Pharma Mar, S.A., Sociedad Unipersonal, Colmenar Viejo, Madrid, Spain
Johnson & Johnson Pharmaceutical Research and Development L.L.C.,
Titusville, NJ, USA

CLINICAL STUDY REPORT

ET-B-028-06

A MULTICENTER PHASE II CLINICAL TRIAL OF NEOADJUVANT TRABECTEDIN (YONDELIS®) IN PATIENTS WITH LOCALIZED MYXOID/ROUND CELL LIPOSARCOMA

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-028-06
Study Start Date:	16 April 2007 (First consent signed)
Study Completion Date:	12 January 2010 (Date of last follow-up)
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Earlier Approved Reports:	None
Version:	Final version
Approval Date:	5 November 2010

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

2. SYNOPSIS

<table>
<tr><td>Name of Sponsor(s)/Company(ies):
PharmaMar S.A., Sociedad Unipersonal
J&JPRD</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of finished product:
YONDELIS®</td></tr>
<tr><td>Name of active ingredient(s):
Trabectedin</td></tr>
<tr><td>Protocol number</td><td colspan="2">ET-B-028-06</td></tr>
<tr><td>Title of the study</td><td colspan="2">A Multicenter Phase II Clinical Trial of Neoadjuvant Trabectedin (Yondelis®) in Patients with Localized Myxoid/Round Cell Liposarcoma</td></tr>
<tr><td>Coordinating Investigator</td><td colspan="2">Alessandro Gronchi, M.D.
Unità Melanomi e Sarcomi. Dipartimento di Chirurgia. Istituto Nazionale per lo studio e la cura dei Tumori, Milano, Italy.</td></tr>
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Dr. Sylvie Bonvalot. Institut Gustave Roussy, Paris, France.
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Dr. Raymond J Hohl. Carver College of Medicin, Division of Hematology, Oncology and Blood and Marrow transplantation, Iowa, United States.
Dr. George Demetri. Dana-Farber Cancer Institute, Boston, United States.</td></tr>
<tr><td>Publication (references)</td><td colspan="2">At the time of this report no articles have been published on the study described herein.
Preliminary results of this study were presented at:
American Society of Clinical Oncology (ASCO) 2009 Meeting. Gronchi A, Le Cesne A, Bui NB, Palmerini E, Demetri G, Hohenberger P, Hohl RJ, Pilotti S, Perez I, Lardelli P. A phase II clinical trial of neoadjuvant trabectedin in patients with nonmetastatic advanced myxoid/round cell liposarcoma (MRCL). J Clin Oncol Vol 27(Suppl 15): page 542s (abstract No.10525).
European Cancer Organization (ECCO) 15-34th European Society for Medical Oncology (ESMO) Meeting, September 20-24, 2009. Berlin. Gronchi A, Palmerini E, Demetri G, Pérez I, Lardelli P, Pilotti S, Hohenberger P, Bui NB, Milhem MM, Bonvalot S. A phase II clinical trial of neoadjuvant trabectedin in patients with non metastatic advanced myxoid/round cell liposarcoma (MRCL). Eur J Cancer Vol 7 Suppl (2): page 590 (abstract No. O9400).
DGHO Deutsche Gesellschaft für Hämatologie und Onkologie, October 2-6, 2009, Heidelberg, Mannheim, Germany. Hohenberger P, Palmerini E, Bonvalot S, Demetri G, Lardelli P, Singer H, Pilotti S, Bui NB, Milhem MM, Gronchi A. A phase II clinical trial of neoadjuvant trabectedin in patients with non metastatic advanced myxoid/round cell liposarcoma (MRCL). Onkologie Vol 32 (Suppl 4): page 139 (abstract No. P511).
35th ESMO Congress, 8-12 October 2010, Milan, Italy. Gronchi A, Tarantino E, Italiano A, Le Cesne A, Hohenberger P, Hohl R, Benlloch S, Lardelli P, Nieto A, Tercero JC. RNA expression of XPG, ERCC1 and BRCA1 in myxoid liposarcoma patients treated neoadjuvant with trabectedin. Ann Oncol 21 (suppl 8); viii412; abstract No. 1358P.
16th Annual Meeting of The Connective Tissue Oncology Society (CTOS), 11-13 November 2010, Paris, France. Gronchi A, Tarantino E, Italiano A, Le Cesne A, Hohenberger P, Hohl RJ, Benlloch S, Lardelli P, Nieto A, Tercero JC. RNA expression of XPG, ERCC1 and BRCA1 in myxoid liposarcoma patients treated neoadjuvant with trabectedin.</td></tr>
<tr><td>Study period:
. First consent signed
. Last consent signed
. First infusion
. Last infusion
. Last follow-up</td><td>
16 April 2007
27 January 2009
20 April 2007
18 June 2009
12 January 2010</td><td>Phase of Development:

Phase II</td></tr>
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Name of finished product: YONDELIS®		
Name of active ingredient(s): Trabectedin		
Study objectives	**Primary:** • To determine the pathological complete response (pCR) rate with trabectedin in patients with localized myxoid/round cell liposarcoma (MRCL). **Secondary:** • To evaluate the objective response rate per the Response Evaluation Criteria in Solid Tumors (RECIST), and to contrast such response with changes in radiological density and tumor pathology. • To describe the incidence and severity of adverse events in this patient population. • Exploratory, hypothesis-generating pharmacogenomic analyses to correlate molecular parameters in patient samples with clinical outcomes (pCR).	
Methodology	This was an open-label, prospective, multicenter phase II clinical trial evaluating the efficacy and safety of neoadjuvant trabectedin 1.5 mg/m^2 24-hour intravenous (i.v.) infusion administered every three weeks (q3wk) in patients with localized MRCL previously untreated with chemotherapy or radiation. Patients with a documented histopathological diagnosis of MRCL and who fulfilled all eligibility requirements were to be entered into the study. They had to receive a minimum of three and a maximum of six trabectedin treatment cycles prior to definitive surgery, in the absence of overt tumor progression or intolerable side effects.	
Number of patients (planned and analyzed)	**Planned number of patients:** A Simon's optimal two-stage design was adopted to test the null hypothesis that p≤0.050 *versus* the alternative that p≥0.300 with a probability for early termination of 0.630. If the drug was actually not effective, there was a 0.02 probability of concluding that it was (target alpha=0.05). If the drug was actually effective, there was a 0.091 probability of concluding that it was not (target beta=0.1). After testing the drug on nine patients in the first stage, the trial was to be terminated if no pCR occurred (the Sponsor had to stop the accrual of patients). The cutoff date for that analysis was to be established once the ninth eligible and evaluable patient had undergone surgery/biopsy post completion of neoadjuvant trabectedin therapy. If the trial went on to the second stage, a total of 22 evaluable patients were to be studied. If the total number of patients achieving a confirmed pCR was three or less, the drug was to be rejected for further study in this clinical setting. **Patients analyzed:** One of the nine patients recruited and treated in the first stage of this study (patient #608) had pCR per central pathology review and, therefore, the studied proceeded to a second stage, with a total of 29 patients enrolled at eight investigational sites in France (n=12 patients; 3 centers), Germany (n=3 patients; 1 center), Italy (n=9 patients; 2 centers) and the U.S. (n=5 patients; 2 centers). Twenty-three of these 29 patients were evaluable for the main endpoint of efficacy (pathological response by central pathology review). All 29 patients were treated with trabectedin and evaluable for safety.	
Diagnosis and main selection criteria	**<u>Inclusion Criteria</u>** Patients who met all following criteria had to participate in the study: • Patient's written informed consent before any study-specific procedure. • Adult patients (≥ 18 years). • Pathological diagnosis of MRCL and availability of pathology specimens for central review and pharmacogenomic studies. • Clinical evidence of locally advanced (stage III), non-metastatic tumor, including locally recurring disease after initial surgery. • Measurable disease (by RECIST). • No prior chemotherapy or radiation (except for adjuvant post-operative radiotherapy).	

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Name of active ingredient(s): Trabectedin		

- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-2.
- Hematological variables:
  - Hemoglobin ≥ 9 g/dl.
  - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l, and
  - Platelet count ≥ 100x 10^9/l.
- Serum creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 30 ml/min.
- Creatine phosphokinase (CPK) ≤ 2.5 x upper limit of normal (ULN).
- Hepatic function variables:
  - Total bilirubin ≤ ULN.
  - Total alkaline phosphatase (AP) ≤ 2.5 x ULN; if AP > 2.5 x ULN, AP liver fraction or gamma-glutamyltransferase (GGT) or 5' nucleotidase had to be ≤ ULN.
  - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN.
- Albumin ≥ 25 g/l.

