Pharma Mar, S.A., Sociedad unipersonal
Colmenar Viejo, Madrid, Spain

CLINICAL STUDY REPORT

ET-B-031-10

Multicenter, Open-Label, Phase II Study of Trabectedin (Yondelis®) in Patients with Hormonal Receptors Positive, HER2 Negative, Advanced Breast Carcinoma, Overexpressing or Underexpressing Xeroderma Pigmentosum G Gene (XPG)

Compound Number:	ET-743
Investigational Medicinal Product:	Trabectedin (YONDELIS®)
Study Design:	Open-label, single-arm, prospective, multicenter, phase II clinical trial
Protocol Number:	ET-B-031-10 (EudraCT: 2010-022968-13)
Study Start Date:	28 March 2011 (First consent signed)
Study Completion Date:	16 November 2012 (Date of last follow-up)
Principal Investigator Name and Affiliation:	**Dr. Ahmad Hussein Awada, M.D.** Institut Jules Bordet, 125 Boulevard Waterloo Brussels 1000 Belgium Phone: +32 2 541 31 89 Fax: +32 2 538 08 58 E-mail: ahmad.awada@bordet.be
Responsible Medical Officer:	**Arturo Soto Matos-Pita, M.D.** Clinical Research and Development Associate Director PharmaMar S.A., Sociedad Unipersonal (abbreviated as PharmaMar in this report) Avenida de los Reyes, 1 Polígono Industrial La Mina-Norte 28770 Colmenar Viejo, Madrid, Spain Phone: +34 918 466 053 Fax: +34 918 234 504 E-mail: asoto@pharmamar.com
Earlier Approved Reports:	None
Version:	Final version
Approval Date:	15 August 2014

2. SYNOPSIS

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<tr><td>Title of the study</td><td colspan="4">Multicenter, Open-Label, Phase II Study of Trabectedin (Yondelis®) in Patients with Hormonal Receptors Positive, HER2 Negative, Advanced Breast Carcinoma, Overexpressing or Underexpressing Xeroderma Pigmentosum G Gene (XPG)</td></tr>
<tr><td>Co-Investigators/Study centers</td><td colspan="4">Dr. Ahmad Hussein Awada, M.D. Institut Jules Bordet, 125, Boulevard Waterloo, Brussels 1000, Belgium
Dr. Javier Cortés, M.D. Hospital Universitario Vall d'Hebron, Passeig Vall d'Hebrón, 119-129, 08035 Barcelona, Spain
Dr. Suzette Delaloge, M.D. Institut Gustave Roussy, 39 Rue Camille Desmoulins, 94805 Villejuif, France
Dr. Miguel Martín, M.D. Hospital General Universitario Gregorio Marañón, C/ Doctor Esquerdo, 46, 28007 Madrid, Spain
Dr. Marc Espie, M.D. Hôpital Sant Louis, 1, Avenue Claude-Vellefaux, 75010 Paris, France</td></tr>
<tr><td>Publication (references)</td><td colspan="4">A phase II trial of trabectedin (T) in patients with hormone receptor-positive, HER2-negative advanced breast cancer, according to Xeroderma Pigmentosum G gene (XPG) expression. A Awada, J Cortes, M Martin et al. 2012 ASCO ASCO Annual Meeting; J Clin Oncol 30, 2012 (suppl; abstr TPS652).
Final results of a phase II trial of trabectedin (T) in patients with hormone receptor-positive, HER2-negative advanced breast cancer, according to Xeroderma Pigmentosum G gene (XPG) expression. A Awada, J Cortes, M Martin et al. 2013 ASCO Annual Meeting; Abstract No: Nº 547; J Clin Oncol 31(15 Supl).</td></tr>
<tr><td>Study period:
. First consent signed
. Last consent signed
. First dose first patient
. First dose last patient
. Last follow-up</td><td colspan="2">28 March 2011
4 April 2012
7 April 2011
25 April 2012
16 November 2012</td><td>Phase of Development:

