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CLINICAL TRIAL PROTOCOL

Non-interventional, multicenter, prospective, European study to describe the effectiveness of trabectedin + PLD in the treatment of relapsed ovarian cancer (ROC) patients by previous usage of an antiangiogenic drug

INVESTIGATIONAL MEDICINAL PRODUCTS: Trabectedin

Protocol No.: ET-D-031-14
Version No.: 4 - Amendment 2
Date Issued: 18 September 2018
NCT Code: 02825420

Clinical Protocol

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Protocol/Amendment Approval Page(s)

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Synopsis

Study Title:	**Non-interventional, multicenter, prospective, European study to describe the effectiveness of trabectedin + PLD in the treatment of relapsed ovarian cancer (ROC) patients by previous usage of an antiangiogenic drug**
Protocol ID:	ET-D-031-14
Trial Centers:	Approximately 70 centers will be identified across 5 European countries (Italy, Spain, Germany, France, Belgium)
Study Objectives:	***Primary Objective:*** To assess the progression-free survival (PFS) according to investigator criteria in relapsed ovarian cancer patients treated with trabectedin + pegylated liposomal doxorubicin (PLD) according to standard local clinical practice following approved Summary of Product Characteristics (SmPC) indication and dose, overall and by previous usage of antiangiogenic drug.
	Secondary Objectives: • To evaluate the response rates (complete response [CR] + partial response [PR]), and disease control rate (DCR; CR + PR + stable disease [SD]) • Overall survival (OS) • To evaluate patient's performance status (PS) • To assess treatment duration and number of cycles, treatment exposure, and time to next treatment • To evaluate the safety of the combination of trabectedin + PLD Secondary objectives will be assessed overall and by previous usage of antiangiogenic drug.
Study Rationale:	To assess the PFS after trabectedin + PLD therapy for the treatment of relapsed ovarian cancer according to standard local clinical practice following approved SmPC indication and dose, while describing patients who were pretreated with an antiangiogenic drug and those not pretreated, in real-life clinical practice.
Study Design:	Non-interventional, multicenter, prospective study of trabectedin + PLD administered according to standard local clinical practice following approved SmPC indication and dose.

Study Population:	Patients with platinum-sensitive relapsed ovarian cancer who are receiving trabectedin + PLD according to standard local clinical practice following approved SmPC indication and dose.
Selection Criteria:	• Women aged 18 years or older. • Presence of platinum-sensitive relapsed ovarian cancer. • Treatment indication according to local label SmPC and reimbursement for trabectedin and PLD treatment. • Prior treatment with a minimum of 1 cycle of trabectedin + PLD before inclusion in the study. • Written informed consent indicating that patients understand the purpose and procedures and are willing to participate in the study.
Study Drug:	Trabectedin (Yondelis®)
Administration:	Trabectedin administered according to standard local clinical practice following approved SmPC indication and dose. The recommended dose of trabectedin for the treatment of relapsed platinum-sensitive ovarian cancer is 1.1 mg/m^2 body surface area (BSA), administered every 3 weeks as a 3-hour infusion immediately after PLD 30 mg/m^2. Pretreatment with corticosteroids (e.g., dexamethasone) is required; additional anti-emetics may be administered in accordance with local practice, as needed, and as specified in the SmPC.

Study Procedures:	Patients will be managed by their treating clinician without any additional instructions. The study will require no additional treatment procedures during patient visits. Patients meeting the selection criteria will be invited to participate in the study. Before any study-specific data are recorded, patients will be provided with all the study details prior to their decision to participate and will be requested to sign an informed consent form (ICF) prior to their participation in the study. Patient's baseline data, safety, and PS (evaluation according to the Eastern Cooperative Oncology Group [ECOG] score) will be collected during the Observation Period (treatment with trabectedin + PLD). Even though baseline data will be collected when patient is under treatment with trabectedin + PLD, it corresponds to data prior to treatment initiation. Response and survival assessments will be collected during the study and include symptomatic response and overall tumor response according to investigator criteria. The preferred method to measure overall response is Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as it is the generally accepted standard criteria; however other criteria used by the investigators will be accepted. Safety, response, reason for discontinuation of treatment and survival will be assessed during the follow-up period (1 month after the end the Observation Period and, for patients who discontinued trabectedin before the end of the 12-month Observation Period, 12 months after the Index date). Subsequent non-trabectedin treatments that the patient received during the follow-up period will also be described.
Study Endpoints:	Study endpoints will be assessed overall and by previous usage of antiangiogenic drug. Primary endpoint: PFS measured as time from first dose of trabectedin to disease progression as reported by the investigator or death regardless of cause. Secondary endpoints: • Response rate (CR+PR) • DCR (CR+PR+SD) • OS • Evolution of the patient's performance status • Treatment duration and number of cycles • Treatment exposure • Time to next treatment • Safety of the combination of trabectedin + PLD

Safety Evaluation:	A solicited reporting system of adverse events (serious and non-serious, related or non-related) on trabectedin.
Pharmacokinetic Considerations:	This is a non-interventional, prospective study and no pharmacokinetic or pharmacodynamic evaluations are planned.
Planned Study Periods:	• Recruitment: 36 months • Observation Period: up to 12 months • Follow-up visits: 1 month after patient last on-study cycle and, for patients who discontinued treatment with trabectedin before the end of the 12-month Observation Period, 12 months after the index date. • Data Base Lock: Nov 2019 • Study Final Report: Jan 2020
Date Issued:	18 Nov 2014
Date Amended:	18 September 2018

List of Abbreviations

Abbreviation	Description
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BSA	Body Surface Area
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DNA	Deoxy ribonucleic acid
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society for Medical Oncology
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FAS	Full Analysis Set
FIGO	International Federation of Gynecology and Obstetrics
GCP	Good Clinical Practice
GVP	Good Pharmacovigilance Practices
h	Hour
HR	Hazard Ratio

Abbreviation	Description
IARC	International Agency for Research in Cancer
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Patient identification number for study participation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
iv	Intravenous
kg	Kilogram
KM	Kaplan-Meier
m^2	Square Meter
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MR	Magnetic Resonance
NCCN	National Comprehensive Cancer Network
ORR	Overall Response Rate
OS	Overall Survival
PD	Progression of Disease
PFS	Progression-Free Survival
PR	Partial Response
PS	Performance Status
q	Every
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SD	Stable Disease

Abbreviation	Description
SmPC	Summary of Product Characteristics
US/USA	United States of America
VEGF	Vascular Endothelial Growth Factor
vs	Versus
WHO	World Health Organization
wk	Week

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1 INTRODUCTION

1.1 Background

1.1.1 Ovarian Cancer

Ovarian cancer is a serious, clinically challenging malignancy with the majority of ovarian malignancies (85%-95%) developing from epithelial cells. Ovarian cancer represents a significant challenge in oncology, being a malignancy that has a mortality rate disproportionate to its incidence. According to the World Health Organization (WHO) International Agency for Research in Cancer (IARC) GLOBOCAN database, ovarian cancer comprised 3.6% of all incident cancer types reported worldwide in 2012, and 4.1% of cancer types across Europe. Yet despite its low incidence, ovarian cancer has the sixth highest cancer-related mortality rate in European women, and is associated with the highest mortality-to-case ratio of all gynecologic malignancies (Holschneider and Berek, 2000; World Health Organization, 2014).

A contributing factor to high mortality rates is the late disease diagnosis. Most women are asymptomatic until the disease has spread, with the majority of cases diagnosed at the advanced stage. In European countries, population-based data indicate that, of the subset of patients with known disease severity, 60% to 74% of cases of ovarian cancer are diagnosed at a FIGO (International Federation of Gynecology and Obstetrics) stage of III or IV (Maringe et al, 2012). Unfortunately, approximately 80% of patients will relapse after first-line platinum-based and taxane-based chemotherapy (National Cancer Institute, 2014). Given that relapsed ovarian cancer is not curable, most women who relapse die from their disease (Della Pepa and Banerjee, 2014). Consequently, developing new therapies for relapsed ovarian cancer is critical.

