RESEARCH PROJECT SUMMARY

I. GENERAL INFORMATION

1. Title: **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		
2. IEO Principal Investigator: Prof. Nicoletta Colombo		
3. Division: Gynaecology Unit, Medical Oncology	4. Sponsor: Mario Negri Gynecologic Oncology Group-MaNGO	
5. Multicentric study Coordinating Centre: Istituto Europeo Oncologico, Milan. Coordination Centre: MaNGO- Istituto di Ricerche Farmacologiche Mario Negri, Milan.		
6. Duration: 6 years and 6 months	7. Expected start date: October 2010	8. Expected end date: December 2016

II. KEY CHARACTERISTICS

1. Pharmacological study
1.1 Study treatment: Trabectedin (Yondelis) in association with PLD.
1.2 Trabectedin mechanism of action: anti-tumour agent that binds to the DNA's minor groove and bends towards the major groove blocking transcription and triggering tumour cell apoptosis.
1.3 Proposed study indication: treatment of advanced, progressive ovarian cancer.
1.4 Approved indication: indicated in combination with pegylated liposomal doxorubicin (PLD) for the treatment of patients with progressive, platinum-sensitive ovarian cancer.
1.5 **Phase III Study**
1.6 Placebo will not be used

III. METHODOLOGICAL APPROACH

1. **Scientific rationale:** there are no comparison data available on Trabectedin and PLD vs. platinum-based chemotherapy. Based on the outcomes of studies OVA-301 and CALYPSO, INOVATYON will investigate the role of a platinum-free treatment regimen in patients with progressive ovarian cancer 6-12 months after completing previous platinum-based chemotherapy. In particular, this study aims at demonstrating that prolonging PFS (progression-free survival) with platinum-free combination therapy (Trabectedin and PLD) will result in prolonged survival in the study population.
2. **Key study objective:** Proving that Trabectedin (Yondelis) and PLD prolong Overall Survival (OS) vs. carboplatin plus PLD, in patients with progressive ovarian cancer 6-12 months after completing previous platinum-based chemotherapy. 3. **Secondary objectives:** - Progression Free Survival (PFS) - Response by treatment arm based on CA-125 levels - Quality of life by treatment arm - Safety
4. **Study design:** The objective of this multicentric, randomised, Phase III study is to demonstrate superiority, in terms of prolonged survival, of trabectedin and PLD vs. carboplatin and PLD. Patients will be randomised to: Arm A: PLD 30 mg/m^2 in 1 hour i.v. infusion followed by 30 min carboplatin AUC 5 i.v. infusion on treatment day 1. Each cycle will last 4 weeks. Arm B: PLD 30 mg/m^2 in 1 hour i.v. infusion followed by 3 hours trabectedin 1.1 mg/m^2 i.v. infusion on treatment day 1. Each cycle will last 3 weeks.
Study treatment: Trabectedin and PLD **Control treatment:** Carboplatin and PLD

IV. STUDY POPULATION

1. **Patients'/subjects' characteristics:** patients over 18 years of age with advanced, progressive ovarian cancer 6-12 months after completion of first line treatment with platinum-based chemotherapy.	
2. Total number of patients/subjects: 588	3. Number of patients/subjects in each centre: Approximately 5

4. **Sample size justification:** This study has been designed to demonstrate a statistically and clinically significant difference in terms of survival (H_o: HR=1, H_1: HR=0.75). In order to identify a significant difference in survival with a 2.5% significance level at least 85% power, 422 events and 588 patients are needed. In order to reject a null hypothesis a 17.34% reduction in mortality risk will be required.

5. **Inclusion criteria:**

- Women age >18
- Patients with cancer of the ovaries, fallopian tubes or primary peritoneal cancer.
- Patients with 6 to 12 months PFS from the date of their last platinum-based treatment cycle to radiologically confirmed progression. Patients may have received more than 2 platinum-based treatment lines; at least one of which must have contained taxanes.
- Measurable or assessable disease, radiologically confirmed by tests such as MRI, CT scan or PET/CT (CA-125 alone is not acceptable) or histological evidence of recurrent ovarian cancer, even in case of absence of post-surgical measurable or assessable lesions.
- ECOG ≤ 2
- Life expectancy ≥ 12 weeks
- Patients willing to commit to treatment and follow-ups.
- Adequate bone marrow, renal and liver function as defined by the following tests (to be carried out 14 days prior to starting 1st treatment cycle):
  i. Haemoglobin ≥ 9g/dl
  ii. Neutrophils ≥ 1,5 x 10^9/L
  iii. Platelets ≥ 100 x 10^9/L
  iv. Glomerular filtration rate calculated using Cockroft-Gault formula > 60 ml/min
  v. Creatine phosphokinase (CPK) ≤ 2.5 x ULN
  vi. Total Bilirubin ≤ ULN
  vii. Total alkaline phosphatase ≤ 2.5 x ULN
  viii. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
- Normal liver function levels
- Patients able to receive desametasone or similar agents
- Written informed consent provided by the patient prior to randomization

