PM1183-C-004-14 (NCT02421588)

Phase III Randomized Clinical Trial of Lurbinectedin (PM01183) *versus* Pegylated Liposomal Doxorubicin or Topotecan in Patients with Platinum-resistant Ovarian Cancer (CORAIL Trial)

STATISTICAL ANALYSIS PLAN

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-Confidential-

TABLE OF CONTENTS

ABBREVIATIONS AND GLOSSARY

AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
AST (SGOT)	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence Interval
CPK	Creatine Phosphokinase
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
DF	Degrees of Freedom
DNA	Deoxyribonucleic Acid
DR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
EPO	Erythropoietin
FU	Follow-up
CSF	Colony Stimulating Factor
HR	Hazard Ratio
IA	Investigator Assessment
IC	Informed Consent
IDMC	Independent Data Monitoring Committee
IORT	Intraoperative Radiation Therapy
IRC	Independent Review Committee
ITT	Intention-to-treat
LR	Log Rank Test
MedDRA	Medical Dictionary for Regulatory Activities
mo	Months
NA	Not Available
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not Evaluable
NOS	Not Otherwise Specified
ORR	Overall Response Rate
OS	Overall Survival
PARPi	Poly(ADP-ribose) Polymerase Inhibitors
PD	Progressive Disease
PLD	Pegylated Liposomal Doxorubicin
PFS	Progression Free Survival
PR	Partial Response
PRO	Patient-Reported Outcomes
PS	Performance Status
PT	Preferred Term

RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SOC	System Organ Class
STD	Standard Deviation
UK	Unknown
USA	United States of America
vs.	versus
WBC	White Blood Cells
WHO	World Health Organization

1 STUDY RATIONALE

Patients with relapsed platinum-resistant ovarian cancer have poor prognosis. New treatment options are needed to treat these patients, particularly agents with novel mechanisms of action.

PM01183 is a new chemical entity that induces double-strand DNA breaks through binding to the DNA minor groove. PM01183 has *in vitro* and *in vivo* anticancer activity in several platinum sensitive and resistant ovarian cancer-derived cell lines.

On the basis of preclinical results, a controlled, phase II exploratory clinical trial including a randomized stage was conducted to evaluate the activity and safety of PM01183 as a single agent in platinum-resistant/refractory advanced ovarian cancer (PM1183-B-002-11). The primary endpoint of the study was the overall response rate (ORR). The global endpoint was met, and the results of the randomized second stage of the study showed PM01183 more active than topotecan in this indication.

Therefore, a randomized trial has been proposed to compare lurbinectedin (PM01183) *vs.* pegylated liposomal doxorubicin (PLD) or topotecan in advanced ovarian cancer patients with platinum-resistant disease.

A full rationale for the study may be found in the appropriate sections of the study Clinical Protocol.

2 OVERALL STUDY DESIGN

Multicenter, open-label, randomized, controlled phase III clinical trial to evaluate the activity and safety of PM01183 *vs.* PLD or topotecan as control arm in patients with platinum-resistant ovarian cancer.

A single-agent PM01183 dose will be explored in the experimental arm (Arm A) *vs.* PLD or topotecan in the control arm (Arm B).

Central randomization will be implemented in all patients who fulfill the inclusion criteria; patients will be assigned to each treatment arm at a 1:1 ratio. If the patient had not previously received PLD or topotecan, the assigned treatment in case the patient is randomized to the control arm (Arm B) will be based on the reported Investigator's preference with regard to each of these two drugs. However, if the number of patients randomized to either PLD or topotecan reaches 60% of the total number of patients expected in the control arm (i.e., 126 patients), then the treatment of choice in the control arm will be restricted to the less frequent control drug until the end of accrual. Once the 60% is achieved for one of the two control agents, the patient will not be eligible for this trial if this agent is the only possible option (e.g., if the patient has been previously treated with topotecan, then PLD is the only possible option if the patient is randomized to Arm B and the patient will not be eligible if an accrual of 60% has been reached for PLD). Stratification will be performed according to Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 vs. ≥1), prior platinum-free interval (1-3 months vs. >3 months) (Platinum Free Interval = PFI: time elapsed between completion of the last platinum-containing regimen and the subsequent relapse or progression) and prior chemotherapy (1-2 vs. 3 lines).

Up to 420 patients with platinum resistant ovarian cancer (disease relapse or progression within one to six months after last platinum-containing chemotherapy) will be included in the trial.

An Independent Data Monitoring Committee (IDMC) will oversee the conduct of the study. Operational details for the IDMC will be detailed in the corresponding charter.