According to treatment guidelines from the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO), primary treatment for advanced ovarian cancer (FIGO stage II, III, IV) consist of surgical staging and cytoreductive surgery followed by a combination of platinum-based chemotherapy, including paclitaxel/carboplatin or docetaxel/carboplatin combination therapies, or bevacizumab-containing regimens (Colombo et al, 2010; National Comprehensive Cancer Network, 2014). According to ESMO clinical practice guidelines, the appropriate therapy for patients with relapsed ovarian cancer is guided by the time to progression since the last platinum-based treatment (referred to as the platinum-free interval). Patients who progress during platinum-based treatment are considered to have platinum-refractory disease, while patients who develop recurrence within 6 months from the completion of first-line platinum chemotherapy are considered to have platinum-resistant disease (Colombo et al, 2010). The prognosis for these patients is poor, with a median overall survival (OS) typically under 12 months. Treatment options include paclitaxel, pegylated liposomal doxorubicin (PLD), topotecan, and gemcitabine (Della Pepa and Banerjee, 2014). However, since response rates are only about 10%, the primary goal of therapy in these patients is palliative care (Colombo et al, 2010).

Patients with relapsed ovarian cancer who progress following an interval greater than 6 months since the last platinum-based treatment (platinum sensitive disease) have 2 categorizations: partially platinum-sensitive patients are those who progress between 6 and 12 months, while fully platinum-sensitive patients progress with a platinum-free interval of more than 12 months (Ledermann et al, 2013). Both types are likely to benefit from further platinum-based therapy. The ESMO clinical practice guidelines recommend that for partially platinum-sensitive and fully platinum-sensitive patients, carboplatin combination therapies are the treatment of choice (Ledermann et al, 2013). Platinum-containing regimens that are effective for these patients include carboplatin with paclitaxel, carboplatin with PLD, carboplatin with gemcitabine, and a combination of carboplatin with gemcitabine and the antiangiogenic agent bevacizumab (see Section 1.1.2) (Della Pepa and Banerjee, 2014; Gonzalez Martin et al, 2013). Surgical resection is also an option in platinum-sensitive patients with prolonged (over 24 months) treatment free-

interval, especially with isolated recurrence and good performance status (Colombo et al, 2010). However, no single therapeutic agent is recommended for relapsed ovarian cancer, and recurrence therapies may include drugs, radiation, or other treatments aimed at reducing tumor burden, control symptoms, or increase length and/or quality of life patients (National Comprehensive Cancer Network, 2014).

Compared with fully platinum-sensitive patients, partially platinum-sensitive patients have a lower response to platinum-based regimens, with shorter progression-free survival (PFS) and OS. Thus, different strategies beyond carboplatin-based regimens are needed. Based on a subgroup analysis of the open-label, multinational, multicenter, phase III OVA-301 study (see Section 1.1.3.1 for additional study details), both ESMO and The Spanish Research Group for Ovarian Cancer (GEICO) recommend the non-platinum-based regimen of trabectedin + PLD for patients with partially platinum-sensitive relapsed ovarian cancer (Gonzalez Martin et al, 2013; Ledermann et al, 2013).

1.1.2 Angiogenesis

Angiogenesis is a key factor contributing to tumor growth and metastases. Since neoplasms are dependent, in part, on the formation of adequate vascular support, there is a focus on therapies targeting angiogenesis to reduce the growth and spread of ovarian cancer. For patients with ovarian cancer, the clinical utility of antiangiogenic therapies is apparent, since the extent of angiogenesis correlates inversely with prognosis (Huang et al, 2000).

Studies have demonstrated a complex relationship underlying angiogenesis and vascular endothelial growth factor (VEGF), a family of ligands that are often overexpressed in women with ovarian cancer, and is an independent prognostic factor for OS (Aravantinos and Pectasides, 2014). Thus, many current therapeutic approaches target the inhibition of VEGF and its receptors (Eisenhauer et al, 2012). Current VEGF-mediated antiangiogenic therapies include biologics that target the ligand, including bevacizumab and aflibercept, and tyrosine kinase inhibitors that target VEGF receptors, such as pazopanib, cediranib, sorafenib, and vandetanib (Slomovitz et al, 2011).

1.1.3 Trabectedin + Pegylated Liposomal Doxorubicin (PLD)

Trabectedin combined with PLD is approved in the EU for the treatment of relapsed platinum-sensitive ovarian cancer. Trabectedin (Yondelis®) is a novel antitumor agent derived from a marine source, the Caribbean tunicate *Ecteinascidia turbinata* and currently produced synthetically (Pommier et al, 1996). Trabectedin is a first-in-class antitumor agent with a complex mechanism of action at the level of gene transcription. Trabectedin binds covalently to the minor deoxyribonucleic acid (DNA) groove and alkylates the N2 amino group of a guanine residue, which bends towards the major groove (Pommier et al, 1996). Cytotoxic concentrations of trabectedin delay cell cycle progression through the S phase and produces arrest at G2/M, ultimately resulting in p53-independent apoptosis (Carter and Keam, 2007; Erba et al, 2001; Martinez et al, 2001; Martinez et al, 2005).

Trabectedin also has selective anti-inflammatory and immunomodulatory properties that affect the tumor microenvironment. Emerging evidence suggests trabectedin has selective cytotoxicity on tumor stroma macrophages, inhibits VEGF, and selectively inhibits inflammatory mediators. These actions collectively inhibit tumor growth, invasion and metastases, while also providing an antiangiogenic effect (Poveda et al, 2014).

PLD is available as doxorubicin hydrochloride in a pegylated liposomal formulation. Pegylation involves encapsulated doxorubicin hydrochloride in liposomes with surface-bound methoxypolyethylene glycol. This process protects liposomes from an immune response, thereby increasing its blood circulation time.

The active ingredient of PLD—doxorubicin hydrochloride—is a cytotoxic anthracycline antibiotic obtained from *Streptomyces peucetius* var. *caesius*. Although the exact mechanism of action is not known, it is generally believed that inhibition of DNA, ribonucleic acid (RNA), and protein synthesis is responsible for the majority of antitumor effects of PLD. This is probably the result of intercalation of the anthracycline between adjacent base pairs of the DNA double helix thus preventing their unwinding for replication. (Caelyx SmPC, 2006)

The recommended dosage for trabectedin in relapsed ovarian cancer is 1.1 mg/m^2 administered as a 3-hour infusion every 3 weeks (3h_q3w), immediately after infusion of 30 mg/m^2 PLD.

1.1.3.1 ***Efficacy***

Several phase I trials extensively evaluated the safety and antitumor activity of trabectedin in patients with advanced solid malignancies using different rates of intravenous (iv) infusion on every-3-week (q3w) schedules (Ryan et al, 2001; Taamma et al, 2001; Twelves et al, 2003; van Kesteren et al, 2000; van Kesteren et al, 2002). In these phase I trials, trabectedin produced objective antitumor responses in heavily-pretreated patients with diverse tumor types.