Phase II</td></tr>
<tr><td>Study objectives</td><td colspan="4">Primary:
• To evaluate the efficacy in terms of progression-free survival rate at 4 months (PFS4) of trabectedin in patients with advanced or metastatic breast cancer (MBC), hormonal receptors positive, HER2 negative, positive or negative for XPG overexpression, who have already received at least two and no more than five lines of chemotherapy for advanced disease (including anthracyclines or taxanes in any setting).
Secondary:
• To compare progression-free survival (PFS), objective response rate (ORR) and duration of response (DR), as defined by the Response Evaluation Criteria in Solid Tumors (RECIST, v.1.1) in patients positive or negative for Xeroderma Pigmentosum G gene (XPG) overexpression.
• To compare overall survival in patients positive or negative for XPG overexpression.
• Safety profile.</td></tr>
<tr><td>Methodology</td><td colspan="4">Multicenter open-label, phase II study of single-agent trabectedin in patients with breast cancer, hormonal receptors positive, HER2 negative, overexpressing or underexpressing XPG, after failure of at least two and no more than five chemotherapy lines (including anthracyclines or taxanes in any setting) in the advanced setting.</td></tr>
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Number of patients (planned and analyzed)	**Planned number of patients:** Sample size calculation was based on the rate of patients free of progression/death at 16 weeks (~ 4 months), PFS4. At a first stage, forty evaluable patients were to be included in two strata: • Stratum A: 20 patients XPG-positive for overexpression (XPG+) ("high XPG"). • Stratum B: 20 patients XPG-negative for overexpression (XPG-) ("low XPG"). A futility analysis based on the primary endpoint (PFS4) was planned for the time when 20 evaluable patients per stratum had been recruited. If more than six of 20 patients in one stratum achieved PFS4, recruitment in this stratum was to continue to a maximum of 50 evaluable patients. The maximum number of evaluable patients was to be 100. **Patients analyzed:** Forty-four (21 high-XPG and 23 low-XPG) patients were included and treated during the first stage. Of these, 20 and 23 patients were evaluable for efficacy, respectively. Recruitment was stopped after the pre-established criterion for the futility analysis (six of 20 patients achieving PFS4) was not met in any stratum.	
Diagnosis and main selection criteria	**Inclusion Criteria** **1.** Age ≥ 18 years. **2.** Voluntary written informed consent, obtained from the patient before the beginning of any specific study procedures. **3.** Histologically proven diagnosis of advanced or MBC. **4.** Patients had to be HER2 negative and hormone receptor (estrogen receptor and/or progesterone receptor) positive. **5.** Failure to at least two but no more than five chemotherapy lines in the advanced setting. **6.** Previous treatment with anthracyclines or taxanes. **7.** XPG RNA expression determined from patient's tumor specimen (paraffin-embedded tissue). **8.** Measurable disease as defined by the RECIST v.1.1. If the only tumor lesion was situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, progression of the lesion had to be demonstrated. **9.** Patients with bone metastases receiving bisphosphonates for palliation were to be eligible if other sites of measurable disease were present. **10.** Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. **11.** Adequate bone marrow, liver and kidney function: • Hemoglobin ≥ 9g/dl. • Neutrophil count ≥ 1.5×10^9/l. • Platelet count ≥ 100×10^9/l • Serum creatinine ≤ 1.5 mg/dl or calculated creatinine clearance ≥ 30 ml/min. • Albumin ≥2.5g/dl. • Total serum bilirubin ≤ upper limit of normal (ULN), except in Gilbert's syndrome. • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3×ULN. • Total alkaline phosphatase (AP) ≤2.5×ULN; if the value was >2.5×ULN, hepatic AP isoenzyme and/or gamma-glutamyltransferase (GGT) and/or 5'nucleotidase had to be evaluated, and values had to be within the ULN	

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(indicating that the elevation of AP was of bone origin).

- Creatine phosphokinase (CPK) ≤2.5×ULN.

12. Life expectancy ≥3 months.

13. Complete recovery to grade ≤ 1 from any toxicity due to previous therapy (except for alopecia and grade 2 neuropathy).

14. Women of child-bearing potential had to have a negative pregnancy test prior to treatment initiation and had to use a medically approved method of contraception during treatment with trial medication and for three months after the last administration of study drug. Fertile men had to use a medically approved method of contraception during treatment with trial medication and for five months after the last administration of study drug.