Exclusion Criteria

Patients who met any of the following criteria were to be excluded from participating in the study:

- Known hypersensitivity to any of the components of the trabectedin i.v. formulation or dexamethasone.
- Pregnant or lactating women, or men and women of reproductive potential who were not using effective contraceptive methods (one or more of the following):
  - Complete abstinence from intercourse, from two weeks prior to the administration of the study drug, throughout the study, and for at least six months after completion or premature discontinuation from the study to account for elimination of the investigational drug; or
  - Patient or patient's partner physical sterilization; or
  - One of the following, for female patients or female partners of male patients:
    - Implants of levonorgestrel; or
    - Injectable progestogen; or
    - Oral contraceptive (combined or progestogen only; subjects taking oral contraceptives should have been on a stable regimen for at least two months prior to screening); or
    - Any intrauterine device (IUD) with published data showing that the lowest expected failure rate is less than 1% per year (not all IUDs meet this criterion); or
    - Double-barrier method (two physical barriers or one physical barrier plus spermicide); or
    - Any other method with published data showing that the lowest expected failure rate for that method is less than 1% per year.
- History of another neoplastic disease (except basal cell carcinoma or cervical carcinoma in situ adequately treated) unless in remission for five years or longer.
- Known distant metastases.
- Other serious illnesses, such as congestive heart failure or angina pectoris, myocardial infarction within one year before enrollment, uncontrolled arterial hypertension or arrhythmias.
- Psychiatric disorder that prevented compliance with protocol.
- Active viral hepatitis or chronic liver disease.
- Active infection.
- Any other unstable medical condition.

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Name of finished product: YONDELIS®		
Name of active ingredient(s): Trabectedin		
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 or 1 mg. The 0.25-mg and 1-mg vials had to be reconstituted by adding 5 ml (0.25-mg vials) or 20 ml (1-mg vials) of sterile water for injection. From a microbiological point of view the reconstituted solution had to be used immediately. If not used immediately, in-use storage times and conditions prior to use could not be longer than 24 hours at 2ºC to 8ºC. The reconstituted solution had to be further diluted in at least 500 ml of normal saline (0.9% NaCl for injection) or 5% glucose (dextrose) solution and had to be administered using a central line. Trabectedin was administered as a **1.5 mg/m^2 24-hour q3wk i.v. infusion**, with prophylactic antiemetic medication [dexamethasone 20 mg i.v. on Day 1 before trabectedin infusion; additional steroids and serotonin (5-HT$_3$) blockers, either oral or i.v. on Day -1, were recommended; other antiemetics, such as lorazepam, prochlorperazine or diphenhydramine, could be used at the Investigator criteria]. The numbers of the trabectedin batches were as follows: • **0.25-mg vial batches:** 05I20, 06L14, 07012, 07A19 and 08030. • **1-mg vial batches:** 05I01, 06K16, 07O27, 07I13, 07I83, 07J18, 08A22, 08C31, 08D24, 08F19 and 08060**.**	
Duration of treatment	The patients had to receive a minimum of three and a maximum of six trabectedin cycles prior to definitive surgery, in the absence of unacceptable toxicity and/or disease progression. In exceptional circumstances, and in agreement with the Sponsor, a patient could receive additional cycles of trabectedin prior to definitive surgery if considered by the Investigator to be in the patient's best interest. Time between last trabectedin cycle and surgery should be three weeks (with a 2-week window), provided there was appropriate recovery of acute side effects from the chemotherapy. The Investigator could decide the need of early tumor surgery during the course of the study. In any case, surgery had to be done in the best time frame for the patient's benefit. Patients whose MRCL had not progressed at the end of the neoadjuvant treatment were to be followed every six weeks until progression, six months post definitive surgery and until resolution of any trabectedin-related adverse events (AEs) and sequelae. Thus, all AEs suspected to be related to the study drug had to be followed after the time off therapy until the event and its sequelae resolve or stabilize at a level acceptable to the Investigator and the clinical monitor or his/her designee. Patients with documented disease progression prior to surgery had to go off-study and then they had to be treated and followed per institutional standards. Patients were to be considered on-study for the duration of their treatment and in the 30 days following treatment discontinuation. Treatment discontinuation was defined as the day of last trabectedin administration.	
Criteria for evaluation **Efficacy**	The primary efficacy evaluation of neoadjuvant trabectedin treatment was the assessment of the pathological complete response (pCR) rate by central pathology review in the tumor surgical specimen. Patients were to be considered evaluable for the primary efficacy endpoint if they had a centrally confirmed diagnosis of MRCL positive for fluorescence *in situ* hybridization (FISH+MRCL), had received at least one infusion of trabectedin and had a central assessment of pathologic response in the surgical specimen (or in a second biopsy for inoperable cases). As a secondary objective, RECIST responses were also to be assessed in those patients who had received at least one cycle of trabectedin and had at least one post-baseline disease assessment. Tumor assessments were to be performed within four weeks prior to the first trabectedin infusion and every six weeks thereafter until disease progression. Objective responses had to be confirmed at least four weeks after the previous assessment. Patients with early disease progression or who died due to disease progression before the first scheduled tumor assessment were also to be included in the analysis.	