A retrospective pooled analysis of 3 phase II studies evaluated the efficacy and safety profile of trabectedin monotherapy as a second- and third-line therapy in patients with relapsed ovarian cancer (del Campo et al, 2013). Three trabectedin dose schedules were investigated: 1.3 mg/m^2 3h_q3w administered to 94 patients , 0.58 mg/m^2 given to 147 patients as a 3-hour weekly infusion for 3 weeks of a 4-week cycle (3h_qw x 3_q4w), and 1.5 mg/m^2 over 24 h every 3 weeks (24h_q3w) administered to 54 patients. Of the combined total of 295 patients, 189 (64%) had platinum-sensitive disease. The primary endpoint in all 3 trials was the overall response rate (ORR, complete response [CR] + partial response [PR]). Among the secondary endpoints was the disease control rate (DCR), defined as the percentage of patients with a CR or PR and/or stable disease (SD) lasting 3 months or more. Compared with the weekly schedule, both q3w regimens showed a significantly higher ORR (36% vs 16%, $P < 0.001$) and DCR (66% vs 46 %, $P < 0.001$), and a longer median PFS (5.6 vs 2.8 months, $P < 0.0001$). Patients with platinum-sensitive disease treated with either q3w schedule had a longer median PFS (24h, 6.2 months; 3h, 6.8 months) versus (vs) the weekly schedule (5.1 months). The median OS for the q3w schedules was also comparable (24h, 20.4 months; 3h, 17.1 months) and longer than the weekly regimen (13.7 months). Patients with platinum-sensitive disease also had a higher median OS (20.4 months) compared with platinum-resistant patients (11.1 months). The analysis demonstrated that trabectedin was an effective monotherapy for the treatment of relapsed ovarian cancer, with better outcomes in patients with platinum-sensitive disease. Given the better safety profile regarding neutropenia, fatigue, and vomiting for the 3h_q3w vs the 24h_q3w schedule, the 3h_q3w schedule (associated with shorter infusion times) was considered the most appropriate regimen.

The key evidence of efficacy of trabectedin + PLD in relapsed ovarian cancer is based on an open-label, multicenter, randomized, phase III study (OVA-301) in 672 patients who experienced either persistent or recurrent disease, or disease progression following a prior platinum-based chemotherapy. Patients also had measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or less. The randomization was stratified according to whether the patient had platinum-sensitive disease or platinum-resistant disease (Poveda et al, 2014). Treatment groups included trabectedin 1.1 mg/m^2 administered as a 3-hour infusion and PLD 30 mg/m^2 administered as a 1.5-hour infusion every 3 weeks, or PLD 50 mg/m^2 administered as a 1.5-hour infusion every 4 weeks. The primary analysis of PFS by independent radiology review was performed on 645 patients. Median PFS for the trabectedin + PLD group (7.3 months) vs PLD alone (5.8 months) translated to a 21% risk reduction for disease progression (Hazard ratio [HR] = 0.79,

95% CI: 0.65-0.96). Secondary analyses of ORR also favored the combination arm (HR = 1.65, 95% CI: 1.14-2.37). In patients with platinum-sensitive relapsed ovarian cancer (65% in trabectedin + PLD; 63% in PLD arm), median PFS was 9.7 months in the trabectedin + PLD arm compared with 7.2 months in the PLD monotherapy arm (HR = 0.66, 95% CI: 0.52-0.85).

A secondary analysis of 214 partially platinum-sensitive patients from the OVA-301 study demonstrated a 35% risk reduction of disease progression or death that significantly favored the trabectedin + PLD combination (HR, 0.65. 95% CI, 0.45-0.92). The trabectedin + PLD group had a median PFS of 7.4 months vs 5.5 months for PLD monotherapy. When PFS results were compared across subsets of patients according to patients' platinum-free interval, the largest benefit with trabectedin + PLD treatment was obtained with partially platinum-sensitive patients (Poveda et al, 2011).

The protocol-defined analysis of OS for OVA-301 did not demonstrate differences across treatment groups: the median OS was 22.2 months for trabectedin + PLD and 18.9 months for PLD (HR = 0.86, $P = 0.08$). However, a significant imbalance of the platinum-free interval across treatment groups (trabectedin + PLD, mean PFI = 10.6 months; PLD, mean PFI = 13.3 months; $P < 0.01$) spurred an exploratory multivariate analysis that considered platinum-free interval and other prognostic factors as covariates, which demonstrated a significant OS advantage in favor of trabectedin + PLD (22.6 vs 19.4 months; HR = 0.82, 95% CI: 0.69-0.98). Further analysis with 430 platinum-sensitive patients showed a median OS of 27.0 months for trabectedin + PLD and 24.1 months for PLD (HR = 0.83; 95% CI: 0.67-1.04). For partially platinum-sensitive patients, the median OS of 22.4 months in the trabectedin + PLD group was significantly longer than in the PLD group at 16.4 months (HR = 0.64; 95% CI: 0.47-0.86) (Monk et al, 2012; Poveda et al, 2014).

Further advantages to OS were demonstrated in a subgroup of 94 patients with partially platinum-sensitive disease from the OVA-301 trabectedin + PLD arm who subsequently received platinum-based chemotherapy at progression. Compared with PLD alone, trabectedin + PLD (followed by subsequent platinum-based therapy) induced a 9-month longer median OS (27.7 vs 18.7 months) and a significant 42% decrease in the risk of death (HR = 0.58; $P= 0.0153$) (Poveda et al, 2014).

Thus, the OVA-301 trial demonstrated a clinical benefit of trabectedin + PLD compared with PLD alone in patients with platinum-sensitive relapsed ovarian cancer.

1.1.3.2 ***Safety***

Myelosuppression, elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and fatigue were the primary dose-limiting toxicities in the dose-finding phase I studies.

Adverse events from the OVA-301 trial, 1 dose-ranging randomized control trial, and 2 nonrandomized trials reported rates of grade 3 (severe) and 4 (life-threatening) adverse events of 89% vs 58% for trabectedin + PLD compared to PLD alone, respectively. The rates of discontinuation due to adverse events were 17% vs 9%, for patients who received trabectedin + PLD vs patients receiving PLD alone (Papaioannou et al, 2011). Adverse events from OVA-301 were collected from 333 patients receiving trabectedin + PLD and 330 patients receiving PLD alone. The most frequent grade 4 hematologic adverse events at least possibly related to treatment with trabectedin + PLD vs PLD included neutropenia (34% vs 8.5%), leukopenia (8.4% vs 2.4%), thrombocytopenia (8.1% vs 0.6%), anemia (3.0% vs 0.3%), and febrile neutropenia (2.4% vs 0.3%). The most frequent grade 4 nonhematologic adverse events that were more common with trabectedin + PLD therapy included increases in ALT (2.4% vs 0%) and AST (0.9% vs 0.3%). The most common adverse events leading to treatment termination or dose adjustment was neutropenia for trabectedin + PLD and hand-foot syndrome for PLD (Monk et al, 2010).

All patients must receive corticosteroids (e.g., 20 mg dexamethasone iv) 30 minutes prior to PLD (in combination therapy) or Yondelis (in monotherapy); not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed (Yondelis SmPC).

1.2 Rationale for the Study

Based on the outcomes of study OVA-301, this non-interventional study will investigate the clinical utility of a platinum-free trabectedin + PLD regimen in patients with progressive ovarian cancer relapsing 6 months or more following the previous platinum-based chemotherapy. This study will assess the value of palliative care by collecting real-life data on the response to trabectedin + PLD, which can be related to the principal objectives of re-treatment for patients with relapsed platinum-sensitive ovarian cancer—to prolong survival, improve quality of life, and alleviate cancer-related symptoms (Poveda et al, 2014).

The aim of this non-interventional, European, multicenter, prospective study is to assess the PFS after trabectedin + PLD therapy for the treatment of relapsed ovarian cancer according to standard local clinical practice following approved SmPC indication and dose, describing patients who were pretreated with an antiangiogenic drug and those not pretreated, in real-life clinical practice.

Patients must have received a minimum of 1 cycle of trabectedin + PLD before their inclusion in the study (Appendix 14.1, Figure 1).

Clinical evidence of PFS, response rate, DCR, survival, treatment parameters, and safety will be obtained in order to evaluate the effectiveness of trabectedin + PLD in patients with relapsed ovarian cancer in Europe.

2 GOALS AND OBJECTIVES

2.1 Primary Objective

To assess the progression-free survival (PFS) according to investigator criteria in relapsed ovarian cancer patients treated with trabectedin + pegylated liposomal doxorubicin (PLD) according to standard local clinical practice following approved Summary of Product Characteristics (SmPC) indication and dose, overall and by previous usage of antiangiogenic drug.