Exclusion Criteria

1. Prior exposure to trabectedin.

2. Treatment with chemotherapy or with biological agents in the two weeks prior to the first dose of the clinical trial drug (six weeks for nitrosoureas or mitomycin C) provided that patients had recovered to grade ≤ 1 from any toxicity due to prior therapy (except alopecia and grade 2 neuropathy)(see inclusion criterion 13).

3. Participation in another clinical trial, or concomitant treatment with any investigational drug, in the four weeks prior to enrollment in the clinical trial.

4. Concomitant administration of any other antineoplastic therapy.

5. Contraindications to corticosteroid use.

6. History of another neoplastic disease (except for basal cell carcinoma of the skin or properly treated carcinoma in situ of the uterine cervix) unless in remission for five years or longer.

7. Presence of cerebral and/or leptomeningeal metastasis, even if they were being treated.

8. Other serious and/or relevant diseases or clinical situations that, in the opinion of the Investigator, were incompatible with the protocol (any of the following):

- History of cardiac disease, such as myocardial infarction, in the year prior to enrollment in the clinical trial; symptomatic/uncontrolled angina pectoris; congestive heart failure or uncontrolled cardiac ischemia; any type of uncontrolled arrhythmia or abnormal left ventricular ejection fraction, or uncontrolled arterial hypertension (according to the standards of the World Health Organization [WHO]).
- History of significant psychiatric disease.
- Active infection requiring antibiotic, antifungal or antiviral treatment that, in the opinion of the Investigator, could compromise the patient's capacity to tolerate the therapy.
- Active liver (hepatitis B or C) or renal disease.
- Major surgery in the two weeks prior to entering the clinical trial, or any other concomitant pathology that could jeopardize the patient's safety or commitment to complete the clinical trial.

9. Pregnant or breastfeeding women (negative pregnancy test in the three days prior to treatment administration required).

10. Inability or refusal to comply with the protocol or with the clinical trial procedures.

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Test product, dose and mode of administration	Trabectedin was supplied by PharmaMar (Madrid, Spain) as a sterile lyophilized product in vials containing 0.25 mg of trabectedin or 1 mg of trabectedin. Vials containing 0.25 mg trabectedin had to be reconstituted in 5 ml of sterile water for injection. Vials containing 1 mg trabectedin had to be reconstituted in 20 ml of sterile water for injection. The reconstituted solution was stable from a chemical and physical point of view for 30 hours at room temperature or refrigerated conditions. Nevertheless, from a microbiological point of view, the recommendation was to use the reconstituted solution as soon as practically possible. If not, in-use storage times and conditions prior to use could be no longer than 24 hours at 2ºC to 8ºC from the reconstitution of the vial. These time and temperature conditions reflect the chemical and physical stability experience with these products. Trabectedin was administered as a **1.3 mg/m^2 3-hour i.v. infusion q3wk**. This schedule was safely evaluated in previous clinical trials on different malignant diseases. Premedication with dexamethasone was mandatory according to the following schedule: 4 mg orally, 24 h and 12 h before the planned trabectedin infusion on day -1, 20 mg i.v. 30 minutes before the planned trabectedin infusion on Day 1 and 4 mg orally, 24 h, 36 h, 48 h, 60 h, and 72 h after start of the trabectedin infusion. In addition, optional anti-emetic prophylaxis could be used in accordance to the American Society for Clinical Oncology (ASCO) guidelines for drugs with moderate emetic risk: 5-HT3 antagonists (ondansetron 8 mg i.v. or granisetron 1 mg i.v. or tropisetron 5 mg i.v.) before the trabectedin infusion and, if necessary, addition of 10 mg of metoclopramide orally every eight hours, extension of the duration of treatment with 5-HT3 antagonists and/or dexamethasone or both options together. Trabectedin batch numbers used were as follows: • **0.25-mg vial batches:** 11B22, 10K14 and 10G09. • **1-mg vial batches:** 10B06, 10B16, 10510, 10613, 91104, 10C31, 10C24, 10B26, 10A22 and 91009.	
Duration of treatment	Administration of the study treatment had to be discontinued if this was considered to be in the best interest of the patient. More specifically, treatment was to be discontinued due to any of the following reasons: disease progression (PD), unacceptable toxicity (including any toxicity leading to the need for a third dose reduction or severe hypersensitivity reactions, except in the event of obvious clinical benefit, in which case the patient could be allowed to remain on treatment after having discussed and agreed on the case with the Sponsor), patient refusal, intercurrent serious illness, protocol deviation with an effect on the risk/benefit ratio of the clinical trial, treatment delay > three weeks (except in case of clear clinical benefit, with the Sponsor's approval), administrative reasons or Sponsor's decision. Regardless of the reason, patients who discontinued treatment could not be re-treated in the context of this study at any time. Any subsequent therapies for the patients could be provided off-study according to Investigator's criteria. After treatment discontinuation, patients had to be followed until all toxicities or their sequelae resolved or stabilized at a level acceptable to the Investigator and the Sponsor. Patients who discontinued treatment without disease progression were to be followed every three months until disease progression, start of other antitumor therapy, death or the date of study termination, whichever occurred first. Patient's survival was to be assessed every three months. During the first stage patients were to be followed for at least four months after the first infusion of the last evaluable patient recruited, during the second stage patients were to be followed up to three months after the last infusion administered in the study. The date of death or the date of the last contact before the end of study was to be collected. Patients who withdrew their consent were not to be followed with any study procedures.	
Criteria for evaluation	The primary endpoint of this study was the progression-free survival rate at 16 weeks	

