Comisión Nacional del Mercado de Valores
Att. Sr. D. Rodrigo Buenaventura
C/ Miguel Ángel 11, 1º
28010 Madrid

Madrid, 13 de Julio de 2009

Muy Sres. Nuestros:

Por la presente les informamos que la FDA ha publicado hoy en su página web, como es habitual antes de cada sesión de su Oncologic Drugs Advisory Comité (ODAC), el material de soporte para la sesión del ODAC del día 15 de julio de 2009, en la que entre otras materias tratará sobre la solicitud de autorización de comercialización de YONDELIS (trabectedin) en combinación con DOXIL, para el tratamiento de pacientes con cáncer de ovario en recaída, solicitud que fue presentada por Centocor Ortho Biotech Products, L.P. el pasado mes de noviembre de 2008. Tal material puede ser consultado en la página web de la FDA (www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm171145.htm), adjuntándose copia del mismo a la presente. Asimismo les acompañamos nota de prensa que al respecto Pharma Mar distribuirá en el día de hoy a los medios de comunicación. Todo lo anterior a fin que sea registrada como **OTRAS COMUNICACIONES.**

Sin otro particular les saluda atentamente,

Sebastián Cuenca Miranda
Secretario del Consejo de Administración

Comunicado sobre las preguntas anunciadas por la FDA sobre la sesión oral de la ODAC acerca del estudio de registro de Yondelis® en combinación con Doxil® para el tratamiento del cáncer de ovario recurrente (OVA-301)

Madrid, 13 de julio 2009*:* Ante la publicación por parte de la FDA de las preguntas que va a realizar al comité de expertos (ODAC) el próximo 15 de julio de 2009 acerca del estudio de registro de Yondelis® en combinación con Doxil® para el tratamiento del cáncer de ovario recurrente (OVA-301), Pharma Mar, S.A. quiere puntualizar lo siguiente:

1. La formulación de preguntas al ODAC forma parte del proceso habitual para la evaluación de productos oncológicos

2. El objetivo primario del ensayo pivotal OVA-301 ha sido alcanzado con resultados positivos, según ya se informó mediante Hecho Relevante núm. 96.581 de 7 de agosto de 2008.

3. En relación con la pregunta nº 4 que la FDA realizará al ODAC relacionada con el análisis final de supervivencia de los pacientes, cabe señalar que esta cuestión se refiere a un objetivo secundario del ensayo pivotal OVA-301. Durante la reunión del ODAC se presentarán datos adicionales que se confía contribuyan a responder dicha pregunta satisfactoriamente.

4. Quisiéramos informar que hasta el momento, las acciones de Johnson&Johnson están teniendo una evolución positiva en la sesión de hoy.

PharmaMar

PharmaMar es una empresa biofarmacéutica española líder mundial perteneciente al Grupo Zeltia, comprometida con el avance en el tratamiento del cáncer mediante el descubrimiento y el desarrollo de nuevos marinos derivados de los medicamentos. El primer producto de PharmaMar, Yondelis®, recibió la Autorización de Comercialización de la Comisión europea en septiembre de 2007 para el tratamiento del sarcoma de tejidos blandos en estado avanzado o metastático. En 2008 se presentó el

FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting

July 15, 2009

NDA 22-447
Yondelis (Trabectedin)
Ortho Biotech Products, L.P.

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1 Proposed Indication

"Indicated in combination with DOXIL® for treatment of patients with relapsed ovarian cancer"

2 Executive Summary

The pivotal study for this NDA is the ET743-OVA-301 study in 672 patients sponsored by the Applicant.

The ET743-OVA-301 study is a multicenter, multinational, open-label, randomized, controlled trial in 672 patients with ovarian cancer previously treated with only 1 platinum based chemotherapy regimen (including adjuvant therapy). Patients had experienced either recurrence or progression after the initial line of platinum-based chemotherapy regimen and were randomized 1:1 to trabectedin plus Doxil or Doxil alone. Both platinum sensitive and platinum resistant patients were included in the trial. The primary efficacy endpoint was initially overall survival but was later changed to progression-free survival (PFS). The secondary endpoint is overall survival (OS). Progression events in the primary analysis were adjudicated by blinded independent radiologists.

FDA would like the ODAC members to consider the following issues:

The **first issue** is the reliability of PFS, the primary endpoint in this trial. PFS is defined as the time between randomization and disease progression or death. The primary analysis of PFS was based on data from an independent radiologic review of patients with measurable disease. Discrepancies between the two independent radiology readers on the progression status or progression date required adjudication by a third independent radiology reader in 252 of the 645 patients (39%). There is also a high degree of discrepancy in the progressive disease (PD) status and PD date between the independent radiologic review and the investigators in 289 of the 456 patients (63%) who were determined to have progressive disease by the investigator. This raises the question whether PFS could be reliably assessed in this clinical trial.

The **second issue** is the inaccuracy of disease progression measured only by imaging studies in an ovarian cancer trial. Many patients progressed clinically or in non-measurable, non-target lesions, and the independent radiology assessments did not confirm the investigator's progressive disease assessments. These patients with disease progression by investigator assessment resulted in a high degree of censoring (40%).

The **third issue** is the clinical relevance of the PFS results. Trabectedin in combination with Doxil was better than Doxil monotherapy as assessed by the independent radiologic review. The median PFS (defined as time to radiologic progression or death) was 7.3 months for the combination versus 5.8 months for Doxil (a difference of 6 weeks) and the hazard ratio (HR) was 0.79 (0.65, 0.96). Whether the addition of 6 weeks to PFS at a cost of additional toxicity is sufficient benefit for approval needs to be discussed with ODAC. The trabectedin combination therapy showed more toxicities compared to Doxil monotherapy. The main trabectedin toxicity is hematologic with grade 3-4 neutropenia in 63% of the patients (22% with Doxil monotherapy) and 8% febrile neutropenia (2% with Doxil monotherapy). Grade 3-4 thrombocytopenia occurred in 18% of patients treated in the trabectedin arm compared to only 3% in the Doxil monotherapy arm. Transaminases increased in 31% of patients treated with trabectedin compared to 1% of patients in the Doxil monotherapy arm and 6 cases in the trabectedin group met Hy's Law criteria. Cardiac adverse events were also increased in the trabectedin combination arm (10%) compared to the Doxil monotherapy arm (3%). Six patients (2%) in the trabectedin combination arm had congestive heart failure compared to one patient (<1%) in the Doxil monotherapy arm.