2.2 Secondary Objectives

The secondary objectives will be to determine the following based on real-life clinical data overall and by previous usage of antiangiogenic drug:

- Response rate (CR + PR) and DCR (CR + PR + SD)
- Overall survival (OS)
- Evolution of the patient's performance status (PS)
- Treatment duration and number of cycles, treatment exposure, and time to next treatment
- Safety of the combination of trabectedin + PLD.

3 METHODS

3.1 Study Design Overview

This will be a non-interventional, prospective, multicenter study in which trabectedin + PLD will be administered according to standard local clinical practice following approved SmPC indication and dose. There will be no involvement with any treatment decisions for the patients included in the study. The choice of therapy must be made prior to the patient's inclusion in the study. Treatment administration will be independent of, and dissociated from participation in the study.

For each patient, the study will consist of a Qualification Period (see Section 6.1), an Observation Period (see Section 6.2) and a Follow-up Period (see Section 6.3). Once treatment with trabectedin is discontinued, patients may be treated with subsequent anticancer therapies or supportive care as per the treating clinician's best clinical judgment. The study design is summarized in Appendix 14.1, Figure 1.

3.2 Estimated Duration of the Study

The study will begin with the enrollment of the first patient. The individual patient study duration will be up to 13 months (12-month Observation Period + 1-month Follow-up Period). Enrollment of patients in the study is expected to be completed within 36 months. This target however, is dependent upon the enrollment rate of each individual study center participating in the study. If the targeted enrollment rate of each individual site participating in the study is lower than expected, additional sites may be added.

The total duration of the study will be 49 months, including the 36-month enrollment period and the 13-month study duration of the last patient enrolled in the study.

The planned study periods are as follows:

- Entire study period: September 2014-January 2020
- First patient in: July 2015
- Last patient in: 31 July 2018
- Last patient last visit: August 2019

Given the variation of clinical practice not only across, but also within countries, a good geographical representation of patients with relapsed ovarian cancer will be attempted by targeting study centers spread across the regions of each of the countries. This variation in clinical practices will contribute to more representative results for each country.

4 STUDY POPULATION

4.1 General Considerations

The study population will include patients with platinum-sensitive relapsed ovarian cancer who are receiving trabectedin + PLD according to standard local clinical practice following approved SmPC indication and dose.

To be enrolled in this study, the patients must meet all inclusion criteria and have none of the exclusion criteria.

4.2 Number of Patients

At least 300 patients will be selected across approximately 70 European sites. Study sites will be located in Germany, Italy, Spain, France, and Belgium.

4.3 Selection Criteria

If patients meet the selection criteria, they will be invited to participate in the study. Before any study-specific data are recorded, patients will be provided with all the study details prior to their decision to participate and will be requested to sign an informed consent form (ICF) prior to their participation in the study.

4.3.1 Selection Criteria

Patients must comply with all of the following criteria in order to be enrolled into the study:

- Patients must be aged 18 years or older.
- Patients must have platinum-sensitive relapsed ovarian cancer, defined as disease relapse that occurs 6 months or more after completion of last platinum-containing therapy.
- Treatment indication according to local label SmPC and reimbursement for trabectedin and PLD treatment.
- Patients must have received a minimum of 1 cycle of trabectedin + PLD before their inclusion in the study.
- Patients must have signed an informed consent document indicating that they understand the purpose and procedures required for the study and are willing to participate in the study.

4.3.2 Failure of Patient Enrollment

The reason(s) for not enrolling a patient in the study (patient declined, no reply, patient not fulfilling the selection criteria) will be recorded in a patient qualification log at each site. This will enable subsequent assessment of potential selection bias necessary for quality assurance of the data collected.

4.4 Discontinuation Criteria

4.4.1 Patient Discontinuation

Patients are free to discontinue the anticancer treatment at any time. Discontinuation of anti-cancer treatment is not considered a study discontinuation and treating clinicians are encouraged to follow the patient as long as possible. Whenever feasible, patients will be followed until death or until end of study.

Patients may request discontinuation from the study at any time. The date and the reason for withdrawal or discontinuation must be recorded in the electronic Case Report Form (eCRF).

4.4.2 Study Discontinuation

The Sponsor has the right to terminate the participation of either an individual site or the study at any time. Reasons for terminating an individual site or the study include, but are not limited to the following:

- Treating clinician does not adhere to the protocol or applicable regulatory guidelines in conducting the study.

5 STUDY MEDICATION AND TREATMENTS

This is a non-interventional, prospective study and no study medication will be provided as part of the study.

5.1 Study Drugs

Trabectedin is administered every 3 weeks as a 3-hour infusion at a dose of 1.1 mg/m^2, immediately after PLD 30 mg/m^2 (see also the SmPC for specific administration advice). To minimize the risk of PLD infusion reactions, PLD infusion should be in accordance with the SmPC. Any dose modifications and/or change in dosing interval should be in accordance with the SmPC and the treating clinician's best clinical judgment.

5.1.1 Duration of Treatment

There is no predefined limit as to the number of cycles of treatment with trabectedin. Treatment may continue as long as the treating physician feels there is benefit, even in the presence of apparent disease progression.

5.1.2 Storage, Dispensing, and Reconciliation of Study Drug

Detailed information on dosing, preparation, handling, storage, and disposal of trabectedin may be found in the SmPC.

5.1.3 Warnings and Precautions

Detailed information regarding warnings and precautions for trabectedin may be found in the SmPC.

5.2 Concomitant Medication

Patients will be allowed to continue with any concomitant medication throughout the duration of this study in accordance with the SmPC and the treating clinician's best clinical judgment.

5.3 Other Treatments

5.3.1 Medical Care

Standard of care will be provided to patients as per their treating clinician's best clinical judgment.

5.3.2 Pre-Existing Medical Conditions

Treatment of any pre-existing medical conditions will be provided according to the SmPC and the treating clinician's best clinical judgment.

5.3.3 Treatment of Emergent Adverse Drug Reaction

Treatment of any emergent adverse drug reaction (ADR) will be provided according to the SmPC and the treating clinician's best clinical judgment.

5.3.4 Laboratory Abnormalities

According to the SmPC and the treating clinician's best clinical judgment, all laboratory tests associated with ADRs and serious adverse drug reactions (SADRs) will be assessed and any necessary medical intervention provided. When available, these will be collected on electronic case report forms (eCRFs).

6 STUDY PROCEDURES

This is a non-interventional study. Prior to the initiation of the qualification process or any study procedures, patients must sign an ICF indicating that they understand the purpose and procedures required for the study and that they are willing to participate in the study. The ICF must be signed 1 or more days following completion of the initial trabectedin + PLD administration (1st treatment cycle). The Study Schedule of Events is noted in Table 1 and Appendix 14.1, Figure 1.

6.1 Qualification Period

The patient's inclusion/exclusion criteria will be evaluated before the patient signs the ICF. The Qualification Period will begin following the signing of the ICF and end with the first on-study trabectedin + PLD administration cycle.

The first on-study trabectedin + PLD administration must follow, but may be on the same day as the signing of the ICF and the evaluation of the patient's inclusion/exclusion criteria

6.2 Observation Period

The Observation Period will begin with the first trabectedin + PLD dose administered after the signing of the ICF and will continue for up to a total of 12 months after that or until trabectedin treatment discontinuation, patient discontinuation for any reason or patient's death. PLD discontinuation is not a reason for Observation Period discontinuation. There are no predefined limits to the number of cycles administered. Trabectedin + PLD treatment can continue at the treating clinician's discretion.

Methods and timing of the imaging procedures will be determined by the treating clinician.

6.2.1 First Study Visit

On the first day of the Observation Period (Index Date) the following data, if available, will be collected:

1. Medical history including baseline imaging evaluation. The patient's baseline tumor imaging evaluation will be the last available imaging evaluation performed prior to the initial trabectedin + PLD administration (1st treatment cycle) or the earliest imaging study following the 1st treatment cycle.