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Efficacy	(~ 4 months) (PFS4), defined as the percentage of patients remaining alive and progression-free at Week 16 after the first treatment dose. Evaluable patients were to be all recruited patients who had received at least one treatment cycle with trabectedin and had undergone at least one radiological post-baseline evaluation (performed a minimum of eight weeks after beginning the therapy). In addition, any patient who had PD, died due to PD, or discontinued treatment due to unmanageable toxicity before evaluation of the response was to be considered evaluable for response and classified as a non-responder. Other efficacy secondary endpoints were: • **Overall response rate (ORR),** defined as the percentage of patients with objective response (OR), either CR or PR response according to RECIST v.1.1. • **Duration of response (DR),** defined as the time between the date when the response criteria (PR or CR, the first that was reached) were fulfilled and the first date when PD, recurrence or death was objectively documented (taking the smallest measurements documented since the treatment started as reference for PD). • **Progression-free survival (PFS),** defined as the time from the first day of study treatment to the day of negative assessment (progression or death) or last tumor evaluation. • **Overall survival (OS),** defined as the time from the first day of treatment to the date of death or last contact. In the first stage of this study, the patients were to be followed at least four months after the first infusion of the last evaluable patient recruited. In the second stage, the patients were to be followed up to three months after the last infusion administered in the study.
Safety	Other secondary endpoints included the analysis of safety. Patients were evaluable for safety if they had received at least part of one trabectedin infusion. Safety was evaluated by clinical examinations, analysis of vital signs, clinical assessment of adverse events (AE), changes in the analytical parameters (hematological and biochemical, including liver function tests), reasons for study discontinuation and any other analyses that could be considered necessary. All drug-related AEs had to be followed-up, even if the administration of chemotherapy had finalized, until the AE or its sequelae had resolved or stabilized to an acceptable level for both the Investigator and the Sponsor. AEs were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.0, and were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 11.0.
XPG RNA analyses	**XPG RNA expression** from paraffin-embedded tissue samples was to be determined by quantitative real time reverse transcription polymerase chain reaction (qRT-PCR) in a centralized laboratory previous to the inclusion of the patient. The methodology for sample collection and shipment and qRT-PCR analysis is described in a separate charter document. Patients were to be stratified according to their XPG RNA expression values: "low XPG" (≤ 3; XPG negative for overexpression) and "high XPG" (> 3; XPG positive for overexpression). Although the patient population in this study had a different cancer subtype than patients treated with trabectedin in the previously conducted ET-B-027-06 study, the initial cutoff point selected to categorize between low and high XPG groups was the XPG RNA median value (actual value is 3.05) obtained in the analysis of the HER2 and BRCA mutated populations in the ET-B-027-06 study.
Statistical methodology	**<u>Stratification of Patients</u>** Patients fulfilling all eligibility criteria were to be stratified according to the expression of XPG RNA from patients' paraffin-embedded tumor samples as XPG positive for overexpression (> 3) ("high XPG") or XPG negative for overexpression (≤ 3) ("low XPG").