ODAC advice is requested on whether these PFS results are reliable, are clinically significant, and are associated with an acceptable benefit:risk ratio.

The **fourth issue** is whether the FDA should wait for the final survival analysis before making a decision on the trabectedin application. An interim OS analysis after 300 (46%) deaths; showed that the median survival for the trabectedin arm is 20.5 months versus 19.4 months for Doxil, HR=0.85; 95% CI:0.67;1.06. The final OS analysis is planned at 520 death events. Whether the final OS analysis will show a significant difference between treatment arms remains to be seen.

The **fifth issue** is the applicability of the subjects' prior platinum treatment to the US standard practice. In this study, approximately 25% of patients received prior platinum-based therapies in the neo-adjuvant setting.

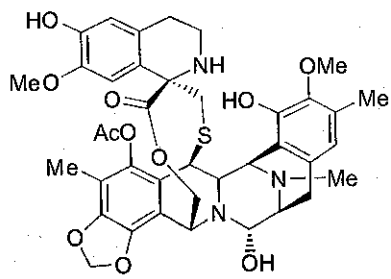
The following additional issues with this application do not require ODAC advice:
First Issue: Trabectedin adsorbs to some infusion set materials during administration, reducing dose delivered. Several non-clinical studies reported this effect with various infusion sets. One study reported that trabectedin losses were reversed (37% to 10%) when polyethylene infusion set materials were replaced with polyurethane. In clinical studies of trabectedin, no investigations were conducted to verify effective dose delivered and no data regarding the material composition of the infusion set materials were collected. This issue has implications on the validity of doses administered in the pivotal clinical study and the entire clinical program. A full study report for an additional chemistry study to carefully evaluate the effect of trabectedin loss to infusion set materials on the clinical dose is expected in June 2009.

Second issue: The CMC section of the NDA contains the results of studies evaluating the compatibility of trabectedin with some infusion set components (bags, tubing, filters, etc.). However, these CMC studies were found to be incomplete in that some materials of component construction used in clinical studies were not evaluated. Also, the preclinical toxicology findings of adsorption were not addressed. As designed and executed, the CMC infusion set compatibility studies overall fail to confidently establish that trabectedin did not adsorb to infusion set materials in clinical studies to an extent which may be considered clinically significant.

The applicant has recently agreed to conduct an additional compatibility study to more thoroughly evaluate adsorption of trabectedin to infusion set materials under clinically relevant conditions. The results of this study are expected to be submitted in June 2009.

2 Drug Description

Trabectedin is a new antineoplastic agent, described chemically as (1'*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12*H*-1,3-dioxolo[7,8]isoquino[3,2-*b*][3]benzazocine-20,1'(2'*H*)-isoquinolin]-19-one. The molecular formula is $C_{39}H_{43}N_3O_{11}S$ and molecular weight is 761.84. The chemical structure is:



Formulation is: sterile single use vial contains 1 mg of trabectedin to be constituted and further diluted for intravenous infusion. Inactive ingredients are sucrose (400 mg), potassium dihydrogen phosphate (27.2 mg), phosphoric acid and potassium hydroxide.

3 Clinical Toxicology

Trabectedin adsorbs to some infusion set materials during administration, reducing dose delivered. While this adsorption is poorly understood, its effect on dose delivered was measured in several non-clinical studies. These studies reported decreases in trabectedin

concentrations (0 to 83%) during infusion through various infusion set materials (plastics, glass, and silicone) and at various infusion solution concentration levels (0.67 to 12 micrograms/mL). One study reported that trabectedin losses were reversed (37% to 10%) when polyethylene infusion set materials were replaced with polyurethane. In other non-clinical studies, trabectedin losses to infusion set materials were not adequately measured and consequently these studies were invalidated. In clinical studies of trabectedin, no investigations were conducted to verify effective dose delivered and no data regarding the material composition of the infusion set materials were collected. This issue has implications on the validity of doses administered in the pivotal clinical study and the entire clinical program.

4 ET743-OVA-301 study

4.1 Study Design

The study is an open-label, multicenter, randomized, controlled Phase 3 study in 672 patients with ovarian cancer previously treated with only one platinum based chemotherapy regimen (including adjuvant therapy) who had experienced either recurrence or progression after the initial line of platinum-based chemotherapy regimen. Patients treated with more than 1 prior chemotherapy regimen, including adjuvant therapy were excluded.

Patients were randomized 1:1 to the combination of Doxil 30 mg/m^2 administered as a 90-minute intravenous infusion followed by trabectedin 1.1 mg/m^2 as a 3-hour IV infusion every 3 weeks or to Doxil alone at a dose of 50 mg/m^2 administered as a 90-minute infusion every 4 weeks. Patients in the trabectedin arm were premedicated with dexamethasone. The stratification factors were based on platinum sensitivity and baseline ECOG performance status (0-1 or 2). Treatment was to be continued until disease progression occurred or until subjects experienced a confirmed complete response (CR) for at least 2 cycles.

The original protocol primary endpoint was overall survival (OS). The protocol was amended on December 2006 (440 subjects were randomized) to change the primary endpoint to progression-free survival (PFS) based on an independent radiologic review. The secondary endpoint was overall survival. The analysis of the primary endpoint, PFS, was planned after at least 415 events (disease progression or death) were observed.

Subjects were followed for disease progression, the start of new therapy (if applicable), and for survival every 8 weeks during the study, as well as after study treatment was permanently discontinued for the first 2 years. Thereafter, follow-up was planned for every 3 months.