2. Complete physical examination (including weight, height, and body surface area [BSA]).

3. Evaluation of performance status using ECOG /World Health Organization (WHO) PS score (Appendix 14.2 Table 2).

4. Date of first trabectedin + PLD administration.

5. Any previous cycles of trabectedin + PLD therapy. If patient enrollment occurs after the second administration of trabectedin + PLD or later, all information should also be retrospectively collected from the time of first administration, when available.

6. Symptomatic response and overall tumor response will be collected for each cycle of treatment with trabectedin + PLD, starting with cycle 2 (except for patients with confirmed progression of disease (PD) at discontinuation or who had started a new treatment). The preferred method to measure overall response is Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as it is the generally accepted standard criteria; however other criteria used by the investigators will be accepted.

7. Safety assessment (all AEs including ADRs and SADRs) at the visit.

8. Laboratory tests will be collected when available and based on the treating clinician's usual practice procedures. Laboratory tests associated with ADRs and SADRs will be collected when available (at the visit and/or any prior cycles of trabectedin +PLD).

9. Description of prior anticancer therapy, including nature of the prior systemic treatment, previous lines of therapy, date of first and last cycles of prior treatment, best response and/or date of progression with prior treatment.

10. BRCA-1/2 status.

Even though baseline data will be collected when patient is under treatment with trabectedin + PLD, it corresponds to data prior to treatment initiation.

6.2.2 Subsequent Visits during Observation Period

Subsequent visits will occur at the treating clinician's typical schedule. On each subsequent visit during the Observation Period, the following data, if available, will be collected:

1. Complete physical examination (including weight, height, and BSA).

2. Evaluation of performance status using ECOG/WHO PS score.

3. Safety assessment (all AEs including ADRs and SADRs).

4. Imaging procedures and results of imaging response evaluations will be collected, if they are available, during each cycle of the Observation Period of the study. Symptomatic response will also be collected.

5. Laboratory tests will be collected when available and based on the treating clinician's usual practice procedures. When available, those laboratory tests associated with ADRs and SADRs will be collected.

6. Data on trabectedin + PLD treatment administration.

6.3 Follow-up Period

A follow-up visit will take place 1 month after the end of the Observation Period. For patients who discontinued trabectedin before 12 months after the Index date, an additional follow-up visit will be performed 12 months after the Index date, except for patients who are dead or have withdrawn consent. Follow-up information may be collected through phone calls with the patient or site visits by the patient.

For each follow-up visit, the following data will be collected, if available:

- Safety assessment (all AEs including ADRs and SADRs). Laboratory tests associated with ADRs and SADRs will be collected when available.

- Reason for discontinuation of treatment with chemotherapy, if applicable. Reason will include the following: treatment completed, PD, toxicity including grade, patient refusal, patient lost to follow-up, withdrawal of consent, inter-current illness of sufficient severity (specify), withdrawal for pregnancy, death (specify the cause), or other (specify).

- Best symptomatic response and best response (except for patients with confirmed PD at discontinuation or who had started a new treatment) and evaluation of treatment duration.
- Survival status.
- Subsequent non-trabectedin anti-cancer treatments that the patient received during the follow-up period, including regimen number, type of therapy, start and stop date, and best response observed for each regimen.

6.4 Study Drug Treatment Procedures

As per the primary objective of the study, patients may or may not have been pretreated with an antiangiogenic regimen. No pretreatment procedures will be specified for this non-interventional study.

Patients will continue to be managed by their treating clinician without any additional instructions. No additional treatment procedures will be undertaken during patient visits.

6.5 Clinical Laboratory Procedures

Any laboratory tests necessary to diagnosis and/or monitor the patient's condition will be performed at the discretion of the treating clinician. Laboratory test results associated with ADRs or SADRs will be collected for the study when available.

7 STUDY ASSESSMENTS

Observations and measurements collected, if available, during each study cycle are described in Table 1 located below and in Appendix 14.1, Figure 1.

Table 1. Study Schedule of Events

Assessment/Activity	Qualification Period		Observation Period		Follow-up Period
	Patient Qualification	ICF Signature Date	Baseline and Cycle 1 Visit	Subsequent Visits	
Review of inclusion/exclusion criteria	X[1]				
Signed Informed Consent Form (ICF)		X			
Medical history			X[2]		
Prior therapies			X		
Initial imaging			X[3]		
Physical examination (BSA, weight, and height)			X	X[4]	
Performance status (ECOG/WHO score)			X	X[4]	
Date of first trabectedin + PLD administration			X[5]		
Prior trabectedin + PLD therapy			X		
Safety assessment (AEs including ADRs and SADRs)			X	X[4]	X
Laboratory tests			X	X[4]	X[6]
Reporting of symptomatic and best response			X[8]	X[4]	X
Additional imaging[7]			X	X[4]	X[7]
Reason for ending treatment with trabectedin + PLD			X	X	
Survival status			X	X	X

Abbreviations: ADRs, adverse drug reactions; AE, Adverse Event; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; SADRs, serious adverse drug reactions; WHO, World Health Organization.

[1]Information must be collected prior to first on-study trabectedin administration (Cycle 2 or later) but may occur on the same day.

[2]This includes relevant prior history, the description of key features of the disease and disease histology.

[3]The patient's baseline tumor imaging assessment will be considered the imaging assessment performed prior to the initial trabectedin + PLD administration (1st treatment cycle) or the earliest imaging study following the 1st treatment cycle.

[4]Repeat at the treating clinician's typical schedule.

[5]If patient enrollment occurs after the second administration of trabectedin + PLD or later, information on physical examination (BSA) and performance status should also be collected for Cycle 1 trabectedin + PLD administration, when available.

[6]Safety assessments include laboratory tests associated with ADRs and SADRs and will be collected when available.

[7]The final imaging assessment will be the imaging assessment performed closest to the Follow-up Visit and prior to initiation of any other chemotherapy treatments.

[8]Collected from cycle 2 and onward.

8 SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Event (AE)

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product that does not necessarily have a causal relationship with treatment [Directive 2001/20/EC Art 2(m)]. An adverse event can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is considered related to the medicinal product.

8.1.2 Serious Adverse Event (SAE)

An adverse event is SERIOUS when the event fulfills 1 of the following criteria:

- Results in DEATH
- Is LIFE-THREATENING (see clarification below)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant DISABILITY or INCAPACITY
- Is a CONGENITAL ANOMALY or BIRTH DEFECT [Directive 2001/83/EC Art 1(12)]
- Is MEDICALLY SIGNIFICANT (see clarification below)
- Is a suspected transmission via a medicinal product of an infectious agent

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see Annex IV, ICH-E2D Guideline).

For medically significant criteria, medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the initial admission, as determined by the investigator or treating physician.

8.1.3 Adverse Drug Reaction (ADR)

An ADR is defined as a response to a medicinal product that is noxious and unintended [Directive 2001/83/EC Art 1(11)]. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (see Annex IV, ICH-E2A Guideline).

ADRs may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure [Directive 2001/83/EC Art 101(1)]. Conditions of use outside the Marketing Authorization include off-label use, overdose, misuse, abuse and medication errors.

For the purpose of this study, an ADR is defined as any undesirable medical occurrence (sign, symptoms, or diagnosis) or worsening of a pre-existing medical condition that occurs after initiation of trabectedin that the treating clinician considers to be associated with the use of trabectedin.

8.1.4 Serious Adverse Drug Reaction (SADR)

An adverse reaction is SERIOUS when the event is considered related to the drug and also fulfills 1 of the criteria described in section 8.1.2.

8.1.5 Misuse of a Medicinal Product

Misuse of a medicinal product is defined as any situation where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.

8.1.6 Occupational Exposure to a Medicinal Product

For the purpose of reporting cases of suspected adverse reactions, is an exposure to a medicinal product as a result of one's professional or non-professional occupation.