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	The initial cut-off value of 3 was selected on the basis of the results of clinical trial ET-B-027-06. However, to avoid possible bias if the median value used to select the XPG strata was not the actual median value for the studied population, a Bayesian 95% credible region calculation was to be implemented after the first 20 patients were recruited. If the actual median XPG value was 3, it was anticipated that approximately 50% of the patients had to be categorized in each stratum. Assuming a non-informative prior distribution if the credible region did not contain the 0.5 probability (five or less patients were allocated in any stratum), then the XPG values were to be re-evaluated to look for the best cutoff available for this population. **Sample Size** Sample size calculation was based on the rate of patients free of progression/death at 16 weeks (~ 4 months), PFS4. At a first stage, forty evaluable patients were to be included in two strata: • **Stratum A:** 20 patients XPG-positive (XPG+) (high XPG). • **Stratum B:** 20 patients XPG-negative (XPG-) (low XPG). A futility analysis based on the primary endpoint (PFS4) was planned. This analysis was to be performed using the O'Brien Fleming boundary once 40 evaluable patients enrolled (i.e., 20 patients per XPG stratum) had had a tumor assessment at Week 16 or PD or died due to PD or discontinued treatment due to unmanageable toxicity, whichever occurred first. The minimum follow-up to do this analysis was to be 16 weeks after the last patient recruited had received the first trabectedin infusion. In the case that the actual number of patients per stratum was 20 and if there were six or less patients achieving PFS4 according to boundaries and sample size assumptions, the alternative hypothesis could be rejected and recruitment in that stratum had to be stopped. If more than six out of 20 patients in one stratum achieved PFS4, recruitment in this stratum was to continue to up to 50 evaluable patients. A maximum number of 50 evaluable patients in each XPG stratum (therefore, a maximum of 100 patients) was to be recruited to test the null hypothesis that $p \leq 0.30$ versus the alternative hypothesis that $p \geq 0.50$. The variance of the standardized test was based on the empirical estimate. The type I probability (alpha) associated with these one-sided tests was 0.025 and the type II probability (beta) was 0.2; hence, statistical power was 80%. With these assumptions, if the number of patients free of progression/death at Week 16 was ≥ 22, then this would allow rejecting the null hypothesis. **Efficacy Analysis** The exact binomial estimator and its 95% confidence interval were to be used in the analysis of the categorical variables: PFS4 and ORR. Time-to-event variables (DR, PFS and OS) and their fixed time estimates (PFS3, PFS6 and OS12) were to be analyzed according to the Kaplan-Meier method. Exploratory hypothesis-generating comparisons of the results in the two XPG strata were to be performed. Comparisons were to be carried out in the case of categorical variables by the Fisher's exact test and by logistic regressions. In the case of time-to-event variables, comparisons were to be carried out by log-rank tests and by Cox regressions. **Safety** Safety analyses were to consider AEs, serious AEs (SAE), analytical results, deaths and reasons for study discontinuations. All AEs and SAEs were to be graded according to NCI-CTCAE, v. 4.0, and were to be coded using MedDRA, v.11.0.	
Results (1): Patient characteristics	A total of 44 patients were included and treated in the study: 21 with high XPG	