4.2 Criteria for Efficacy Assessment

Per protocol the following are the criteria for efficacy assessments:

- Baseline imaging studies were to be obtained within 2 weeks before administration of the first dose of study medication. All measurable lesions, up to a maximum of 5 per organ (total of 10), were identified as target lesions.
- Patients with known bone metastases had bone scans and associated bone imaging to confirm metastasis according to the required schedule and as clinically indicated. Bone scans and bone imaging to confirm metastasis were not required for other subjects unless clinical symptoms suggested bone metastases.
- A single elevated CA-125 was not considered evidence of disease progression, nor did it trigger unscheduled assessments of tumor status.
- Unplanned imaging assessments to evaluate disease progression were to be triggered by the following:
  - Escalating pain not referable to another cause
  - Increased ascites
  - Protracted nausea and vomiting despite treatment
  - Declining performance status or
  - Examination findings consistent with disease progression.

4.3 Primary Endpoint: PFS

PFS was defined as the time between randomization and disease progression or death. Thoraco-abdominal and pelvic CT scans or MRI were sent for central review. Although there were differences in cycle length (trabectedin +Doxil combination every 3 weeks and Doxil monotherapy every 4 weeks), tumor assessments were to be done every 8 weeks for both treatment arms. Measurable disease and response criteria used in the protocol were per RECIST guidelines and were to be based on radiologic assessments only.

The primary PFS analysis was based on all patients with measurable disease and was assessed by independent radiologists using imaging only. Overall assessment of response was determined by 2 independent radiologists, blinded to treatment arm and clinical data, who assessed tumor response for all of the images submitted using RECIST criteria. When the 2 radiologists disagreed, a 3rd radiology adjudicator read the scan and provided the final result. Secondary analyses were done per independent oncology reviewer and investigator.

Censoring rules applied to the protocol are as follows:

- Patients who neither progressed nor died were censored at the date of the last tumor assessment.

- Patients who were lost to follow up or started subsequent therapy for ovarian cancer were censored at the date of the last tumor assessment.
- Patients with missed assessments with a gap between assessments ≥ 18 weeks were censored at the date of the last tumor assessment.

Statistical Plan:
The protocol was to target a sample size of 650 patients. The number of patients enrolled in the platinum-resistant group were not to exceed 50% of the study population.

The study was powered to detect a difference in median PFS from 16 weeks to 22 weeks with at least 90% power. The study was also powered to detect a difference in median overall survival from 62.7 weeks to 83.4 weeks with a 90% power. The statistic for sample size calculation was the log rank statistic. It was anticipated that the final OS analysis would be performed at approximately 4.5 years from the start of randomization.

The number of events required for the final analysis was at least 415 events (progression or death) for analysis of progression-free survival for accelerated approval; 520 observed deaths for analysis of overall survival for regular approval. The actual PFS analysis was done at 389 PFS events. An interim analysis of OS was done at the time of final PFS analysis; 300 deaths were observed.

4.4 Study Results

Study results were based on a cut-off date of May 15, 2008. Enrollment occurred between April 2005 and May 2007. A total of 672 patients were enrolled, 335 in the Doxil arm and 337 in the trabectedin arm. The study was conducted in 21 countries at 124 sites. Most of the study sites were foreign sites with 82% of the patients accrued in foreign countries.

Table 1 ET743-OVA-301 Enrollment by Country

Country	No. Subjects Enrolled, N (%)
US	121 (18)
Russia	108 (16)
Poland	86 (13)
China	73 (11)
Canada	56 (8)
U.K.	38 (6)
Hong Kong	25 (4)
Belgium/Luxemburg	25 (4)
Germany	19 (3)
Korea	28 (4)
Brazil	21 (3)
Spain	17 (3)
Sweden	14 (2)
Italy	7 (1)
Argentina	7 (1)
Australia	7 (1)
Chile	3 (<1)
France	2 (<1)
Taiwan	9 (1)
Netherlands	5 (1)
Singapore	1 (<1)
TOTAL	**672**

Table 2 shows the patient population. Of the 672 patients randomized, 9 were not treated. The efficacy population consisted of 645 patients who had measurable disease at baseline. The safety population consisted of 663 treated patients.

Table 2 Patient Population

Population	Doxil n (%)	Trab/Doxil n (%)	Total n (%)
Randomized	335 (100)	337 (100)	672 (100)
Not Treated	6 (2)	3 (1)	9 (1)
Treated	329 (98)	334 (99)	663 (99)
Measurable Disease	317 (95)	328 (97)	645 (96)

Patient demographics and disease characteristics were well balanced between treatment arms. Two thirds of the patients in both arms had papillary serous histology. The remaining one third of the patients had other histologies, including endometrioid, clear cell, mixed epithelial cell, peritoneal, and fallopian tube carcinoma. Most of the patients in both groups had 1-3 sites of disease.

Table 3 Patient Demographics and Disease Characteristics

	Doxil (n=335)	**Trabectedin/Doxil (n=337)**
Age		
Mean	58.2	56.8
Range	27-87	26-82
Race		
White	259 (77%)	265 (79%)
Asian	71 (21%)	66 (20%)
Black	3 (1%)	2 (1%)
Baseline ECOG		
0	192 (57)	230 (68)
1	132 (39)	98 (29)
2	11 (3)	9 (3)
Histology		
Papillary/Serous	230 (69%)	225 (67%)
Other	105 (31%)	111 (33%)
Sites involved at baseline		
1-3	295 (89%)	278(84%)
≥3	37 (11%)	53 (16%)

Table 4 shows the available information on prior ovarian cancer chemotherapy. Thirty five percent to 37% of the patients in each group had a platinum-free interval of <6 months, and were therefore platinum-resistant. There was a slight imbalance in the 6-<12 month platinum-free interval between treatment arms, 37% in the trabectedin combination arm and 27% in the Doxil monotherapy arm.

Most of the patients (80%) had prior taxane therapy. Only 20% of the patients received their prior platinum regimen in the metastatic setting, the other 80% of the patients had

their prior platinum based chemotherapy as adjuvant or neo-adjuvant. There is no information on stage of disease at the time of first platinum therapy.