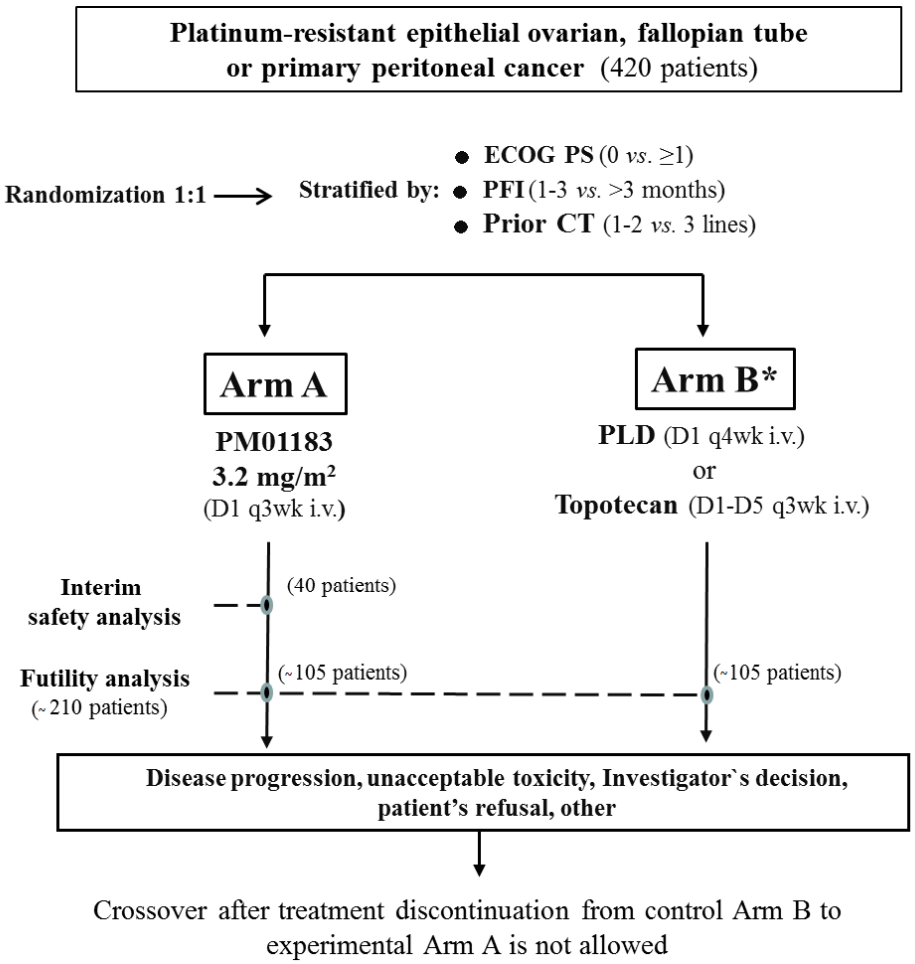
An Independent Review Committee (IRC) will determine the best patient's response and assign the date of objective response or progression/censoring according to Response Evaluation Criteria In Solid Tumors (RECIST) v.1.1. Operational details for the IRC, the algorithm and its validation by an expert panel is described in detail in the IRC charter.

An interim safety analysis will be performed in the PM01183 arm only (Arm A) when 40 patients are enrolled in this arm. Based on the results of this analysis, the IDMC may provide recommendations on the primary prophylactic use of colony stimulating factors (CSFs) as part of the therapy in the experimental Arm A. The recruitment in both treatment arms will not be stopped during the conduct of the interim safety analysis.

A futility analysis will be performed when 210 patients are recruited. The recruitment will not be put on hold. The IDMC will review efficacy and safety data available at that time and, based on the observed results, might recommend stopping the trial; no claim for efficacy in comparison with the control arm will be made at this analysis.

Crossover after treatment discontinuation from the control Arm B to the experimental Arm A is not allowed.

A summary of the study design is shown in the below figure.



*If the patient had not previously received PLD or topotecan, the assigned treatment in case that the patient is randomized to the control arm (Arm B) will be based on the reported Investigator's preference with regard to each one of these two drugs. However, if the number of patients randomized to either PLD or topotecan reaches the 60% of the total number of patients expected in the control arm (i.e., 126 patients), then the treatment of choice in the control arm will be restricted to the less frequent control drug until the end of accrual.

Patients will receive the study treatment while it is considered to be in their best interest. Specifically, treatment will continue until disease progression, unacceptable toxicity, intercurrent illness of sufficient magnitude to preclude safe continuation of the study, Investigator's decision, patient refusal, non-compliance with the study requirements, a major protocol deviation that may affect the risk/benefit ratio for the participating patient, or requirement of > two dose reductions.

All adverse events (AEs) will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4. Treatment delays, dose reduction requirements and reason for treatment discontinuation will be monitored throughout the study. The safety profile of patients will be monitored throughout the treatment and up to 30 days after the last treatment infusion (end of treatment, EOT), until the patient starts a new antitumor therapy or until the date of death, whichever occurs first. Any treatment-related AEs will be followed until recovery to at least grade 1 or stabilization of symptoms, whichever occurs first.

Patients will be evaluated at scheduled visits on three study periods: Pre-treatment, Treatment and Follow-up. This clinical trial will finish (clinical cutoff) 24 months after randomization of the last patient.

3 PATIENTS EVALUABILITY CRITERIA

Patients must fulfill all the inclusion/exclusion criteria to be eligible to participate in the study. Randomized patients will not be replaced.

