CLINICAL STUDY REPORT SYNOPSIS

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Name of Sponsor/Company	Ortho Biotech Oncology Research & Development, Unit of Johnson & Johnson Pharmaceutical Research & Development, L.L.C. and Pharma Mar S.A.	
Name of Finished Product	YONDELIS®	
Name of Active Ingredient(s)	trabectedin	

Protocol No.: ET743-OVA-301

Title of Study: An Open-Label, Multicenter, Randomized, Phase 3 Study Comparing the Combination of YONDELIS® With DOXIL®/CAELYX® or DOXIL/CAELYX Alone in Subjects With Advanced Relapsed Ovarian Cancer

Principal Investigator: Bradley J. Monk, M.D., F.A.C.O.G., F.A.C.S. – Associate Professor, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of California, Irvine, UCI Medical Center, 101 The City Drive, Bldg. 56, Suite 260, Orange, CA 92868-3298, United States

Study Period: Date study initiated: 20 April 2005 Clinical cutoff: 15 May 2008	**Phase of Development:** Phase 3

Objectives:

The primary objective of this study was as follows:

- compare PFS of the combination of trabectedin + DOXIL with DOXIL 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 DOXIL in each respective 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.

Methodology:

This was an open-label, multicenter, randomized, controlled Phase 3 study comparing the combination of DOXIL, 30 mg/m^2, administered as a 90-minute intravenous infusion (i.v.) followed by trabectedin, 1.1 mg/m^2, as a 3-hour i.v. infusion, every 3 weeks, with DOXIL alone at a dose of 50 mg/m^2, administered as a 90-minute i.v. infusion every 4 weeks.

Number of Subjects (planned and analyzed):

Approximately 650 subjects were to be randomly assigned to 1 of the treatment arms over 2 years. The analysis of the primary endpoint, PFS, was to be conducted after at least 415 events (disease progression or death) were observed. An interim analysis of safety was to be performed when approximately 100 subjects were randomly assigned.

Diagnosis and Main Criteria for Inclusion:

Female subjects 18 years of age or older who had been previously treated for advanced ovarian cancer, and for whom first-line platinum-based chemotherapy regimen had failed, were enrolled. The subjects had to meet all of the inclusion criteria and none of the exclusion criteria. At the time of randomization, subjects were to be stratified on the basis of platinum sensitivity of disease (sensitive or resistant) and baseline Eastern Cooperative Oncology Group (ECOG) performance status score (0 to 1, or 2).

SYNOPSIS (CONTINUED)

Test Product, Dose and Mode of Administration:

Trabectedin was supplied in sterile, single-use vials containing 0.25 mg or 1.0 mg of trabectedin. Inactive ingredients are sucrose, potassium dihydrogen phosphate as a buffering agent, phosphoric acid, and potassium hydroxide for pH adjustment.

DOXIL was provided in glass single-use vials containing sterile translucent red liposomal dispersion for infusion. Each vial contained either 20 mg in 10 mL or 50 mg in 25 mL of doxorubicin HCl at a concentration of 2 mg/mL. Sites were provided the DOXIL package insert.

Batch No.:

Identity of Trabectedin and DOXIL Investigational Product
(Study ET743-OVA-301)

Trabectedin Lyopholized Powder/Formulation	Manufacturer Lot Number	Packaging Lot Number
0.25 mg/ 10 mL vial	4M102	V05PD9618
	4M102	V05PC9195
	4M102	V05PE9239
	4M102	V05PK9387
	4M102	V05PK9402
	4M102	V06PC9592
	4M102	V06PC9614
	4M101	V06PD9644
	4M101	V06PD9655
	4M101	V06PH9793
	4M101	V06PJ9813
	5E105	V07PC9991
	5E103	V07PC9992
	5E103	V07PC7000
	5E104	V07PD7009
	5E103	V07PD7010
	5E104	V07PE7049
	5E104	V07PE7051
1.0 mg/25 mL vial	4M203	V05PD9619
	4M203	V05PC9196
	4M203	V05PE9240
	4L202	V05PK9388
	4L202	V05PK9403
	4M203	V06PC9615
	4L202	V06PD9657
	5E206	V06PJ9814
	5K209A	V07PH7109
	5K209A	V07PJ7131
DOXIL/CAELYX		
20mg/10mL vial	0420003	R13171
	0420003	R13200
	0429272	R13381
	0429272	R13482
	0503051	R13692
	0503051	R13772
	0526366	R13947
	0526366	R13948
	0526366	R13924
	0625023	350524
	0625023	350522
	0625023	350759