Table 4 Prior Ovarian Cancer Chemotherapy Treatment

	Doxil (N= 335) N (%)	**Trab + Doxil (N=337) N (%)**
Time to End of plat tx to PD		
Platinum Resistant		
<6	124 (37)	118 (35)
Platinum Sensitive	212 (63%)	218 (65%)
6-<12	**90 (27)**	**123 (37)**
12-<24	76 (23)	70 (21)
≥24	45 (13)	25 (7)
Prior Taxane	271 (81)	269 (80)
Therapeutic Phase of prior chemotherapy		
Adjuvant	245 (73)	231 (69)
Neo-adjuvant	91 (27)	82 (24)
Advanced/metastatic	60 (18)	72 (21)

Table 5 shows the therapeutic phase for which patients received their prior platinum therapy. Most of the patients received prior platinum in the adjuvant setting alone or subsequent to neo-adjuvant therapy. Approximately 25% of the patients received platinum based therapy in the neo-adjuvant setting and 17% of the patients in the metastatic setting. According to the study protocol, patients treated with more than 1 prior chemotherapy regimen, including adjuvant therapy were excluded. However, 15% of the study patients received more than 1 prior chemotherapy regimen.

Table 5 Therapeutic Phase of Prior Platinum Chemotherapy

	Doxil n=317 (%)	Trabectedin/Doxil n=328 (%)	Total n (%)
Adjuvant	182 (57)	183 (56)	365 (57)
Neoadjuvant	32 (10)	39 (12)	71 (11)
Neoadjuvant and adjuvant	49 (15)	38 (12)	87 (13)
Neoadjuvant and advanced metastatic	3 (◁)	3 (◁)	6 (◁)
Advanced metastatic	48 (15)	60 (18)	108 (17)
Adjuvant and advanced metastatic	4 (1)	2 (◁)	6 (◁)

Table 6 shows the major protocol violations and deviations which were higher in the trabectedin study arm. Most of them were treatment deviations such as wrong treatment, incorrect dose, or length of infusion. However, these deviations probably do not affect the study results.

Table 6 Protocol Violations/Deviations

	Doxil N= 335	Trab/Doxil N=337
Patients with deviations	**32 (9)**	**43 (13)**
Treatment deviation	9 (3)	24 (7)
Not withdrawn per protocol	8 (2)	4 (1)
Efficacy assessment dev.	8 (2)	8 (2)
Selection criteria not met	7 (2)	9 (3)

4.5 Efficacy Results

Progression-Free Survival

The primary analysis results of PFS based only on radiologic progressions or deaths, shows that the combination of trabectedin has a median PFS of 7.3 months compared to 5.8 months for the Doxil monotherapy arm. The Hazard Ratio is 0.79 in favor of combination of trabectedin and Doxil arm. These results are shown in Table 7 and Figure 1. Sixty percent of the patients had an event and 40% were censored.

Table 7 PFS Results Based on Independent Radiology Assessments (Measurable Disease)

	Doxil (n=317)	Trabectedin/Doxil (n=328)
PFS Events (%)	194 (61.2)	195 (59.5)
Death	24 (12.4)	14 (7.1)
PD	170 (87.6)	181 (92.8)
Censored (%)	123 (38.8)	133 (40.5)
Median PFS (95% CI)	5.8 (5.5; 7.1)	7.3 (5.9; 7.9)
P-value	0.019	
Hazard Ratio (95% CI)	0.79 (0.65, 0.96)	

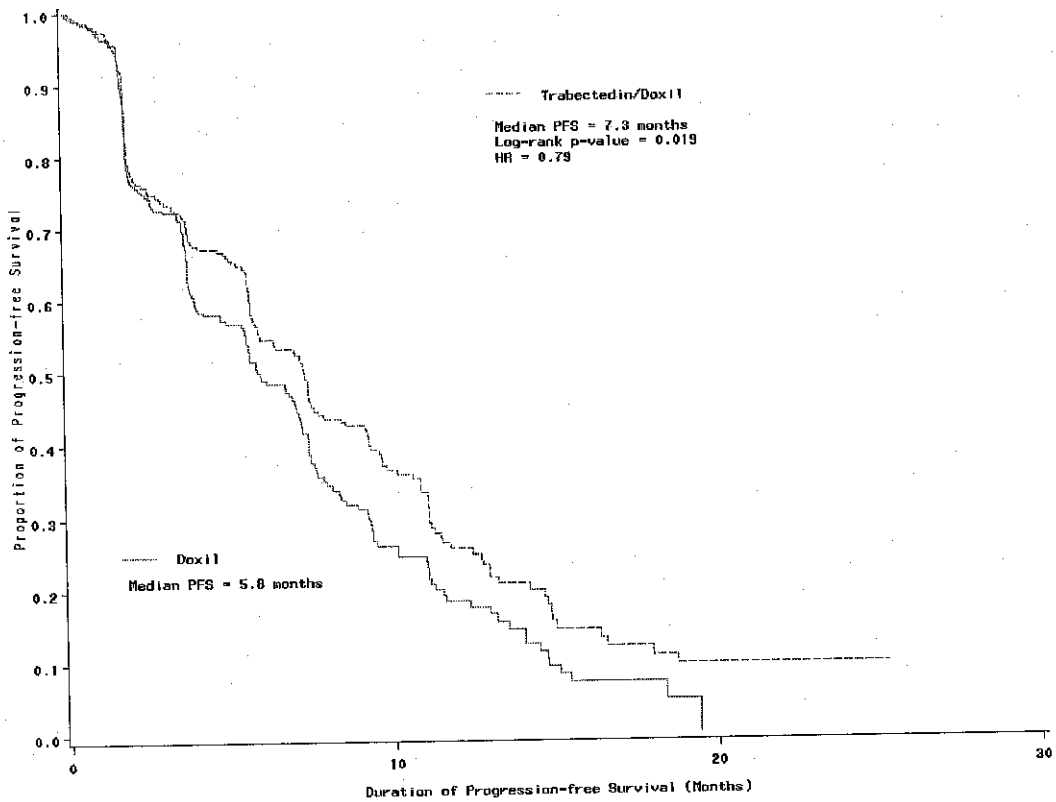


Figure 1 Kaplan-Meier Curve of PFS (Independent Radiologic Review on All Measurable Disease Patients)

PFS results based on investigator and independent oncologist assessments are consistent with the results based on Independent Radiologist.