3.1 Intention-to-Treat (ITT) Population

All patients randomized to either treatment arm independent of whether they received study drug or not, and analyzed in the group where they were allocated.

3.2 Safety Population

Safety population or "all treated patients" population will be defined as patients who have received at least part of one infusion of the investigational agents, and analyzed in the group where they were treated.

4 OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

- To determine a difference in progression-free survival (PFS) between lurbinectedin (PM01183) and PLD or topotecan in platinum-resistant ovarian cancer patients according to RECIST v.1.1.

4.2 Secondary Objectives

To evaluate:

- Overall survival (OS).
- Antitumor activity.
- Safety profile.
- Patient-reported outcomes (PRO).
- To characterize the plasma pharmacokinetics (PK) of PM01183 using a sparse sampling scheme in the PM01183 treatment arm (Arm A).
- Subgroup analyses of the PM01183 arm *vs.* PLD or topotecan.

- To conduct an exploratory pharmacogenetic and pharmacogenomic (PGx) sub-study.

4.3 Endpoints

Primary endpoint:

- **Progression-free survival (PFS) by IRC** is defined as the time from the date of randomization to the date of documented progression per RECIST v.1.1 or death (regardless of the cause of death). If the patient receives further antitumor therapy or is lost to follow-up before PD, PFS will be censored at the date of last tumor assessment before the date of subsequent antitumor treatment.

Secondary endpoints:

- **Progression-free survival (PFS) per RECIST v.1.1 by Investigator's Assessment (IA).**
- **Overall survival (OS)** will be calculated from the date of randomization to the date of death (death event) or last contact (in this case, survival will be censored on that date).
- **Landmark analyses:**
  - **PFS at 6 and 12 months by IRC/IA** will be the Kaplan-Meier estimates of the probability of being free from progression (per RECIST v.1.1) and death at these time points.
  - **OS at 12 and 24 months** will be the Kaplan-Meier estimates of the probability of being alive at these time points.
- **Best antitumor response by IRC/IA** will be the best response obtained in any evaluation according to the RECIST v.1.1. before progressive disease. Irrespectively of treatment arm, radiological and clinical tumor assessment will be performed symmetrically at baseline and every eight weeks from randomization until evidence of PD. Patients who finish treatment without PD will continue with the tumor assessments every eight weeks (± two weeks) from randomization until PD, start of a new antitumor therapy, death or date of study termination (clinical cut-off), whichever occurs first.
- **Duration of response (DR) by IRC/IA** will be calculated from the date of first documentation of response per RECIST v.1.1 (complete or partial response, whichever comes first) to the date of documented PD or death. The censoring rules defined above for PFS will be used for duration of response.
- **Best response according to tumor marker evaluation (CA-125)** will be the best response obtained according to GCIG criteria. Irrespectively of treatment arm, tumor marker assessment will be performed symmetrically at baseline and every eight weeks from randomization until evidence of PD.
- **Treatment safety profile:** AEs, serious adverse events (SAEs) and laboratory abnormalities will be coded by the Medical Dictionary for Regulatory Activities (MedDRA), graded according to the NCI-CTCAE v. 4 and analyzed. Dose reductions or delays required due to treatment-related AEs, and reasons for treatment discontinuations will be also assessed.
- **Patient-reported outcomes (PRO):** To measure the quality of life of patients, EORTC QLQ-C30 and EORTC QLQ-OV28 questionnaires will be completed by the patients every eight weeks in all three treatment arms.

- **Plasma pharmacokinetics (PK) of PM01183** will be evaluated using a sparse sampling scheme in the PM01183 treatment arm (Arm A). Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.
- **Subgroup analyses:** Subgroup analyses of the PM01183 arm *vs.* PLD or topotecan outcomes will be performed.
- **Pharmacogenetics:** This analysis will be performed in those patients who signed the IC for the PGx sub-study. The presence or absence of known polymorphisms from a single sample collected just before the PM01183 treatment start will be assessed to explain the individual variability in the main PK parameters.
- **Pharmacogenomics:** This exploratory analysis will be performed in those patients treated in any arm who signed the IC for the PGx sub-study. Samples from Arm B will be used as controls in order to differentiate between the prognostic or predictive value of any obtained finding. mRNA or protein expression levels of factors involved in DNA repair mechanisms, or related to the mechanism of action of PM01183 or to the pathogenesis of the disease, will be evaluated from prior available tumor tissue samples obtained at diagnosis or relapse. Their mutational status might also be analyzed. Their correlation with the clinical response and outcome after treatment will be assessed.

5 SAMPLE CONSIDERATIONS

5.1 Randomization and Stratification

Central randomization will be implemented in all patients who fulfill the eligibility criteria. Randomization of patients should occur as close in time as possible to the administration of the first dose of study drug. Patients will be assigned to each treatment arm (Arm A or Arm B) at a 1:1 ratio. If the patient had not previously received PLD or topotecan, the assigned treatment in case that the patient is randomized to the control arm (Arm B) will be based on the reported Investigator's preference with regard to each one of these two drugs. However, if the number of patients randomized to either PLD or topotecan reaches the 60% of the total number of patients expected in the control arm (i.e., 126 patients), then the treatment of choice in the control arm will be restricted to the less frequent control drug until the end of accrual. Stratification will be performed according to ECOG PS (0 *vs.* ≥1), prior platinum-free interval [PFI] (1-3 months *vs.* >3 months) and prior chemotherapy (1-2 *vs.* 3 lines).