SYNOPSIS (CONTINUED)

Identity of Trabectedin and DOXIL Investigational Product (Continued)
(Study ET743-OVA-301)

Trabectedin Lyopholized Powder/Formulation	Manufacturer Lot Number	Packaging Lot Number
	0625023	350523
	0625023	350758
	635745	352648
	635745	350649
	635745	350651
50mg/25mL vial		
	0412850	R13063
	0412850	R13172
	0535886	R13950
	0535886	R13949
	0535886	R13988
	0535886	R14200
	0535886	R14199
	0535886	R14175
	0616730	350057
	0616730	350058
	0616730	350059
	0616730	350211
	0616730	350210
	0616730	350655
	0616730	351626
	0616730	350653
	0625173	350654
	0625173	352492
	0625173	352493

Duration of Treatment:

Trabectedin + DOXIL arm: trabectedin q3wk;3-h and DOXIL q3wk;90 minutes i.v. infusion until disease progression or death.

DOXIL monotherapy arm: q4wk; 90-minute i.v. infusion until disease progression or death.

Criteria for Evaluation:

Pharmacokinetics/ Pharmacodynamics/ Pharmacogenomics: provided in separate reports

Efficacy:

The primary objective was to demonstrate the superiority of the combination therapy over the single agent control therapy in PFS. The secondary objectives were to compare the treatments with respect to OS, ORR, and duration of response, safety profile, and overall clinical benefit. Clinical benefit was to have been assessed by the following: change in analgesic use, weight change, change in ECOG performance status score, frequency of hospitalization, tumor-related symptoms (i.e., pain, dyspnea, cough, ascites, and pleural effusion) and PRO.

Safety:

Safety evaluations included adverse events, deaths, cardiovascular safety, clinical laboratory data, vital signs, and physical findings. Data for these safety variables were recorded in the CRFs. Adverse event severity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 3.0) classification.

Statistical Methods:

The statistical methods used to analyze the study data are summarized in the Statistical Analysis Plan.

Efficacy

All analyses were performed as planned. However, the number of subjects with an ECOG performance status score of 2 was limited in this study, therefore, the ECOG stratification factor was excluded in the stratified log-rank test. For ECOG grouping for multivariate analysis, baseline ECOG performance status score (0 versus greater than 0) was used instead of baseline ECOG performance status score (0 or 1 versus 2). If there were discrepancies between IVRS and CRF for 2 stratification factors (platinum sensitivity and baseline ECOG performance status score), then CRF data were used for the analysis.

SYNOPSIS (CONTINUED)

Safety

The safety analysis was based on the All-Treated Subject analysis set, where the grouping into the different arms was based on the treatment received during Cycle 1. All safety analyses were performed as planned.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

The results of Study ET743-OVA-301 demonstrate that subjects with relapsed ovarian cancer who were treated with trabectedin in combination with DOXIL have better clinical outcomes compared with those who were treated with DOXIL monotherapy. The analysis of PFS by independent radiologists, the primary endpoint, demonstrates that the combination treatment with trabectedin + DOXIL arm results in a 21% risk reduction of disease progression or death compared with DOXIL monotherapy (HR=0.79; 95% CI: 0.65;0.96; p=0.0190). This result, derived from the independent radiologist review, was consistent with the independent oncologist review (HR=0.72; 95% CI: 0.60;0.88; p=0.0008), which took into account clinical, as well as imaging, data in the assessment of progression. The independent oncologist review is well matched with assessments by the study investigators (HR=0.72; 95% CI: 0.61;0.86; p=0.0002). Therefore, all 3 measures of PFS demonstrate clinically meaningful and statistically significant improvement in the primary endpoint, PFS. In addition, the median CA-125 PFS was longer in the trabectedin + DOXIL arm than in the DOXIL monotherapy arm. These results are consistent with the overall efficacy outcomes. These results are supported by an increased response rate with the use of the combination therapy versus monotherapy (28% versus 19%, respectively). While overall survival data are 55% censored, there is a trend toward benefit in the combination arm (15% risk reduction). In addition the PRO analysis show there is no unfavorable effect when adding trabectedin to DOXIL for the treatment of ovarian cancer

SAFETY RESULTS:

Six hundred seventy-two subjects were randomized, 337 subjects in the trabectedin + DOXIL arm and 335 subjects in the DOXIL arm. The study was conducted in a total of 21 countries at 124 sites worldwide. Nine subjects did not receive study drug (6 subjects in the DOXIL monotherapy arm and 3 in the trabectedin + DOXIL arm). The remaining 663 randomized subjects received at least 1 dose of study medication (trabectedin + DOXIL, 334; DOXIL alone, 329) and comprise the All-Treated Subjects safety analysis population.