Table 8 PFS Results Based on Investigator and Independent Oncologist Assessments

	Investigator		Independent Oncologist	
	Doxil (n=317)	**Trabec/Doxil (n=328)**	**Doxil (n=317)**	**Trabec/Doxil (n=328)**
PFS Events (%)	236 (74.5)	220 (67.1)	213 (67.2)	202 (61.6)
Censored (%)	81 (25.6)	108 (32.9)	104 (32.8)	126 (38.4)
Median PFS (95% CI)	5.7 (5.5; 7.1)	7.7 (7.3; 9.3)	5.8 (5.5; 7.1)	7.3 (5.9; 7.9)
P-value	<0.0001		0.0004	
Hazard Ratio (95% CI)	0.69 (0.57, 0.83)		0.71 (0.58, 0.86)	

The results of an exploratory subgroup analysis using the stratification factors of platinum-sensitive and platinum-resistant are shown in Table 9. There was no improvement in PFS with the trabectedin combination compared to Doxil monotherapy in patients who were platinum-resistant. The combination of trabectedin and Doxil did result in a statistically significant improvement in PFS over Doxil alone in patients who were platinum-sensitive (median PFS 9.2 vs. 7.5 months, Hazard Ratio 0.73).

Table 9 Subgroup PFS Analysis by Platinum Sensitivity (IR)

	Platinum-Resistant		Platinum-Sensitive	
	Doxil (n=115)	**Trabectedin/Doxil (n=113)**	**Doxil (n=202)**	**Trabectedin/Doxil (n=215)**
PFS Events (%)	83 (72.2)	80 (70.8)	111 (55.9)	115 (53.5)
Censored (%)	32 (27.8)	33 (29.2)	91(45.1)	100 (46.5)
Median (95% CI)	3.7 (3.0, 5.5)	4.0 (2.9, 5.6)	7.5 (7.0, 9.1)	9.2 (7.4, 11.1)
P-value	0.75		0.017	
Hazard Ratio (95% CI)	0.95 (0.70, 1.30)		0.73 (0.56, 0.95)	

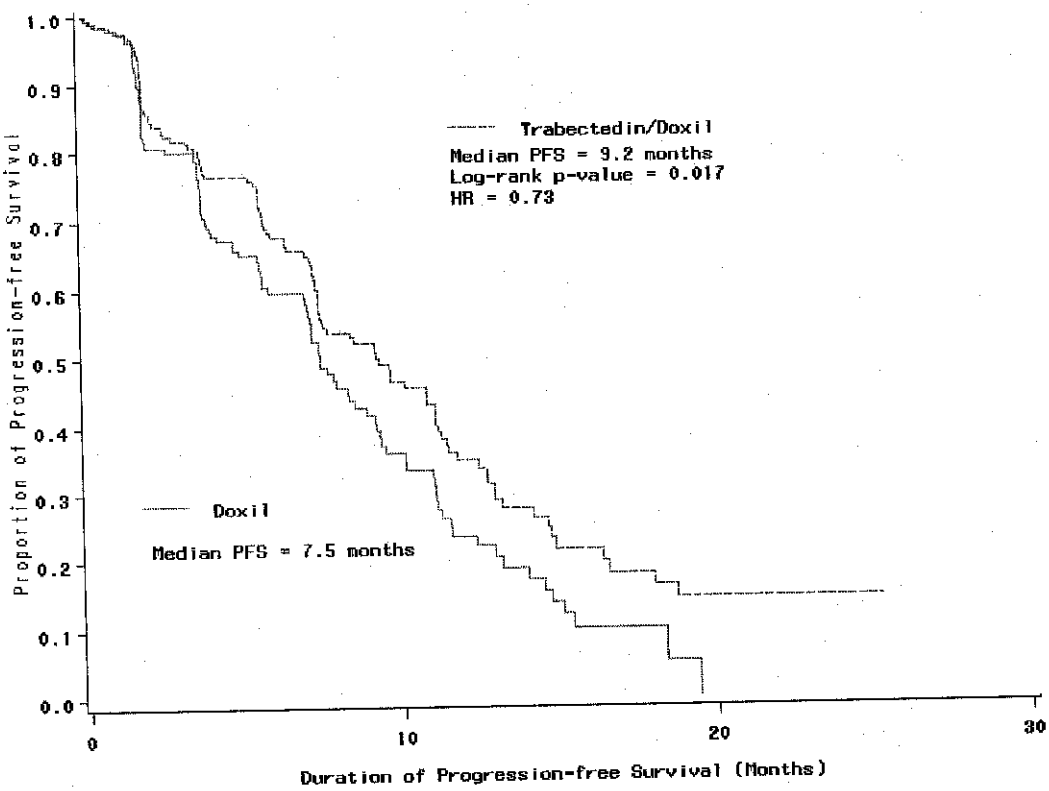


Figure 2 Kaplan-Meier Curve of PFS in Platinum-Sensitive Patients (Independent Radiologist Review on All Measurable Disease Patients)