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	expression and 23 with low XPG expression. Median age for all patients was 56.5 years (range, 34-81 years) and 22 patients (50.0%) had ECOG PS=1. Forty-two of all tumors (95.5%) were ductal carcinomas, 42 (95.5%) were estrogen receptor positive, 29 (65.9%) were progesterone receptor positive and 27 (61.4%) were estrogen/progesterone receptor positive. The median value of XPG expression was 2.8 (range, 0.8-10.6), the median number of sites involved at baseline was 2.0 (range, 1-6 sites), being liver the most common one, and 11 patients (25%) had stage IV at diagnosis. Median time from the first diagnosis to the first trabectedin infusion was 85.1 months (range, 18.4-264.4 months) and the median time from the last disease progression to the first trabectedin infusion was 1.0 month (range, 0.3-2.7 months). All patients had received prior chemotherapy. Forty-one (93.2%) had received prior radiotherapy, 40 patients (90.9%) had had previous surgery, 42 patients (95.5%) had received hormonal therapy and 27 patients (61.4%) had received biological therapy. All 44 treated patients had received chemotherapy in the advanced setting, and 12 patients (27.3%) and 26 patients (59.1%) had received chemotherapy in the neoadjuvant and adjuvant settings, respectively. Most patients (n=31, 70.5%) had received more than two prior lines of chemotherapy in the advanced setting, with a median of three prior lines (range, 1-5 lines) per patient. The median time to progression to the last prior chemotherapy was 4.4 months (range, 1- 31 months).	
Results (2): Efficacy	**High-XPG:** at the time of the futility analysis, 20 of the 21 enrolled patients were evaluable for efficacy. Four of them (20%) achieved PFS4. Therefore, the protocol criterion for further recruitment (more than six patients achieving PFS4) was not met and recruitment was stopped. The median PFS in this stratum was 1.9 months (95% CI: 1.4-3.5 months), PFS at three months (PFS3) was 35% (95% CI: 14.1-55.9%) and PFS at six months (PFS6) was 15% (95% CI: 0-30.6%). One patient had a partial response (PR), with a duration of 1.02 months. The ORR in this stratum was therefore 5% (95%CI: 0.1-24.9%). With a median follow-up of 10.9 months (range, 10.1-13.4 months), the median overall survival (OS) was 11.8 months (95% CI: 7.4-not reached) and OS at 12 months (OS12) was 42.4% (95% CI: 16.4-68.4%). **Low-XPG:** at the time of the futility analysis, all 23 treated patients were evaluable for efficacy. Six of them (26.1%) achieved PFS4. Therefore, the protocol criterion for further recruitment (more than six patients achieving PFS4) was not met and recruitment was stopped. The median PFS in this stratum was 2.3 months (95% CI: 1.7-3.8 months), PFS3 was 40.9% (95% CI: 20.4-61.5%) and PFS6 was 13.6% (95% CI: 0-28.0%). One patient had a complete response (CR) and two patients had PRs. The ORR in this stratum was therefore 13% (95%CI: 2.8-33.6%). The duration of the CR was 4.57 months and the two PRs lasted 1.81 and 3.65 months, respectively. With a median follow-up of 10.9 months (range, 10.1-13.4 months), the median OS was not reached (95% CI: 6.7-not reached) (due to data censoring) and OS12 was 51.7% (95% CI: 26.0-77.4%). Comparison of the main efficacy parameters (PFS4, ORR, DR, PFS and OS) between the two pre-selected strata, i.e., high XPG and low XPG patients, showed no statistically significant differences. ORR in the whole efficacy population (i.e., 43 patients) was 9.3% (95% CI: 2.6-22.1%). The median PFS and OS in the whole efficacy population were 1.9 months (95% CI: 1.8-3.5 months) and 11.8 months (95% CI: 7.4-not reached), respectively.	
Results (3): Safety	All 21 high-XPG and 23 low-XPG treated patients received at least part of one trabectedin infusion and were therefore evaluable for safety. The median number of cycles per patient was 3 (range, 1-15 cycles). The median dose intensity was 0.4 mg/m^2/week (range, 0.3-0.4 mg/m^2/week) and the median relative dose intensity of 89.5% (range, 63.2-102.3%). The most common AEs related (or of unknown relationship) to trabectedin were fatigue (75.0%), nausea (61.4%), constipation (56.8%), vomiting (47.7%), decreased	

