction (≥ 25,000/ mm^3). **Section 4.4: Special warning and precautions for use** Thrombocytopenia […] Yondelis should not be administered to patients with baseline […] platelets count of less than 100,000 cells/ mm^3. **Section 4.8: Undesirable effects** Thrombocytopenia related events are labelled and incidences given for monotherapy and combination with PLD, including differences between white and non-white populations.
Anaemia		SPC **Section 4.2: Posology and method of administration** Patients must meet specific criteria on haemoglobin (≥ 9 g/dl) to start and continue treatment with Yondelis. Weekly haematology monitoring is

		required during first 2 cycles and at least once between subsequent cycles. There are strict criteria for dose reduction (any grade 3 or 4 adverse reaction). **Section 4.8: Undesirable effects** Anaemia related events are labelled and incidences given for monotherapy and combination with PLD, including differences between white and non-white populations.
CPK elevations/ Rhabdo-myolysis		SPC **Section 4.2: Posology and method of administration** Patients must meet specific criteria on CPK values (≤ 2.5 x ULN) to start and continue treatment with Yondelis. Weekly CPK monitoring is required during first 2 cycles and at least once between subsequent cycles. Any grade 3 or 4 adverse reaction requires dose reduction. **Section 4.4: Special warning and precautions for use** Trabectedin must not be used in patients with CPK > 2.5 ULN (see section 4.2). Rhabdomyolysis has been uncommonly reported, usually in association with myelotoxicity, severe liver function test abnormalities and/or renal or multiorgan failure. Therefore, CPK should be closely monitored whenever a patient may be experiencing any of these toxicities, muscle weakness or muscle pain. If rhabdomyolysis occurs, supportive measures such as parenteral hydration, urine alkalinisation and dialysis should be promptly established, as indicated. Treatment with Yondelis should be discontinued until the patient fully recovers. Caution should be taken if medicinal products associated with rhabdomyolysis (e.g. statins), are administered concomitantly with trabectedin, since the risk of rhabdomyolysis may be increased. **Section 4.8: Undesirable effects** CPK increases and rhabdomyolysis are labelled.
Emesis		SPC **Section 4.2: Posology and method of administration** All patients must receive corticosteroids e.g. dexamethasone intravenously 30 minutes prior to PLD (in combination therapy) or Yondelis (in monotherapy). Additional anti-emetics may be administered as needed. **Section 4.4: Special warning and precautions for use** Anti-emetic prophylaxis with corticosteroids such as dexamethasone must be administered to all patients). **Section 4.8: Undesirable effects** Nausea and vomiting are labelled.
Respiratory events		SPC **Section 4.8: Undesirable effects** Dyspnoea, cough, pulmonary embolism and pulmonary oedema are labelled.
Local infusion reactions		SPC **Section 4.2: Posology and method of administration** Administration through a central venous line is strongly recommended (see *Section 6.6*). **Section 4.4: Special warning and precautions for use** Patients may develop a potentially severe injection site reaction when trabectedin is administered through a peripheral venous line. New added wording proposed and accepted from 2nd PSUR: There have been few reported cases of trabectedin extravasation, with subsequent tissue necrosis requiring debridement. There is no specific antidote for extravasation of trabectedin. Extravasation should be managed by local standard practice.

