CLINICAL TRIAL PROTOCOL

- INOVATYON -

Phase III international, randomized study of Trabectedin plus Pegylated Liposomal Doxorubicin (PLD) versus Carboplatin plus PLD in patients with ovarian cancer progressing within 6-12 months of last platinum (ENGOT-ov5)

Protocol No.: ET-D-009-10
EudraCT: 2010-022949-17
Version n.1: UK ONLY: 16 September 2010 - Final Revised 25 October 2010_draft

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

Confidentiality Statement

The information and data included in this protocol contain trade secrets and privileged or confidential information which is the property of the Sponsor. No person is authorized to make it public without written permission of the Sponsor. These restrictions on disclosure will apply equally to all future information supplied to you which is indicated as privileged or confidential. This material may be disclosed to and used by your staff and associates as it may be necessary to conduct the clinical study.
<table>
<thead>
<tr>
<th>STUDY CONTACTS</th>
<th>NAME AND ADDRESS</th>
<th>PHONE AND FAX NUMBER AND E-MAIL ADDRESS</th>
</tr>
</thead>
</table>
| Principal Investigator | Nicoletta Colombo, MD  
Associate Professor  
Department of Surgery Science  
University of Milan “Bicocca”  
Director of Gynecology Unit  
Istituto Europeo di Oncologia  
Via Ripamonti, 435  
20141 Milan, Italy | Phone: +39 02-57489543  
Fax: +39 02-94379222  
E-mail: nicoletta.colombo@ieo.it |
| Study Coordinator   | Roldano Fossati, MD  
Department of Oncology  
Istituto Mario Negri  
Via La Masa, 19  
20156 Milan, Italy | Phone: +390239014467  
Fax: +390233200231  
E-mail: roldano.fossati@marionegri.it |
| Project Manager     | Elena Biagioli, Chem.Pharm.D.  
Department of Oncology  
Istituto Mario Negri  
Via La Masa, 19  
20156 Milan, Italy | Phone: +390239014650  
Fax: +390233200231  
E-mail: elena.biagioli@marionegri.it |
| Pharmacovigilance Contact | Marlen Llerena Mesa, Pharm.D.  
Department of Oncology  
Istituto Mario Negri  
Via La Masa, 19  
20156 Milan, Italy | Phone: +390239014638  
Fax: +390233200231  
E-mail: marlen.llerena@marionegri.it |
Department of Oncology  
Istituto Mario Negri  
Via La Masa, 19  
20156 Milan, Italy | Phone: +390239014695  
Fax: +390233200231  
E-mail: irene.floriani@marionegri.it |

Steering Committee’s members, AVERION CRO’s referents and the list of investigators are reported in the Operative Manual.
INVESTIGATOR AGREEMENT

Sponsor and author approval:
This clinical study protocol has been reviewed and approved by a sponsor representative, and the authors of sections pertaining chemotherapy and/or oncologic aspects listed below.

Roldano Fossati (Sponsor representative)  __________________________      ___________
Signature    Date

Nicoletta Colombo (Principal investigator)    __________________________      ___________
Signature    Date

Investigator signature:
I have read the contents of this protocol and agree to abide by all provisions set for therein. I agree to personally conduct or supervise this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki and with the International Conference on Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable Italian regulatory requirements. I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. I agree to make available to sponsor personnel, their representatives and relevant regulatory authorities, my subject’s study records in order to verify the data that I have entered into the case report forms.

__________________________________               __________________________         ___________
Print name  Signature        Data
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## SYNOPSIS

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<th>TITLE</th>
<th>Phase III international, randomized study of Trabectedin plus Pegylated Liposomal Doxorubicin (PLD) versus Carboplatin plus PLD in patients with relapsed ovarian cancer progressing within 6-12 months of last platinum</th>
</tr>
</thead>
</table>
| PROTOCOL NAME | IN-OVA-T-YON  
Refers to: INternational OVArian cancer patients Treated with YONdelis. |
| CODE NUMBER | ET-D-009-10 |
| INVESTIGATORS / TRIAL LOCATION | Prof. Dr. Nicoletta Colombo, IEO Milan, Italy and TBD / Italy, nicoletta.colombo@ieo.it  
Other EU countries |
| STUDY OBJECTIVES | **Primary:**  
- To demonstrate that the combination of trabectedin (Yondelis®) and pegylated liposomal doxorubicin (PLD) prolongs overall survival (OS) over carboplatin and PLD in patients with relapsed ovarian cancer progressing within 6-12 months after end of last platinum.  
**Secondary:**  
- To evaluate the time from randomization to subsequent chemotherapy and the overall survival counted from the administration of subsequent chemotherapy.  
- To evaluate serological response of CA-125 in each arm.  
- To compare the quality of life (QoL) in each arm using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 (QLQ-C30) and the Quality of Life Questionnaire-OV28 (QLQ-OV28).  
- To compare safety profile, progression free survival (PFS), objective response rate (ORR), the type and length of remission (response rate and PFS) after subsequent therapies following each of the two combinations.  
- Sub-study in selected centers: To perform pharmacokinetic (PK) analyses in both plasma and ascites in a subset of patients receiving trabectedin and PLD. |
| RATIONALE | The standard carboplatin and paclitaxel therapy for patients with advanced ovarian carcinoma relapsing after six months of previous platinum-based chemotherapy resulted from the ICON4/OVAR 2.2 trial (1), in which the addition of a taxane led to an extension of PFS and patient survival as compared to a conventional platinum-based chemotherapy, in patients with platinum-sensitive, recurrent ovarian cancer.  
Platinum re-administration is the most common option in patients with |
platinum-sensitive disease, with progression-free interval (PFI) of more than six months after the last date of platinum-based chemotherapy: it is standard in patients with PFI > 12 months, and frequently used in patients with partially platinum-sensitive disease with PFI 6-12 months. However, clinically significant sequelae such as hypersensitivity reactions (~20% of ovarian cancer patients) (2), residual neurotoxicity (~23%) (3) and other clinically significant sequelae are common, underscoring the need for an efficacious non-platinum regimen, particularly in the PFI 6-12 subset.

PLD is an active agent in second-line therapy for ovarian carcinoma. Gordon et al compared topotecan with PLD in a randomized phase III trial and demonstrated improved efficacy, favorable safety profile, and convenient dosing, supporting the regulatory approval of PLD in both platinum-resistant and platinum-sensitive recurrent ovarian cancer (4). Subsequently, PLD plus carboplatin was safe and induced a high response rate and possibly prolonged PFS in a phase II trial (5).

A recently reported large phase III trial (CALYPSO) comparing carboplatin + PLD vs. carboplatin + paclitaxel showed non inferior PFS results (hazard ratio [HR]: 0.82; median 11.3 months for carboplatin + PLD vs. 9.4 months for carboplatin + paclitaxel) (6, 7). Of note, in the PFI 6-12 month subset carboplatin + PLD achieved better PFS results (HR: 0.73; median: 9.4 vs. 8.8 months; p=0.004 [superiority]), suggesting improved benefits over standard carboplatin + paclitaxel chemotherapy although overall survival data are not yet available (8).

The recent phase III trial OVA-301 demonstrated that trabectedin + PLD significantly prolonged PFS over PLD alone, with a particularly enhanced benefit in the platinum-sensitive stratum (PFI > 6 months, n=430), where a median PFS of 9.2 months for the combination vs. 7.5 months for PLD was reported (9, 10). In the partially platinum-sensitive subset (PFI 6-12 months, n=214), trabectedin + PLD resulted in a 35% risk reduction of disease progression or death (HR=0.65; p=0.0152; median PFS 7.4 vs. 5.5 months). Interim overall survival (OS) data with 419 events (520 required for the final OS analysis) show a positive trend favoring the combination arm (HR: 0.85; p=0.09) in the overall population: median OS was 22.4 months in the trabectedin + PLD arm vs. 19.5 months with PLD. Patients with PFI > 6 months randomly assigned to the trabectedin combination had an 18% reduction in the risk of death (HR: 0.82) and a nearly three-month prolongation in median survival. In the PFI 6-12 subset, there was a significant 41% decrease in the risk of death (HR=0.59; p=0.0015; the median survival was 23.0 months in the trabectedin + PLD arm vs. 17.1 months in the PLD arm).

In OVA-301 study, similar proportions of patients received subsequent therapy in each arm (76% vs. 77%) (11). In the PFI 6-12 month cohort, subsequent platinum-based chemotherapy was delayed by a median of 1.9 months (HR=0.64; p=0.0167) favoring the trabectedin + PLD arm. Importantly, in these patients, OS counted from the administration of subsequent platinum was significantly extended, with a 37% reduction in the risk of death (HR=0.63; p=0.0357) and a 3.5 months longer median OS (13.3 months vs. 9.8 months) (11). Therefore, the OVA-301 data
support the hypothesis that extending the PFI may improve patient sensitivity to subsequent platinum (12). Hence, an effective non-platinum combination, such as trabectedin + PLD, may provide additional benefit in this subset.

Trabectedin safety profile is well characterized and relies on data in over 6000 patients from clinical trials and from an expanded access program, plus an increasingly large post-marketing experience since the initial approval in September 2007.

In the OVA-301 trial, the safety profile of the trabectedin + PLD combination compares favorably with that for established regimens and appears better than that with single-agent topotecan in this population (4, 10). Adverse events were consistent with those known for each single agent and no new or unexpected toxicities emerged. More frequent grade 3/4 neutropenia and transaminase elevations occurred, but these were generally transient, manageable and not associated with serious sequelae. Cumulative myelosuppression, cardiotoxicity, neurotoxicity, ototoxicity, hypersensitivity reactions and alopecia were not a concern. Overall, this therapy was well tolerated by the patients in the OVA-301 trial.

No decrement in QoL occurred in the trabectedin + PLD combination arm vs. PLD alone, as assessed by patient-reported outcomes (PRO) (13).

Regarding CALYPSO, carboplatin + paclitaxel was associated with more severe toxicities (carboplatin hypersensitivity, long-lasting neuropathy) and alopecia. On the other hand, moderate reversible palmar-plantar erythrodysesthesia, mucositis and nausea/vomiting were more frequent with carboplatin + PLD.

No data are available comparing trabectedin + PLD to a platinum-based regimen. Based on data from OVA-301 and CALYPSO the proposed INOVATYON trial will investigate the role of a non-platinum combination for the treatment of ovarian cancer patients relapsing between six and twelve (6-12) months after last platinum-based chemotherapy for whom there is need for new treatment options. Specifically, the present trial is aimed at demonstrating that extending the PFI with a non-platinum combination prolongs survival in patients with relapsed, partially platinum-sensitive ovarian cancer.

### PATIENT ELIGIBILITY

<table>
<thead>
<tr>
<th><strong>Inclusion criteria:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Female, aged ≥ 18 years</td>
</tr>
<tr>
<td>2. Histologically and/or cytologically proven epithelial ovarian, epithelial fallopian tube cancer or primary peritoneal cancer</td>
</tr>
<tr>
<td>3. Progression free interval between six and twelve (6-12) months (calculated from the first day of the last cycle of the last platinum-based chemotherapy until the date of progression confirmation through radiologic imagery). Patients may have received up to two platinum-based chemotherapy lines, of which at least one must have contained a taxane</td>
</tr>
<tr>
<td>4. Measurable or evaluable disease confirmed by radiological imaging, such as magnetic resonance imaging (MRI), computed tomography (CT) scan, or PET/CT scan at study entry (CA-125 rise not supported</td>
</tr>
</tbody>
</table>
by radiological evidence of disease is not accepted as criteria for defining progression) or histological proven recurrent ovarian cancer even in the absence of postoperatively measurable or evaluable lesions.

5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2

6. Estimated life expectancy ≥ 12 weeks

7. Patients must be accessible for treatment and follow-up

8. Adequate organ function within 14 days prior to first cycle as evidenced by:
   a. Peripheral blood counts and serum chemistry values:
      i. Hemoglobin ≥ 9 g/dl
      ii. Absolute neutrophil count (ANC) ≥ 1,500/μl
      iii. Platelet count ≥ 100,000/μl
      iv. Estimated glomerular filtration rate > 60 ml/min according to the Cockcroft-Gault formula
      v. Creatine phosphokinase (CPK) ≤ 2.5 x ULN
   b. Hepatic function variables:
      i. Total bilirubin ≤ ULN
      ii. Total alkaline phosphatase ≤ 2.5 ULN (consider hepatic isoenzymes 5-nucleotidase if the elevation could be osseous in origin)
      iii. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) must be ≤ 2.5 x ULN

9. Patients must be able to receive dexamethasone or its equivalent, which is required if randomly assigned to treatment with trabectedin plus PLD

10. Informed consent of the patient

Exclusion criteria:

1. Non epithelial ovarian or mixed epithelial/non epithelial tumors (e.g., Mullerian tumors)

2. Patients who did not respond to last platinum-based therapy or in whom last relapse occurred < 6 months or > 12 months from the last dose of platinum

3. Bowel obstruction, sub-occlusive disease or the presence of symptomatic brain metastases

4. Pre-existing grade > 1 motor or sensory neuropathy according to the National Cancer Institute Common Toxicity Criteria Adverse Event (NCI-CTCAE) version 4.0

5. Myocardial infarct within six months before enrolment, New York Association (NYHA) Class II or worse heart failure (Appendix 1. The New York Heart Association), uncontrolled angina, severe uncontrolled ventricular arrhythmias, clinically significant pericardial disease, or electrocardiographic evidence of acute ischemic or active conduction system abnormalities

6. History of liver disease

7. Concurrent severe medical problems or any unstable medical
condition unrelated to malignancy, which would significantly limit full compliance with the study or expose the patient to extreme risk or decreased life expectancy
8. Breastfeeding women and women of child bearing potential must use effective contraception during treatment and 3 months thereafter, which may include prescription contraceptives (oral, injection, or patch), intrauterine device, double-barrier method or male partner sterilization (not applicable to patients that are surgically sterile)
9. Prior exposure to trabectedin
10. Prior resistance to anthracyclines or PLD defined as a progression during anthracycline-based chemotherapy or a recurrence within 6 months from its ending
11. Prior severe PLD related toxicity
12. Prior exposure to cumulative doses of doxorubicin >400mg/m² or epirubicin >720mg/m²
13. Treatment with any investigational product within 30 days prior to inclusion in the study
14. Patients with known hypersensitivity to Trabectedin and any of its excipients or yellow fever vaccine
15. Patients with concurrent serious or uncontrolled infection
16. Patients in need of yellow fever vaccine while on study chemotherapy

**STUDY DESIGN**

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLD 30 mg/m² 1-hour i.v. + Carboplatin AUC 5 30-60 min i.v. on Day 1 q4w</td>
<td>PLD 30 mg/m² 1-hour i.v. + Trabectedin 1.1 mg/m² 3-hour i.v. on Day 1 q3w</td>
</tr>
<tr>
<td>Up to 6 Cycles or PD</td>
<td>Up to 6 Cycles or PD</td>
</tr>
</tbody>
</table>

At PD, subsequent therapy at Investigator discretion
At PD, subsequent platinum rechallenge is mandatory unless refused by the patient

*Stratification factors:*
- Center
- Line of ChT: 2nd/3rd
- Measurable disease: y/n
- Previous anthracyclines:y/n

*Ratios 1:1*

**Schedule of evaluations by study period**

Patients will be evaluated at scheduled visits in three study periods:
**Pretreatment:** from signature of informed consent to first study drug
infusion.

**Treatment:** from first study drug infusion to 30 days after last dose of study drugs, unless the patient dies or starts subsequent anticancer therapy outside this clinical trial (in which case the date of death or the date of administration of such subsequent therapy will be considered the date of treatment discontinuation). An end-of-treatment visit will be performed within 30 days after last dose administration.