5.2 Sample Size

This phase III clinical trial is designed to determine a statistically significant difference in PFS by IRC between PM01183 and a control arm with PLD or topotecan in ovarian cancer patients with platinum-resistant disease.

Patients will be randomized to receive PM01183 given as 3.2 mg/m^2 (Arm A) or either topotecan or PLD (Arm B).

The prospective assumptions are a 30% reduction in the relative risk of progression or death (HR=0.7) to be achieved with the experimental arm (PM01183), at a one-sided 2.5% significance level with at least 90% power, following exponential distributions and fulfilling the proportional hazard assumption. Median PFS with control arm is expected to be around 3.5 months. It is forecasted that an observed HR of approximately 0.8 will have enough power to reject the null hypothesis (HR=1).

Approximately 420 patients with platinum resistant ovarian cancer will be necessary to stratify and randomize at a 1:1 ratio over 18 months (~23 patients/month). The required 332 PFS events are expected to occur around six months after randomization of the last patient. Therefore, the IDMC meeting after the IRC review to test PFS is expected to occur about one year after randomization of the last patient.

With the prospective assumptions above mentioned, about 175 PFS events are expected in the control arm and 157 in the PM01183 treatment arm.

The IDMC will review the results of the analyses. The IRC will determine the patient's best response and assign the date of objective response or progression/censoring according to the RECIST v.1.1.

5.2.1 Futility Analysis

A futility analysis will be performed when 210 patients are recruited (i.e., ~105 patients enrolled in each arm). The recruitment will not be put on hold.

In the futility analysis, the sponsor will make no claim of efficacy, consequently this futility analysis and the final analysis to reject the null hypothesis (HR=1) are planned; the significance level will be determined by the actual number of observed events by IR. To maintain scientific integrity, type II error will be controlled by a spending function defined by O'Brien-Fleming boundaries. Following the prospective assumptions, the interim analysis will occur at less than one year after start of recruitment. At this moment, with the available information collected after balancing efficacy and safety, the IDMC might recommend stopping the trial.

The IDMC may request to review other preliminary safety/efficacy parameters, but no claim of superiority will be done; therefore, no type I/II error corrections will be applied.

5.2.2 Interim Safety Analysis

An interim safety analysis, performed when 40 patients are enrolled in Arm A, will test if the addition of primary CSF prophylaxis might be necessary in this arm. With the information available at that time, a Bayesian test assuming non-informative prior distribution will be done to assess the null hypothesis of febrile neutropenia ≤ 20% *vs.* the alternative hypothesis of febrile neutropenia >20%. If the probability associated with the alternative hypothesis is higher than 50% (e.g., 8 cases out of 40 patients), the addition of primary CSF prophylaxis will be considered necessary.

At the time of the interim safety analysis, recruitment in Arm B (PLD or topotecan) is also expected to be approximately 40 patients.

The IDMC may request to review other preliminary safety/efficacy parameters, but no claim of superiority will be done; therefore, no type I/II error corrections will be applied.

6 STATISTICAL METHODOLOGY FOR EFFICACY

6.1 Efficacy Definitions

Primary endpoint.

Progression-free survival (PFS) by IRC is defined as the time from the date of randomization to the date of documented progression per RECIST v.1.1 or death (regardless of the cause of death). If the patient receives further antitumor therapy or is

lost to follow-up before PD, PFS will be censored at the date of last tumor assessment before the date of subsequent antitumor treatment.

Irrespectively of treatment arm, radiological and clinical tumor assessment will be performed symmetrically at baseline and every eight weeks from randomization until evidence of PD is found. Patients who finish treatment without radiological PD will continue with the tumor assessments every eight weeks (± two weeks) from randomization until PD, start of a new antitumor therapy, death or date of study termination (clinical cut-off), whichever occurs first.

After radiological PD is documented or a new antitumor therapy is started, patients will be followed for survival at least every three months (± two weeks) from the end-of-treatment visit until death or date of study termination, whichever occurs first. Once the whole recruitment is completed, the 3-month follow-up for patients who discontinue treatment due to PD will be performed according to calendar time. Follow-up for survival, after radiological PD is documented or new therapy is started, may be made by telephone calls to the investigational sites.

The date of clinical and/or radiological PD and the date of death will be registered and documented as appropriate.

Copies of CT scans, MRIs and any other documented means to evaluate tumor response or progression should be available for external radiological review by an IRC. The IRC will determine the patient's best response, and assign the date of objective response or progression/censoring according to RECIST v.1.1.

Crossover after treatment discontinuation from Arm B to Arm A is not allowed.

Secondary endpoints.