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	appetite (29.5%) and diarrhea (22.7%). AEs ≥ grade 3, related to trabectedin consisted of nausea, fatigue and decreased appetite (n=3; 6.8% each), diarrhea, intestinal obstruction, myositis, rhabdomyolysis, febrile neutropenia, syncope, renal failure and respiratory failure (n=1; 2.3% each). Three patients discontinued treatment due to trabectedin-related AEs: one patient died due to rhabdomyolysis, one patient had grade 3 fatigue and grade 4 thrombocytopenia and one patient had grade 3 myositis. Six patients had a total of 13 trabectedin-related SAEs: one patient had grade 5 rhabdomyolysis, grade 4 respiratory failure, grade 4 renal failure, grade 3 febrile neutropenia and grade 3 thrombocytopenia. Grade 3/4 CPK increases were reported in two patients. One patient presented grade 3 myositis, which resulted in treatment discontinuation. One patient had grade 4 thrombocytopenia and grade 3 fatigue, both leading to treatment discontinuation, and one patient presented grade 4 leukopenia and grade 3 intestinal obstruction. All twenty deaths but one occurring during this study were due to progression of the malignant disease. One patient died due to trabectedin-related rhabdomyolysis. The most common hematological abnormalities were lymphopenia (97.7%), leukopenia (90.9%), neutropenia (77.3%) and anemia (75.0%). Grade 4 hematological abnormalities consisted of neutropenia (31.8%), thrombocytopenia and leukopenia (13.6% each), and lymphopenia (6.8%). Hematological abnormalities resulted in treatment discontinuations in three patients: one patient had grade 4 thrombocytopenia, one patient had grade 4 neutropenia and thrombocytopenia and one patient had continuous grade 2/3 neutropenia. Neutropenia occurred in 34 patients and reached grade 3/4 in 24 of them. One case of grade 3 febrile neutropenia was reported as a trabectedin-related SAE. Overall, grade 3/4 neutropenia appeared on Day 14 after dosing (range, 6-21), returned to grade ≤ 1 by Day 24 (range, 16-33), and lasted a median of eight days (range, 2-19 days). The most frequent biochemical abnormalities were ALT increased (100.0%), GGT increased (97.6%), AST increased (95.5%), creatinine increased (84.1%) and AP increased (81.8%). Grade 4 biochemical abnormalities consisted of GGT increased (17.1%), CPK increased (9.1%), ALT increased (6.8%) and AST increased (2.3%). Biochemical abnormalities resulted in treatment discontinuation in one patient with grade 2 AP increase. ALT increases were reported in all patients (n=44) and reached grade 3/4 in 32 of them. AST increases were reported in 42 patients and reached grade 3/4 in 15 of them. Overall, grade 3/4 transaminases increases appeared on Days 6-7 (range, 3-39) after dosing, returned to 2.5 x ULN by Days 14-18 (range, 8-35) and lasted a median of 7-11 days (range, 4-27). Grade 2/3 ALT increases were the cause of trabectedin dose delays in three patients and caused trabectedin dose reductions in two patients. AST increases did not cause any trabectedin dose delays or reductions. Nineteen patients (43.2%) had dose administration delays due to trabectedin-related toxicity. Transient severe neutropenia was the most common cause of trabectedin dose delays. Eleven of 44 treated patients (25.0%) had trabectedin-related dose reductions. Four of the 44 treated patients (9.1%) had dose reductions due to hematological toxicity (grade 2/4 neutropenia). Seven patients (15.9%) had dose reductions due to non-hematological toxicity, mostly due to transaminases increase. Three patients (6.8%) discontinued treatment due to trabectedin-related AEs: grade 5 rhabdomyolysis, grade 3 myositis, and grade 3 fatigue and grade 4 thrombocytopenia, respectively.	
Conclusions	The current phase II study was terminated due to a negative futility analysis of the primary endpoint in both groups of patients, over and under-expressing XPG. ORR and especially PFS were poor in the whole patient population. The level of mRNA expression of the nucleotide excision repair system member XPG did not seem to represent a prognostic or predictive factor to patients' outcome after trabectedin treatment in this setting. The safety profile of trabectedin administered as 1.3 mg/m^2 3-hour i.v. infusion q3wk in patients with hormonal receptor positive, HER-2 negative,	

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	advanced breast carcinoma was similar to that of this compound administered as single agent in other indications. However, there was a higher rate of drug administration delays due to trabectedin toxicity as compared to prior studies, as well as a higher incidence of muscular disorders, including one fatal rhabdomyolysis. These findings might be partially the result of the poor underlying condition of this patient population. Trabectedin at a dose of 1.3 mg/m^2 as a 3-hour i.v. infusion, q3wk will not be considered for further clinical development in patients with hormonal receptor-positive, HER2-negative, advanced breast carcinoma.	
Date of report (final version)	15 August 2014	