**Follow-up:** after treatment discontinuation, patients will be followed every 12 weeks during the first two years and every six months thereafter. Subsequent therapies and disease evaluations will be recorded in the electronic case report form (eCRF) until death or until the date of study termination, whichever occurs first. For the evaluation of OS, after disease assessments living patients will be followed up to the date of death or the date of last contact.

Patients will be considered to be **on-study** from the date of signature of the informed consent to the end of the follow-up period. Patients will be considered to be **on-treatment** for the duration of the study drug treatment and until treatment discontinuation. **Treatment discontinuation** will be defined as 30 days after the last dose of the study drug administration, unless the patient dies or starts subsequent anticancer therapy outside this clinical trial, in which case the date of death or the date of administration of such new therapy will be considered as date of treatment discontinuation.

Patients will receive the study medications up to six cycles or PD, however if it is considered to be in their best interest treatment will continue until:
- Six cycles of treatment, although patients with clinical benefit may continue therapy beyond Cycle 6.
- Disease progression.
- Unacceptable toxicity.
- Intercurrent illness of sufficient severity to preclude a safe continuation of the study.
- Patient refusal and/or non compliance with study requirements.

### STUDY POPULATION

Patients with advanced ovarian cancer with recurrence or progression between six and twelve (6-12) months after end of first or second line platinum-based regimen, of which at least one must have contained a taxane.

### No. of patients

Approximately 588 patients will be enrolled in this trial (see Statistical Methods).

### STUDY DRUG Formulation

**Group A:** Carboplatin + PLD  
PLD 30 mg/m² followed by carboplatin area under the curve (AUC) 5. Carboplatin AUC dose will be calculated according to the Calvert’s formula (14): Dose (mg) = target AUC x (glomerular filtration rates [GFR] + 25) (15).  
**Group B:** Trabectedin + PLD  
PLD 30 mg/m² infusion followed by trabectedin 1.1 mg/m² infusion.
Trabectedin should be diluted in normal saline according to the preparation guidelines.

<table>
<thead>
<tr>
<th>Treatment schedule and route of administration</th>
<th>Group A: PLD 30 mg/m² intravenous (i.v.) as a 1-hour infusion followed by carboplatin AUC 5 i.v. as a 30-min infusion on Day 1 every four weeks up to six cycles or until progressive disease (PD), whichever occurs first. A 4-week schedule defines a cycle of treatment in this group. Group B: PLD 30 mg/m² i.v. infusion immediately followed by trabectedin 1.1 mg/m² as a 3-hour continuous i.v. infusion on Day 1 every three weeks up to six cycles or until PD, whichever occurs first. The use of central venous access is strongly recommended. A 3-week schedule defines a cycle of treatment in this group. Patients with clinical benefit from either group may continue therapy beyond Cycle 6.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria for treatment continuation</td>
<td>In order to be re-treated on Day 1 of a new cycle, patients will have to fulfill the same entry criteria (see inclusion criterion 8). If these criteria are not met on Day 1 of a new cycle, treatment administration may be delayed for a maximum of two weeks in Group A and three weeks in Group B and reevaluated weekly. The new cycle will start upon recovery of these parameters, according to the same criteria. A maximum delay of two weeks in Group A and three weeks in group B is allowed for recovery from drug-related AEs. If toxicities have not recovered within the allowed timeframe, the patient should discontinue treatment. In the event of obvious clinical benefit, the patient may remain on treatment upon agreement with the Sponsor, provided that all parameters have recovered according to the aforementioned criteria.</td>
</tr>
<tr>
<td>Concomitant therapies</td>
<td>Oral ketoconazole, fluconazole, ritonavir, clarithromycin, aprepitant, co-administered with trabectedin, should be used with caution. If such combinations are needed, close monitoring of toxicities is required. Inhibitors of P-gp, e.g. cyclosporine and verapamil should be administered as concomitant therapies only with extreme caution. Combination of trabectedin with phenytoin or live attenuated vaccines are not recommended. Caution with concomitant administration of medicinal products associated with rhabdomyolysis. The use of medicinal products known to interact with doxorubicin hydrochloride or substances reported to be cardiotoxic or cardiologically active must to be used with caution. Concomitant therapy with other liposomal or lipid-complexed substances or intravenous fat emulsions could change the pharmacokinetic profile of PLD. Nephrotoxic compounds could be used with caution because their renal effect may be potentiated by Carboplatin and patients receiving concomitant therapy with nephrotoxic agents are likely to experience more severe and prolonged myelotoxicity. The concurrent administration of carboplatin and chelating agents should be avoided.</td>
</tr>
</tbody>
</table>
A decrease in phenytoin serum levels has been observed in case of concurrent administration of carboplatin and phenytoin. This may require an increase of phenytoin dosages.

**Prophylactic medication**

Patients in **Group A** will receive prophylactic medication according to the Investigator criteria.

Patients in **Group B** will be pre-medicated with 20 mg dexamethasone i.v. 30 minutes before the PLD infusion. If dexamethasone is not available, an equivalent can be used. Further steroid pre-medication can be used at the discretion of the Investigator.

Secondary prophylaxis with colony-stimulating factors such as granulocyte (G-CSF) or granulocyte-macrophage (GM-CSF) colony-stimulating factors may be used in both groups according to the American Society of Clinical Oncology (ASCO) or institutional guidelines (16).

**Dose reduction**

Dose reductions will be based on the worst drug-related toxicity that occurred since the last dose administration. Once a dose has been reduced because of toxicity, there will be no dose re-escalation in subsequent cycles. A maximum of two dose reductions are allowed regardless of the type of toxicity. Study treatment will be permanently discontinued for any patient who required a third dose reduction.

**Group A**

The following dose levels will be used in modifying PLD and/or carboplatin doses after Cycle 1 according to toxicity.

<table>
<thead>
<tr>
<th>PLD + Carboplatin dose reduction</th>
<th>Dose level 0</th>
<th>Dose level –1</th>
<th>Dose level –2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLD 30 mg/m²</td>
<td>PLD 25 mg/m²</td>
<td>PLD 20 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Carboplatin AUC 5</td>
<td>Carboplatin AUC 4</td>
<td>Carboplatin AUC 4</td>
<td></td>
</tr>
</tbody>
</table>

If a further dose reduction from level -2 is specifically required for PLD despite adequate countermeasures and/or cycle delays, PLD must be permanently discontinued and the patient should be treated with carboplatin AUC 4 alone. Any patient who does not tolerate the carboplatin dose level -2 shall be treated at the discretion of the investigator. The patient will go off protocol treatment and will be followed as any other patient.

**Group B**

The following dose levels will be used in modifying PLD and trabectedin doses after Cycle 1 according to toxicity.

<table>
<thead>
<tr>
<th>PLD + Trabectedin dose reduction</th>
<th>Dose level 0</th>
<th>Dose level –1</th>
<th>Dose level –2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLD 30 mg/m²</td>
<td>PLD 25 mg/m²</td>
<td>PLD 20 mg/m²</td>
<td></td>
</tr>
</tbody>
</table>
In case of recurrent toxicity after two dose reductions of one of the agents, the other non-reduced compound may be continued for patients with clinical benefit. Thus, for patients continuing on single-agent trabectedin 1.3 mg/m\(^2\), the first and second reduced doses will be 1.1 mg/m\(^2\) and 0.9 mg/m\(^2\), respectively. For patients continuing on single-agent PLD 35 mg/m\(^2\), the first reduced dose will be 30 mg/m\(^2\) and the second reduced dose will be 25 mg/m\(^2\).

**EFFICACY EVALUATIONS**

All randomized patients to either treatment arm, regardless of whether they received any study drug or not, will be analyzed on the basis of the intention-to-treat principle.

The primary endpoint (OS) will be measured from the date of randomization up to the date of death due to any cause or, for living patients, the date of last contact.

PFS will be counted as time from randomization until progression or death due to any cause. For subsequent therapies PFS will be calculated from the date of first dose until progression or death due to any cause.

Response and progression will be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

For the determination of PFS, the following events will be taken into account:

- Death
- Radiological tumor progression by RECIST 1.1
- Objective clinical progression (such as progressive peritoneal carcinomatosis with increasing bowel dysfunction, increased ascites requiring palliative drainage, emerging surgical procedure due to bowel obstruction)

The planned analysis of OS and PFS will include all randomized patients (on the basis of the intention-to-treat principle).

Disease evaluations will be performed symmetrically in both arms at 12 and 24 weeks including physical exam, radiology (CT scan or MRI, or PET/CT scan; regardless of the number of administered cycles) and CA-125 serum levels. The same method of assessment will be used to determine the disease status at baseline and at 12 and 24 weeks. Afterwards, pelvic examination and CA-125 levels will be performed every 12 weeks for the first 2 years and every 6 months thereafter, until evidence of PD or death.

**Subsequent treatment**

All patients must have documented disease progression before the administration of subsequent anticancer therapy. Agents administered, date of initiation, best response and progression date with subsequent therapies will be collected in the eCRF.

**Group A:** Subsequent therapies after carboplatin + PLD will be administered according to Investigator’s discretion (including the possibility of trabectedin treatment).

**Group B:** Subsequent platinum rechallenge is mandatory unless
refused by the patient.

**Follow-up**

Every patient must be followed until death regardless of the treatments received during the evolution of her disease. Follow-up will be performed every 12 weeks during the first two years and every six months thereafter. Subsequent therapies and disease evaluations will be recorded in the eCRF until death or study termination, whichever occurs first.

### SAFETY EVALUATIONS

All patients who have received at least part of one cycle of treatment will be included in the safety analysis. Safety will be evaluated by clinical examination, assessment of clinical AEs, changes in laboratory parameters (blood counts, clinical chemistry including liver function tests), and other tests as appropriate. AEs will be graded according to the NCI-CTCAE version 4.0 and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 11.0.

### PHARMACOKINETIC EVALUATIONS (at selected institutions)

The aim of the pharmacokinetic (PK) study is to quantify the trabectedin concentrations in ascites and to evaluate its relationship with plasma concentrations. Approximately 10 patients recruited in selected sites and presenting ascites at baseline will be sampled for trabectedin PK analysis in plasma and ascites. Additional information on the collection and processing of PK samples may be found in Appendix 2. Pharmacokinetic Sub-study.

### QoL EVALUATIONS

Two patient-reported outcome (PRO) instruments will be administered in this study: the EORTC QLQ-C30 and QLQ-OV28. Both PRO instruments will be completed by each patient at screening (before randomization) and, if not progressing, within 4 weeks from the end of the sixth cycle of chemotherapy or at the time of progression, whichever occurs first.

### STATISTICAL METHODS

**Sample size**

This study is designed to demonstrate a statistically and clinically significant difference in OS, (H₀: hazard ratio=1, H₁: hazard ratio=0.75). The primary OS analysis will be conducted when 442 events are observed; 588 patients are estimated to be enrolled to allow the demonstration of a statistically significant difference in the OS at a one-sided 2.5% significance level with at least 85% power. With these assumptions a reduction in the relative risk of death of at least 17.34% would allow the null hypothesis rejection.

**Interim analyses**

A futility analysis of the primary end point (OS) to reject H₁ is planned. This interim analysis will be conducted with approximately 100 events, which are estimated to occur ~28 months after start of study enrolment (assuming 10 patients/month and median OS=18-24 months in the control group). The trial will be stopped in case of clear OS advantage in the control arm. No claim for superiority is planned in this analysis.

A second interim analysis to test superiority will be performed when two
thirds of the death events are observed (approximately at the end of
recruitment period according to the sample size assumptions) with the
significance level determined by the actual observed number of events and
alpha spending function defined by the O'Brien-Fleming boundary.

Analysis methods
Primary analysis: OS between treatment arms will be compared by the
log-rank test.

Time-to-event variables (OS, PFS, response duration and length of
remission to subsequent therapies) and their fixed-time estimates will be
calculated according to the Kaplan-Meier method. The log-rank test will
also be used for the comparison of PFS and response of duration, as well
as the length of remission to subsequent therapies. For the categorical
variables (ORR and serological response) binomial exact estimates and
confidence interval at 95% will be calculated. For comparisons between
arm A and B, the Fisher exact test will be performed. Descriptive statistics
will be used to contrast baseline characteristics and safety profile between
both arms. PRO comparisons will be carried out using t-tests and mixed-
effects models.

Randomization
Randomization procedure will have a 1:1 ratio, using a biased-coin
minimization procedure and the following stratification factors: center,
line of chemotherapy (2nd vs. 3rd), measurable disease (yes vs. no) and
previous anthracyclines-based chemotherapy (yes vs. no).

<table>
<thead>
<tr>
<th>PLANNED TRIAL PERIODS</th>
<th>Study start: October 2010.</th>
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<tbody>
<tr>
<td></td>
<td>• First patient included: December 2010.</td>
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<td></td>
<td>• Three and a half years of recruitment.</td>
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# SCHEDULE OF ASSESSMENTS AND PROCEDURES

<table>
<thead>
<tr>
<th>Assessment / Activity</th>
<th>Screening</th>
<th>Treatment*</th>
<th>Follow-up</th>
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<tr>
<td></td>
<td>Evaluation within 14 days before first dose</td>
<td>Prior to each cycle</td>
<td>At treatment discontinuation (within 4 weeks)</td>
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<tr>
<td>Informed consent</td>
<td>X †</td>
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<td>Medical history</td>
<td>X †</td>
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<td>Physical/Pelvic examination</td>
<td>X †</td>
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<tr>
<td>ECOG performance status</td>
<td>X †</td>
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<tr>
<td>BSA, height and weight</td>
<td>X †</td>
<td>X</td>
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<tr>
<td>Vital signs</td>
<td>X †</td>
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<tr>
<td>Cardiac function</td>
<td>X b, †</td>
<td>X c</td>
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<tr>
<td>Symptoms/AEs</td>
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<td>QoL patient-reported outcomes instruments d</td>
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<td>Hematology</td>
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<td>Pregnancy test †</td>
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<tr>
<td>Pharmacokinetic sampling ‡</td>
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* A 3-day window is allowed for the different tests and procedures (unless otherwise specified).
† Within four weeks prior to Day 1 of Cycle 1.
‡ A limited PK sampling schedule will be implemented at selected sites. Nine blood and ascites samples will be obtained from approximately 10 consenting patients included in Arm B who present ascites at baseline. PK samples are to be collected at baseline (with a -1 day window) and on Days 1, 2, 3 and 8 of Cycle 1. Additional information on the collection and processing of PK samples may be found in Appendix 2. Pharmacokinetic Sub-study.
a. BSA may be calculated once, either at screening or Cycle 1, Day 1. It is not necessary to recalculate the patient BSA at each cycle unless required by the institution. BSA, height and weight may be evaluated at treatment discontinuation if clinically indicated.
b. Baseline cardiac function evaluation must be performed by ECG and echocardiography or MUGA to assess LVEF within 4 weeks prior to Day 1 of Cycle 1.
c. ECG must be performed in both arms at the end of study treatment or earlier if clinically indicated. Echocardiography or MUGA should be performed periodically in both arms during treatment: timing at investigators discretion. The evaluation of LVEF must be performed every cycle once cumulative doxorubicin or epirubicin dose exceeds 450 mg/m² or 810 mg/m², respectively
d. Patients reported outcome instruments will be completed by each patient before starting the treatment and within four
weeks after Cycle 6 or at the time of progression, whichever occurs first.

e. Including differential WBC (neutrophils, lymphocytes), hemoglobin and platelets must be performed at screening,
weekly for the first two cycles and then once between cycles in subsequent cycles.

f. Bilirubin, alkaline phosphatase, aminotransferases, creatinine, and CPK should be monitored at screening, weekly
during the first two cycles of therapy, and at least once between treatments in subsequent cycles.

g. CA-125 should be tested before each cycle of therapy (with a 3-day window) according to institutional policy while on
therapy, every 12 weeks in the first two years of follow up and every six months thereafter.

h. Baseline disease evaluations, including clinical exam and radiology (CT or MRI or PET/CT), must be performed within
4 weeks prior to Day 1 of Cycle 1. During the study disease evaluations will be performed symmetrically in both arms
at week 12 and 24 (regardless of the number of administered cycles). The same method of assessment will be used to
determine the disease status at screening and at the efficacy evaluations at week 12 and 24 weeks. After the first 24
weeks, disease assessment will be done with physical/pelvic examination and CA-125 measurements only. Further
radiological imaging is left at clinical discretion.

i. If PD has not occurred at treatment discontinuation, then disease assessment should continue every six months until
evidence of PD or death, or until the clinical data cutoff date, or until the clinical data cutoff date, or until the start of
first subsequent anticancer therapy, whichever is earlier. For the evaluation of OS, after disease assessments living
patients will be followed up to the date of death due to any cause or the date of last contact.

j. Pregnancy test if indicated (serum or urine).