Most subjects in the DOXIL monotherapy and trabectedin + DOXIL arms had 1 or more adverse events assessed by the investigator as drug related. Deaths during the study due to treatment-emergent adverse events occurred in 1 (<1%) subject in the DOXIL monotherapy arm and 5 (2%) subjects in the trabectedin + DOXIL arm.

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

	DOXIL (N=330) n (%)	Trabectedin/DOXIL (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	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

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SYNOPSIS (CONTINUED)

The safety profile of the combination used in this study is consistent with the well-characterized toxicities seen with each agent alone. Treatment with the combination of trabectedin + DOXIL primarily results in additional myelosuppression and liver enzyme abnormalities, both of which do not usually result in serious clinical sequelae.

The incidence of Grades 3 and 4 adverse events for neutropenia is higher in the trabectedin + DOXIL arm (63%) compared with DOXIL monotherapy (22%). In the trabectedin + DOXIL arm 8% of subjects developed grade 3-4 neutropenic fever compared with 2% in DOXIL monotherapy arm. Two subjects in the combination arm developed neutropenic sepsis and 1 subject experienced sepsis. Neutropenia was managed by dose delays (18% versus 53%, respectively), reductions (3% versus 13%, respectively), as well as the use of colony stimulating agents (17% versus 42%, respectively).

The incidence of ALT Grade 3 or 4 toxicity was 1% in the DOXIL monotherapy arm and 31% in the trabectedin + DOXIL arm. This was not unexpected, because acute, transient transaminase elevation has been associated commonly with single-agent trabectedin in prior studies. Transaminase elevations were generally of short duration, usually returning to normal before the next cycle. In addition, in most cases, it decreased in incidence and magnitude in subsequent cycles, and did not result in severe liver toxicity or failure. Transaminase elevations were generally managed by protocol-defined dose reductions and delays. The potential for severe liver toxicity is low, as demonstrated by the analysis of patients who fulfilled the criteria of Hy's Law. Three subjects (0.9%) in the trabectedin + DOXIL arm experienced abnormalities that fulfill the criteria for Hy's law, which predicts for severe liver toxicity. In all 3 subjects the acute transaminitis resolved, with all 3 able to continue with study therapy or receive subsequent therapy. Neither of the deaths for the 2 subjects were considered to be drug-related.

The incidence of cardiac dysfunction or failure was not significantly increased nor was there any impact on left ventricular ejection fraction by adding trabectedin to DOXIL. One patient discontinued treatment due to congestive heart failure, but there were no patients with congestive heart failure leading to death in the trabectedin + DOXIL arm.

The incidence of hand-foot syndrome, stomatitis, mucosal inflammation, and abdominal pain are all reduced, as might be expected with the lower dose of DOXIL in the trabectedin + DOXIL arm compared with the DOXIL monotherapy arm. The incidence of cholestasis, neuropathy, nephropathy, rhabdomyolysis, alopecia, and ototoxicity were low or absent in both treatment arms.

CONCLUSION:

Study ET743-OVA-301 met its primary endpoint. The effect of adding trabectedin to DOXIL was consistent across the primary endpoint, PFS, as assessed by the independent radiologists, independent oncologists, or investigators. An improved ORR and favorable trend in OS seen in the combination therapy arm support the PFS results.

The lower dose of DOXIL used in the combination may be the reason for the decreased incidence of DOXIL-related toxicity on the combination arm in this study. Toxicities seen with trabectedin in the combination arm are consistent with its single agent safety profile. Quality-of-life assessments showed no unfavorable effect when adding trabectedin to DOXIL.

The results of Study ET743-OVA-301 demonstrate that trabectedin in combination with DOXIL results in increased efficacy, without substantial worsening of clinical safety. Given the results of this study, and its favorable comparison with recent reports of other agents currently used in relapsed ovarian cancer, the combination of trabectedin + DOXIL could be an important new, non-platinum containing treatment option for patients with recurrent ovarian cancer.

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