Hyper-sensitivity		SPC **Section 4.3: Contraindications** Contraindicated in patients with hypersensitivity to trabectedin or to any of the excipients.
Cardio-vascular events		SPC **Section 4.8: Undesirable effects** Left ventricular dysfunction is included as observed in <1% of patients receiving the combination Yondelis+ PLD (Caelyx) treatment for ovarian cancer.
Foetal exposure to trabectedin through parental exposure		SPC **Section 4.3: Contraindications** Contraindicated when breast-feeding . **Section 4.4: Special warning and precautions for use** Men in fertile age and women of childbearing potential must use effective contraception during treatment and 3 months thereafter for women and immediately inform the treating physician if a pregnancy occurs, and 5 months after treatment for men. **Section 4.6: Pregnancy and lactation** No sufficient clinical data on exposed pregnancies are available. However based on its known mechanism of action, trabectedin may cause serious birth defects when administered during pregnancy. Trabectedin should not be used during pregnancy unless clearly necessary. If it is used, the patient must be informed of the potential risk to the foetus (see *Section 5.3*) and be monitored carefully. If trabectedin is used at the end of pregnancy, potential adverse reactions should be monitored carefully in the newborns Men in fertile age and women of childbearing potential must use effective contraception during treatment and 3 months thereafter for women and immediately inform the treating physician if a pregnancy occurs (see *Section 5.3*) and 5 months after treatment for men (see *Section 4.4*). Trabectedin can have genotoxic effects. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with Yondelis. If pregnancy occurs during treatment the possibility of genetic counselling should be considered. Genetic counselling is also recommended for patients wishing to have children after therapy. It is not known whether trabectedin is excreted in human milk. […] Breast-feeding is contraindicated during treatment and 3 months thereafter (see *Section 4.3*).
Patients with severe renal impairment		SPC **Section 4.2: Posology and method of administration** Patients must meet specific criteria on creatinine clearance ≥ 30 ml/min (monotherapy), serum creatinine ≤ 1.5 mg/dl (≤ 132.6 µmol/l) or creatinine clearance ≥ 60 ml/min (combination therapy) to start and continue treatment with Yondelis. Weekly monitoring of creatinine is required during first 2 cycles and at least once between subsequent cycles. Studies including patients with renal insufficiency (creatinine clearance < 30 ml/min for the monotherapy, and < 60 ml/min for the combination regime) have not been conducted and therefore Yondelis must not be used in this patient population (see *Section 4.4*) […] **Section 4.4: Special warning and precautions for use** Creatinine clearance must be monitored prior to and during treatment. Yondelis monotherapy and combination regimes must not be used in patients with creatinine clearance < 30 ml/min and < 60 ml/min respectively (see *Section 4.2*).
Patients with hepatic impairment.		SPC **Section 4.2: Posology and method of administration** No studies with the proposed regime have been conducted in patients with liver dysfunction. Thus, data are not available to recommend a lower

		starting dose in patients with hepatic impairment. However, special caution is advised and dose adjustments may be necessary in these patients since systemic exposure is probably increased and the risk of hepatotoxicity might be increased. Patients with elevated bilirubin must not be treated with Yondelis (see *Section 4.4*). **Section 4.4: Special warning and precautions for use** Patients must meet specific criteria on hepatic function parameters to start treatment with Yondelis. Since systemic exposure to trabectedin is probably increased due to hepatic impairment and therefore the risk of hepatotoxicity might be increased, patients with clinically relevant liver diseases, such as active chronic hepatitis, must be closely monitored and the dose adjusted if needed. Patients with elevated bilirubin must not be treated with trabectedin (see *Section 4.2*). **Section 4.8: Undesirable effects** Hepatic events are labelled
Potential risks		
Myelo-dysplasia Acute Myeloid Leukaemia	Enhanced monitoring	Insufficient evidence of risk to warrant SPC information at present.
Potential risk of interactions		SPC **Section 4.4: Special warning and precautions for use** Co-administration of Yondelis with potent inhibitors of the enzyme CYP3A4 should be avoided (see *Section 4.5*). If this is not possible, close monitoring of toxicities are required and dose reductions of trabectedin should be considered. Caution should be taken if medicinal products associated with hepatotoxicity are administered concomitantly with trabectedin, since the risk of hepatotoxicity may be increased. Concomitant use of trabectedin with phenytoin may reduce phenytoin absorption leading to an exacerbation of convulsions. Combination of trabectedin with phenytoin or live attenuated vaccines is not recommended and with yellow fever vaccine is specifically contraindicated (see *Sections 4.3 and 4.5*). The concomitant use of trabectedin with alcohol must be avoided (see *Section 4.5*). Caution should be taken if medicinal products associated with rhabdomyolysis (e.g. statins), are administered concomitantly with trabectedin, since the risk of rhabdomyolysis may be increased. **Section 4.5: Interaction with other medicinal products** In vivo interaction studies have not been performed. Since trabectedin is metabolised mainly by CYP3A4, co-administration of substances that inhibit this isoenzyme e.g. ketoconazole, fluconazole ritonavir or clarithromycin could decrease metabolism and increase trabectedin concentrations. If such combinations are needed, close monitoring of toxicities is required (see *Section 4.4*). Likewise co-administration with potent inducers of this enzyme (e.g. rifampicin, phenorbarbital, Saint John's Wort) may decrease the systemic exposure to trabectedin. Alcohol consumption must be avoided during treatment with trabectedin due to the hepatotoxicity of the medicinal product (see *Section 4.4*). Preclinical data have demonstrated that trabectedin is a substrate to P-gp. Concomitant administration of inhibitors of Pgp, e.g. cyclosporine and verapamil, may alter trabectedin distribution and/or elimination. The relevance of this interaction e.g. CNS toxicity has not been established. Caution should be taken in such situations. New added wording proposed and accepted from 2nd PSUR: Aprepitant added as another example of CYP3A4 inhibitors.