AE(s), adverse event(s); BSA, body surface area; CPK, creatine phosphokinase; CR, complete response; CT, computed
tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection
fraction; MRI, magnetic resonance imaging; MUGA, multigate angiography; PD, Progressive Disease; PK,
pharmacokinetic; PLD, pegylated liposomal doxorubicin; PR, partial response; QoL, quality of life; RECIST, Response
Evaluation Criteria in Solid Tumors; WBC, white blood cells.
1. INTRODUCTION

1.1. OVARIAN CANCER

Ovarian cancer remains the second most lethal gynecologic malignancy after cervical cancer, with approximately 125,000 deaths annually worldwide (17). Primary therapy for advanced disease includes maximal surgical debulking followed by platinum/taxane chemotherapy (18, 19). In spite of ~80% response rates to primary therapy (20), most women eventually suffer recurrent disease and die.

1.1.1. Treatment of Recurrent Ovarian Cancer

Recurrent ovarian cancer represents a major clinical challenge; few compounds have shown activity in large randomized trials (21). Approved agents in Western countries include carboplatin/cisplatin, paclitaxel, altretamine, topotecan, pegylated liposomal doxorubicin (PLD), and gemcitabine (with carboplatin). Treatment option of recurrent ovarian cancer has traditionally been based on platinum responsiveness of recurrent disease as assessed by the progression-free interval (PFI). Platinum rechallenge is the most common option in patients with platinum-sensitive disease, with PFI > 6 months after the last date of platinum-based chemotherapy. PFI seems to predict the activity of all active agents in this setting, not just platinum compounds, and reflects a spectrum of activity rather than a dichotomy as measured by the six month PFI (20, 22). Non-platinum monotherapy is the preferred treatment for patients with platinum-resistant disease (PFI < 6 months) (22), and many clinicians also consider its use in patients with PFI > 6 months as a potential means of increasing the benefit of subsequent platinum-based treatment, or in patients with platinum hypersensitivity or other toxic sequelae from initial platinum.

Four major positive phase III randomized trials have been reported in the second-line recurrent ovarian cancer setting, leading to the regulatory approval of a new agent or altering the existing treatment paradigm. The study by Bokkel Huinink et al (23) randomized 235 patients to either topotecan or paclitaxel and showed that the former had efficacy at least equivalent to paclitaxel, resulting in a higher overall response rate (ORR) and longer time to progression. Gordon et al (4, 24) compared topotecan to PLD. This randomized phase III trial demonstrated improved efficacy, favorable safety profile, and convenient dosing, supporting regulatory approval of PLD in both platinum-resistant and -sensitive recurrent ovarian cancer.

The standard carboplatin and paclitaxel therapy for patients with advanced ovarian carcinoma relapsing after six months of previous platinum-based chemotherapy resulted from the ICON4/OVAR 2.2 (1), in which the addition of a taxane led to a longer progression-free survival (PFS) (hazard ration [HR] 0.76, p= .0004) and overall survival (OS) (HR 0.82, p=.02) over a conventional platinum-based chemotherapy in patients with platinum-sensitive, recurrent ovarian cancer.

Pfisterer et al (25) confirmed that combination therapy, in this case carboplatin + gemcitabine, prolongs PFS over a platinum single agent. With a median follow-up of 17 months, median PFS was 8.6 months for gemcitabine plus carboplatin vs. 5.8 months for
carboplatin alone, HR 0.72, p=0.0031. No survival differences were found in this trial.

1.1.2. New Approaches for the Partially Platinum Sensitive Population (PFI 6-12 months).

Platinum rechallenge is the most common option in patients with platinum-sensitive disease, with PFI > 6 months: it is standard in patients with PFI > 12 months, and frequently used in patients with partially sensitive disease (PFI 6-12 months). However, hypersensitivity reactions (~20% of ovarian cancer patients) (2, 26, 27), residual neurotoxicity (~23%) (3) and other clinically significant sequelae are common, underscoring the need for an efficacious non-platinum regimen, particularly in the PFI 6-12 months subset of patients.

PLD is an active agent in second-line therapy for ovarian carcinoma which obtained regulatory approval in both platinum-resistant and platinum-sensitive recurrent ovarian cancer (4). The combination of PLD plus carboplatin was shown to be safe and active in a phase II trial (5).

A recently reported large phase III trial (CALYPSO) comparing carboplatin + PLD vs. carboplatin + paclitaxel showed non inferior PFS results (hazard ratio [HR]: 0.82; median 11.3 months for carboplatin + PLD vs. 9.4 months for carboplatin + paclitaxel) (6, 7). Of note, in the PFI 6-12 subset carboplatin + PLD achieved better PFS results (HR: 0.73; median: 9.4 vs. 8.8 months; p=0.004 [superiority]), suggesting improved benefits over standard carboplatin + paclitaxel chemotherapy although overall survival data are not yet available (8).

The recent phase III trial OVA-301 demonstrated that trabectedin + PLD significantly prolonged PFS over PLD alone, with particularly enhanced benefits in patients with PFI > 6 months (n=430), where a median PFS of 9.2 months for the combination vs. 7.5 months for PLD was reported (9, 10). In the 6-12 months cohort (n=214), trabectedin + PLD resulted in a 35% risk reduction of disease progression or death (HR=0.65, 95% CI, 0.45-0.92; p=0.0152; median PFS 7.4 vs. 5.5 months). Interim OS data with 419 events (520 required for the final OS analysis) show a positive trend favoring the combination arm (HR: 0.85; p=0.09) in the overall population: median OS was 22.4 months in the trabectedin + PLD arm vs. 19.5 months with PLD. Patients with PFI 6-12 randomly assigned to the trabectedin combination had an 18% reduction in the risk of death (HR: 0.82) and a nearly three-month prolongation in median survival. The OS results were especially striking in patients with PFI 6-12, with a 41% reduction in the risk of death (HR=0.59; p=0.0015) and a 6-month prolongation in median survival (23.0 months in the trabectedin + PLD arm vs. 17.1 months in the PLD arm).

In OVA-301 study, similar proportions of patients received subsequent therapy in each arm (76% vs. 77%), although patients in the trabectedin + PLD arm had a slightly lower proportion of further platinum (49% vs. 55%) (11). After OVA-301 study, patients in the trabectedin + PLD arm received subsequent chemotherapy and, specifically, subsequent any platinum-based chemotherapies (i.e., as first, second or further lines) at a later time with median delays of 2.5 and 6 months vs. PLD arm, respectively. In addition, when only patients who received platinum as first line subsequent chemotherapy were analyzed, the
Protocol: INOVATYON

difference in median time to subsequent platinum, was 2.7 months; 10.3 months in trabectedin + PLD arm vs. 7.6 months in PLD arm; HR=0.80 (95%CI, 0.64-0.99); p=0.0361 (28).

In all randomized patients, median OS counted from the administration of subsequent platinum was identical at 14.9 months in each arm, and 1-year survival rates were 58% (PLD arm) and 60% (trabectedin + PLD arm). Thus, the delay in the administration of subsequent platinum does not appear to have exerted an influence on overall survival. An analysis per platinum-sensitivity evidenced that in patients with PFI 6-12, time from randomization to OVA-301 to subsequent platinum-based chemotherapy was delayed by a median of 1.9 months (9.8 vs. 7.9 months; HR=0.64; p=0.0167) favoring the trabectedin + PLD arm. Importantly, in these patients, OS counted from the administration of subsequent platinum was significantly extended, with a 37% reduction in the risk of death (HR=0.63; p=0.0357) and a 3.5 months longer median OS (13.3 months vs. 9.8 months) (11).

Additionally, differences were larger in patient subset with PFI 6-12 when only data of patients who received platinum as first line subsequent therapy were analyzed: platinum rechallenge was delayed a median of 4 months (HR=0.61; p=0.0203) and OS from first platinum was significantly extended by a median of 8.7 months (HR=0.54; p=0.0169) (28). Thus, the superior results obtained with trabectedin + PLD over single-agent PLD in OVA-301 trial cannot be explained by differences in the extent or nature of subsequent therapies administered to the patients after completion of on-study therapy. The enhanced survival with trabectedin + PLD over single-agent PLD in OVA-301, particularly in patients with PFI 6-12, may be due to an extension of the PFI coupled with longer survival after the start subsequent platinum-based chemotherapy. Consequently, the hypothesis that extending the PFI may improve the outcomes with subsequent platinum possibly by reversing the partial resistance pattern (12) is further supported by OVA-301 data. Hence, an effective non-platinum combination, such as trabectedin + PLD, may provide such additional benefit.

Concerning the safety results, in the trabectedin + PLD combination there was an increase in neutropenia (92% vs. 74% of patients) and neutropenic fever (7% vs. 2%)(11). Colony-stimulating agents were given to 17% and 42% of patients (8% compared to 25% by cycle) in the PLD and trabectedin + PLD arms, respectively (10). Grade 3/4 transaminase elevations were also more common with the combination but were transient, non-cumulative, and not associated with any major clinical consequence such as increased bilirubin or liver failure. Hand-foot syndrome (HFS) and mucositis paralleled the dose intensity of PLD and were lower with trabectedin + PLD compared to PLD alone. There were one related adverse event-related death due to sepsis in the PLD arm and three in the combination arm (neutropenic sepsis, pancytopenia and sepsis, and thrombocytopenia and febrile neutropenia in one patient each). Of note, the overall health status was maintained in patients treated with trabectedin + PLD vs. PLD alone, as assessed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 (QLQ-C30), the Quality of Life Questionnaire-OV28 (QLQ-OV28) and European Quality of Life-5 Dimensions (EQ-5D) questionnaires (13). The magnitude of the PFS and ORR differences in patients with sensitive relapse in the OVA-301 trial are in line with those reported in other positive trials in this setting as outlined above. Although the trabectedin + PLD combination provides a new option for
platinum-sensitive relapsed ovarian cancer, platinum rechallenge remains an established approach in this setting. Therefore, the comparison of the trabectedin + PLD combination vs. a platinum-containing regimen is warranted.

1.2. TRABECTEDIN

Trabectedin is an antineoplastic agent with a unique mechanism of action. It binds covalently to the minor groove of DNA, bending DNA towards the major groove, and disrupts transcription leading to G2-M cell cycle arrest and ultimately apoptosis (29).

The United States National Cancer Institute (NCI) conducted many of the early preclinical studies with trabectedin, and PharmaMar subsequently selected the compound for clinical development. Trabectedin is being co-developed by Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD), pursuant to a licensing agreement with PharmaMar. The clinical development program was focused primarily on ovarian cancer and soft tissue sarcoma (STS), where trabectedin demonstrated activity at very low concentrations in both preclinical models and humans. Trabectedin is also being investigated in lung, prostate, and breast cancers.

Trabectedin received marketing authorization in the European Union (EU) in 2007 for the treatment of patients with advanced STS after failure of anthracyclines and ifosfamide. Also, trabectedin in combination with PLD was approved for patients with relapsed platinum-sensitive ovarian cancer by the European Medicines Agency (EMA) in 2009.

Further information regarding trabectedin may be found in the Summary of Product Characteristics (SPC).

1.2.1. Clinical Data

As of September 2009, approximately > 6000 patients with advanced malignancies have been treated with trabectedin, administered either as a single agent or in combination with other chemotherapeutic agents. In addition to the subjects treated in clinical studies conducted by J&JPRD and PharmaMar, approximately 4000 patients received trabectedin under expanded access or compassionate use programs.

1.2.1.1. Efficacy Data as Single-agent

Phase II and III clinical studies of trabectedin in STS and ovarian cancer demonstrated efficacy in these tumor types and suggested a lack of cross-resistance with other chemotherapeutic agents. Therefore, trabectedin has the potential to be combined with other chemotherapeutic agents.

1.2.1.2. Clinical Safety Data as Single-agent

Trabectedin is well tolerated with prolonged administration. Myelosuppression, with neutropenia as its primary component, elevated transaminases (ALT, AST) and fatigue were the major dose-limiting toxicities reported in phase I studies. Anemia, thrombocytopenia and lymphopenia were less common. Although neutropenia is commonly reported with trabectedin, severe, drug-related infections, mucositis and stomatitis are infrequent. No evidence of cumulative toxicity has been noted.
Mild or moderate, transient and reversible elevations of serum creatine phosphokinase (CPK) were observed in 18.5% of patients, and grade 3 in 2.4% and grade 4 in 1.7% of treated patients according to laboratory data. Irreversible renal failure and fatal rhabdomyolysis were rarely reported. Rhabdomyolysis is an uncommon event with an incidence of approximately 0.5%, which has decreased in recent years following rigorous adherence to dose adjustment recommendations. Adequate monitoring of CPK serum levels is warranted.

Trabectedin is a moderately emetogenic drug, although treatment discontinuations because of gastrointestinal toxicity are rare. Prophylactic antiemesis with dexamethasone or equivalent is recommended. Mild to moderate asthenia/fatigue is common in patients who receive trabectedin. Trabectedin-associated neuropathy and alopecia are infrequent events. Local toxicity consists mainly of phlebitis, pain at the site of injection and possibly extravasation. These findings were infrequent and managed by local standard practice (the use of central venous access is strongly recommended).

1.2.1.3. Pharmacokinetic Properties

Systemic exposure after i.v. administration as a constant rate i.v. infusion is dose proportional at doses up to and including 1.8 mg/m². The pharmacokinetic profile of trabectedin is consistent with a multiple-compartment disposition model, including a terminal half-life in plasma of 175 hours. The concentrations of trabectedin in plasma do not accumulate when administered every 3 weeks.

**Distribution**

Trabectedin has a large volume of distribution (>5,000 l), consistent with extensive distribution into peripheral tissues. Trabectedin is highly bound to plasma proteins. The mean free (unbound) fraction in plasma is 2.23% and 2.72% at a total plasma concentration of 10 ng/ml and 100 ng/ml, respectively.

**Metabolism**

Trabectedin is extensively metabolized. Cytochrome P450 3A4 is the major cytochrome P450 isozyme responsible for the oxidative metabolism of trabectedin at clinically relevant concentrations. The contribution of other P450 enzymes to the metabolism of trabectedin cannot be ruled out. No appreciable glucuronidation of trabectedin has been observed.

**Elimination**

The mean (standard deviation) recovery of total radioactivity was 58% (17%), and 5.8% (1.73%) in the feces (24 days) and urine (10 days), respectively, after a dose of radiolabeled trabectedin was administered to 8 cancer subjects. Negligible quantities (<1% of the dose) of unchanged drug are excreted in the feces and in urine. The clearance of trabectedin in whole blood is approximately 35 l/hour. This value is approximately one-half the rate of human hepatic blood flow. Thus, the trabectedin extraction ratio can be considered moderate. The interpatient variability of the population estimate for plasma clearance of trabectedin was 51% and intrapatient variability was 28%.

**Special populations**

A population pharmacokinetic analysis indicated that the plasma clearance of trabectedin is not influenced by total body weight (range: 36 to 148 kg), body surface area (range: 0.9 to
2.8 m³), age (range 19 to 83 years), or gender. The effects of race and ethnicity on trabectedin pharmacokinetic (PK) have not been studied.