Progression-free survival (PFS) by IA will be calculated using the same methodology as explained above for IRC assessment but following investigator assessments.

Overall survival (OS) is defined as the time from the date of randomization to the date of death (death event) or last contact (in this case, survival will be censored on that date). If applicable and more than one OS analysis is performed type I error will be controlled by spending function defined by O'Brien-Fleming boundaries. Counting out subsequent therapies impact, sample size is powered to detect OS differences in the 20-30% range. Final OS analysis is planned 24 months after randomization of last patient (planned end of study date).

Landmark analyses of PFS at 6/12 months by IRC/IA and OS at 12/24 months will be the Kaplan-Meier estimates of the probability of being free from progression and/or alive at these time points.

Best antitumor response by IRC/IA will be the best response obtained in any evaluation according to RECIST v.1.1.

Radiological antitumor activity will be assessed using the RECIST v. 1.1 on a set of measurable lesions identified at baseline as target lesions, and/or non-measurable lesions (if any) identified at baseline as non-target lesions and followed until disease progression (PD) by the appropriate method [computed tomography (CT) scan or magnetic resonance imaging (MRI)].

Duration of response (DR) will be calculated from the date of first documentation of response (complete or partial response, whichever comes first) to the date of documented PD or death. The censoring rules defined above for PFS will be used for duration of response.

Assessments must be done consistently in both treatment arms to ensure a symmetrical assessment of tumor response and progression. Every effort should be made to ensure

that these assessments are done on the required date. Time to n^{th} (i.e. 1, 2, 3…) disease assessment is defined as weeks between randomization and the recorded date of the n^{th} radiology assessment after randomization.

Best response according to tumor marker evaluation (CA-125) will be the best response obtained according to GCIG criteria[(1)]. Irrespectively of treatment arm, tumor marker assessment will be performed symmetrically at baseline and every eight weeks from randomization until evidence of PD.

6.2 Efficacy Analysis Methods

Time-to-event variables (PFS, OS and DR) and their set time estimates (i.e., PFS 6/12 and OS 12/24) will be analyzed according to the Kaplan-Meier method.

The stratified log-rank test, using actual values for all randomization strata variables, on the ITT population will be primarily used to compare the time-to-event variables. If the actual value is not a pre-defined category the value will be added to the most similar category (e.g., patients with more than three prior chemotherapy lines will be included in the 3-lines category).

Unstratified log-rank tests will also be calculated as supportive analyses.
The symmetry of tumor evaluations between the different arms will be examined. Wilcoxon test to compare time to disease assessments between treatment arms will be used to assess symmetry of evaluations. Moreover, Kaplan-Meier curves of the time from randomization and first and second disease assessment will be plotted. If necessary, internal symmetry between the two different treatments in the control arm will be checked following the same approach.

Cox regression will be used to calculate the risk reduction (PFS, OS and DR) and to evaluate the influence of the stratification variables and other potential prognostic factors on the time-to-event efficacy endpoints.

Counts and percentages, with their corresponding exact 95% confidence intervals, will be calculated for the binomial endpoints (i.e., response rate). The Fisher's exact test (univariate analyses) and logistic regressions will be used to compare the response rates.

Waterfall plots will be used to describe the best variation of the sum of target lesions diameters during the treatment.

Multivariate models (main effects or including interaction terms, if appropriate) will include all stratification factors and/or prognostic factors/covariates widely reported and recognized by the scientific community: treatment (PM01183 *vs.* control), ECOG PS (0 *vs.* ≥1 or coded as 0 *vs.* 1 *vs.* 2) prior platinum-free interval (1-3 months *vs.* >3 months or used as continuous variable), prior chemotherapy (1-2 *vs.* 3 lines or coded as 1 *vs.* 2 *vs.* 3) , geographical area (USA *vs.* Europe *vs.* rest of the world), investigator's preference for the control arm (Topotecan vs. PLD), age, age at diagnosis, race (caucasian *vs.* other), histology type (serous/papillary *vs.* other), histology grade (poorly/undifferentiated *vs.* other), primary tumor site (ovarian *vs.* other), FIGO stage at diagnosis (metastatic/locally advanced [stage III] *vs.* other), FIGO stage at study entry (metastatic *vs.* locally advanced [stage III]/other), BRCA status (mutated *vs.* other), clinical/radiological signs of intestinal subocclusion at entry (yes *vs.* no), site of current disease: lung/liver (yes *vs.* no), liver metastases (yes *vs.* no), number of prior metastatic sites (≤2 *vs.* >2), body mass index (BMI), height, weight, body surface area (BSA), time from diagnosis to first infusion, prior cytoreduction (optimal *vs.* suboptimal *vs.* no surgery), prior radiotherapy (yes *vs.* no), platinum resistance (primary *vs.* secondary), clinically evidence of ascites at baseline (yes *vs.* no), time elapsed from last dose of last prior platinum-containing regimen to randomization, prior antiangiogenic treatment

with bevacizumab (yes *vs.* no), prior PARPi (yes *vs.* no), presence of any bulky (< 50 mm *vs.* ≥ 50 mm) lesion at baseline, measurable disease (yes *vs.* no), sum of all target lesion diameters, baseline CA-125, albumin value at baseline, PFS prior line, response to last platinum therapy (yes *vs.* no) and baseline global QoL. In addition, continuous variables categorized as discrete variables will also be investigated in the continuum range and if the adjustment is better then the continuous variable will be selected in the model.

