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

CLINICAL STUDY REPORT

ET-B-029-07

PHASE II CLINICAL TRIAL OF TRABECTEDIN AFTER PROGRESSION ON PLATINUM-BASED ANTITUMORAL THERAPY IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) WITH XPG AND/OR ERCC1 OVEREXPRESSION AND BRCA1 UNDEREXPRESSION (*STRACT* CLINICAL TRIAL)

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-029-07
Study Start Date:	27 March 2009 (First consent signed)
Study Completion Date:	9 September 2010 (Date of last follow-up)
Principal/Coordinating Investigator Name and Affiliation:	**Dolores Isla Casado, M.D.** Servicio de Oncología Médica Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain. Phone: +34 97 676 5746 Fax: +34 97 635 4212 E-mail: lola.isla@gmail.com
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:	5 July 2011

This study was conducted in compliance with Good Clinical Practice (GCP)

2. SYNOPSIS

Name of Sponsor/Company: PharmaMar S.A., Sociedad Unipersonal **Name of finished product:** YONDELIS® **Name of active ingredient(s):** Trabectedin	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(*For National Authority Use only*)**
Protocol number	ET-B-029-07	
Title of the study	Phase II clinical trial of trabectedin after progression on platinum-based antitumoral therapy in patients with advanced non-small-cell lung cancer (NSCLC) with XPG and/or ERCC1 overexpression and BRCA1 underexpression (*STRACT* clinical trial).	
Coordinating investigator	**Dolores Isla Casado, M.D.** Servicio de Oncología Médica Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain.	
Co-investigators / Study centers	**Bartomeu Massuti Sureda, M.D.** Hospital General Universitario de Alicante, Alicante, Spain. **Carlos Camps Herrero, M.D.** Hospital General Universitario de Valencia, Valencia, Spain. **Manuel Cobo Dols, M.D**. Hospital Regional Universitario Carlos Haya, Malaga, Spain. **Manuel Dómine Gómez, M.D.** Fundación Jiménez Díaz, Madrid, Spain. **Mariano Provencio Pulla, M.D.** Hospital Universitario Puerta de Hierro-Majadahonda, Majadahonda, Madrid, Spain. **Nuria Viñolas Segarra, M.D.** Hospital Clínico y Provincial de Barcelona, Barcelona, Spain. **Vicente Alberola Candel, M.D.** Hospital Arnau de Vilanova, Valencia, Spain.	
Publication (references)	At the time of this report no articles have been published on the study described herein.	
Study period: **. First consent signed** **. Last consent signed** **. First dose first cycle** **. First dose last cycle** **. Last follow-up**	 27 March 2009 2 June 2010 31 March 2009 7 June 2010 9 September 2010	**Phase of Development:** Phase II
Study objectives	**Primary:** • To evaluate the efficacy of trabectedin in patients with NSCLC, who have XPG and/or ERCC1 overexpression (XPG > 0.99 and/or ERCC1 > 3.47), and BRCA1 underexpression (BRCA1 < 12), after the failure of standard platinum-based treatment. Efficacy was evaluated by determining the progression-free survival rate of patients at 12 weeks (3 months), PFS3. **Secondary:** In addition, the following parameters were evaluated: • Efficacy: o Overall response rate (ORR). o Duration of response (DR). o Progression-free survival (PFS). o Overall survival (OS). • Safety profile: o Rate of adverse events (AEs). • Pharmacogenomic profile: o Hypothesis-generating exploratory pharmacogenomic analyses were planned to correlate the molecular parameters of patients' tumor specimens with the clinical results of the medicinal product under study.	
Methodology	Open-label, single-arm, prospective, multicenter, phase II clinical trial. Screening had to include analysis of the levels of XPG, ERCC1, and BRCA1 expression in the tumor specimens obtained at the time of diagnosis.	
Number of patients (planned and analyzed)	**Planned number of patients:** A Simon's optimal two-stage design was used. A minimum PFS3 of 10% and an objective PFS3 of 30% were required to recommend further evaluation of trabectedin	