**Impaired renal function**

There is no relevant influence of renal function measured by creatinine clearance on trabectedin PK within the range of values (≥30.3 ml/min) present in the subjects included in the clinical studies. No data are available in subjects with a creatinine clearance of <30.3 ml/min. The low recovery (<9% in all studied subjects) of total radioactivity in the urine after a single dose of 14C-labelled trabectedin suggests that renal impairment would have little influence on the elimination of trabectedin or its metabolites.

**Impaired hepatic function**

The clearance of trabectedin may be decreased in subjects with hepatic impairment; resulting in higher concentrations of trabectedin in plasma. Close monitoring of toxicity is warranted when administering trabectedin to subjects with impaired hepatic function.

### 1.3. PEGYLATED LIPOSOMAL DOXORUBICIN (PLD)

Doxorubicin is an anthracycline class with broad spectrum of antineoplastic activity. Pegylated liposomal doxorubicin (PLD; Caelyx®, Doxil®) is doxorubicin hydrochloride encapsulated in Stealth® liposomes aimed at escaping recognition and uptake by the mononuclear phagocyte system. This i.v. formulation has a long circulation time, and the liposomes eventually extravasate through the abnormally permeable vessels characteristic of many tumors. Once concentrated in tumors, PLD can deliver high levels of doxorubicin to malignant cells with less damage to normal tissues. PLD safety profile is improved over doxorubicin, with less cardiotoxicity, nausea vomiting and alopecia.

The major toxicity is on the bone marrow, limiting the dose. Irreversible cumulative cardiac toxicity limits the total deliverable dose as well. Special attention must be given to the myocardial damage that may be associated with cumulative doses of doxorubicin and caution should be observed in patients who have received other anthracyclines. PLD is approved both in the United States (Doxil®) and in Europe (Caelyx®) for patients with recurrent ovarian cancer after initial standard chemotherapy. The approved dose of PLD as a single agent for the treatment of ovarian carcinoma is 50 mg/m² administered every 4 weeks.

### 1.4. TRABECTEDIN IN COMBINATION WITH PLD

#### 1.4.1.1. Preclinical Studies of the Combination of Trabectedin and Doxorubicin

The orphan nuclear receptor SXR is involved in the regulation of various enzymes (e.g., CYP3A4, 2C8) and transporters (e.g., P-gp, MRP2) and trabectedin has been shown to antagonize SXR at clinically relevant concentrations. PLD is principally metabolized by CYP3A4 and its PK could be theoretically affected by trabectedin co-administration through SXR antagonism. It should be noted that, at present, there are no preclinical or clinical data available that demonstrate a lack of metabolism-based interaction between trabectedin and PLD.

Trabectedin did not alter the activity of the CYP3A enzymes during in Vitro studies. Other
potential effects at the level of transcription or translation of the CYP enzymes are being investigated.

1.4.1.2. Clinical Efficacy Data of the Trabectedin Plus PLD Combination

The efficacy of trabectedin + PLD combination in relapsed ovarian cancer is based on OVA-301, a randomized phase III study of 672 patients who were randomly assigned to receive either trabectedin (1.1 mg/m²) and PLD (30 mg/m²) every three weeks or PLD (50 mg/m²) every four weeks (Table 1). The primary analysis of PFS was performed in 645 patients with measurable disease and assessed by independent radiology review. Treatment with the combination arm resulted in a 21% risk reduction for disease progression or death (PFS) compared to PLD alone (HR=0.79, CI: 0.65-0.96, p=0.0190). Secondary analyses of PFS and response rate also favored the combination arm.

Based on independent oncology review, patients with PFI < 6 months (35% in trabectedin + PLD and 37% in PLD arm) had similar PFS in the two arms with both showing median PFS of 3.7 months (HR=0.89, CI: 0.67-1.20). In patients with PFI ≥ 6 months (65% in trabectedin + PLD and 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, CI: 0.52-0.85).

In the interim analysis, the effect of the trabectedin + PLD combination on overall survival was more pronounced in patients with PFI ≥ 6 months (27.0 vs. 24.3 months, HR=0.82, CI: 0.63-1.06) than in those with PFI < 6 months (14.2 vs. 12.4 months, HR=0.90, CI: 0.68-1.20).

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<tr>
<th>Table 1. Efficacy analyses from OVA-301.</th>
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<td><strong>Trabectedin + PLD</strong></td>
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<td><strong>Progression Free Survival</strong></td>
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<td>Independent radiology review, measurable disease*</td>
</tr>
<tr>
<td>Median PFS (95% CI) (months)</td>
</tr>
<tr>
<td>12 months PFS rate (95% CI) (%)</td>
</tr>
<tr>
<td>Independent oncology review, all randomized</td>
</tr>
<tr>
<td>Median PFS (95% CI) (months)</td>
</tr>
<tr>
<td>Overall Survival (Interim analysis - n=419 events, 38% censoring)</td>
</tr>
<tr>
<td>All randomized</td>
</tr>
<tr>
<td>Median OS (95% CI) (months)</td>
</tr>
<tr>
<td>Overall Response Rate</td>
</tr>
<tr>
<td>Independent radiology review, all randomized</td>
</tr>
<tr>
<td>ORR (95% CI) (%)</td>
</tr>
</tbody>
</table>

*Primary efficacy analysis. aLog rank test; bFisher’s test

In the multivariate analyses including PFI, treatment effect was statistically significant favoring the trabectedin + PLD combination (PFS, p=0.0157; OS, p=0.0407).
1.4.1.3. **Safety Data of the Trabectedin Plus PLD Combination**

The most common grade 3/4 adverse events (AEs) and other AEs of interest at least possibly related to treatment are summarized in Table 2.

Grade 3/4 neutropenia and ALT elevations were more frequent with trabectedin + PLD. HFS, mucosal inflammation and stomatitis were more common with PLD.

Nineteen patients died during treatment (PLD = 8; trabectedin + PLD = 11). Six deaths in each group were from progressive disease (PD), with two deaths in the PLD group (one due to an AE, one unknown cause) and five in the trabectedin + PLD group (due to AE). No significant difference in LVEF reduction (> 15%) was noted between treatments (PLD = 8; trabectedin + PLD = 7) although seven cases of non-fatal congestive heart failure (CHF)-related diagnoses, irrespective of causality, were reported (PLD = 1 [1 CHF]; trabectedin + PLD = 6 [1 CHF, 3 ventricular dysfunction, 2 cardiac failure]).

**Table 2.** Drug-related grade 3/4 adverse events in ≥ 5% of patients (all treated patients) and other drug-related adverse events of interest (all grades).

<table>
<thead>
<tr>
<th>Grade 3/4 Toxicity</th>
<th>PLD (n = 330)</th>
<th>Trabectedin + PLD (n = 333)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td><strong>Hematological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>46</td>
<td>13.9</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>24</td>
<td>7.3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Anemia</td>
<td>15</td>
<td>4.5</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>6</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Non-hematological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFS</td>
<td>61</td>
<td>18.5</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>19</td>
<td>5.8</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>16</td>
<td>4.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8</td>
<td>2.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>2.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7</td>
<td>2.1</td>
</tr>
<tr>
<td>AST increase</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>ALT increase</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Other events of interest (any grade)</strong></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>44</td>
<td>13</td>
</tr>
<tr>
<td>Alkaline phosphatase increase</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>Bilirubin conjugated increase/hyperbilirubinemia</td>
<td>18</td>
<td>5</td>
</tr>
</tbody>
</table>

1.5. **CARBOPLATIN PLUS PLD COMBINATION**

The combination of carboplatin area under the curve (AUC) 5 and PLD (30 mg/m²) was examined in a phase II study conducted by Ferrero JM *et al* (5) on 105 patients with ovarian cancer, progressing after at least 6 months following a first or a second line treatment including a platinum and a taxane. Response rate was 63% including 38% complete responses (CR). Median PFS was 9.4 months and median OS was 32 months,
similar to the ICON4/OVAR2.2 trial figures.

The multicenter phase III study CALYPSO compared the efficacy and safety of carboplatin/paclitaxel (C/P) with carboplatin/PLD (C/D) in 976 relapsed platinum-sensitive ovarian cancer patients with recurrent OC > 6 months after first- or second-line platinum-based therapy (7). The primary endpoint (non-inferiority design) was PFS, with secondary endpoints of toxicity, quality of life (QoL) and survival. Patients were randomized to six cycles of carboplatin AUC 5 + PLD 30 mg/m² i.v. Day 1 q4wks, or carboplatin AUC 5 i.v. + paclitaxel 175 mg/m² i.v. Day 1 q3wks. PFS was prolonged with carboplatin/PLD over carboplatin/paclitaxel (median 11.3 vs 9.4 months; HR 0.821, 95%CI 0.72-0.94; p=0.005), and there were lower rates of severe and long-lasting (neuropathy) toxicities (Table 3). Survival data from this trial are not yet available.

**Table 3. Summary of results from the CALYPSO trial**

<table>
<thead>
<tr>
<th></th>
<th>C/D arm</th>
<th>C/P arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (months), median after 824 events, HR 0.821 (95% CI:0.72-0.94); p=0.005</td>
<td>11.3</td>
<td>9.4</td>
</tr>
<tr>
<td>Neutropenia grade ≥4</td>
<td>35%</td>
<td>46%</td>
</tr>
<tr>
<td>Thrombocytopenia grade ≥4</td>
<td>16%</td>
<td>6%</td>
</tr>
<tr>
<td>Any non-hematological toxicity grade ≥4</td>
<td>28%</td>
<td>37%</td>
</tr>
<tr>
<td>Hypersensitivity grade &gt;2</td>
<td>5%</td>
<td>18%</td>
</tr>
<tr>
<td>Alopecia grade &gt;2</td>
<td>7%</td>
<td>84%</td>
</tr>
<tr>
<td>Neuropathy grade &gt;2</td>
<td>4%</td>
<td>27%</td>
</tr>
<tr>
<td>Hand-foot syndrome grade &gt;2</td>
<td>13%</td>
<td>2%</td>
</tr>
<tr>
<td>Mucositis grade &gt;2</td>
<td>14%</td>
<td>7%</td>
</tr>
<tr>
<td>Early treatment discontinuation (toxicity related)</td>
<td>7%</td>
<td>15%</td>
</tr>
</tbody>
</table>

1.6. **TRIAL RATIONALE**

The large CALYPSO trial has demonstrated non inferior PFS results with carboplatin + PLD over carboplatin + paclitaxel (6, 30) with a favorable safety profile. In this trial, the subpopulation of patients with PFI 6-12 months also obtained better PFS outcomes with the carboplatin + PLD combination (8).

The phase III trial OVA-301 demonstrated the superiority of the trabectedin + PLD combination over single agent PLD in the overall population of recurrent ovarian cancer, with striking differences in outcomes, including statistically significant survival advantage in the subset of patients with PFI 6-12 months. This may be explained, at least in part, by the fact that patients in the trabectedin + PLD arm received subsequent chemotherapy at a later time than those in the PLD arm. After OVA-301 study, all randomized patients in the trabectedin + PLD arm received subsequent chemotherapy and, specifically, any subsequent platinum-based chemotherapies (i.e., as first, second or further lines), at a later time with median delays of 2.5 and 6 months vs. PLD arm, respectively. Subsequent platinum as first line subsequent chemotherapy was delayed by a median 2.7 months in the trabectedin + PLD arm: HR=0.80; p=0.0361 (28). In the PFI 6-12 month cohort time from randomization to subsequent platinum was delayed by a median of 1.9 months (9.8 vs. 7.9 months; HR=0.64; p=0.0167) favoring the trabectedin + PLD arm. Importantly, OS counted from the administration of subsequent platinum was significantly prolonged, with a 37%
reduction in the risk of death (HR=0.63; p=0.0357) and a 3.5 months longer median OS (13.3 months vs. 9.8 months). Even larger differences in the PFI 6-12 subset were found in patients who received platinum as first-option subsequent therapy, with a median of 4 months delay (HR=0.61; p=0.0203) and a median of 8.7 months longer OS from first platinum (HR=0.54; p=0.0169).

Trabectedin safety profile is well characterized and relies on data in > 6000 patients from clinical trials and from an expanded access program, plus an increasingly large post-marketing experience since the initial approval of this agent in September 2007.

The safety profile of the trabectedin + PLD combination compares favorably with that for established regimens and appears better than that with single-agent topotecan in this population (4, 21). Adverse events in OVA-301 were consistent with those known for each single agent and no new or unexpected toxicities emerged. More frequent grade 3/4 neutropenia and transaminase elevations occurred, but these were generally transient, manageable and not associated with serious sequelae. Cumulative myelosuppression, cardiotoxicity, neurotoxicity, ototoxicity, hypersensitivity reactions and alopecia were not a concern. No decrement in QoL occurred with the combination, as assessed by QoL/PRO (13). Overall, this therapy was well tolerated by the patients in the OVA-301 trial.

Regarding CALYPSO, carboplatin + paclitaxel was associated with more severe toxicities (carboplatin hypersensitivity, long-lasting neuropathy) and alopecia. On the other hand, moderate reversible palmar-plantar erythrodysesthesia, mucositis and nausea/vomiting were more frequent with carboplatin + PLD.

No data are available comparing trabectedin + PLD to a platinum-based regimen. Based on data from OVA-301 and CALYPSO the proposed INOVATYON trial will investigate the role of a non-platinum combination for the treatment of ovarian cancer patients relapsing between six and 12 months after last platinum-based chemotherapy for whom there is need for new treatment options. Specifically, the present trial is aimed at demonstrating that extending the PFI with a non-platinum combination prolongs survival in patients with relapsed, partially platinum-sensitive ovarian cancer with PFI 6-12 months. If so, such novel treatment strategy would fulfill the requirement for a much needed alternative treatment in this patient population.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

- To demonstrate that the combination of trabectedin (Yondelis®) and pegylated liposomal doxorubicin (PLD) prolongs overall survival (OS) over carboplatin and PLD in patients with relapsed ovarian cancer progressing within 6-12 months after end of last platinum.

2.2. SECONDARY OBJECTIVES

- To evaluate the time from randomization to subsequent chemotherapy and the overall survival counted from the administration of subsequent chemotherapy.
- To evaluate serological response of CA-125 in each arm.
To compare the QoL in each arm using the EORTC Quality of Life Questionnaire-C30 (QLQ-C30) and the Quality of Life Questionnaire-OV28 (QLQ-OV28).

To compare safety profile, PFS, ORR, the type and length of remission (response rate and PFS) after subsequent therapies following each of the two combinations.

Sub-study in selected centers: To perform PK analyses in both plasma and ascites from a subset of patients receiving trabectedin and PLD.

3. STUDY DESIGN

This is a multicenter, randomized phase III study of trabectedin plus PLD vs. carboplatin plus PLD in patients with advanced ovarian cancer who experience PD between six and twelve (6-12) months from last platinum-based regimen. Patients may have received up to two platinum-based regimens, of which at least one must have contained a taxane.

Patients will be randomly allocated to either of the following treatments (Figure 1):

**Group A:** PLD 30 mg/m² i.v. as a 1-hour infusion followed by carboplatin AUC 5 i.v. as a 30 min infusion on Day 1 every 4 weeks. A 4-week schedule defines a cycle of treatment.

**Group B:** PLD 30 mg/m² i.v. infusion immediately followed by trabectedin 1.1 mg/m² 3-hour i.v. infusion on Day 1 every 3 weeks. A 3-week schedule defines a cycle of treatment.

*Figure 1.* Design and randomization chart.