Medication errors including overdose		SPC **Section 4.2: Posology and method of administration** Detailed posology, dosage adjustment, preparation instructions are provided. **Section 4.9: Overdose** There is limited data on the effects of trabectedin overdose. The major anticipated toxicities are gastrointestinal, bone marrow suppression and hepatic toxicity. There is no specific antidote for trabectedin currently available. In the event of an overdose, patients should be closely monitored and symptomatic supportive care measures instituted as required. **Section 6.6: Special precautions for disposal and other handling** Instructions for reconstitution and dilution, including correct volume calculation algorithm are provided.
Off-label use including paediatric use		SPC **Section 4.1: Therapeutic indications** Approved indications are specified. **Section 4.2: Posology and method of administration** The safety and efficacy of trabectedin in paediatric patients have not yet been established. Therefore this medicinal product must not be used in children and adolescents until further data becomes available. Some paediatric trials are ongoing.
Common to all safety concerns	Routine PhV	Legal status: Restricted prescription Cytotoxic for specialist use only

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

1.6. Benefit-risk assessment

Benefits

In a well-conducted phase III trial (OVA-301) comparing Caelyx with Caelyx/trabectedin in 663 patients with relapsed ovarian cancer, the primary efficacy endpoint PFS showed a clear advantage for the combination therapy whichever dataset was used. With the most conservative assessment (independent radiologist in patients with measurable disease) a 21% risk reduction for the PFS endpoint could be considered evidence of activity of trabectedin (this is also supported by phase II data). However, the absolute magnitude of PFS prolongation (about 1.5 months) from 5.8 months to 7.3 months is not impressive considering that there is no clear support of overall survival prolongation. Final overall survival analysis is pending, since it will only be performed when 520 deaths are observed. The increase in PFS is not linked to an improvement in QoL. The QoL data neither support nor challenge the efficacy/safety assessment. The pivotal study was not blinded and QoL data are often not very sensitive. However, the addition of trabectedin does not seem to worsen the QoL.

The magnitude of PFS gain (6-8 weeks) and the HR (0.72-0.79) in favour of the combination of trabectedin + PLD observed in the OVA-301 trial do not differ from efficacy results of other randomised trials in comparable populations of women with ovarian carcinoma. A number of sensitivity analyses support the robustness of the PFS endpoint. However, the importance of the imbalanced prognostic factors observed (Age, ECOG and ascites) on the PFS and OS was further analysed. Results seem to be robust in the sense that the imbalances do not affect the global PFS results.

As previously stated there is clear evidence of antitumour activity of the combination of PLD and trabectedin and provided that a significant improvement in overall survival support the PFS endpoint this would be considered sufficient evidence of benefit in terms of efficacy.

Thus, further reassurance on the maturity of the OS data was needed. The protocol-specified interim analysis of overall survival (OS) was carried out with 300 events, and even though the data are clearly immature, a favourable trend appears for the combination (HR=0.85) and survival curves remain separated throughout the entire observation period. The MAH conducted an *ad hoc* interim analysis of the secondary endpoint OS with a prospectively established cutoff date of 31 May 2009 when a total of 419 death events (215 in the PLD monotherapy arm and 204 in the trabectedin + PLD combination arm) had occurred. This represents 81% of the 520 death events required for the final OS analysis, or 62% of the 672 randomised population. Current follow-up ranges from April 2005 to May 2009. The trabectedin + PLD combination resulted in a 15% decrease in the risk of death compared with PLD alone [HR=0.85 (95% CI, 0.70-1.03); p=0.0920]. The median OS was 19.5 months (95% CI, 17.4-22.1) in the PLD monotherapy arm and 22.4 months (95% CI, 19.4-25.1) in the combination arm

The study OVA 301 was not powered to detect differences in outcome according to platinum-resistance status. The results of a multivariate analysis indicate that treatment effect and platinum sensitivity acted as independent factors with influence on PFS. Although a long platinum-free interval points to a better outcome in terms of PFS as compared to a short interval (platinum-resistance) the CHMP agree that the benefit in the platinum-resistant subset cannot be ruled out.