8.1.7 Off-label Use

Off-label use is defined as any situation where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.

8.1.8 Overdose

Administration of a quantity of a medicinal product given per administration or cumulatively that is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.

8.1.9 Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects [Directive Art 1].

8.1.10 Lack of Efficacy/Effect

Evidence of less than the expected effect of a product (Online Medical dictionnary for regulatoy activities; Whetzel et al, Epub 2011).

8.1.11 Medication Error

Medication error refers to any unintentional error in the prescribing, dispensing, administration [including preparation for administration] or monitoring of a medicinal product while in control of the healthcare professional, patient or consumer.

8.2 Collection and Reporting of Safety Information for Study Investigators

A solicited reporting system of all Adverse Events (serious and non-serious, related and not-related) will be used during this study, from the beginning of trabectedin + PLD treatment. Whenever possible the investigator will record the diagnosis instead of the signs and symptoms.

To properly classify each adverse event, the treating physician should assess seriousness, causal relationship to study drugs (trabectedin + PLD), and severity (grade).

Seriousness assessment will take into account criteria described in Section 8.1.2.

The investigators must provide an assessment of the causal relationship for all AEs with the study treatment according to the following scale:

- Related (Y): there is a reasonable possibility that the study treatment caused the AE (i.e., an ADR).
- Not related (N): there is no reasonable possibility that the study treatment caused the AE and other causes are more probable.
- Unknown (Unk): Only to be used in exceptional situations where the investigator has insufficient information (i.e., the patient was not seen at his/her center) and if none of the above can be used

The grade will be assessed by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE Version 4.0) in force at time of study database development. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guide:

- Grade 1 = mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 = moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[1]
- Grade 3 = severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2]
- Grade 4 = life-threatening consequences; urgent intervention indicated
- Grade 5 = death related to AE

[1] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[2] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.2.1 Reporting of Safety Information to Pharmacovigilance Department

The investigators will notify to PharmaMar Pharmacovigilance Department:

1. ALL serious ADRs (SADRs). For the other drugs the reporting will be performed by the investigator to the applicable Marketing Authorization Holder (MAH). When possible, diagnosis should be reported instead of the signs and symptoms.
2. ALL SPECIAL SITUATIONS included below, leading or not to an ADR (serious or non-serious):

- Use during pregnancy or breastfeeding
- Lack of efficacy
- Overdose
- Misuse
- Medication errors
- Off-label use
- Abuse
- Occupational exposure

The information will be reported immediately by the investigator and always **within 24 hours** of awareness on the electronically available PharmaMar´s "**Adverse Event Report form**" or the "**Pregnancy form for spontaneous and non-interventional studies**". The forms should be reported in English to the PharmaMar Pharmacovigilance Department by e-mail (phv@pharmamar.com) and a copy sent to the Mapi site monitor.

In the case that electronic reporting is not possible, a paper "**Adverse Event Report form**" and "**Pregnancy form for spontaneous and non-interventional studies**" will be handed out at the beginning of the non-interventional study and remain at doctors' disposal at the investigator's file for notification by conventional fax (PharmaMar **fax number: 00 34 91 846 6004**) or e-mail (phv@pharmamar.com).

Additional information have to be provided when PharmaMar Pharmacovigilance Department request it and also if new significant information on the case is available. This additional information should always be provided in a serious adverse event (SAE) form ("follow-up" field of the SAE form should be ticked).

8.2.1.1 Pregnancy Reporting

No sufficient clinical data on exposed pregnancies are available. However, based on its known mechanism of action, trabectedin may cause serious birth defects when administered during pregnancy. Trabectedin should not be used during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the fetus and be monitored carefully. If trabectedin is used at the end of pregnancy, potential adverse reactions should be monitored carefully in the newborns.

To ensure patient safety, each pregnancy in a female patient or in a female partner of a male subject diagnosed during the Observation Period or within 6 months after last trabectedin administration must be reported to the sponsor within 24 hours of learning of its occurrence.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital

abnormalities, or maternal and/or new-born complications. The new-born will be followed at least up to 1 year after the delivery.

8.2.1.2 Exemptions from Reporting

The event of "disease progression" and events due to "disease progression", even though these fulfill any seriousness criterion (i.e., fatal, requiring hospitalization, etc.), are exempted from reporting to PharmaMar Pharmacovigilance Department and will only be collected in the applicable CRF page. Death, as such, is the outcome of an ADR and should not be reported as the ADR itself. Instead the cause of death should be recorded as the ADR term.

Hospitalizations that do not meet criteria for SADR reporting are:

- Hospitalization or prolonged hospitalization for technical, practical or social reasons, in absence of an AE.
- Pre-planned hospitalizations: Any pre-planned surgery or procedure must be documented in the source documentation. Only if the pre-planned surgery needs to be performed earlier due to a worsening of the condition, should this event (worsened condition) be reported as a SADR.
- An emergency visit due to an accident where the patient is treated and discharged.
- When the patient is held 24 hours for observation and finally is not admitted.
- Planned treatments at sites not associated to a hospital and generally considered as minor surgical procedures (i.e., laser eye surgery, arthroscopy, etc.).

8.2.2 Collection of Safety Information in the eCRF

The investigators are responsible for ensuring that all AEs (serious and non-serious, related and not-related) that occur after first dose of trabectedin until 30 days after last dose administered are reported using the applicable eCRF page within 15 calendar days from its knowledge. Beyond this period of time, only ADRs suspected to be related to trabectedin will be reported to the PharmaMar Pharmacovigilance Department.

All SADR with the study treatment must be followed after discontinuation until the event or its sequelae resolve or stabilize at an acceptable level to the treating physician.

Non-serious ADRs also will be collected in the pharmacovigilance database. The non-serious ADR will be retrieved by the Contract Research Organization (CRO) from the CRF and will be provided in a line listing on a monthly basis.

8.3 Reporting to the Competent Regulatory Authorities

PharmaMar is responsible for all applicable reporting and notifications to the competent Regulatory Authorities, if required.

9 DATA MANAGEMENT

9.1 Data Collection

The CRO (Mapi) will be required to have a web-based electronic data capture (EDC) system and provide an integrated, transparent tool to facilitate subject selection and study progress at country, center and subject level. The EDC system will include eCRFs, which will be developed by the CRO in conjunction with the Sponsor to allow the capture of all study data. Local center staff will be trained to enter study data into the eCRFs. Paper CRFs will not be provided. Alternatively, CRO staff could perform this function, subject to any additional informed consent, patient confidentiality, and data protection requirements.

The study will be monitored by monthly telephone calls to the treating clinicians and on-site visits (if required) by the clinical study monitor from the CRO. During the telephone calls the monitor will discuss study status as well as any potential problems with data completeness or practical study conduct.

9.1.1 Data Monitoring

All data entered into the EDC system by site study staff will be pseudonymized to ensure patient confidentiality and compliance with country ethical and data regulations. No patient-identifying information will be available to the Sponsor or the CRO. There will be no formal source data verification. However, the structure and programming of the EDC system will permit remote monitoring of the pseudonymized data by the Sponsor or the CRO as the study data accrue in real time, allowing data queries to be raised with sites.

Where feasible, given the limitations of non-interventional data collection, queries will be reconciled prior to database acceptance. Data will be clarified with the sites by phone, fax, email or completion of data clarification and/or quality control reconciliation forms. All queries and their reconciliations will be documented and an audit trail of any changes will be kept on file. Sites with high query rates will be identified and provided additional training. A quality control plan will be documented prior to the go-live date.

9.2 Site Monitoring

During the site visit, the study monitor should review source documents (including original patient records) and document retention (study file). Additionally, the monitor will discuss any problem with the treating clinicians.

Adequate time for these visits should be allocated by the treating clinicians. The treating clinicians should also ensure that the monitor is given direct access to source documents (i.e., hospital or private charts, original laboratory records, appointment books, etc.) of the patient, which support data recorded on eCRFs.