**Relapsed ovarian cancer with a progression-free interval of 6-12 months after the end of 1st or 2nd line platinum-based therapy**

**Group A**
- PLD 30 mg/m² 1-hour i.v. +
- Carboplatin AUC 5 30-60 min
- i.v. on Day 1 q4w
- Up to 6 Cycles or PD

**Group B**
- PLD 30 mg/m² 1-hour i.v. +
- Trabectedin 1.1 mg/m² 3-hour i.v.
- on Day 1 q3w
- Up to 6 Cycles or PD

*At PD, subsequent therapy at Investigator discretion*

**Stratification factors:**
- Center
- Line of ChT: 2nd/3rd
- Measurable disease: y/n
- Previous anthracyclines: y/n

**Tumor evaluation at wk12-24**

At PD, subsequent platinum rechallenge is mandatory unless refused by the patient.

Dexamethasone pre-medication mandatory.

**Afterwards, pelvic examination and CA-125 levels will be performed every 12 weeks for the first two years and every six months thereafter, until evidence of PD or death. Further radiological imaging is left to clinical discretion.**

i.v., intravenous; ChT, chemotherapy; PD, progressive disease; PFI, progression-free interval; R, randomization.
Disease evaluations will be performed symmetrically in both arms at week 12 and 24 including physical exam, radiology (CT scan or MRI, or PET/CT scan; regardless of the number of administered cycles) and CA-125 serum levels. The same method of assessment will be used to determine the disease status at baseline and at week 12 and 24. Afterwards, physical and pelvic examination and CA-125 levels will be performed every 12 weeks for the first two years and every six months thereafter, until evidence of PD or death. Further radiological imaging is left at clinical discretion.

Every patient must be followed until death regardless of subsequent treatments received during the evolution of her disease. Follow-up will be scheduled every 12 weeks during the first two years and every six months thereafter.

All patients must have documented disease progression before the administration of subsequent anticancer therapy which will be as follows:

**Group A:** Subsequent therapies after carboplatin + PLD will be administered according to Investigator’s discretion (including the possibility of trabectedin treatment).

**Group B:** Subsequent platinum rechallenge is mandatory unless refused by the patient.

Agents administered, date of initiation, best response and progression date with subsequent therapies will be collected in the electronic case report form (eCRF).

### 4. PATIENT SELECTION

#### 4.1. INCLUSION CRITERIA

To be eligible for the trial, patients must fulfill all of the following criteria:

1. Female, aged ≥ 18 years
2. Histologically and/or cytologically proven epithelial ovarian, epithelial fallopian tube cancer or primary peritoneal cancer
3. Progression free interval between six and twelve (6-12) months (calculated from the first day of the last cycle of the last platinum-based chemotherapy until the date of progression confirmation through radiologic imagery). Patients may have received up to two platinum-based chemotherapy lines, of which at least one must have contained a taxane
4. Measurable or evaluable disease confirmed by radiological imaging, such as magnetic resonance imaging (MRI), computed tomography (CT) scan, or PET/CT scan at study entry (CA-125 rise not supported by radiological evidence of disease is not accepted as criteria for defining progression) or histological proven recurrent ovarian cancer even in the absence of postoperatively measurable or evaluable lesions.
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2
6. Estimated life expectancy ≥ 12 weeks
7. Patients must be accessible for treatment and follow-up
8. Adequate organ function within 14 days prior to first cycle as evidenced by:
a. Peripheral blood counts and serum chemistry values:
   i. Hemoglobin ≥ 9 g/dl
   ii. Absolute neutrophil count (ANC) ≥ 1,500/μl
   iii. Platelet count ≥ 100,000/μl
   iv. Estimated glomerular filtration rate > 60 ml/min according to the Cockroft-Gault formula
   v. CPK ≤ 2.5 x ULN.

b. Hepatic function variables:
   i. Total bilirubin ≤ ULN
   ii. Total alkaline phosphatase ≤ 2.5 ULN (consider hepatic isoenzymes 5-nucleotidase, if the elevation could be osseous in origin)
   iii. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) must be ≤ 2.5 x ULN

9- Patients must be able to receive dexamethasone or its equivalent, which is required if randomly assigned to treatment with trabectedin plus PLD

10- Informed consent of the patient

4.2. **EXCLUSION CRITERIA**

Patients fulfilling any of the following criteria will not be included into the trial:

1- Non epithelial ovarian or mixed epithelial/non epithelial tumors (e.g., Mullerian tumors)

2- Patients who did not respond to last platinum-based therapy or in whom last relapse occurred < 6 months or > 12 months from the last dose of platinum

3- Bowel obstruction, sub-occlusive disease or the presence of symptomatic brain metastases

4- Pre-existing grade > 1 motor or sensory neuropathy according to the National Cancer Institute Common Toxicity Criteria Adverse Event (NCI-CTCAE) version 4.0

5- Myocardial infarct within six months before enrolment, New York Association (NYHA) Class II or worse heart failure (Appendix 1. The New York Heart Association), uncontrolled angina, severe uncontrolled ventricular arrhythmias, clinically significant pericardial disease, or electrocardiographic evidence of acute ischemic or active conduction system abnormalities

6- History of liver disease

7- Concurrent severe medical problems or any unstable medical condition unrelated to malignancy, which would significantly limit full compliance with the study or expose the patient to extreme risk or decreased life expectancy

8- Breastfeeding women and women of child bearing potential must use effective contraception during treatment and 3 months thereafter, which may include prescription contraceptives (oral, injection, or patch), intrauterine device, double-barrier method or male partner sterilization (not applicable to patients that are
surgically sterile)

9- Prior exposure to trabectedin.

10- Prior resistance to anthracyclines or PLD defined as a progression during anthracycline-based chemotherapy or a recurrence within 6 months from its ending

11- Prior severe PLD related toxicity

12- Prior exposure to cumulative doses of doxorubicin >400mg/m² or epirubicin >720mg/m²

13- Treatment with any investigational product within 30 days prior to inclusion in the study

14- Patients with known hypersensitivity to Trabectedin and any of its excipients or yellow fever vaccine

15- Patients with concurrent serious or uncontrolled infection

16- Patients in need of yellow fever vaccine while on study chemotherapy

4.3. **Duration of Study (Whole Population)**

This study will commence in October 2010. The primary endpoint of this study is OS, which will be measured from the date of randomization up to the date of death due to any cause or, for living patients, the date of last contact.

The total duration of the study includes about three and a half years of active recruitment.

4.4. **Duration of Study and Treatment (Per Patient)**

Patients will be evaluated at scheduled visits in three study periods:

- **Pretreatment**: from signature of informed consent to first study drug infusion.
- **Treatment**: from first study drug infusion to 30 days after last dose of study drugs, unless the patient dies or starts subsequent anticancer therapy outside this clinical trial (in which case the date of death or the date of administration of such subsequent therapy will be considered the date of treatment discontinuation). An end-of-treatment visit will be performed within 30 days after last dose administration.
- **Follow-up**: after treatment discontinuation, patients will be followed every 12 weeks during the first two years and every six months thereafter. Subsequent therapies and disease evaluations will be recorded in the eCRF until death or until the date of study termination, whichever occurs first. For the evaluation of OS, after disease assessments living patients will be followed up to the date of death or the date of last contact.

Patients will be considered to be on-study from the date of signature of the informed consent to the end of the follow-up period. Patients will be considered to be on-treatment for the duration of the study drug treatment and until treatment discontinuation. Treatment discontinuation will be defined as 30 days after the last dose of the study drug administration, unless the patient dies or starts subsequent anticancer therapy outside this
clinical trial, in which case the date of death or the date of administration of such new therapy will be considered as date of treatment discontinuation.

4.4.1. Discontinuations

4.4.1.1. Treatment Discontinuation

Patients will receive the study medications up to six cycles or PD, however if it is considered to be in their best interest treatment will continue until:

- Six cycles of treatment, although patients with clinical benefit may continue therapy beyond Cycle 6.
- Disease progression.
- Unacceptable toxicity.
- Intercurrent illness of sufficient severity to preclude a safe continuation of the study.
- Patient refusal and/or non compliance with study requirements.

Treatment discontinuation occurs when an enrolled patient ceases to receive the study medication, regardless of the circumstances. The primary reason for any discontinuation will be recorded on the patient’s eCRF.

If a patient discontinues treatment, every effort should be made to complete the scheduled assessments. Subsequent therapies for the patients may be provided as suggested in Section 3.

4.4.1.2. Study Discontinuation

Study discontinuation occurs when an enrolled patient ceases to participate in the study, regardless of the reason. Patients have the right to withdraw consent at any time; if this is the case, no further follow-up should be performed. The study may be terminated following administrative reasons or a decision by the Sponsor to discontinue the study.

The date and reason for study discontinuation will be clearly documented on the patient’s notes and eCRF.

4.5. Screening Evaluation

During the pre-treatment period, and once the patient has signed the Informed Consent Form, the Investigator will confirm the patient’s eligibility for the study by conducting the following assessments listed in Table 4.

<table>
<thead>
<tr>
<th>ASSESSMENT</th>
<th>TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. History and clinical examination</td>
<td>* Written informed consent. Prior to any specific study procedures.</td>
</tr>
<tr>
<td></td>
<td>* Medical history:</td>
</tr>
<tr>
<td></td>
<td>o Date of diagnosis of the primary disease. Within four weeks prior to Day 1 of Cycle 1.</td>
</tr>
<tr>
<td></td>
<td>BSA can be calculated once, either at</td>
</tr>
</tbody>
</table>
## ASSESSMENT

<table>
<thead>
<tr>
<th>Demographic information.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior treatments (surgery, radiotherapy, chemotherapy, immunotherapy), specifying the best response and the date of disease progression.</td>
</tr>
<tr>
<td>Complete physical and pelvic examination.</td>
</tr>
<tr>
<td>Performance status (ECOG PS; see Appendix 3. ECOG Performance Status Assessment Scale).</td>
</tr>
<tr>
<td>Weight, height and BSA.</td>
</tr>
<tr>
<td>Concomitant diseases and treatments.</td>
</tr>
<tr>
<td>Vital signs: heart rate, blood pressure.</td>
</tr>
<tr>
<td>Symptoms/ adverse events.</td>
</tr>
</tbody>
</table>

### TIME

 screening or Cycle 1, Day 1. It is not necessary to recalculate the patient BSA at each cycle unless required by the institution.

### 2. Cardiac function

<table>
<thead>
<tr>
<th>ECG, and</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF by ECHO (preferentially) or MUGA.</td>
</tr>
</tbody>
</table>

Within four weeks prior to Day 1 of Cycle 1.

### 3. Laboratory tests

**Hematology**: differential WBC (neutrophils, lymphocytes), hemoglobin and platelets.

**Biochemistry**: liver function test (ALT, AP, AST, total bilirubin), creatinine and creatinine clearance and CPK.

Within 14 days prior to Day 1 of Cycle 1. Creatinine clearance will be calculated according with Cockroft-Gault formula (15).

### 4. Pregnancy test

Pregnancy test (serum or urine). Within 14 days prior to Day 1 of Cycle 1 if indicated.

### 5. CA-125

In addition to appropriate imaging. Within four weeks prior to Day 1 of Cycle 1.

### 6. Tumor measurement

Measurable or evaluable disease either by radiological imaging, such as MRI, CT scan, or PET/CT scan

Within four weeks prior to Day 1 of Cycle 1.

### 7. QoL/ PRO instruments

Two PRO instruments will be administered in this study: the EORTC QLQ-C30 and QLQ-OV28. PRO instruments will be completed by the patient at screening (before randomization) (this is, before knowing the treatment arm).

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BSA, body surface area; CPK, creatine phosphokinase; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition; PD, progressive disease; PRO, patient-reported outcomes; PS, performance status; QoL, quality of life; QLQ-C30, Quality of Life Questionnaire-C30; QLQ-OV28, Quality of Life Questionnaire-OV28; WBC, white blood cells.

A limited PK sampling schedule will be implemented at selected sites. Nine blood and ascites samples will be obtained from approximately 10 consenting patients included in Arm B and who present ascites at baseline. Pharmacokinetic samples will be collected at Day 1 of Cycle 1 (with a -1 day window). Additional information on the collection and processing of PK samples may be found in Appendix 2. Pharmacokinetic Sub-study.

### 4.6. PATIENT RANDOMIZATION

After obtained informed consent to participate, eligible patients will be randomized. At that moment information regarding relevant demographic characteristics and stratification variables must be available and randomization form should be completely filled in.
A system that automates the random assignments of treatment groups will be used. The random application and tutorial can be downloaded at this URL: http://lsi.marionegri.it/trials/inovatyon

Each investigator will have a personal **username** (provided as soon as the Sponsor has obtained the information about the independent ethics committee [IEC] / institutional review board [IRB] approval of the protocol) and a **password** (remember that the randomizer is case sensitive, therefore username and password should be entered always in compliance with the first capital/small letter format: e.g., ‘ABC’ is different from ‘abc’). **Please note:** these credentials are strictly personal and must not be given up to other people.

All randomized patients will receive a unique patient identification 7-digit trial code: the first 2 digits stand for the country, the next 2 for the site and the last 3 for the patient inclusion number. This number will be used to identify patients throughout the clinical study and must be used on all study documentation related to that patient.

At the end of the randomization process, the notification of randomization page should be printed and archived in the investigator site file (ISF).

**4.7. EVALUATIONS DURING TREATMENT**

The following assessments will be done while the patient is on treatment (Table 5).

A 3-day window is allowed for the different tests and procedures (except where otherwise specified).

<table>
<thead>
<tr>
<th><strong>ASSESSMENT</strong></th>
<th><strong>TIME</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Clinical examination</strong></td>
<td><strong>Complete physical and pelvic examination.</strong>&lt;br&gt;<strong>Performance status (ECOG PS; see Appendix 3. ECOG Performance Status Assessment Scale).</strong>&lt;br&gt;<strong>Vital signs: heart rate, blood pressure</strong>&lt;br&gt;<strong>Weight, height and BSA.</strong>&lt;br&gt;<strong>Intercurrent events, concomitant disease and treatments.</strong></td>
</tr>
<tr>
<td><strong>2. Cardiac function</strong></td>
<td><strong>ECG, and</strong>&lt;br&gt;<strong>LVEF by ECHO (preferentially) or MUGA.</strong></td>
</tr>
</tbody>
</table>

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Version n1: UK ONLY: 16 September 2010 - Final Revised 25 October 2010 _draft_
### 3. Laboratory tests

**Hematology:**
- Differential WBC (neutrophils, lymphocytes), hemoglobin and platelets.

**Biochemistry:**
- Liver function test (ALT, AP, AST, total bilirubin), creatinine or creatinine clearance and CPK.

Laboratory test must be performed weekly for the first two cycles and then once between subsequent cycles.

Creatinine clearance will be calculated according with Cockroft-Gault formula (15).

**Laboratory test must be performed weekly for the first two cycles and then once between subsequent cycles.**

### 4. Pregnancy test, if indicated
- Pregnancy test (serum or urine).

If indicated.

### 5. CA-125
- In addition to appropriate imaging.

Prior to each cycle (with a 3-day window).

### 6. Tumor measurement
- Measurable or evaluable disease either by radiological imaging, such as MRI, CT or PET/CT scan.

At week 12 and 24 (regardless of the number of administered cycles). The same method of assessment will be used to determine the disease status at screening and at the efficacy evaluations through the study and follow-up. After the first 24 weeks, disease assessment will be done with physical/pelvic examination and CA-125 measurements only. Further radiological imaging is left at clinical discretion.

### 7. QoL/PRO instruments
- Two PRO instruments will be administered in this study: the EORTC QLQ-C30 and QLQ-OV28.

Patients reported outcome instruments will be completed by each patient before starting the treatment and within four weeks after the 6th cycle or at the time of progression, whichever occurs first.

### 8. Survival status
- Every patient should be followed until death.

Throughout the study. After treatment discontinuation, patients will be followed every 12 weeks during the first two years from randomization and every six months thereafter. For the evaluation of OS, living patients will be followed up to the date of death or the date of last contact.