All variables with a good percentage of valid cases (approximately ≥ 90%) will be included in the multivariate analysis. Within the multivariate stepwise Logistic/Cox regression analysis, the chosen significance level for entering an explanatory variable into the model will be 0.05 (for all variables not in the model, the one with the smallest p-value will be entered if the p-value is less than or equal to the specified significance level). The significance level for removing an explanatory variable from the model will be 0.05 (for all variables in the model, the one with the largest p-value will be removed if the p-value exceeds the specified significance level). The parameter estimates, hazard ratios/odds ratios and p-values of the variables retained in the model will be presented.

Forest plots for PFS and OS summarizing main results, stratification and factors/covariates used in multivariate analyses will be plotted[2].

Median follow-up (FU) time for PFS and OS will be calculated in the descriptive way, only taking into account the censored values and using the Kaplan-Meier method for reversing the censoring values as described by Parmar[3].

Concordance between IRC and IA PFS assessments will be evaluated by means of Kaplan-Meier curves. Forest plots for response will also be performed adapting them to show relevant information (e.g. percentages will be shown instead of medians).

Sensitivity analyses for different PFS censoring will be performed. The following approaches will be calculated: 1) Date of progression based on scheduled time instead of recorded date (e.g. if progression occurs in the eleventh week and assessment would have to be done in the eighth week then the expected date is used instead of the actual date); 2) First date of progression combining IRC and IA assessments (e.g. the lowest date between IRC and IA is used); and 3) Date of progression moved to the prior tumor assessment date (e.g. if progression has not been documented in the second assessment and is documented in the third assessment then progression date is moved to the second assessment).

Proportional hazard assumption for PFS and OS will be checked by means of a Cox regression including treatment and its interaction with survival time[4]. In case of strong rejection of proportionality, then restricted mean survival estimates will also be calculated in addition to HR[5,6].

Main summary of efficacy analyses

Endpoint	Population	Statistics
PFS by IRC (primary endpoint)	ITT population	-Stratified log rank test
OS	ITT population	-Stratified log rank test -Unstratified log rank test -Kaplan Meier estimates -Univariate Cox regression -Multivariate Cox regression
PFS by IRC/IA	ITT population	-Stratified log rank test (IA) -Unstratified log rank test -Kaplan Meier estimates -Univariate Cox regression -Multivariate Cox regression

Endpoint	Population	Statistics
Response rate by IRC/IA	ITT population	-Fisher exact test -Logistic regression
Duration of response by IRC/IA	ITT population (in patients achieving a response)	-Unstratified log rank test -Kaplan Meier estimates

ITT: Intention-to-treat; IRC: Independent Review Committee; IA: Investigator Assessment; PFS: Progression Free Survival; OS: Overall Survival

7 STATISTICAL METHODOLOGY FOR SAFETY

7.1 Toxicity and Adverse Events

Patients will be evaluable for safety if they have received any partial or complete treatment infusion. All AEs will be graded according to the NCI-CTCAE v.4. Treatment delays, dose reduction requirements and reason for treatment discontinuation will be monitored throughout the study.

The safety profile of patients will be monitored throughout the treatment and up to 30 days after the last treatment infusion (end of treatment, EOT), or until the patient starts a new antitumor therapy or until the date of death, whichever occurs first.

Any AEs will be coded using to the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-related AEs will be followed, whenever possible, until recovery to at least grade 1 or stabilization of symptoms, whenever possible.

Summary of overall AEs will be done by body system and preferred term, by severity (worst toxicity grade) and by relationship. Tables will be sorted by body system/preferred term.

A frequency table will be made for the AEs leading to cycle delay, dose reduction, skipped dose (topotecan only), or withdrawal of study medication. AEs leading to permanent treatment stop and AEs with outcome of death will also be presented by relationship to drug.

Exploratory Fisher's exact tests will be performed to compare the incidence of grade 4 or grade 3/4 AEs between treatment arms.

7.2 Clinical Laboratory Evaluation

Laboratory results will be classified according to the NCI-CTCAE v.4.

The worst grade per patient will be tabulated during overall treatment and per cycle for hematology values [white blood cells (WBC), absolute neutrophil count (ANC), lymphocyte count, platelet count and hemoglobin] and for the following biochemistry tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (AP), creatine phosphokinase (CPK), creatinine, glucose, sodium, potassium and albumin.

Exploratory Fisher's exact tests will be performed to compare the incidence of grade 4 or grade 3/4 laboratory evaluations between treatment arms.

7.3 Physical Examination Findings

Tables summarizing the performance status (PS), height, body weight and BSA (according to the Dubois and Dubois formula) at baseline will be prepared.

In addition, changes in the ECOG PS and body weight of each patient during the treatment compared to baseline will be presented.