The fact that patients with platinum sensitive disease (as measured by a long platinum-free interval) still have the option to be retreated with a platinum-containing regimen should not per se be an obstacle for approving the combination of PLD and trabectedin. PLD was approved for" *treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen*". The registration study for PLD with topotecan as comparator also included patients with both platinum-sensitive and platinum-refractory disease. However, it is unfortunate that the performance of trabectedin + PLD against common practice (retreatment with platinum) is unknown. Superiority against the approved PLD has been demonstrated. The design and inclusion criteria of the pivotal trial OVA-302 have been sufficiently detailed in section 5.1 of the SPC. In the updated analysis the survival benefit appears enhanced in the stratum of platinum-sensitive patients, where PFS HR was 0.73 (p=0.0170) and OS HR was 0.82 (p=0.1259) in the updated analysis. Of interest, in the subpopulation of patients with intermediate platinum-sensitivity (PFI 6-12 months), an exploratory analysis shows the largest differential effect favouring the trabectedin combination with a 41% reduction in the risk of death (HR=0.59; p=0.0015) and a 6 month increase in median survival.

Risks

No new or unexpected serious adverse events were seen with the trabectedin + Caelyx combination relative to administration of Caelyx monotherapy or trabectedin alone.

The overall clinical safety assessment of the proposed combination of trabectedin + Caelyx does not cause any major concern per se since the toxicity profile is predictable from the known safety profiles of both substances and such toxicity is routine management in oncology centres. The most important additive toxicity is neutropenia and infection-related adverse events due to neutropenia with increasing frequency and severity with the combination as compared to both agents used as monotherapy. Any potential safety concern of the combination should be evaluated in the context of risk/benefit. Two percent (2%) of subjects in the Caelyx arm developed Grade 3 or 4 febrile neutropenia versus 8% in the trabectedin + Caelyx arm. Sepsis, septic shock, or sepsis syndrome were reported in 4 subjects (1.2%) in the Caelyx monotherapy arm and 2 subjects (0.6%) in the trabectedin + Caelyx arm.

Other concerns are more thrombocytopenia with the combination, more elevations in liver transaminases and more elevations in CPK (and rhabdomyolysis in rare cases) due to the toxicity of trabectedin. These aspects have been sufficiently addressed in the RMP and the SPC.

Balance

The magnitude of PFS gain (6-8 weeks) and the HR (0.72-0.79) in favour of the combination of trabectedin + PLD observed in the OVA-301 trial do not differ from efficacy results of other randomised trials in comparable populations of women with ovarian carcinoma. A number of sensitivity analyses support the robustness of the PFS endpoint. As previously stated there is clear evidence of antitumour activity of the combination of PLD and trabectedin. The updated *ad hoc* interim analysis on overall survival provided further reassurance on the validity of the PFS endpoint.
Further, the MAH has made a commitment to provide the final results from the ongoing study OVA-301 for review by CHMP when available.

It is agreed that although toxicity of the two-drug combination is more pronounced than with PLD alone it is not very different from the toxicity seen after other two-drug combinations for the same therapeutic indication. The safety profile of trabectedin and the combination is by no means unusual or frightening considering the therapeutic indication.

The benefit-risk balance of *Yondelis in combination with pegylated liposomal doxorubicin (PLD) in the treatment of patients with relapsed platinum-sensitive ovarian cancer*, is considered positive.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SPC have been updated. The Package Leaflet has been updated accordingly. Further, annex II has been updated to include the agreed version 6.0 of the RMP.

Furthermore, the CHMP reviewed the data and justifications submitted by the MAH taking into account the provisions of Article 14(11) of Regulation (EC) No. 726/2004, and taking into account the provisions of the "*Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period (November 2007)*", and did not consider that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies. (EMEA note: This refers to the extension of the marketing protection but has no impact on the orphan status and its incentives, which is reviewed by the COMP.)