### 9. AEs
- As per NCI-CTCAE v.4.0.

Until treatment discontinuation

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BSA, body surface area; CPK, creatine phosphokinase; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition; NCI-CTCAE, National Cancer Institute Common Toxicity Criteria Adverse Event; PD, progressive disease; PRO, patient-reported outcomes; PS, performance status; QoL, quality of life; QLQ-C30, Quality of Life Questionnaire-C30; QLQ-OV28, Quality of Life Questionnaire-OV28; WBC, white blood cells.

For PK sub-study, a total of nine samples will be obtained for blood and ascites analyses during the first cycle. Samples for plasma PK will have a volume of 5 ml of blood and those for ascites PK will have a volume of 10 ml (see Appendix 2. Pharmacokinetic Sub-study).

#### 4.8. Evaluation at Treatment Discontinuation

Treatment discontinuation will be counted 30 days after last dose of study drug (a window of ± 3 days is allowed), unless the patient dies or starts a subsequent antitumor therapy outside this clinical trial, in which case the date of death or the date of administration of this new therapy will be considered the date of treatment discontinuation.

Regardless of the reason for discontinuation, the same complete workup conducted at study...
entry (except for medical history) will be done at the end-of-treatment visit. This will include the following assessments:

- Complete physical examination, which may include weight, height and BSA, if clinically indicated
- Vital signs
- ECOG PS
- Hematology
- Safety assessment (AEs)
- QoL patient-reported outcomes.

Adverse events must be reported for 30 days after the last study drug administration. All serious adverse events (SAEs) occurring within 30 days of the last study drug administration will be reported. Beyond this period of time, only those SAEs suspected to be treatment-related will be reported (see Section 7).

The Sponsor will evaluate all safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

4.9. FOLLOW-UP AFTER TREATMENT DISCONTINUATION

The date and reason of the study discontinuation will be recorded on the patient’s eCRF (see Section 4.4.1.1).

Every patient must be followed regardless of the treatments received during the evolution of her disease. Follow-up will be performed every 12 weeks during the first two years and every six months thereafter. Subsequent therapies and disease evaluations will be recorded in the eCRF until death or study termination, whichever occurs first. For the evaluation of OS, after disease assessments living patients will be followed up to the date of death or the date of last contact.

Follow-up evaluations will include the following:

- Complete physical examination
- ECOG PS
- Safety assessment (AEs)
- Evaluation of CA-125 serum levels.

Patients who withdraw consent will not be followed with any study procedures. Patients withdrawn with ongoing study drug-related AEs (including SAEs) will be followed-up until the events or their sequelae resolve or stabilize at a level acceptable to the Investigator and the Sponsor.

Additional parameters will be assessed and/or the frequency of observations will be increased at the Investigator’s discretion and according to the nature of the observed AEs. When available, autopsy data should be provided.

5. TREATMENT
5.1. DESCRIPTION OF TREATMENT

**Group A: Carboplatin plus PLD**

PLD 30 mg/ m² followed by carboplatin AUC 5. Carboplatin area under the curve (AUC) dose will be calculated according to the Calvert’s formula (14):  \[ \text{Dose (mg)} = \text{target AUC} \times \text{GFR}^{\frac{1}{2}} + 25. \]

Detailed information on preparation, handling, storage and disposal of carboplatin and PLD may be found in their SPCs (for PLD please see: http://www.ema.europa.eu/humandocs/PDFs/EPAR/Caelyx/H-089-PI-en.pdf), which are provided as separate documents.

**Group B: Trabectedin plus PLD**

PLD 30 mg/m² infusion followed by trabectedin 1.1 mg/m² infusion. Trabectedin should be diluted in normal saline according to the preparation guidelines.

Detailed information on preparation, handling, storage and disposal of trabectedin and PLD may be found in their SPCs (for trabectedin please see: http://www.ema.europa.eu/humandocs/Humans/EPAR/yondelis/yondelis.htm), which are provided as separate documents.

5.2. ADMINISTRATION OF STUDY MEDICATION

5.2.1. Dose Schedule

**Group A:** PLD 30 mg/m² i.v. as a 1-hour infusion followed by carboplatin AUC 5 i.v. as a 30 min infusion on Day 1 every 4 weeks. A 4-week schedule defines a cycle of treatment.

**Group B:** PLD 30 mg/m² i.v. as a 1-hour infusion followed by trabectedin 1.1 mg/m² 3-hour i.v. infusion on Day 1 every 3 weeks. The use of central venous access is strongly recommended. A 3-week schedule defines a cycle of treatment.

In both arms patients will be treated during six cycles (or more in case of clinical benefit) or until PD, whichever occurs first.

5.2.2. Criteria for Treatment Continuation

Patients will remain on treatment for six cycles in the absence of confirmed progression or unacceptable toxicity that is not resolved after applying the appropriate dose reductions. Patients with clinical benefit may continue therapy beyond cycle 6 according to the Investigator criteria.

In order to be re-treated on Day 1 of a new cycle, patients will have to fulfill the same entry criteria (see inclusion criterion 8; 4.1). If these criteria are not met on Day 1 of a new cycle, treatment administration may be delayed for a maximum of two weeks in Group A and three weeks in Group B and reevaluated weekly. The new cycle will start upon recovery of these parameters, according to the same criteria.

*Calculated according to Cockroft-Gault formula.
A maximum delay of two weeks in Group A and three weeks in group B is allowed for recovery from drug-related AEs. If toxicities have not recovered within the allowed timeframe, the patient should discontinue treatment. In the event of obvious clinical benefit, the patient may remain on treatment upon agreement with the Sponsor, provided that all parameters have recovered according to the aforementioned criteria.

5.2.3. **Dose Reduction**

Dose reductions will be based on the worst drug-related toxicity that occurred since the last dose administration. The criteria for dose delay/reduction in either group are defined in Table 6 and Table 7. Once a dose has been reduced because of toxicity, there will be no dose re-escalation in subsequent cycles. A maximum of two dose reductions are allowed regardless of the type of toxicity. Study treatment will be permanently discontinued for any patient who required a third dose reduction.

5.2.3.1. **Group A: Carboplatin plus PLD**

The following dose levels will be used in modifying PLD and carboplatin doses after Cycle 1 according to toxicity (Table 6).

**Table 6. Carbo"platin + PLD dose reduction due to toxicity.**

<table>
<thead>
<tr>
<th>Dose Level 0</th>
<th>Dose Level –1</th>
<th>Dose Level –2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLD 30 mg/m²</td>
<td>PLD 25 mg/m²</td>
<td>PLD 20 mg/m²</td>
</tr>
<tr>
<td>Carboplatin AUC 5</td>
<td>Carboplatin AUC 4</td>
<td>Carboplatin AUC 4</td>
</tr>
</tbody>
</table>

If a further dose reduction from level -2 is specifically required for PLD despite adequate countermeasures and/or cycle delays, PLD must be permanently discontinued and the patient should be treated with carboplatin AUC 4 alone. Any patient who does not tolerate the carboplatin dose level -2 shall be treated at the discretion of the investigator. The patient will go off protocol treatment and will be followed as any other patient.

5.2.3.2. **Group B: Trabectedin plus PLD**

The following dose levels will be used in modifying PLD and trabectedin doses after Cycle 1 according to toxicity (Table 7).

**Table 7. Trabectedin + PLD dose reduction due to toxicity.**

<table>
<thead>
<tr>
<th>Dose Level 0</th>
<th>Dose Level –1</th>
<th>Dose Level –2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLD 30 mg/m²</td>
<td>PLD 25 mg/m²</td>
<td>PLD 20 mg/m²</td>
</tr>
<tr>
<td>Trabectedin 1.1 mg/m²</td>
<td>Trabectedin 0.9 mg/m²</td>
<td>Trabectedin 0.75 mg/m²</td>
</tr>
</tbody>
</table>

In case of recurrent toxicity after two dose reductions of one of the agents, the other non-reduced compound may be continued for patients with clinical benefit. Thus, for patients
continuing on single-agent trabectedin 1.3 mg/m², the first and second reduced doses will be 1.1 mg/m² and 0.9 mg/m², respectively. For patients continuing on single-agent PLD 35 mg/m², the first reduced dose will be 30 mg/m² and the second reduced dose will be 25 mg/m².

5.2.3.3. Dose Reduction for Hematological Toxicity

For details see Table 8.

Table 8. Dose reductions for hematological toxicity.

<table>
<thead>
<tr>
<th>Nadir Toxicity</th>
<th>Nadir value</th>
<th>All drugs in either Group A and B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil count</td>
<td>&lt; 1000/µl with fever (≥38.5°C)/infection</td>
<td>Decrease by 1 level</td>
</tr>
<tr>
<td></td>
<td>&lt; 500/µl lasting more than 5 days</td>
<td>Decrease by 1 level</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&lt; 25,000/µl or bleeding requiring platelet transfusion</td>
<td>Decrease by 1 level</td>
</tr>
</tbody>
</table>

5.2.3.4. Dose reduction for Non-hematological toxicity

Table 9 presents the dose reduction schedule for non-hematological toxicity.

Table 9. Dose reductions due to non-hematological toxicity.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Worst CTC grade</th>
<th>All drugs in either Group A and B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea or vomiting despite adequate treatment</td>
<td>≥3</td>
<td>Decrease by 1 level</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>≥3</td>
<td>Decrease by 1 level</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• First occurrence</td>
<td>≥3</td>
<td>Decrease by 1 level</td>
</tr>
<tr>
<td>• Any occurrence after first occurrence of grade 3/4</td>
<td>≥1</td>
<td>Decrease by 1 level</td>
</tr>
<tr>
<td>Conjugated bilirubin &gt;ULN at any time</td>
<td>≥1</td>
<td>Decrease by 1 level</td>
</tr>
<tr>
<td>Transaminase elevation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Recovery to grade 1 by Day 1 of the next cycle or within 3 weeks after this date</td>
<td>≥3</td>
<td>Decrease by 1 level</td>
</tr>
<tr>
<td>• No recovery to grade 1 or less by Day 1 of the next cycle or within 3 weeks after this date</td>
<td>≥3</td>
<td>Treatment termination</td>
</tr>
<tr>
<td>Alkaline phosphatase of non-osseous origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• First occurrence</td>
<td>1</td>
<td>No reduction</td>
</tr>
<tr>
<td>• Second occurrence or more</td>
<td>1</td>
<td>Decrease by 1 level</td>
</tr>
<tr>
<td>• First occurrence</td>
<td>≥2</td>
<td>Decrease by 1 level</td>
</tr>
</tbody>
</table>

Note: Dose reduction for any other severe toxicity not listed in this table needs to be discussed with the sponsor

5.3. Prophylactic Medication

Patients in Group A will receive prophylactic medication according to the Investigator criteria.

Patients in Group B will be pre-medicated with 20 mg dexamethasone i.v. 30 minutes before the PLD infusion. If dexamethasone is not available, an equivalent can be used.
Further steroid pre-medication can be used at the discretion of the investigator. Secondary prophylaxis with colony-stimulating factors such as granulocyte (G-CSF) or granulocyte-macrophage (GM-CSF) colony-stimulating factors may be used in both groups according to the American Society of Clinical Oncology (ASCO) or institutional guidelines (16).

5.4. CONCOMITANT THERAPIES

The concentrations of trabectedin in plasma are likely to be increased in patients who are co-administered drugs that potently inhibit the activity of CYP3A4. For this reason caution should be used with the following drugs: oral ketoconazole, fluconazole, ritonavir, clarithromycin or aprepitant. If such combinations are needed, close monitoring of toxicities is required.

Concomitant administration of trabectedin and inhibitors of P-gp, e.g. cyclosporin and verapamil, may modify trabectedin distribution or elimination. Combination of trabectedin with phenytoin or live attenuated vaccines is not recommended. Caution should be exercised with concomitant administration of trabectedin and medicinal products associated with rhabdomyolysis.

Medicinal products known to interact with standard doxorubicin hydrochloride such as streptozocin, phenobarbital, phenytoin and warfarin should be used with extreme caution. Concomitant treatment with other substances reported to be cardiotoxic or with cardiologically active substances (e.g. calcium antagonists) may increase the risk for cardiotoxicity, for this reason the co-administration of these substances during the study treatment is not recommended. Concomitant therapy with other liposomal or lipid-complexed substances or intravenous fat emulsions could change the pharmacokinetic profile of PLD.

Nephrotoxic compounds should be used with caution because their renal effect may be potentiated by Carboplatin.

Patients receiving concomitant therapy with other nephrotoxic agents are likely to experience more severe and prolonged myelotoxicity.

The concurrent administration of carboplatin and chelating agents should be avoided as it can theoretically lead to a decrease of the antineoplastic effect of carboplatin.

A decrease in phenytoin serum levels has been observed in case of concurrent administration of carboplatin and phenytoin. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.

5.5. PACKAGING AND LABELING

5.5.1. Carboplatin

Commercially available carboplatin will be utilized in this study. Carboplatin will be administered according to the directions of the prescribing information. Dose will be calculated according to Calvert’s formula (14) to obtain an AUC = 5 mg/ml*min for Group A. For more details see http://www.drugs.com/pro/carboplatin.html and the carboplatin Package Insert.
5.5.2. Pegylated Liposomal Doxorubicin (PLD)
Commercially available PLD (Caelix®) will be utilized in this study. See the Caelix® Package Insert, for more details.

5.5.3. Trabectedin
Trabectedin will be provided by the manufacturer as a sterile lyophilized product in vials containing 1.0 mg of trabectedin (Yondelis®). Before lyophilization, sufficient quantities of monopotassium phosphate and phosphoric acid were added to the process solution for pH adjustment. See the Yondelis® Package Insert, for more details.

5.6. Drug Accountability
Pharmacist and/or investigator will be responsible for receipt, proper storage, preparation (reconstitution and dilution) and usage of study medication. Proper drug accountability will be done by the clinical trial monitor. Each study site will keep records to allow a comparison of quantities of drug received and used at each site. All unused drug will be properly destroyed at the study site. Documentation of this procedure must be provided to the clinical trial monitor.

5.7. Treatment Compliance
The Investigator is responsible for supervising compliance with the instructions described in this study protocol.

6. Study Evaluations

6.1. Efficacy
All randomized patients to either treatment arm, regardless of whether they received any study drug or not, will be analyzed on the basis of the intention-to-treat principle for all the efficacy analyses.

The primary endpoint (OS) will be measured from the date of randomization up to the date of death due to any cause or, for living patients, the date of last contact.

PFS will be counted as time from randomization until progression or death due to any cause. For subsequent therapies PFS will be calculated from the date of first dose until progression or death due to any cause.

Response and progression will be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

For the determination of PFS, the following events will be taken into account:
- Death.
- Radiological tumor progression by RECIST version 1.1.
- Objective clinical progression (such as progressive peritoneal carcinomatosis with increasing bowel dysfunction, increased ascites requiring palliative drainage, emerging surgical procedure due to bowel obstruction).
The planned analysis of OS and PFS will include all randomized patients (on the basis of the intention-to-treat principle).

Disease evaluations will be performed symmetrically in both arms at week 12 and 24 including physical exam, radiology (CT scan or MRI, or PET/CT scan; regardless of the number of administered cycles) and CA-125 serum levels. The same method of assessment will be used to determine the disease status at baseline and at week 12 and 24. Afterwards, pelvic examination and CA-125 levels will be performed every 12 weeks for the first two years and every six months thereafter, until evidence of PD or death. Further radiological imaging is left at clinical discretion.

The time from randomization to subsequent chemotherapy and the overall survival counted from the administration of subsequent chemotherapy will be evaluated as an exploratory analysis.

6.2. SAFETY

All patients who have received at least part of one cycle of treatment will be included in the safety analysis. Safety will be evaluated by clinical examination, assessment of clinical AEs, changes in laboratory parameters (blood counts, clinical chemistry including liver function tests), and other tests as appropriate.