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Name of finished product: YONDELIS®		
Name of active ingredient(s): Trabectedin		
	An exploratory assessment of changes in radiological density in contrast with the tumor response by RECIST and pathological changes was to be carried out in patients with available material. Only a description of the findings (without a formal analysis) was to be provided due to lack of standardized methodology for this activity.	
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, laboratory measurements, clinical examinations, deaths and study discontinuations.	
Pharmacogenomics	Samples required for pharmacogenomic analyses were paraffin-embedded tumor blocks or tissue slices mounted in microdissection slides from both the initial diagnostic biopsy and the surgical specimen for central pathology review and pharmacogenomic tests in all patients (whenever available, fresh frozen or RNAlater® preserved tissue were to be preferred to characterize the translocation type, i.e., II vs. III) and one pre-treatment serum sample (5 ml) for methylation analysis. The pharmacogenomic analyses included: • Evaluation of mRNA expression of DNA repair-related genes (BRCA1, ERCC1 and XPG) in paraffin-embedded tumor samples. Quantitative reverse transcription-polymerase chain reaction (qRT-PCR) was to be used for determining the mRNA expression. • The t(12;16) and t(12;22)(q13;q12) chromosomal translocation was to be determined by FISH analysis in paraffin-embedded tissue. The analysis of the FUS-CHOP fusion protein variants was to be determined by polymerase chain reaction (PCR) amplification and sequencing of RNA extracted from fresh frozen or RNAlater® preserved patient tumor tissue. • Methylation status of BRCA1 promoter was to be analyzed by PCR amplification with methylated/unmethylated specific primers in paired paraffin-embedded tumor samples and circulating tumor DNA in patient serum. • Patients' paraffin-embedded tissue blocks/slides were to be used to construct a tissue microarray (TMA). TMA sections were to be analyzed by immunohistochemistry (IHC) using DNA repair proteins' specific antibodies. • Sections of paraffin-embedded tumor blocks were to be used for the pathological comparison of pre- and post-treatment tissue samples for cellular viability, proliferation index and vascularization.	
Statistical methodology	**Demographics** Descriptive statistics were to be used for this open, non-comparative study. Non-continuous variables were to be described in frequency tables using counts and percentages. Continuous variables were to be described by median, minimum and maximum. **Efficacy** For evaluation of the main endpoint (centrally-assessed pathologic response), binomial exact estimator and its 95% CI were to be calculated. **Safety** Descriptive statistics were to be employed to characterize the toxicity, drug-related deaths, serious adverse events (SAEs) and toxicity-related treatment discontinuation profiles. AEs were to be 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.6.1. **Pharmacogenomics** The parameters to be analyzed are shown in the Section below.	
Results (1): Patient characteristics	Most patients were Caucasian (96.6%), more than half of them (55.2%) were male, their median age was 47 years (range, 23-75 years), and the majority (79.3%) had ECOG PS=0. Twelve patients (41.4%) had myxoid liposarcoma with round cells. Primary tumors	