7.4 Deaths and other Serious Adverse Events

Deaths, and other serious adverse events will be tabulated following the same pattern than AEs.

8 OTHER ANALYSES

Non-continuous variables will be described in frequency tables using counts and percentages. Continuous variables will be described by median, mean, standard deviation (STD), minimum and maximum.

8.1 Baseline and Demographic Data

Baseline data such as demographics, cancer history, number of organs involved and sites of disease, prior therapy, laboratory values at baseline, prior relevant history, signs and symptoms, electrocardiogram, and concomitant medication [Anatomical Therapeutic Chemical – World Health Organization (ATC-WHO) coded] will be described following standard tables (detailed in Appendix I) for all randomized patients.

For pre-treatment characteristics with multiple measurements per patient before the start of treatment (e.g. laboratory assessments, vital signs), the baseline measurement will be considered the last value prior to or on the first day of treatment for tabulation and analysis. However all the baseline assessments will be listed (see section 13).

8.2 Protocol Deviations

Analysis of protocol deviations following the 'Protocol Deviation and Non-Compliance Management Plan' will be done as described in Appendix I.

8.3 Treatment Administration

Total cumulative dose, time on treatment, dose intensity and relative dose intensity, administration delay, and dose reductions/omissions will be described following standard tables (detailed in Appendix I) and the reported cycle information on the case report form (CRF) pages will be used for the analyses.

Total cumulative dose by drug, expressed in mg, is the sum of all the product doses from the first cycle until the last cycle, including the dose received in the last cycle.

Time on treatment, expressed in weeks, is defined as last infusion date minus first infusion date plus 30 days, except if the patient dies or starts a new antitumor therapy within 30 days from the last infusion date, in which case the time on treatment will be the date of death or the date of the start of a new antitumor therapy minus the date of the first infusion.

Intended dose intensity is the planned dose per cycle divided by the planned number of weeks by cycle.

Absolute dose intensity is the actual cumulative dose divided by the number of weeks of treatment. As a convention, for this calculation, the duration of the last cycle will be the predefined cycle length (i.e., 21 days or 28 days in case of PLD). Relative dose intensity (%) is the ratio of absolute dose intensity divided by the intended dose intensity.

The items « Infusion delayed: yes/no» and « Dose reduced: yes/no» present on the drug

administration CRF page will be used to calculate delays and dose reductions, respectively. For cycles considered as delayed by the Investigator, the length of the delay will be calculated as:

Duration of cycle delay: Date of the current drug administration – Date of the previous drug administration – the predefined cycle length (i.e., 21 days if PM01183/topotecan or 28 days if PLD).

8.4 Patient-reported Outcomes (PRO)

To measure the quality of life of patients, EORTC QLQ-C30 and EORTC QLQ-OV28 questionnaires will be analyzed every eight weeks from randomization and while on treatment.

PRO will be analyzed by means of longitudinal modelling and T-test comparisons to determine if efficacy and side effects are accompanied by measurable changes. The analysis will be performed on summary scores of EORTC QLQ-C30 and EORTC QLQ-OV28 questionnaires, as well as on subscales and individual symptoms.

8.5 Subsequent Therapies

A table summarizing the subsequent therapies received after discontinuation will be shown. Special attention will be focused on patients receiving any platinum compound as first subsequent treatment, and analyses to test between treatment arms if potential platinum-free interval prolongation is associated with survival.

8.6 Imputation in Incomplete Dates

Dates of certain historical or current clinical activities are key component for statistical analysis. An incomplete date results from a missing day, month or year; in that case, the missing figure can be imputed allowing for the calculation of variables, such duration and time to certain event. However, when all of them, day, month and year, are missing no imputation will be done.

<u>Before randomization</u>

All variables needed to summarize for example prior information (e.g. first diagnosis date) where partial information is available will be subject of imputation by means of SAS programming. If the day of a date is unknown then the imputed day will be 1, if the month is also unknown then the imputed date will 1/July. This assumption will be valid if the imputed date is earlier than the randomization date; otherwise, the imputed date will be the first day of the randomization month date (i.e. 01/Randomization month date/year).

<u>Between treatment start and end of treatment</u>

All date variables during treatment where information is needed and is not fully available, for example adverse events or concomitant medications, will be subject of imputation by means of SAS programming. If the day of a date is unknown then the imputed day will be 1, if the month and/or year is also unknown then the imputed date will 1/January (this assumption will be valid if the imputed date is earlier than the treatment start date; otherwise, the imputed date will be the treatment start date).

After end of treatment

A conservative approach for the variables collecting information after end of treatment where partial information is available (e.g., main time-to-event variables; PFS and OS) will be imputed by means of SAS programming. The following rules will be implemented: if the day of a date is unknown then the imputed day will be 1; if the month is also unknown, then the imputed date will be 1/July. This assumption will be valid if the imputed date occurs later than the last drug administration date; otherwise, the imputed date will be the last drug administration date plus 1 day.