6. **Exclusion criteria:**

- Non epithelial or mixed ovarian cancer (Epithelial/non epithelial)
- Patients who did not respond to last platinum-based treatment or patients who have experienced progression after less than 6 months or after more than 12 months from last dose of platinum-based treatment.
- Intestinal occlusion or subocclusion or symptomatic brain metastasis
- Pre-existing sensitive/motor neurological disorder, NCI-CTCAE degree > 1
- Patients who have suffered myocardial infarction 6 months prior to enrolment (NYHA ≥ 2), angina pectoris, severe ventricular arrhythmia, clinically significant pericardial disease or acute ischemic disease confirmed by ECG.
- History of liver disease
- Severe comorbidities that are not cancer related and which would significantly limit full compliance to protocol, or that would put patients at risk or limit their life expectancy.
- Pregnant or nursing women; women of childbearing age must use adequate contraception.
- Patients previously exposed to Trabectedin
- Resistance to treatment with anthracycline or PLD, i.e. progression within 6 months of completing treatment with these agents.
- Patients with demonstrated severe PLD related toxicity.
- Previous exposure to cumulative doses of doxorubicin > 400mg/m^2 or epirubicin > 720 mg/m^2
- Patients treated with one of the study drugs 30 days prior to enrolment.

7. General criteria for efficacy evaluation: Overall Survival and Progression Free Survival.

8. General criteria for tolerability evaluation: toxicity assessed according to the Common Terminology Classification for Adverse Events (CTCAE) version 4.0 of the National Cancer Institute (NCI).

9. **Statistical methodology:** The statistical analysis will be carried out on the intention to treat population.
The end-points (OS and PFS) will be shown using Kaplan-Meier curves and the comparison between the two treatments will be carried out by means of Log-Rank test.
In order to assess the impact of stratification variables on survival (investigating centre, chemotherapy line, measurable disease, and earlier anthracycline based chemotherapy) and of other potential prognostic factors, Cox semiparametric model will be used.

V. RISK/BENEFIT EVALUATION

1. Possible benefits: prolonged survival using platinum-free pharmacological treatments.

2. Possible drawbacks and risks: Clinical non-superiority of platinum-free pharmacological treatment for those patients in the trabectedin+PLD treatment arm; trabectedin+PLD toxicity profile not yet directly compared to other platinum-based standard treatments.
3. Diagnostic/treatment alternatives: treatment of progression with other standard chemotherapy regimens (carboplatin+PLD or carboplatin+taxol)
4. Study procedures: Treatment arm allocation will be centralised and randomised. The randomization system will be accessible online. Treatment duration for both arms will be 6 cycles; patients benefitting from treatment will be able to extend treatment. In case of progression, patients may receive further chemotherapy treatment with other regimens (trabectedin+PLD arm will receive compulsory platinum-based treatment). Patients in both arms will have disease assessed by diagnostic imaging 12 and 24 weeks after starting study treatment. At the end of the treatment, patients will attend regular follow-up visits (every 12 weeks for the first 2 years and every 6 months thereafter). In order to evaluate overall survival, patient will have to attend follow-up visits until death or until the end of the study.
5. Patients'/subjects' safety precautionary measures: For the duration of the study, an independent Data Safety Monitoring Committee (DSMC) will keep the Steering Committee informed on the efficacy and safety aspects of all study treatments.
6. Overall risk/benefit evaluation: Both study regimens have been thoroughly assessed in Phase III international clinical trials and have shown clinical efficacy and good tolerability. Direct comparison between these two regimens could prove that prolonging 'platinum- free interval' using a platinum-free regimen (trabectedin+PLD), may result in prolonged survival in patients with 'partially platinum-sensitive' ovarian cancer.