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Name of finished product: YONDELIS®		
Name of active ingredient(s): Trabectedin		
	were more frequently located in the lower extremities (n=23; 79.3%), their location was generally deep (T2B in 23 patients; 79.3%), their most frequent stage was III (n=25; 86.2%) and they usually had a size larger than 5 cm (n=27; 93.1%). The median number of sites involved per patient was 1 (range, 1-2 sites), with the thigh being the most common disease location (n=14, 48.3%). All patients (n=29, 100.0%) had undergone previous surgery, usually diagnostic/exploratory (biopsy was done in all but one patients). One patient had received external radiotherapy in the right thigh after surgery (compartment resection).	
Results (2): Efficacy	With respect to the primary endpoint of efficacy, three of 23 evaluable patients had pCR according to central pathology review (13.0%; 95% CI, 2.8-33.6%). In these cases, tumor cells and associated blood vessels disappeared, being present cicatricial tissue and fibrosis at the end of trabectedin neoadjuvant treatment. These three complete pathological responses occurred in patients with myxoid liposarcoma (n=2) and myxoid liposarcoma with round cells (n=1). The patients had no prior curative surgery, their tumors were located in the lower extremities (lower leg, calf and knee, respectively), with tumor size between 5 and 10 cm, and received four (n=2) and six cycles (n=1) of trabectedin. In addition, per central review, very good and moderate histological response was observed in two and ten patients, respectively, and seven patients had a low histological response. Histological responses comprised reduction in the cellular and vascular component of the tumor, and maturation of tumor cells to lipoblasts, even in some patients with the more aggressive tumors (i.e., with the round cell component). According to the Investigator's opinion, ten patients had pathological response (41.7%; 95% CI, 22.1-63.4%), although the diagnosis of myxoid liposarcoma could not be confirmed in one of them. With respect to the secondary endpoint of efficacy, seven patients had radiological PR according to the RECIST (objective response rate of 24.1%; 95% CI, 10.3-43.5%). The rate of tumor growth control, which included patients with objective response or those with stable disease ≥ 3 months, was 72.4% (95% CI, 52.8-87.3%). Hypodensity was observed in the radiological images of two of three patients with pCR per central pathology review (data not available for the third patient) and in five of seven patients with PR per RECIST (data not available for one of the two other patients).	
Results (3): Pharmacogenomics	Although the number of patients evaluated in the pharmacogenomic substudy was low (paraffin-embedded tissue samples were available for 23 patients and 15 patients were evaluable for RNA expression analysis), the results show that patients with MRCL had an increased expression of XPG RNA when compared to other STS subtypes (4.47 vs. 1.55; i.e., a 3-fold XPG expression increase). Median RNA expression values for ERCC1 (6.11) and BRCA1 (2.85) were only slightly increased (≅ 20%) compared to other STS subtypes (4.99 and 2.36, respectively). The two complete pathological responses per central pathology review that had XPG determined; 4 of the 6 pathological responses per Investigator; all three complete cellular and all two vascular regressions observed, and all three PRs per RECIST were found in patients with high XPG RNA expression (i.e., ≥ the median value of 4.47). These findings suggest that higher XPG RNA expression is associated to a better response to trabectedin treatment. No association of ERCC1 or BRCA1 expression with trabectedin treatment outcome was observed. All patients with transcript type data determined in the pre-treatment tumor sample had the FUS-CHOP transcript type II, expected to be sensitive to trabectedin according to previous retrospective studies. No other transcription types were identified in these samples. Post-treatment tumor samples were not adequate for the determination of FUS-CHOP transcript type.	
Results (4): Safety	All 29 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 6 (range, 1-8).	

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Name of finished product: YONDELIS®		
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The AEs most commonly related to trabectedin neoadjuvant treatment were nausea (75.9% of patients/38.5% of cycles), fatigue (62.1% of patients/33.8% of cycles), vomiting (27.6% of patients/11.5% of cycles) and constipation (17.2% of patients/6.1% of cycles). Eight (27.6%) of 29 treated patients had trabectedin-related AEs grade ≥ 3, which comprised fatigue (n=5 patients), vomiting (n=2), nausea (n=2), abdominal pain, constipation, hepatic failure, renal failure, rhabdomyolysis and stomatitis (n=1 each). Most patients were able to continue the study treatment. Only one patient (3.4%) discontinued trabectedin treatment due to trabectedin-related AEs (grade 3 hepatic failure and fatal rhabdomyolysis and renal failure). This patient died due to these treatment-related AEs, being this the sole case of death reported during this clinical trial.