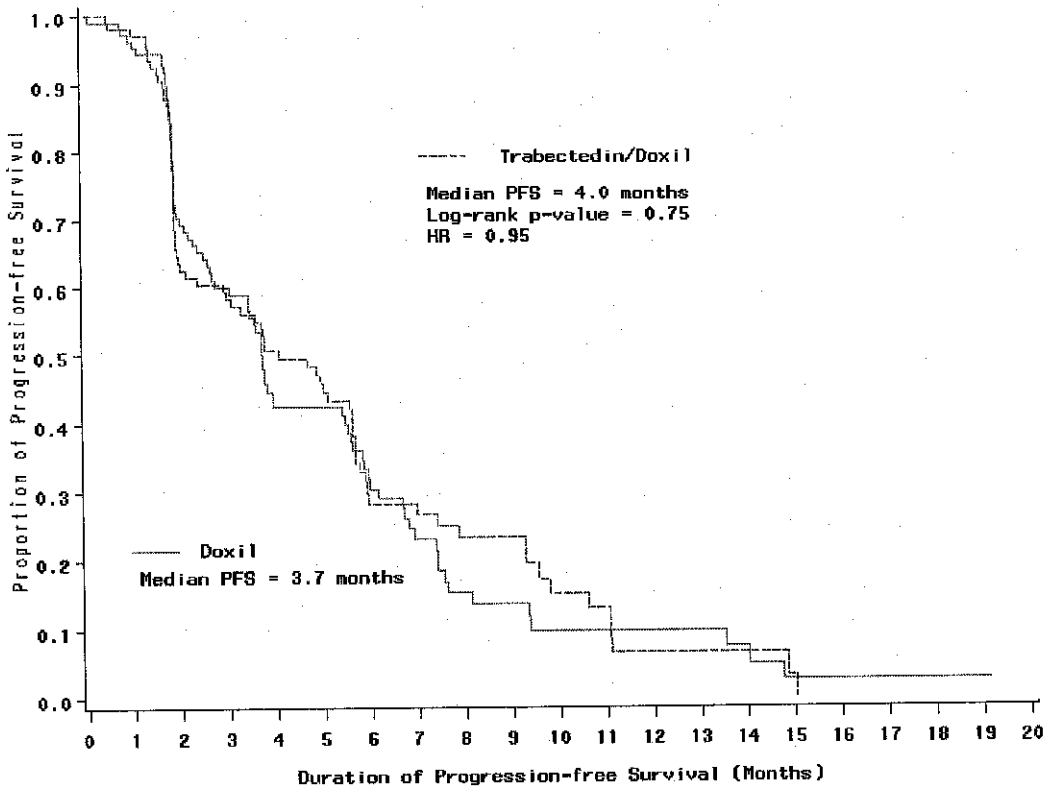


Figure 3 Kaplan-Meier Curve of PFS in Platinum-Resistant Patients (Independent Radiologist Review on all Measurable Disease Patients)

As shown in Table 10, the two independent radiology reviewers disagreed on the progression status of 39% (252 of 645) of the patients with measurable disease, requiring adjudication by a third radiologist. There was a 27% (172 of 645) disagreement on progressive disease status and 12% (80 of 645) disagreement on the date of disease progression. This raises the question whether progression could be reliably assessed in this trial.

Table 10 Adjudicated Independent Radiologist Assessments

Progression	Number	Doxil (n=317)	Trabectedin/Doxil (n=328)
Radiologic Progression	389	194 (61%)	195 (60%)
Number adjudicated	**252 (39%)**	**131 (41%)**	**121 (37%)**
Disagreement on PD	172 (27%)	91 (29%)	81 (25%)
Disagreement on PD date	80 (12%)	40 (13%)	40 (12%)

There are also a high number of discrepancies (63%) between the investigator and independent radiologist's assessments.

Table 11 Discrepancies Between Independent Radiologist and Investigator Assessments

	Doxil (n=317)	Trabectedin/Doxil (n=328)
	Number of Patients (%)	
Progressive disease by INV	236	220
Disagreement w/ IR on PD status or date	**143 (61)**	**146 (66)**
Disagreement w/ IR on PD status	65	62
Disagreement w/ IR on PD date	78	84

Survival

The interim survival analysis results are shown in the tables and figures below. The difference in OS between treatment arms is very small, with a median OS of 20.5 months in the trabectedin combination group and 19.4 months in the Doxil monotherapy group, HR 0.85, p=0.15. Whether the modest 6 week improvement in PFS will result in a survival effect at the time of final OS analysis remains to be seen.

Table 12 Survival Interim Analysis (ITT population)

	Doxil (n=335)	**Trabectedin/Doxil (n=337)**
Death (%)	155 (46.3.1)	145(43.0)
Censored (%)	180 (53.7)	192(57.0)
Median OS (95% CI)	19.4 (17.3, 21.7)	20.5 (18.7, 24.2)
P-value	0.15	
Hazard Ratio (95% CI)	0.85 (0.67, 1.06)	