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	in the study population. In a first stage of the study, at least 3 of 18 patients had to reach PFS3. In that case, recruitment was to be expanded in a second stage to include up to 30 patients (12 additional patients). If seven or more of these 30 evaluable patients achieved PFS3, further development of trabectedin in this indication would be considered justified. **Patients analyzed:** All 18 patients enrolled in the first stage were evaluable for efficacy and safety. Two of these 18 patients reached PFS3 and, therefore, the study was finalized at this stage.	
Diagnosis and main selection criteria	**Inclusion Criteria** Patients who met all following criteria participated in the study: **1.** Informed consent form signed by the patient before beginning any clinical trial-related procedure. **2.** Patients of both genders, with age ≥ 18 years. **3.** Histological or cytological diagnosis of non-resectable/inoperable or metastatic, locally advanced NSCLC, which also met the following conditions: • Overexpression of XPG and/or ERCC1, and underexpression of BRCA1, according to the median expression values in lung cancer, as determined by quantitative reverse transcription-polymerase chain reaction (qRT-PCR), and defined as: XPG>0.99 and/or ERCC1>3.47 and BRCA1<12. • Patient's diagnostic tumor specimen (paraffin block) available. In the absence of a tumor specimen, the corresponding RNA or cDNA extracted from the tumor specimen from previous molecular studies had to be available. • Recurrent or persistent NSCLC after a previous line of platinum-based cytotoxic chemotherapy. **4.** Presence of at least one unidimensionally or bidimensionally lesion measurable by computed tomography (CT), located in non-irradiated areas and measured properly within the four weeks before treatment. **5.** Adequate kidney, liver and bone marrow function: • Hemoglobin ≥ 9 g/dl. • Neutrophil count ≥ 1.5×10^9/l. • Platelet count ≥ 100×10^9/l. • Calculated creatinine clearance ≥ 30 ml/min. • Serum bilirubin ≤ upper limit of normal (ULN). • Total alkaline phosphatase (AP) ≤ 2.5 × ULN; if AP > 2.5 x ULN, AP liver fraction and/or gamma-glutamyltransferase (GGT) and/or 5' nucleotidase had to be ≤ ULN. This would indicate that the elevation of AP was of bone origin. • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN. • Albumin ≥ 2.5 g/dl. • Creatine phosphokinase (CPK) ≤ 2.5 × ULN. **6.** Functional status [Eastern Cooperative Oncology Group (ECOG) performance status] ≤ 1. **7.** Life expectancy ≥ 3 months. **8.** Complete recovery from any toxicity due to previous therapy (except for grade 1 neuropathy and/or alopecia). **Exclusion Criteria** Patients who met any of the following criteria were to be excluded from participating in the study: **1.** Treatment with chemotherapy or with biological agents within the four weeks prior to the first dose of the clinical trial drug (six weeks for nitrosoureas or mitomycin C). **2.** Participation in another clinical trial, or concomitant treatment with any investigational drug within the 30 days prior to enrollment in the clinical trial. **3.** Concomitant administration of any other antineoplastic therapy. **4.** Previous treatment with more than one line of platinum-based chemotherapy for	

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	advanced disease (additional regimens like neoadjuvant or adjuvant therapy were allowed). **5.** Contraindications for the use of corticosteroids. **6.** History of another neoplastic disease (except for skin cancer other than melanoma or cervical carcinoma *in situ* adequately treated). **7.** Presence of cerebral and/or leptomeningeal metastases, even if they were under treatment. **8.** Presence of uncontrolled pleural effusion. **9.** Other serious and/or relevant diseases or clinical situations that, in opinion of the Investigator, were incompatible with the study protocol (any of the following): • History of cardiac disease, such as myocardial infarction, within a 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 neurological (other than metastasis) or psychiatric disorders. • 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. • Clinically relevant active liver disease. • Major surgery within the two weeks prior to entering the clinical trial, or any other concomitant pathology that could jeopardize the patient's safety or its commitment to completing the clinical trial. **10.** Pregnant or breast-feeding women (negative pregnancy test within three days prior to treatment administration was required), or men or women of reproductive potential who were not using effective contraceptive methods. **11.** Inability or refusal to comply with the protocol or clinical trial procedures.
Test product, dose and mode of administration	Trabectedin was supplied by PharmaMar (Colmenar Viejo, Madrid, Spain) as a sterile lyophilized powder for concentrate for solution for infusion, available in vials with two strengths: 0.25 mg (with 100 mg of sucrose and 2 mg of potassium) or 1 mg (with 400 mg of sucrose and 8 mg of potassium). Each vial had to be reconstituted with 5 ml (for 0.25-mg vials) and 20 ml (for 1-mg vials) of sterile water for injection, respectively, before i.v. infusion. If administration had to be via a central venous line, the reconstituted solution had to be further diluted in an infusion bag with at least 500 ml of normal saline solution for infusion (0.9% NaCl for injection) or in 50 mg/l (5%) for infusion. If a central venous line could not be used and a peripheral venous line was to be used, the reconstituted solution had to be added to an infusion bag containing at least 1,000 ml of normal saline solution for infusion (0.9% NaCl for injection) or 50 mg/ml (5%) glucose solution for infusion. Trabectedin was administered as a **1.3 mg/m^2 3-hour q3wk i.v. infusion**, with prophylactic antiemetic medication, including dexamethasone (4 mg orally, 24 and 12 hours before trabectedin infusion; 20 mg i.v., 30 min before trabectedin infusion, and 4 mg orally 24, 36, 48, 60 and 72 hours after trabectedin infusion). Additional antiemetics such as serotonin (5-HT$_3$) blockers, lorazepam, prochlorperazine and/or diphenhydramine could be used at the Investigator criteria, prior to and/or following trabectedin administration. The numbers of the trabectedin batches were as follows: • **0.25-mg vial batches:** 07A19 and 08A16. • **1-mg vial batches:** 09C11 and 08D24.
Duration of treatment	Trabectedin treatment had to continue until disease progression, in the absence of unacceptable toxicity, or whenever considered of clinical benefit for the patient. Patients were to be evaluated every six weeks until disease progression, even if trabectedin treatment had been stopped. After disease progression, patients were to be