A total of 10 trabectedin-related SAEs were reported in five patients (17.2%): grade 5 (fatal) renal failure, grade 5 rhabdomyolysis, grade 3 ALT increase, grade 3 AST increase, grade 3 constipation, grade 3 fatigue, grade 3 hepatic failure, grade 3 liver function test abnormal (ALT and AST increase), grade 3 nausea and grade 3 stomatitis (n=1 each).

The most common hematological abnormality was neutropenia (93.1% of patients/66.9% of cycles; grade 3/4 in 51.7% of patients/31.8% of cycles), but none of these episodes required hospitalization or were reported as SAEs. No cases of febrile neutropenia were reported. Overall, grade 3/4 neutropenia appeared on Day 15 (range, 8-23) after dosing, and most cases (78.7%) returned to grade ≤ 2 before Day 29, with the majority of episodes (89.4%) lasting less or equal than 15 days. Transient severe neutropenia was the most common cause of dose delay in this study (31 of 52 cycles delayed), alone (n=22 cycles) or concomitant with leukopenia (n=2) or non-hematological toxicity (n=7). Transient severe neutropenia was also the cause of dose reduction in four cycles: three alone and one concomitant with non-hematological toxicity. No treatment discontinuations occurred due to neutropenia. Other hematological abnormalities included anemia 86.2% of patients/75.0% of cycles; grade 3 in 3.4% of patients/0.7% of cycles), leukopenia (82.8% of patients/70.3% of cycles; grade 3/4 in 31.0% of patients/16.9% of cycles), lymphopenia (62.1% of patients/42.6% of cycles; grade 3 in 13.8% of patients/4.1% of cycles) and thrombocytopenia (37.9% of patients/20.3% of cycles; grade 3/4 in 6.9% of patients/2.0% of cycles). Overall, apart from two dose delays due to leukopenia concomitant to neutropenia, no modifications of trabectedin treatment due to these other hematological abnormalities were reported.

The most frequent biochemical disorder was transaminases increase. ALT increase occurred in 100.0% of patients/97.3% of cycles (grade 3/4 in 62.1% of patients/35.4% of cycles) and AST increase occurred in 100.0% of patients/81.6% of cycles (grade 3/4 in 31.0% of patients/11.6% of cycles). Two grade 3 ALT/AST increases and one case of grade 3 liver function test abnormal were reported as SAEs. Overall, grade 3/4 ALT appeared on Day 7 (range, 3-9) after dosing, and most cases (75.0%) returned to grade 1 before Day 28, with the majority of episodes (76.9%) lasting less or equal than 24 days. Grade 3/4 AST appeared on Day 6 (range, 3-8) after dosing, and most cases (94.1%) returned to grade 1 before Day 22, with the majority of episodes (82.4%) lasting less or equal than 15 days. Transient ALT increase caused nine cycle delays (four of them due only to ALT increase, and five concomitant with neutropenia) and three dose reductions. No dose delays were caused by AST increases, while one patient had dose reduction due to “hepatic toxicity”, term which includes ALT/AST increase. One treatment discontinuation occurred due to ALT increase. The next most common biochemical abnormality was GGT increase (100.0% of patients/89.6% of cycles; grade 3 in 45.0% of patients/23.6% of cycles), which caused a dose decrease concomitant with neutropenia and AP increase. Other biochemical abnormalities (AP, CPK, creatinine or total bilirubin increases) were less common, with few episodes reaching grade 3: two for total bilirubin and one for CPK and creatinine. In most cases, these other biochemical laboratory abnormalities did not cause changes on trabectedin

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Name of active ingredient(s): Trabectedin		
	treatment. Bilirubin increase led to one dose delay of 20 days in one patient with concomitant neutropenia, and one dose reduction in other patient; CPK increase concomitant with neutropenia caused one dose delay in one patient, and AP increase caused one dose decrease concomitant with other toxicities, as described above.	
Conclusions	Trabectedin 1.5 mg/m^2 given as a 24-hour i.v. infusion every three weeks is a therapeutic option of interest in the neoadjuvant setting in patients with MRCL.	
Date of report (final version)	5 November 2010.	