9.3 Data Quality Assurance

Systems with procedures will be implemented to ensure the quality of every aspect of the study.

The CRO maintains high data quality standards and utilizes processes and procedures to repeatedly ensure that the data are as clean and as accurate as possible when presented for analysis. Data quality is enhanced through a series of programmed data quality checks that automatically detect and prevent the entry of out-

of-range or anomalous data. A remote data quality audit will be performed at various times throughout the study on collected data.

9.4 Site Inspection

During the course of the study, the Quality Assurance Department of the Sponsor or external auditors contracted by the Sponsor may conduct an on-site audit visit.

Participation in this study implies acceptance of potential inspection by national or foreign health authorities.

9.5 Database Quality Assurance and Data Protection

The EDC system meets approved established standards for the security of health information and is validated. The system also meets the International Conference on Harmonization (ICH; http://www.ich.org) guideline E6R1 regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained.

Access to the EDC system will be controlled via a hierarchical user-name and password control. Subject data will be pseudonymized through design of data entry fields that do not permit the entry of identifying information such as initials, date of birth, or center-assigned patient identifiers. Site staff only will enter data into eCRFs. Subject's ages in whole years, but not date of birth, will be entered. No patient identifiers used by centers will be entered; rather the EDC program will automatically assign a study identification number (ID) to each case. The pseudonymized data as entered into the EDC system will be visible to the CRO and the Sponsor, but only center staff will be able to trace a case ID back to a patient identity, a necessary measure to allow center staff to respond to data queries raised by the CRO later. Detailed explanation of data protection and patient confidentiality measures will be included in each application for local ethics approval. Where necessary, these will include country-specific measures.

9.6 Data Retention

All treating clinician's completed forms, original ICFs, and essential documents will be maintained at the study site according to pertinent regulations.

10 STATISTICAL ANALYSIS

10.1 Sample Size/Power Considerations

At least 300 patients are to be selected. With this number it is judged that PFS after treatment with trabectedin + PLD will be estimated with sufficient accuracy.

10.2 Interim Analysis

An interim analysis after 50% (i.e., ~150 patients) of the recruitment will be performed in order to obtain a first approach of the results.

10.3 Study Endpoints

The primary endpoint is the PFS measured as time from first dose of trabectedin to disease progression as reported by the investigator or death regardless of cause.

The secondary endpoints include the following:

1. Response rate (CR + PR)
2. Disease control rate (CR + PR + SD)
3. OS
4. ECOG/WHO PS
5. Treatment duration (number of cycles)
6. Treatment exposure
7. Time to next treatment
8. Safety of the combination of trabectedin + PLD

10.4 Data Analysis

All analyses will be based on the full analysis set (FAS), consisting of all the patients enrolled into the study and who have at least one administration of trabectedin. The FAS will be the primary analysis set for the safety analyses and for analyses assessing effectiveness. All endpoints will be summarized overall and by prior antiangiogenic drug usage.

Frequency tables will be prepared for categorical variables. Continuous variables will be described by median, mean, standard deviation, minimum and maximum.

For the analyses of time-to-event data, methods that take into account censored observations will be used (Kaplan-Meier estimates). Non-informative censoring will be assumed.

10.4.1 Disposition

Number and percentage of patients enrolled, reasons for non-participation in the study, patient disposition over the course of the study, inclusion/exclusion criteria, the number of patients included in the FAS, number of trabectedin cycles received before ICF was signed, reasons for treatment discontinuation and

for not completing the study will be summarized. In addition survival status at end of study, number of deaths including cause of death will also be presented.

10.4.2 Analysis of Baseline and Demographic Data

Descriptive statistics will be presented for the information specified and will include the following:

1. Relevant prior patient history and general patient characteristics (age, gender, disease status, co-morbidity).
2. Clinical evaluation.

10.4.3 Analysis of the Primary Endpoint

PFS and their fixed-time estimations will be analyzed using the Kaplan-Meier (KM) method. KM estimates and 95% CIs will be calculated based on estimated variance for log-log transformation of the estimate.

10.4.4 Analysis of Secondary Endpoints

Response

Response rate will be summarized. Response is defined as a best tumor response of complete or partial response as reported by the investigator. Patients without an assessment of disease response will be treated as non-responders. Descriptive statistics will be provided for best overall tumor response and response rate (CR + PR) and two-sided exact binomial 95% confidence intervals will be presented.

Disease Control

It is defined as a best tumor response assessment of CR, PR, or SD. Patients without a post-baseline tumor disease assessment will be considered to not have disease control. The disease control rate will be presented along with two-sided exact binomial 95% confidence intervals.

Overall Survival

OS will be descriptively analyzed as done for the primary endpoint PFS.

ECOG

ECOG/WHO performance status scores will be summarized at baseline, worst/best scores under treatment, and scores at end of treatment. The change in scores from baseline to best/worst and end of treatment scores will also be summarized presenting categories: <0 (indicating an improvement), 0-2, >2-4, and >4 (indicating worst deterioration).

Treatment Exposure

Trabectedin and PLD administration history will be summarized presenting the number of previous cycles received prior to IC. Descriptive statistics will be calculated for total number of cycles started, administration setting (inpatient/ outpatient), administered dose per infusion (mg), cycle duration (days), and treatment duration. Cumulative dose administered, dose intensity (mg) / week, relative weekly dose intensity (%), and total dose administered (mg) per cycles will also be presented. The number and percentage of patients with modifications (including dose missed, reductions, dose delays, or doses withheld) from the investigator reported schedule will be summarized by type of dose modification and

reason for the dose modification. The number of dose missed/reductions/interruptions/delays per patient will also be summarized.

Subsequent Anti-Cancer Treatment

Exposure to subsequent anticancer drugs will be described. Time from last dose of trabectedin, type of therapy, setting (single, combo), number of cycles, and best response will be described by regimen number, including number and percentage of patients in each regimen.

10.4.5 Safety Analysis

Descriptive summaries presenting all AEs (serious and non-serious, related and not related) reported from Day 1 of study treatment to 30 days post last dose of study treatment. Patient incidence of adverse drug reactions related to trabectedin and related to PLD, respectively, will be summarized by system organ class, preferred term and severity grade for all drug reactions and serious drug reactions. The corresponding summaries will also be presented for ADRs and SADRs grade 3 or higher.

10.4.6 Other Data

The number and percentage of patients with clinically significant laboratory results, symptomatic response, concomitant medications, physical examination, and exposure to subsequent surgery will also be summarized.

10.4.7 Pharmacokinetic / Pharmacodynamic Analysis

No pharmacokinetic or pharmacodynamic evaluations are planned.

11 ETHICAL, ADMINISTRATIVE, AND REGULATORY REQUIREMENTS

This study will comply with ethical and regulatory requirements for each participating country.

11.1 Conduct of Study

This study will comply with the definition of the non-interventional study provided in Article 2(c) of Directive 2001/20/EC and the Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (EMA/876333/2011) and GVP Module VI (EMA/873138/2011).

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki (located at http://www.wma.net/en/30publications/10policies/b3/) and will be consistent with the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences [CIOMS], 2002; located at http://www.cioms.ch/publications/layout_guide2002.pdf) and the Good Clinical Practices (GCP; located at http://www.emea.europa.eu) guidelines. The study will also follow the International Society of Pharmacoepidemiology, Guidelines for Good Pharmacoepidemiology Practices (2008), the International Ethical Guidelines for Epidemiological Studies (CIOMS, 2009), as well as all other applicable regulatory requirements.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s).

11.2 Patient Information and Informed Consent

The rights, safety, and well-being of the trial patients are the most important considerations and should prevail over interests of science and society.

The Patient Information Sheet will include all elements required according to the GCP guidelines and applicable regulatory requirements.