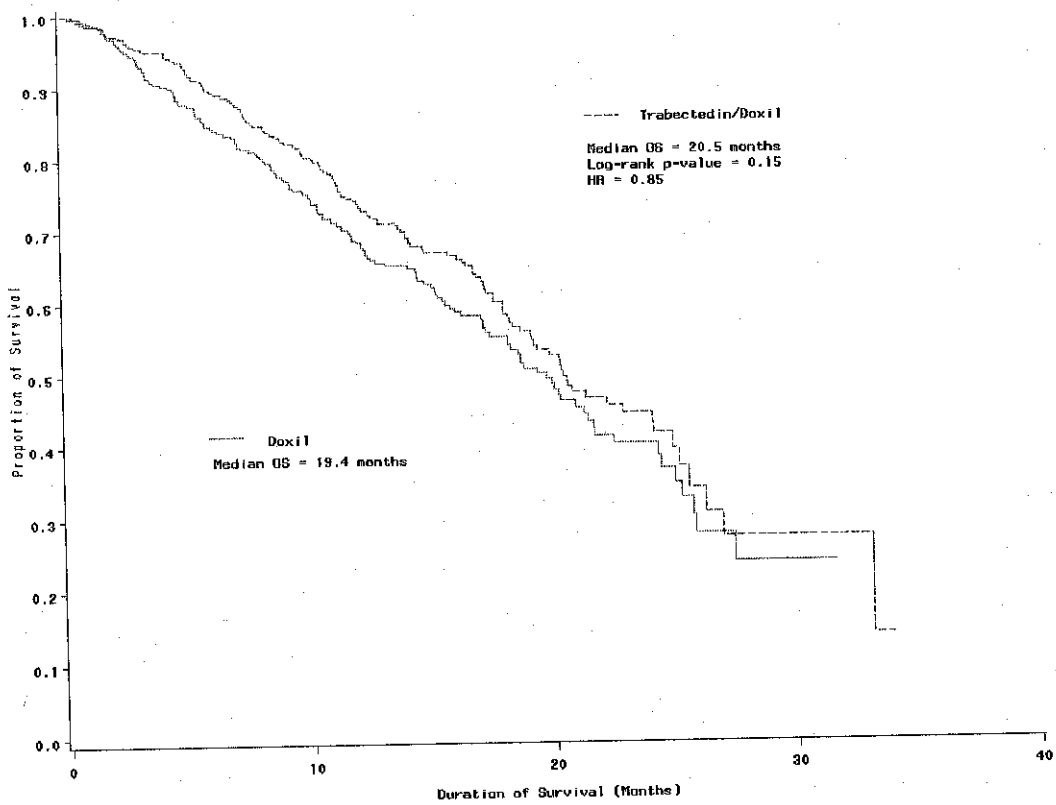


Figure 4 Kaplan-Meier Curve of Interim Survival

Table 13 Survival Interim Analysis by Platinum Sensitivity

	Platinum Sensitive		Platinum Resistant	
	Doxil (n=212)	**Trabec/Doxil (n=218)**	**Doxil (n=123)**	**Trabec/Doxil (n=119)**
Death (%)	78 (36.8)	75 (34.4)	77 (63%)	70 (59%)
Censored (%)	134 (63.2)	143 (65.6)	46 (37.4)	49 (41.2)
Median OS (95% CI)	24.3 (20.1, 25.8)	25.0 (21.4, 27.0)	12.4 (11.0, 15.2)	14.0 (11.1, 17.1)
P-value	0.22		0.56	
Hazard Ratio (95% CI)	0.82 (0.60, 1.13)		0.91 (0.66, 1.3)	

Tumor Response

Objective tumor response evaluated by blinded independent radiologists showed that the combination of trabectedin +Doxil in patients with measurable disease has an increased overall response rate compared to Doxil monotherapy (28% versus 19%, p=0.0080). The median duration of response was 7.9 months in the trabectedin combination arm compared to 7.7 months in the Doxil monotherapy arm.

Table 14 Tumor Response by Independent Radiology Assessment

	Doxil (n=335)	Trabectedin/Doxil (n=337)
CR+PR n (%)	63 (19)	93 (28)
P-value	0.008	
Duration of Response in Months (95% CI)	7.7 (6.5, 9.0)	7.9 (7.4, 9.2)

Post study chemotherapy

Post study chemotherapy was administered to 233 (69%) of the patients in the trabectedin combination arm and 240 (72%) of the patients in the Doxil arm. Apparently there were no crossovers. Forty-seven percent of the patients were treated with platinum compounds and 23% with taxanes.

4.6 Safety Results

Table 15 shows the adverse events occurring in at least 10% of patients. The trabectedin combination arm had a higher incidence of neutropenia, leucopenia, anemia and thrombocytopenia. Increased transaminases were higher in the trabectedin combination arm, 31% Grade 3-4 ALT elevations compared to 1% in the Doxil monotherapy arm.

Table 15 Adverse Events in ≥ 10 % of Patients

Adverse Drug Reaction System Organ Class Preferred Term	TRADENAME®+ DOXIL® (n=333) %			DOXIL® (n=330) %		
	Any (%)	Grade 3	Grade 4	Any (%)	Grade 3	Grade 4
Blood and Lymphatic System						

Adverse Drug Reaction System Organ Class Preferred Term	TRADENAME®+ DOXIL® (n=333) %			DOXIL® (n=330) %		
	Any (%)	Grade 3	Grade 4	Any (%)	Grade 3	Grade 4
Disorders						
Neutropenia	77	**29**	**34**	38	14	8
Leukopenia	48	**25**	**8**	26	7	3
Anemia	48	**10**	3	25	5	1
Thrombocytopenia	36	**10**	**8**	8	2	1
Metabolism and Nutrition Disorders						
Hypokalemia	11	4	<1	8	1	0
Anorexia	32	2	0	26	3	<1
Psychiatric Disorders						
Insomnia	10	0	0	5	0	0
Nervous System Disorders						
Headache	16	1	0	8	<1	0
Respiratory, Thoracic and Mediastinal Disorders						
Dyspnea	15	3	<1	10	2	<1
Cough	12	0	0	12	0	0
Gastrointestinal Disorders						
Nausea	74	**10**	0	42	4	0
Vomiting	56	**12**	<1	30	4	0
Constipation	32	2	0	28	2	0
Diarrhea	26	2	0	19	2	0
Abdominal Pain	20	1	0	33	5	<1
Stomatitis	20	1	0	33	5	<1
Dyspepsia	13	<1	0	11	1	0
Hepatobiliary Disorders						
Hyperbilirubinemia	16	1	0	7	1	0
Skin and Subcutaneous Tissue Disorders						
Hand-foot syndrome	24	4	0	54	18	1
Alopecia	12	0	0	14	<1	0
Rash	11	0	0	17	1	0
General Disorders and Administration Site Conditions						
Pyrexia	20	1	0	13	1	0
Fatigue	46	8	<1	36	5	<1
Asthenia	17	2	0	12	2	0
Mucosal inflammation	12	2	0	19	6	0
Laboratory						
Alanine aminotransferase increased	55	**29**	2	9	1	0
Aspartate aminotransferase increased	40	**6**	1	10	1	<1
Blood alkaline phosphatase increased	23	1	0	8	1	0

Cardiac Adverse Events:
Study ET743-OVA-301 excluded patients with history of myocardial infarction within 6 months of enrollment, New York Heart Association Class II or greater heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, pericardial disease or electrocardiographic evidence of acute ischemic or conduction abnormalities. Patients enrolled were to have a normal LVEF at baseline and at the end of study therapy. All patients with a history of cardiac disease or a cumulative anthracycline dose that exceeded 360 mg/m^2 were to have a follow-up LVEF assessment every 2 cycles of therapy.

Cardiac adverse events were higher in patients treated in the trabectedin combination arm (10%) compared to the Doxil monotherapy arm (3%). Six patients (2%) in the trabectedin combination arm had congestive heart failure compared to one patient (<1%) in the Doxil monotherapy arm.

Table 16 Cardiac Adverse Events

	Doxil (n=330)	**Trabectedin/Doxil (n=333)**
Patients with adverse events in MedDRA Cardiac Soc	12 (3)	**30 (10)**
Congestive Heart Failure	1 (<1)	**6 (2)**
Patients with baseline and post baseline LVEF assessments	190 (58)	223 (67)
LVEF Decline		
Absolute decrease ≥ 15%	28(15)	**40 (18)**
Less than lower limit of normal and absolute decrease ≥ 5%	10 (5)	16 (7)

Forty (18%) patients in the trabectedin combination group had a LVEF decline of ≥15% compared to 28 (15%) patients in the Doxil monotherapy group. These data are incomplete since only 58% to 67% of the study patients had a baseline and a final LVEF assessment.