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	followed every three months to allow evaluation of survival. Independently of the state of the disease, trabectedin treatment was to be permanently discontinued for those patients meeting any of the following criteria: existence of excessive toxicity that precluded continuing treatment, according to the opinion of the Investigator responsible for the patient; toxicity requiring trabectedin dose reduction in more than two levels; delay in the dose administration longer than three weeks due to trabectedin-related adverse events, except for those cases in which continuation of treatment could offer a clear benefit for the patient; development of clinically important organ dysfunction; refusal of the patient; lack of compliance by the patient or another medical reason which required the patient's discontinuation, according to the Investigator criteria. Patient withdrawal occurred when an enrolled patient ceased participation in the study, regardless of the circumstances, prior to completion of the protocol. Reasons for withdrawal included major protocol deviations, such as administration of another anticancer treatment including chemotherapy, hormone therapy or radiotherapy, or experimental antineoplastic agents; patient's refusal, administrative reasons, or Sponsor's decision.	
Criteria for evaluation **Efficacy**	The primary analysis of efficacy was based on progression-free survival rate at 12 weeks (3 months) (PFS3) in the *efficacy population* (i.e., all patients with a pathological diagnosis of NSCLC, and XPG and/or ERCC1 overexpression, and BRCA1 underexpression, who had received at least two cycles of treatment and had undergone at least one radiological post-baseline evaluation, done at least six weeks after starting the treatment). PFS3 data were also to be shown as an additional analysis in the *treated population* (i.e., all patients treated with trabectedin). Finally, all 18 enrolled patients were treated and evaluable, and therefore only one analysis is shown in this report (both populations were the same). Secondary endpoints of efficacy were ORR, DR, PFS and OS. PFS and ORR were to be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.0.	
Safety	All patients who had received at least a part of one trabectedin infusion were evaluable for safety. Safety parameters included the description of AEs, serious adverse events (SAEs), laboratory measurements, clinical examinations, toxic deaths and study discontinuations.	
Pharmacogenomics	Pharmacogenomic analyses were a secondary endpoint of this phase II trial. However, tumor tissue specimens and blood samples were available from ten and 17 patients, respectively. Due to the low number of samples, these analyses were finally not conducted.	
Statistical methodology	Descriptive statistics were used for this open, non-comparative study. Non-continuous variables were described in frequency tables using counts and percentages. Continuous variables were described by median, minimum and maximum. **<u>Efficacy Analysis</u>** For evaluation of the main efficacy endpoint (PFS3) and ORR, binomial exact estimator and its 95% CI were calculated. The time-to-event variables (DR, PFS, and OS) and their fixed-time estimates (PFS6 and OS12) were to be analyzed using the Kaplan-Meier method. **<u>Safety</u>** Descriptive statistics were employed to characterize the toxicity, drug-related deaths, SAEs and toxicity-related treatment discontinuation profiles. AEs were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) v.3.0 and coded with the Medical Dictionary for Regulatory Activities (MedDRA) v.11.0.	
Results (1): <u>Patient characteristics</u>	All patients were Caucasian, 88.9% of them were males, their median age was 66 years (range, 52-81 years), and the majority (83.3%) had ECOG PS=1.	