The treating clinicians or their designee must provide the patients with a copy of the consent form and written full information about the study in a language that is non-technical and easily understood. The treating clinicians should allow enough time for the patients or their legally acceptable representative to inquire about the details of the study. Then, the ICF must be freely signed and personally dated by the patients and by the person who conducted the informed consent discussion before the beginning of the study. The patients should receive a copy of the signed ICF and any other written information prior to participation in the trial.

During their participation in the trial, any updates to the consent form and to the written information have to be provided to the patients.

If a new consent needs to be obtained from the patients, the treating clinicians or their designee should inform the patient of any new information relevant to his/her willingness to continue participation in the study before obtaining the new written consent.

11.3 Confidentiality

The collection and processing of personal data from patients enrolled into this study will be limited to those data that are necessary to investigate the effectiveness, safety, quality, and utility of trabectedin or any other active treatment for ovarian cancer. It is the treating clinician's responsibility that sufficient information related to the identity of the patients will be retained. The clinical trial monitor, the Sponsor auditor, the EC or the regulatory authorities should have direct access to all requested trial-related records and should agree to keep the identity of study patients confidential.

The data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

Explicit consent for the processing of personal data will be obtained from the participating patients before collection of data, and such consent should also address the transfer of the data to other entities and to other countries.

The Sponsor will comply with Directive 95/46/EEC of the European Parliament and the Council dated 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data for all data collected before 25 May 2018. After this date, the Sponsor will comply with Regulation (EU) 2016/679 dated 27 April 2016, repealing Directive 95/46/EEC.

11.4 Ethics Committee Review

The protocol, any amendments, and the ICF will receive Independent Ethics Committee ([IEC] or Institutional Review Board [IRB] or Research Ethics Board [REB]) approval/favorable opinion prior to initiation of the study. Treating clinicians under the jurisdiction of a local IEC must obtain approval of the protocol, ICF, and patient enrollment materials prior to initiating the study at the site.

The CRO in charge of the study management will coordinate the submissions to the IECs and any other necessary authorities, as per international and local requirements.

The decision of the IEC concerning the conduct of the study will be made in writing to the treating clinicians. A copy of the IEC approval letter, IEC committee member roster, and the IEC approved ICF must be submitted to the Sponsor prior to initiating any study procedures at a site and retained in the site files.

The treating clinicians and/or the Sponsor is/are responsible for keeping the IEC informed of significant new information about study drug.

11.5 Protocol Adherence and Modifications

The study will be conducted in accordance with the current protocol or protocol amendments. All protocol and protocol amendments will be agreed upon by the Sponsor and the treating clinicians.

Amendments to the protocol may only be made by the Sponsor. All protocol amendments must be signed and dated by the treating clinicians, and submitted and approved by the IEC and any other local authority as necessary, prior to implementation of the amendment.

Administrative changes of the protocol are minor corrections and/or clarifications that have no impact on the way the study is to be conducted.

11.6 Records Retention

The treating clinicians must maintain all essential documents until notified by the Sponsor and in accordance with all local laws and regulations. The Sponsor and the CRO in charge of the study will follow their applicable standard operating procedures regarding retention of records.

11.7 Insurance

The Sponsor will provide insurance or indemnity in accordance with pertinent regulatory requirements.

11.8 Use of Study Information and Publications

Results of this clinical study will be disclosed by posting a summary online at www.clinicaltrialsregister.eu within 12 months of the last patient last visit.

Before the treating clinicians of this study submit a manuscript/paper or abstract for publication or otherwise publicly disclose information concerning trabectedin, the Sponsor must be provided with at least 60 days to review and approve the proposed publication or disclosure in order to ensure that confidential and proprietary data are protected. If the Sponsor determines that patentable matters are disclosed in the proposed, it shall be withheld for a period of time considered convenient. If the study is part of a multicenter study, publications of the study shall be prepared in conjunction with the treating clinicians and the institutions from all appropriate sites contributing data, analysis, and comments.

12 Investigator Agreement

I have read the foregoing protocol "*Non-interventional, multicenter, prospective, European study to analyze if the effectiveness of trabectedin + PLD in the treatment of relapsed ovarian cancer (ROC) patients regardless of previous use of an antiangiogenic drug*", Version 4 Amendment 2, dated 18 September 2018, and agree to abide by all provisions set forth therein.

I agree to comply with the ICH Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

1. Me (including, if applicable, my spouse [or legal partner,] and dependent children),
2. My sub-investigators (including, if applicable, their spouses [or legal partners], and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

_____

Investigator's name (block letters)

_____ _____

Investigator's signature Date (dd/mmm/yyyy)

13 References

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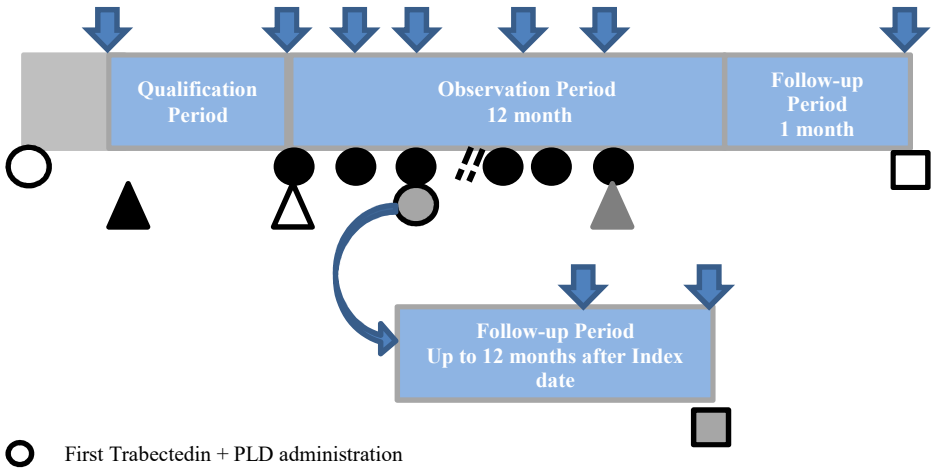
14 Appendices

Appendix 14.1	Study Period Design
Appendix 14.2	Performance Status
Appendix 14.3	Response Criteria: RECIST version 1.1

14.1 Appendix – Study Period Design

Figure 1: Study design schematic



First Trabectedin + PLD administration

Additional trabectedin + PLD administrations

Last trabectedin + PLD administration

Index Date (First administration of trabectedin + PLD while on study)

Informed consent signature

End of Observation Period (12 month s after index date, end of treatment with trabectedin, patient discontinuation for any reason, progression of disease (PD) or patient's death

End of Study - 13 months after Index date

End of Study - 12 months after Index date

1. The informed consent must be signed at least 1 day following completion of the first trabectedin + PLD administration.
2. There are no predetermined numbers of study cycles.
3. A study cycle will be determined according to trabectedin SmPC and treating physician's practice.
4. There may be additional trabectedin + PLD administrations following the first administration prior to signing the informed consent. Patients must have received a minimum of 1 cycle of trabectedin + PLD before their inclusion in the study.
5. The signing of the informed consent, screening, and index date (administration of the second or subsequent dose of trabectedin + PLD) may all be on the same day.
6. Final data collection for an individual patient will coincide with the study's last follow-up visit (at 13 months for a patient who completed the 12-month Observation Period or at 12 months for patients who had their last dose of trabectedin before the end of the 12-month Observation Period), or at the end of Observation Period for patients who died or who discontinued the study.

14.2 Appendix – Performance Status

Performance status evaluated according to the Eastern Cooperative Oncology Group (ECOG) score (also known as the World Health Organization [WHO] score) is shown in Table 2.

Table 2. ECOG Performance Status

Grade	ECOG Score Description*
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
* As published in American Journal of Clinical Oncology: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. Dec 1982;5(6):649-655.	

The ECOG Performance Status is in the public domain therefore available for public use. Credit is given to the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

14.3 Appendix – Response Criteria: RECIST Version 1.1