Hepatic Toxicity:
Liver function test abnormalities were the most frequent adverse events. Hy's Law criteria were used to predict hepatotoxicity. Hy's Law predicts for potential severe liver toxicity when the following criteria are met:

- AST or ALT elevations ≥3 times the ULN; and
- Total bilirubin >2 times the ULN and ALP ≤2 times the ULN; and
- No other clinical explanation

Table 17 summarizes the patients who met the criteria for Hy's Law. The applicant identified 3 patients all in the trabectedin combination arm and the FDA identified 3 additional cases.

Table 17 Hy's Law Cases

Subject ID	ALT/AST		Tbili		Alk Phos	Liver Metastases	Identified by the Applicant
	≥3xULN	Cycle #	≥2xULN	Cycle #	≤2xULN		
240016	Yes	3	Yes	3	Yes	No	Applicant
250005*	Yes	2	Yes	2	Yes	No	Applicant
280005	Yes		Yes		Yes	No	Applicant
200033	Yes	1,2	Yes	2	Yes	No	FDA
220089	Yes	1	Yes	1	Yes	No	FDA
270005	Yes	2,3	Yes	6	Yes	No	FDA

* This patient got an overdose of trabectedin

Addendum
to the

FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting
July 15, 2009
NDA 22-447
Yondelis (Trabectedin)
Ortho Biotech Products, L.P.

This addendum pertains to the **second issue** listed on page 7 of the FDA Briefing Document under the section entitled "*The following additional issues with this application do not require ODAC advice:*"

New CMC studies have been submitted since the FDA Briefing Document was prepared. Preliminary review of these CMC studies indicate that they provide evidence that, at the proposed clinical dose, trabectedin does not adsorb to infusion set materials to an extent which may be considered clinically relevant. Whether the evidence is sufficient to address this CMC issue remains to be determined as this CMC review is still in-process.

ERRATA

to the

FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting
July 15, 2009
NDA 22-447
Yondelis (Trabectedin)
Ortho Biotech Products, L.P.

Oncologic Drugs Advisory Committee
July 15, 2009

Page 5, paragraph 4, sentence 4:

"Discrepancies between the two independent radiology readers on the progression status or progression date required adjudication by a third independent radiology reader in 252 of the 645 patients (39%)."

Corrected to read:
"Discrepancies between the two independent radiology readers on the progression status or progression date required adjudication by a third independent radiology reader in **247** of the 645 patients (**38%**).

Page 10, paragraph 4, 1st sentence:

"The number of events required for the final analysis was at least 415 events (progression or death) for analysis of progression-free survival for accelerated approval; 520 observed deaths for analysis of overall survival for regular approval."

Corrected to read:

"The number of events required for the final analysis was at least 415 events (progression or death) for analysis of progression-free survival; 520 observed deaths for analysis of overall survival."

Page 14, Table 5:

	Doxil n=317 (%)	Trabectedin/Doxil n=328 (%)	Total n (%)
Adjuvant	182 (57)	183 (56)	365 (57)
Neoadjuvant	32 (10)	39 (12)	71 (11)
Neoadjuvant and adjuvant	49 (15)	38 (12)	87 (13)
Neoadjuvant and advanced metastatic	3 (<1)	3 (<1)	6 (<1)
Advanced metastatic	48 (15)	60 (18)	108 (17)
Adjuvant and advanced metastatic	4 (1)	2 (<1)	6 (<1)

Corrected to read:

	Doxil n=317 (%)	Trabectedin/Doxil n=328 (%)	Total n (%)
Adjuvant	182 (57)	183 (56)	365 (57)
Neoadjuvant	32 (10)	39 (12)	71 (11)
Neoadjuvant and adjuvant	49 (15)	38 (12)	87 (13)
Neoadjuvant and advanced metastatic	3 (<1)	3 (<1)	6 (<1)
Advanced metastatic	48 (15)	60 (18)	108 (17)
Adjuvant and advanced metastatic	**2 (<1)**	**4 (1)**	6 (<1)
Neoadjuvant, adjuvant and advanced metastatic	**1 (<1)**	**1 (<1)**	**2 (<1)**

Page 19, 1st parragraph:

"As shown in Table 10, the two independent radiology reviewers disagreed on the progression status of 39% (252 of 645) of the patients with measurable disease, requiring adjudication by a third radiologist."

Corrected to read:
"As shown in Table 10, the two independent radiology reviewers disagreed on the progression status of **38%** (**247** of 645) of the patients with measurable disease, requiring adjudication by a third radiologist."

Page 20, Table 10:

Progression	**Number**	**Doxil (n=317)**	**Trabectedin/Doxil (n=328)**
Radiologic Progression	389	194 (61%)	195 (60%)
Number adjudicated	**252 (39%)**	**131 (41%)**	**121 (37%)**
Disagreement on PD	172 (27%)	91 (29%)	81 (25%)
Disagreement on PD date	80 (12%)	40 (13%)	40 (12%)

Corrected to read:

Progression	**Number**	**Doxil (n=317)**	**Trabectedin/Doxil (n=328)**
Radiologic Progression	389	194 (61%)	195 (60%)
Number adjudicated	**247 (38%)**	**128 (40%)**	**119 (36%)**
Disagreement on PD	**171** (27%)	**90** (28%)	81 (25%)
Disagreement on PD date	**76** (12%)	**38 (12%)**	**38 (12%)**

Page 25, paragraph 3, sentence 2:

"These data are incomplete since only 58% to 67% of the study patients had a baseline and a final LVEF assessment."

Corrected to read:
"These data are incomplete since only 58% to 67% of the study patients had a baseline and a **post-baseline** LVEF assessment.

dossier de registro ante la Agencia europe del Medicamento (EMEA) y la Food and Drug Administration (FDA, EEUU) para Yondelis® administrado en combinación con Doxil®/Caelyx™ para el tratamiento de mujeres con cáncer de ovario recurrente. Yondelis también se encuentra en ensayos de Fase II para próstata, mama y cáncer de pulmón. Tres compuestos, Aplidin® ®, Zalypsis ®, Irvalec® y PM01183 son nuevos agentes de origen marino en diferentes fases de desarrollo clínico.

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