AEs will be graded according to the NCI-CTCAE version 4.0 (31) and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 11.0.

6.3. QUALITY OF LIFE

Health related quality of life will be assessed using the EORTC QLQ-C-30 and OV-28 questionnaire. Both questionnaires will be evaluated using the scoring manuals provided by the EORTC QoL unit. The Sponsor of the study will provide both questionnaires in local languages. The EORTC QoL unit has given a written agreement to the Scientific Coordinator of the study leading group for using the questionnaire QLQ C-30 and OV-28.

Both PRO instruments will be completed by each patient at screening (before randomization) and within four weeks from the end of the sixth cycle or at the time of progression, whichever occurs first.

7. ADVERSE EVENTS REPORTING

7.1. DEFINITIONS

7.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or a clinical investigation patient administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), or a disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any event involving adverse drug reactions, illnesses with onset during the study or
exacerbations of pre-existing illnesses should be recorded, including but not limited to clinically significant changes in physical examination findings and abnormal objective test findings (e.g., x-Ray, ECG). The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- The test result is associated with clinically significant symptoms, and/or,
- The test result leads to a change in the study dosing or discontinuation from the clinical trial, significant additional concomitant drug treatment or other therapy, and/or,
- The test result leads to any of the outcomes included in the definition of a SAE, and/or,
- The test result is considered to be an AE by the Investigator.

7.1.2. **Serious Adverse Event**

A Serious Adverse Event (SAE) is any adverse experience occurring at any dose that:

- Results in death (is fatal),
- Is life-threatening,
- Requires or prolongs inpatient hospitalization,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly or birth defect,
- Is medically significant, or
- Is any suspected transmission of an infectious agent via a medicinal product.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations such an important medical event that may not be immediately life-threatening or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the above definition.

Disease progression will be reported as SAE term.

7.1.2.1. **Death**

Death as such is the outcome of a SAE and should not be used as the SAE term itself. Instead, the cause of death should be recorded as the SAE term.

7.1.2.2. **Life-threatening Event**

Any event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

7.1.2.3. **Hospitalization or Prolongation of Hospitalization**

Any AE requiring hospitalization (or prolongation of hospitalization) that occurs or worsens during the cycle of a patient’s participation in a clinical trial must be reported as a
SAE unless exempted from SAE reporting (see Section 7.2.2). 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 by the treating physician.

Hospitalizations that do not meet criteria for SAE reporting are:

a. Reasons described in protocol (e.g., investigational medicinal product [IMP] administration, protocol-required intervention/investigations, etc). However, events requiring hospitalizations or prolongation of hospitalization as a result of a complication of therapy administration or clinical trial procedures will be reported as SAEs.

b. Hospitalization or prolonged hospitalization for technical, practical or social reasons, in absence of an AE.

c. 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 SAE.

Other situations that MUST NOT be considered as hospitalizations are the following:

d. An emergency visit due to an accident where the patient is treated and discharged.

e. When the patient is held 24 hours for observation and finally is not admitted.

f. Planned treatments at sites not associated to a hospital and generally considered as minor surgical procedures (e.g., laser eye surgery, arthroscopy, etc).

7.1.3. Unlisted/Unexpected Adverse Event

Unlisted or unexpected AE is an AE with the nature or severity of which is not consistent with the applicable reference safety information. The SPC or its national equivalent document will be used by the Sponsor as the reference safety information for the evaluation of listedness/expectedness of AEs.

7.1.4. Adverse Events Related to Study Drug/s (IMP)

An AE is considered related to a study drug/IMP if the Investigator’s assessment of causal relationship to the IMP is “Y” (yes).

The Investigator will assess the causal relationship of each of the IMPs to the SAE.

The Sponsor may also consider related to the study drug/IMP those events for which the Investigator assesses the causal relationship with the IMP as “Uk” when it cannot rule out a role of the IMP in the event. See Section 7.1.6 for causality scale.

7.1.5. Expedited Reporting

The Sponsor is responsible for the appropriate expedited reporting of SAEs to the Regulatory Authorities. The Sponsor will also report all SAEs that are unlisted and related to the study drug/s (IMP/s), to the Investigators and to the IECs/IRBs according to the current legislation unless otherwise required and documented by the IECs/IRB.

7.1.6. Assessment of Causal Relationship to the Study Drug/IMP
The Investigator must provide an assessment of causal relationship of each of the clinical trial IMPs (including combination and comparator products) to each SAE according to the following scale:

- **Y** There is a reasonable possibility that the IMP/s caused the SAE.
- **N** There is no reasonable possibility that the IMP/s caused the SAE and other causes are more probable.
- **Uk.** Only to be used in special situations where the Investigator has insufficient information (i.e., the patient was not seen at his/her centre) if none of the above can be used.

7.2. PROCEDURES

7.2.1. Reporting Adverse Events

The Sponsor will collect AEs until 30 days after administration of the last dose of study drug/IMP or until the start of a new antitumor therapy, whichever occurs first. All AEs suspected to be related to the study drug/IMP must be followed after the time of therapy discontinuation until the event or its sequelae resolve or stabilize at an acceptable level to the Investigator and the Sponsor.

All AEs must be recorded using medical terminology in the source document and the eCRF. Whenever possible, the Investigator will record the main diagnosis instead of the signs and symptoms normally included in the diagnoses.

Investigators must assess severity (grade) of the event following the NCI-CTCAE v.4.0 and assign relationship to each study drug/IMP; pursue and obtain information adequate both to determine the outcome and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the Sponsor or its designated representative. The Investigator must provide any relevant information as requested by the Sponsor in addition to that on the eCRF.

Abnormal laboratory tests occurring during the study are AEs, but they should be collected only in the AE section of the eCRF in some cases (please refer to the eCRF guidelines for comprehensive information).

7.2.2. Reporting Serious Adverse Events

The Sponsor will collect SAEs from the signing of the Informed Consent Form. All identified SAEs must be recorded and described on the appropriate SAE pages of the eCRF.

SAEs will be collected until 30 days after administration of the last dose of study drug/IMP or until the start of a new antitumor therapy, whichever occurs first. Beyond this period of time, only those SAEs suspected to be related to the IMP/s need to be reported. Nonetheless, the Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

All forms of SAEs (as defined above) regardless of treatment group or relationship to the study drug/IMP must be dated and signed by the responsible investigator or one of her/his authorized staff members and sent by fax within 24 hours of the initial observation of the
event to:

Sponsor safety desk:

Dr. Marlen Llerena Mesa
Fax: +39 02 33200231
E-mail: marlen.llerena@marionegri.it

An initial report must be followed by a completed “Serious Adverse Event Form” from the investigational staff within one working day.

All SAEs suspected to be related to the IMP/s must be followed until the event or its sequelae resolves or stabilizes at an acceptable level by the Investigator and the clinical monitor or his/her designated representative.

Death as such, is the outcome of a SAE and should not be used as the SAE term itself. Instead the cause of death should be recorded as the SAE term. When available, the autopsy report will be provided to the Sponsor.

7.2.3. Reporting Pregnancy Cases Occurred Within the Clinical Trial

National regulations require that clinical trial Sponsors collect information on pregnancies occurring during clinical trials, in which exposure to the IMPs at any time during pregnancy, is suspected.

Therefore, pregnancy and suspected pregnancy (including a positive pregnancy test regardless of age or disease state) occurring while the patient is on study drug, or within 30 days of the patient’s discontinuation visit, are considered immediately reportable events.

The Investigator will report the following events immediately and always within 24 hours from first knowledge:

- Any occurrence of a pregnancy where any kind of exposure to the IMP/s is suspected.
- Possible exposure of a pregnant woman (female who came in contact with the clinical trial IMP/s).
- All reports of elevated/questionable or indeterminate beta human chorionic gonadotrophins (βhCGs).

Immediately after detecting a case of suspected pregnancy in a clinical trial patient, the decision on her continued participation in the clinical trial will be jointly taken by the trial patient, the Investigator and the Sponsor, with the patient’s best interest in mind. A decision to continue the pregnancy will require immediate withdrawal from the trial. If the trial is blinded, the Investigator will open the blind whenever the treatment information is needed for the management of the patient.

Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Sponsor Pharmacovigilance immediately by fax. The Investigator will follow the pregnancy until its outcome, and must notify the Sponsor Pharmacovigilance the outcome of the pregnancy within 24 hours of first knowledge as a follow-up to the initial report.

For any event during the pregnancy, which meets a seriousness criterion (including fetal or neonatal death or congenital anomaly), the Investigator will also follow the procedures for
reporting SAEs (complete and send the SAE form to the Sponsor Pharmacovigilance by facsimile within 24 hours of the Investigator’s knowledge of the event).

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death at any time thereafter that the Investigator suspects is related to the exposure to the study drug/IMP should also be reported to the Sponsor Pharmacovigilance by facsimile within 24 hours of the Investigators’ knowledge of the event.

8. STATISTICAL METHODS

The statistical analysis will be done by the Sponsor or under the Sponsor’s authority.

8.1. Sample Size

This study is designed to demonstrate a statistically and clinically significant difference in OS, \((H_0: \text{hazard ratio}=1, H_1: \text{hazard ratio}=0.75)\). The primary OS analysis will be conducted when 442 events are observed; 588 patients are estimated to be enrolled to allow the demonstration of a statistically significant difference in the OS at a one-sided 2.5% significance level with at least 85% power. With these assumptions a reduction in the relative risk of death of at least 17.34% would allow the null hypothesis rejection.

8.2. Randomization

Randomization procedure will have a 1:1 ratio, using a biased-coin minimization procedure having as stratification factors center, line of chemotherapy (2\(^{nd}\) vs. 3\(^{rd}\)), measurable disease (yes vs. no) and previous anthracyclines-based chemotherapy (yes vs. no). A system that automates the random assignment of treatment groups will be used. The random application is accessible 24 hours a day, seven days a week.

8.3. Interim Analyses

A futility analysis of the primary end point (OS) to reject \(H_1\) is planned. This interim analysis will be conducted with approximately \(~100\) events, which are estimated to occur \(~28\) months after start of study enrolment (assuming 10 patients/month and median OS~18-24 months in the control group). The trial will be stopped in case of clear OS advantage in the control arm. No claim for superiority is planned in this analysis.

A second interim analysis to test superiority will be performed when two thirds of the death events are observed (approximately at the end of recruitment period) with the significance level determined by the actual observed number of events and alpha spending function defined by the O’Brien-Fleming boundary.

8.4. Endpoints

8.4.1. Primary Endpoint

Overall survival (OS): will be measured from the date of randomization up to the date of
death due to any cause or, for living patients, the date of last contact.

8.4.2. Secondary Endpoints

**Efficacy:**
- PFS: will be measured from the date of randomization to the date of documented PD or death (regardless of cause of death). All patients should have documented disease progression before the administration of subsequent anticancer therapy although if a patient receives further antitumor therapy before PD, PFS will be censored on the date of administration of this antitumor therapy.

For the determination of PFS, the following events will be taken into account:
- Death due to any cause.
- Radiological tumor progression by RECIST v.1.1.
- Objective clinical progression (such as progressive peritoneal carcinomatosis with increasing bowel dysfunction, increased ascites requiring palliative drainage, emerging surgical procedure due to bowel obstruction).
- Objective RR will be the best response obtained in any evaluation according to RECIST 1.1.
- CA-125 serological response will be the best response obtained in each arm.
- Duration of response: will be calculated from the date of first documentation of response (CR or partial response [PR], whichever occurs first) to the date of documented PD or death.
- The time from randomization to subsequent chemotherapy and the overall survival counted from the administration of subsequent chemotherapy will be evaluated as an exploratory analysis.
- For subsequent therapies the best response obtained (CR, PR, stable disease [SD] or PD) and PFS will be calculated from the date of first dose until progression or death due to any cause.

Treatment drugs, date of initiation, best response achieved and progression date of subsequent therapies in both arms will be also collected in the eCRF. Type and length of remission (response and PFS) after subsequent therapies following each of the two combinations will be evaluated using the same procedures.

**Safety:**
- Clinical and laboratory toxicities, SAEs and toxicities leading to dose delays, dose modifications and treatment discontinuations.

**Others:**
- QoL according to the EORTC QLQ-C30 and QLQ-OV28.
- PK profile (in selected sites only) to quantify the trabectedin concentrations in ascites and to evaluate its relationship with plasma concentrations (Appendix 2. Pharmacokinetic Sub-study).

8.5. Statistical Analysis
Continuous variables will be tabulated and presented with summary statistics (i.e., mean, standard deviation, median and range). Categorical variables will be summarized in frequency tables by means of counts and percentages.

8.5.1. **Efficacy Analysis**

The all randomized population (on the basis of the intention-to-treat principle) will be used for all the efficacy analyses.

Time-to-event variables (OS, PFS, response duration and length of remission to subsequent therapies, the time from randomization to subsequent chemotherapy and the overall survival counted from the administration of subsequent chemotherapy and their fixed-time estimates) will be calculated according to the Kaplan-Meier method.

For the primary analysis, OS between treatment arms will be compared by the log-rank test. The log-rank test will also be used for the comparison of PFS and response of duration, as well as the length of remission to subsequent therapies. Cox regression will be used to calculate the risk reduction and to evaluate the influence of the randomization variables and other potential prognostic factors on the time to event endpoints.

For the categorical variables (ORR and serological response) binomial exact estimates and confidence interval at 95% will be calculated. For comparisons between arm A and B, the Fisher exact test will be performed.

8.5.2. **Safety Analysis**

All patients who have started their allocated treatment receive at least part one cycle of treatment (all treated population) will be included in the safety analysis.

Descriptive statistics will be used to contrast baseline characteristics and safety profile between both arms.

The AEs, SAEs, laboratory evaluations, deaths and the reason for study discontinuations will be analyzed. All AEs and SAEs will be classified according to the NCI-CTCAE v.4.0, and will be coded using the MedDRA, v.11.0.

8.5.3. **Patient Reported Quality of Life**

The patient-reported QoL will be measured by the QLQ-C30, expanded with the QLQ-OV28 questionnaires.

Both PRO instruments will be completed by each patient at screening (before randomization) and, if not progressing, within 4 weeks from the end of the sixth cycle of chemotherapy or at the time of progression, whichever occurs first.

The profiles of the change from baseline will be carried out using t-tests and mixed-effects models.

9. **ADMINISTRATIVE SECTION**

9.1. **ETHICS AND REGULATORY COMPLIANCE**

This study will be conducted in compliance with the protocol, the ethical principles that
have their origin in the Declaration of Helsinki (59th World Medical Association General Assembly, Seoul October 2008) (see Appendix 4. Declaration of Helsinki), the International Conference on Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (CPMP/ICH/135/95), and applicable local regulatory requirement(s).

9.1.1. **Patient Confidentiality**

The investigators and the Sponsor will preserve the confidentiality of all patients taking part in the study, in accordance with ICH/Good Clinical Practice (GCP) and local regulations.

The Sponsor will observe the rules laid down in the European Data protection Directive 95/46/EC, national regulations and following additions on the protection of individuals with regard to the processing of personal data and the free movement of such data.

The investigator must ensure that the patient anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, patients should be identified by a unique patient code. Documents that are not for submission to the Sponsor (e.g., signed informed consent form) should be kept in strict confidence by the investigator.

In compliance with local regulations/ICH/GCP guidelines, it is required that the investigator and institution permit authorized representatives of the Sponsor, of the regulatory agency(s), and the IEC/IRB direct access to review the patient original medical records for verification of study-related procedures and data. The investigator is obliged to inform the patient that her/his study related-records will be reviewed by the above named representatives without violating the confidentiality of the patient.