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	Primary tumors included mostly adenocarcinoma (n=8; 44.4%) and epidermoid carcinoma (n=8; 44.4%). The median number of sites involved per patient was 2 (range, 1-4 sites), with lung (n=17; 94.4%) and lymph nodes (n=12; 66.7%) being the most common disease locations. Five patients (27.8%) had previously received external radiotherapy. Seven patients (38.9%) had undergone previous surgery. All 18 patients had previously received chemotherapy, either alone (n=13; 72.2%) or plus biological therapy (n=5; 27.8%). Chemotherapy was administered in the advanced setting in all patients. The median number of lines and agents of prior chemotherapy was 1 (range, 1-4 lines) and 2 (range, 2-5 agents), respectively. As defined per protocol, all patients had received prior platinum-based chemotherapy (cisplatin in 13 patients and carboplatin in six patients).	
Results (2): Efficacy	The primary analysis of efficacy was based on PFS3 in the *efficacy population* with an additional supportive analysis in the *treated population.* Finally, all 18 enrolled patients were treated and evaluable (both populations were the same), and therefore only one analysis is shown in this report. Two of 18 patients (11.1%; 95% CI, 1.38-34.7%) achieved PFS3. According to the Simon's optimal two-stage design used in this phase II trial, a minimum PFS3 of 10% and an objective PFS3 of 30% were required to recommend further evaluation of trabectedin in the study population. In a first stage of the study, at least 3 of 18 patients had to reach PFS3. As the primary objective was not met during the first stage (only two patients reached PFS3), the study was finalized without opening the second stage. No objective responses per RECIST were achieved. Four patients (22.2%) had stable disease. Median PFS (11.1% censored data) was 1.3 months (95% CI, 1.2-1.6 months). Median OS (44.4% censored data) was 5.9 months (95% CI, 2.5 months-not reached).	
Results (3): Safety	All 18 included patients received at least one infusion of trabectedin in this study and therefore were evaluable for safety. The median number of cycles administered per patient was 2 (range, 1-6). The most common AEs related to the study treatment were fatigue (11 patients), nausea (eight patients), anorexia (six patients) and vomiting (five patients). Six of 18 treated patients had trabectedin-related AEs grade ≥ 3, which comprised fatigue (n=2), cellulitis, febrile neutropenia, nausea, pancytopenia, phlebitis, respiratory failure, and vomiting (n=1 each). Most patients were able to continue treatment. Two patients discontinued the study treatment due to trabectedin-related AEs: grade 4 respiratory failure, and grade 3 nausea, grade 3 vomiting and grade 3 asthenia. No deaths due to adverse events were reported. A total of eight trabectedin-related SAEs were reported in four patients: grade 4 thrombocytopenia (n=2), grade 4 febrile neutropenia, grade 4 pancytopenia, grade 4 respiratory failure, grade 3 neutropenia (n=2), and grade 2 hemoptysis. All eight SAEs resolved, usually without requiring any action (one patient required trabectedin treatment discontinuation). The most common hematological abnormality was anemia (16 patients; grade 3 in three patients), followed by lymphopenia (13 patients; grade 3 in five patients), and leukopenia (12 patients; grade 3/4 in six patients). None of these laboratory abnormalities caused changes in study treatment. Neutropenia (ten patients; grade 3/4 in eight patients) was reported as trabectedin-related SAE in two patients. One case of grade 4 febrile neutropenia was also reported as trabectedin-related SAE. Overall, grade 3/4 neutropenia appeared on Day 15 (range, 11-22) after dosing, and in most cases returned to grade ≤ 2 before Day 28, with the majority of episodes lasting less or equal than 15 days. Transient severe neutropenia was the most common cause of dose delay in this study, but no dose reductions or treatment discontinuations occurred due to neutropenia. Thrombocytopenia was the less common of the hematological abnormalities (ten patients; grade 3/4 in four patients). Two transient episodes of grade 4 thrombocytopenia were reported as trabectedin-related SAEs. No effects of thrombocytopenia on trabectedin treatment were reported.	

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	The most frequent biochemical abnormality was transaminases increases. ALT increase occurred in 14 patients (grade 3 in eight patients), and AST increase occurred in 13 patients (all grade 1/2). Overall, grade 3 ALT appeared on Day 8 (range, 5-15) after dosing, and most cases returned to grade 1 before Day 22, with the majority of episodes lasting less or equal than 15 days. Transient grade 1 ALT, concomitant with grade 2 GGT increase, caused a dose reduction in one patient and one cycle. Other biochemical abnormalities (AP, CPK, creatinine or total bilirubin increases) were less common, with no episodes reaching grade 3, and without requiring changes in trabectedin treatment.	
Conclusions	No recommendation is given for further evaluation of trabectedin 1.3 mg/m^2 3-hour q3wk as treatment of NSCLC patients pretreated with platinum and with XPG and/or ERCC1 overexpression, and BRCA1 underexpression. This trabectedin schedule has an acceptable tolerability, with mostly moderate to mild, reversible and predictable adverse reactions. The safety profile was similar to that of this compound administered as single agent for other indications, and no new safety issues were identified.	
Date of report (final version)	5 July 2011.	