9.1.2. **Informed Consent Procedure**

Before a patient participation in the study, it is the investigator responsibility to obtain freely given consent, in writing, from the patients after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. The written informed consent form (ICF) must be prepared in the local language of the potential patient population.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements, and adhere to ICH/GCP and to the ethical principles that have their origin in the Declaration of Helsinki (59th World Medical Association General Assembly, Seoul October 2008) (see Appendix 4. Declaration of Helsinki). The ICF and any revision(s) must be approved by the IEC/IRB prior to being provided to potential patients.

The patient written informed consent should be obtained prior to her/his participation in the study, and should be documented in the patient medical records. The ICF should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily the principle investigator, but an authorized medical staff member). The original signed ICF should be retained in accordance with institutional policy, and a copy should be provided to the patient. The date that informed consent was given must be recorded on the eCRF.

If the patient cannot read, then according to ICH/GCP guideline, an impartial witness should be presented during the entire informed consent discussion. This witness should sign
the ICF after the patient has orally consented to the patient participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the patient and that informed consent was freely given by the patient.

Suggested model text for the ICF for the study and any applicable subparts (PK) are provided in the Sponsor ICF template for the investigator to prepare the documents to be used at her/his site. Updates to applicable forms will be communicated from the Sponsor.

9.1.3. Regulatory Compliance

The study protocol, proposed patient information, QoL questionnaires and ICF, the investigator brochure, any written instructions to be given to the patient, available safety information, and any other relevant documents must be submitted to the IEC/IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

The investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the ICF. The investigator should notify the IEC/IRB of severe adverse drug reactions (SADRs) occurring at the site and other SADR reports received from the Sponsor, in accordance with local procedures.

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation, and that the implementation of changes to the initial protocol and other relevant study documents happen only after approval by the relevant regulatory bodies.

9.1.4. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the investigator by the Sponsor. Also, the Sponsor will assure the timely submission of amendments to regulatory authorities and IEC/IRB.

Global protocol amendments will affect study conduct at all sites. Such amendments will be incorporated into a revised protocol document. Changes made by such amendments will be documented in a summary of changes document. These protocol amendments will undergo the same review and approval process as the original protocol in accordance with local requirements. A protocol amendment may be implemented only after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for patient safety.

9.2. Study Administrative Information

INOVATYON is an international and collaborative study between several equal participating groups. The common organs of the inter-group study will be the Steering Committee (SC), an independent Data Safety and Monitoring Committee (DSMC) and the coordinating data centre.

9.2.1. Steering Committee (SC)

The study will have oversight in a blinded manner by the SC, composed by gynecologists
and oncologists. For practical reasons the SC will identify a restricted sub-committee, composed by gynecologists and oncologists in charge of making all not-substantial decisions and to ensure the smooth running of the study. The SC will receive twice yearly information about:

- Accrual rate and description of protocol violations;
- Group allocation;
- Toxicity data;
- Incidence of the events (aggregated data).

The members of the SC will receive the survival curves of the whole population of the interim analysis in blinded form (curves not divided by treatment arms).

All scientific decisions concerning stopping, continuation or any amendment of the study will be made by the SC after discussion with the DSMC.

### 9.2.2. Data Safety and Monitoring Committee (DSMC)

An independent DSMC composed of three international experts (two gynecologists and one statistician), not involved in the study and with no conflict of interest with respect of study results will monitor the progress of the study on ethical and scientific basis.

Two interim analyses and a final analysis are planned (see Section 8.3). The results of interim analyses will remain confidential. On the basis of these analyses, the DSMC may recommend whether the study should continue or whether it should be changed or terminated prematurely. Specific tasks of DSMC will be:

- To review study progress (i.e., accrual rate, protocol compliance, event rate);
- To examine interim efficacy data. Results of interim analyses will be presented unblinded by the study statistician to the DSMC. The DSMC may also ask for any additional information, if considered appropriate. The DSMC is requested to submit a report to the SC summarizing recommendations for the study prosecution and possible protocol modification;
- To monitor toxicity. Every six months the study statistician will circulate a report to the members of the DSMC about toxicity. The DSMC will review these interim toxicity data although this is primarily the responsibility of the SC. This biannual procedure prevents against problems of major toxicity;
- To examine other trials. The DSMC will review reports of related studies performed by other groups or organizations to determine whether such information affects the aims or preliminary findings of the trial;
- To review any major modification to the study proposed by the SC prior to its implementation.

### 9.3. Coordinating Data Centre

The clinical trial laboratory of the Istituto di Ricerche Farmacologiche “Mario Negri” will
play the role of coordinating data centre together with the Contract Research Organization (CRO), which will provide study monitoring and coordinating. Specific tasks of the coordinating data centre will be as follows:

- To draw up the study documentation (e.g., study protocol, eCRF, ICF) cooperating with the investigators;
- To initiate the study (e.g., to submit study authorization application to local authorities and IEC/IRB);
- To implement randomizing algorithm, to create the eCRF and to maintain the system for the study duration;
- To coordinate the study conduction;
- To comply with SAE monitoring and handling;
- To perform interim and final statistical analyses;
- To draw the study final report.

9.4. **DATA INTEGRITY AND QUALITY ASSURANCE**

The investigator/investigational site will permit study-related monitoring, audits, IRB/IEC review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

9.4.1. **Monitoring, auditing and Inspecting**

The monitors/auditors of the Sponsor and regulatory authority are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs, source data, and other pertinent documents).

The monitor is responsible for visiting sites at regular intervals (as detailed in the monitoring plan) throughout the study to verify adherence to the protocol (completeness, accuracy and consistency of the data) and adherence to ICH/GCP and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

The monitor will communicate deviations from the protocol, standard operating procedures (SOPs), ICH/GCP and applicable regulations to the investigators and will ensure that appropriate action designed to prevent recurrence of the detected deviations is taken and documented.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are documented and addressed.

9.4.2. **Data Collection**

Patient randomization and data collection will be performed using a clinical trial
management system internally developed by the Sponsor and able to fully operate via Web. Moreover, the system holds these features:

- Each user enabled to the access is identified through his account (username/password);
- Each user is enabled to read his case of competence;
- Every modification to the fields of the eCRF is traced;
- Every patient is identified by a trial code generated from the system during the registration phase.

The eCRF should be kept current to enable the monitor to review the patient status throughout the study. The eCRF will be completed, reviewed and electronically signed by the investigator.

9.4.3. **Data Management**

Edit checks and data clarification forms (DCFs) will be built into the data management plan (DMP), describing also the post-entry validation.

Each patient will be identified in the database by a unique patient identifier, as defined by the Sponsor (see also Section 4.6).

To ensure the quality of clinical data across all patients and sites, a review will be performed on patient data according to specifications given in a data validation plan.

Data will be checked both electronically and manually using Statistical Analysis System software, throughout programmed data rules within the application. During this review, patient data will be checked for consistency, omissions and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and ICH/GCP. To resolve any questions arising from review process, queries generated by rules and mentioned by reviewers will be raised and resolved.

9.4.4. **Study Documentation and Storage**

The investigator will maintain a signature list of appropriately qualified people to whom she/he has delegated study duties. All people authorized to make entries on eCRFs must be included on the signature list. Source documents are original documents, data and records from which the patient eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, QoL patient-reported outcomes instruments, microfiches, X-rays and correspondence.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system, the Investigator Site File (ISF) of all study-related documentation, suitable for inspection at any time by representative from the Sponsor and/or applicable regulatory authorities. In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

All essential documentation will be retained by the institution until told otherwise by the Sponsor. No study documents should be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, she/he must notify the Sponsor in writing of the new responsible person and/or the new location.
9.4.5. Record Keeping

Records of patients, source documents, monitoring visit logs, DCFs, eCRFs, inventory of study product, regulatory documents (e.g., protocol and amendments, IRB/IEC correspondence and approvals, approved and signed ICFs, investigator agreement, clinical supplies receipts, distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the site. Source documents include all recordings and observations of notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

9.5. FINANCING AND INSURANCE

9.5.1. Finances

The study is sponsored by the Istituto di Ricerche Farmacologiche “Mario Negri”, which plays the role of not-for-profit Sponsor.

Pharma Mar, S.A., sociedad unipersonal (thereafter PharmaMar) supports the study, providing the economical support for costs related to data management, local and central monitoring, statistical analysis and the recruitment of patients.

9.5.2. Insurance

The Sponsor of the study agrees to take out adequate clinical insurance to cover its obligations, including but not limited to provide compensation to patients in the study suffering injury of death or loss caused by the administration of drugs or any clinical intervention or procedure in accordance with the relevant protocol and all legal requirements. All patients participating in this clinical trial will therefore be covered by a civil liability policy in accordance to the local laws.

9.6. PUBLICATION POLICY

Every publication of the study results will be written on the basis of the analyses performed by the coordinating data center and approved by the SC. Publications will be decided by the SC. Authors to be reported in the front page will be selected on the basis of the specific contribution or the number of enrolled patients and/or on the consistency, completeness and accuracy of the data. Furthermore, the specification “on behalf of INOVATYON Study Group” will be added. The name list of each article will include:

- For each experimental centre at least one investigator;
- For the Sponsor the responsible, the statistician, the statistician in charge of interim analysis, the data manager, the responsible of informatics, the local monitors and the responsible of safety desk;
- DSMC members;
- SC members;
- At least one of the relevant PharmaMar personnel who have participated in the study.

Furthermore, all manuscripts will include an appropriate acknowledgment section,
mentioning all persons who have made substantial contributions to the work but who are not authors and sources of funding and support. Rules for abstract presentation will be the same as for extended papers.

10. ACKNOWLEDGEMENT
This study is generously funded by PharmaMar.

11. REFERENCES


Appendix 1. The New York Heart Association

The New York Heart Association (NYHA) classification grades the severity of heart failure symptoms as one of four functional classes. The NYHA classification is widely used in clinical practice and in research because it provides a standard description of severity that can be used to assess response to treatment and to guide management. It is less useful for prognosis because symptoms can fluctuate and the severity of symptoms does not always reflect the severity of the underlying heart problem — people with severe heart disease can have mild symptoms, and vice versa.

NYHA classification of heart failure symptoms [American Heart Association, 1994]:

- **NYHA class I:** asymptomatic left ventricular dysfunction is included in this category:
  - No limitations. Ordinary physical activity does not cause fatigue, breathlessness, or palpitation.

- **NYHA class II: symptomatically 'mild' heart failure:**
  - Slight limitation of physical activity. Such people are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, breathlessness, or angina pectoris.

- **NYHA class III: symptomatically 'moderate' heart failure:**
  - Marked limitation of physical activity. Although people are comfortable at rest, less than ordinary physical activity will lead to symptoms.

- **NYHA class IV: symptomatically 'severe' heart failure:**
  - Inability to carry on any physical activity without discomfort. Symptoms of cardiac failure are present even at rest.

Source:
http://www.cks.nhs.uk/heart_failure_chronic/background_information/nyha_classification_of_symptoms#-380908
Appendix 2. Pharmacokinetic Sub-study

At selected sites, blood and ascites samples will be obtained from approximately 10 patients included in the arm B presenting ascites at baseline. Both blood and ascites samples will be obtained at the time points detailed in Table 1 during and after the first trabectedin infusion, to evaluate the PK of trabectedin in plasma and ascites after its i.v. administration. All sample collection dates and times will be recorded on the PK sampling sheet.

Table 1. Pharmacokinetic sampling schedule of blood and ascites samples.

<table>
<thead>
<tr>
<th>Sample number</th>
<th>Day</th>
<th>Sampling time relative to the trabectedin infusion</th>
<th>Decimalized hours relative to the start of trabectedin infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Pre-infusion (-1 day window)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1.5h after SOI</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>5 min before EOI</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>15 min after EOI</td>
<td>3.25</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1h after EOI</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>3h after EOI</td>
<td>6</td>
</tr>
<tr>
<td>7 *</td>
<td>2</td>
<td>24h after EOI (±2 hours)</td>
<td>27</td>
</tr>
<tr>
<td>8 *</td>
<td>3</td>
<td>48h after EOI (±2 hours)</td>
<td>51</td>
</tr>
<tr>
<td>9 **</td>
<td>8</td>
<td>168h after EOI (±24 hours)</td>
<td>171</td>
</tr>
</tbody>
</table>

SOI, start of infusion; EOI, end of infusion; min, minutes; h, hour(s).

During the infusion with PK sampling, the infusion rate will be established so that it ensures that the total trabectedin dose is infused in 3 hours. Trabectedin will be infused with a pump at a constant rate throughout the 3 hours. In order to obtain reliable PK information, the infusion rate should not be modified once the infusion begins. If a variation in the infusion time eventually occurs, it is very important to reflect it in the eCRF, writing clearly the time of the beginning and the end of the infusion. The infusion rate should not be changed to maintain the scheduled duration of infusion. It would be enough just to record the actual duration in the PK sheet. The accurate recording of actual dosing and sampling times is much more important than the strict adherence to the scheduled times.

1.1. Blood samples

A total of 9 blood samples for PK analysis will be obtained at the time points detailed in Table 1 through a peripheral vein located in the contralateral side to that of infusion. In any case, the sampling vein has to be different to that in which drugs are infused. Even the last sample must never be collected from the catheter used for drug infusion. The volume of blood to be extracted is 5 ml for each sample.

If the blood sample is obtained from a catheter, the first milliliter of blood will be discarded.
to avoid dilution of the sample with the solution used to keep it clean. Heparin (10 U/ml in normal saline solution) or a slow drip of normal saline solution (10 ml/h) can be used to keep the catheter permeable between extractions.

1.2. **ASCITES SAMPLES**

A total of nine ascites samples will be taken at the time points detailed in Table 1 from the peritoneal cavity using a temporary indwelling catheter commonly used for drainage of ascites. The catheter has to be flushed with heparin after each sample collection to prevent blockage upon lock. The volume of ascites to be extracted is 10 ml for each sample.

To properly assess the trabectedin PK in ascites, it is very important to **avoid** palliative drainage of the ascitic fluid for the duration of the PK sampling (eight days after the first trabectedin infusion). However, in case of increased ascites requiring palliative drainage during the PK sampling period it is very important to reflect the time of extraction and quantity of removed ascites in the eCRF.

1.3. **SAMPLE MANAGEMENT**

Ascites and blood samples should be collected in a 10 ml sodium heparin tubes and centrifuged (2500 x g for 15 minutes at 4°C). If immediate centrifugation is not possible, the tubes containing the blood or ascites samples must be placed in an ice bath at 0-4°C for a maximum of 30 minutes. After centrifugation, supernatant will be transferred to the provided polypropylene tubes and stored at -20°C until the shipping to the analysis laboratory. The cell pellet should be discarded. All the tubes (nine vacuum tubes for blood, nine vacuum tubes for ascites, 9 polypropylene tubes for plasma and 9 polypropylene tubes for ascites supernatant) will be provided by PharmaMar.

PK samples could be stored up to a maximum of two months before shipment.

PK sampling sheets should be sent at the same time, but never in contact with the dry ice.

Samples will be identified with the following data: study reference, matrix, drug, patient number, cycle, sample number, date and time of collection. The confidentiality of patients’ data will be maintained at all times.

Samples will be destroyed following the appropriate laboratory procedures, after the approval of the final analytical study report by the Sponsor.

A manual of instructions for sample collection, labeling, storage, and shipment will be provided (Instruction Manual for the Collection, Labeling, Storage and Shipment of Pharmacokinetic Samples).

1.4. **PHARMACOKINETIC ANALYSIS**

Pharmacokinetic parameters in both plasma and ascites will be calculated using non-compartmental methods. If the quality of the PK data allows for it, the relationship between plasma and ascites concentrations will also be evaluated using compartmental methods.
Appendix 3. ECOG Performance Status Assessment Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Able to carry on all normal activities without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out light work.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
</tbody>
</table>
Appendix 4. Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and...
treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the Sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be
made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-
written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the
extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
   a. The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
   b. Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.