If the date of subsequent therapy is incomplete (day or month is missing) and the patient had documented disease progression, the date of subsequent therapy will be imputed to the end of the month when the progression occurred. If the subsequent therapy is given before progression to the study treatment, the rules specified above will apply.

8.7 Variable Unit Standardization

Variables reported with different units will be homogenized to standardized variables following the International System of Units (e.g. laboratory tests, biometrical assessments...) unless otherwise specified in the following sections.

8.8 Decimal Places, Missing Values and Allowed Assessment Windows

By default, all results will be rounded to one decimal place, except when variables are integer, which will be reported without decimals (e.g., age in years, number of sites, etc.). For representing p-values four decimals will be selected as default but they could be rounded to fewer decimals if necessary.

Missing values will not be included in the calculation of outputs. Assessment windows as specified in the clinical protocol will be respected.

8.9 Subgroup Analyses

Subgroup analyses implemented a posteriori based on clinically findings will have an exploratory nature.
Some exceptions are the upfront preplanned exploratory analyses, such as efficacy subgroup analyses based on comparison of PM01183 with PLD or topotecan, subgroup analyses for stratification factors, and the analysis of the subset of patients who received a platinum compound as first subsequent treatment.

Pre-specified safety subgroup analyses are: by age (<65 years-old *vs.* ≥65 years-old), by race (white *vs.* other), by number of prior chemotherapy lines (1-2 *vs.* 3 lines) and by geographical area (USA *vs.* Europe *vs.* rest of the world).

8.10 Pharmacokinetic, Pharmacogenetic and Pharmacogenomic Analyses

These analyses will be detailed and reported in separate documents.

9 STATISTICAL SOFTWARE

Medidata Rave® EDC will be used for data entry and clinical data management.

Medidata Balance® will be used for randomization design and management.

EAST® v.6.3 has been used to calculate sample size[7].

SAS® version 9.2 or superior will be used for all statistical analyses[8].

REFERENCES

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2. Qinghua (Kathy) Chen. Incorporating Graphics into Summary Report Tables using ODS and GTL. PharmaSUG2011 – Paper SP02.

3. Parmar M. Machin D. Survival analysis. A practical approach. Wiley, Chichester, 1995.

4. Introduction to SAS. UCLA: Statistical Consulting Group. from http://www.ats.ucla.edu/stat/sas/notes2/ (accessed November 13, 2013). http://www.ats.ucla.edu/stat/examples/asa/test_proportionality.htm(accessed November 13, 2013).

5. Patrick Royston and Mahesh K. B. Parmar. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. Statist. Med. 2011, 30 2409–2421.

6. Klein et al. SAS and R Functions to Compute Pseudo-values for Censored Data Regression. Comput Methods Programs Biomed. 2008 March ; 89(3): 289–300.

7. EAST manual.

8. SAS OnlineDoc.

APPENDIX I

Applicable outputs will also be created at the time of interim analyses. They will be specified as an appendix to the IDMC charter.

10 Study Patients

Study patient analysis will be carried out on the ITT population except for screening failures where no randomization is performed.

10.1 Patient Disposition

Main characteristics concerning inclusion in the study, end of treatment, withdrawal of the study and protocol deviations will be displayed in this section.

Table 10.1.1 Disposition of screened patients

Screening failure	Total	
	N	%
Yes		
No (Patient randomized)		

Listing 10.1.2 Screening failures

Patient	Inclusion/Exclusion criteria not met

Table 10.1.3 Disposition of patients

	PM01183		Control		Total	
	N	%	N	%	N	%
Randomized patients (ITT population)						
Treated patients (Safety population)						

Table 10.1.4 Disposition of patients in the control arm

	Topotecan		PLD		Total	
	N	%	N	%	N	%
Randomized patients (ITT population)						
Treated patients (Safety population)						

Listing 10.1.5 Randomized patients who were not treated

Treatment arm*	Patient	Reason

*PM01183/PLD/Topotecan

Table 10.1.6 Patients accrual by institution

			PM01183	Control	Total
No. Randomized	Country 1	Institution 1			
		…			
		Total			
	…	Institution 1			
		…			
		Total			
	Total	Institution 1			
		…			
		Total			
No. treated	Country 1	Institution 1			
		…			
		Total			
	…	Institution 1			
		…			
		Total			
	Total	Institution 1			
		…			
		Total			

Table 10.1.7 Study dates

	Date
Date of first consent	
Date of first randomization	
Date of first dose of first patient	
Date of last consent	
Date of last randomization	
Date of first dose of last patient	
Date of last dose	
Last follow-up date	

Listing 10.1.8 Patients assigned to incorrect strata at the time of randomization

Treatment arm*	Patient	Actual stratum (Screening form)	Strata reported at randomization (Randomization form)

*PM01183/PLD/Topotecan

Table 10.1.9 Investigator's preference for the control arm

	PM01183		Topotecan		PLD	
	N	%	N	%	N	%
Topotecan						
PLD						

10.2 Reasons for Treatment Discontinuation

Table 10.2.1 Treatment discontinuation

Reason	PM01183		Control	
	N	%	N	%
Progressive disease (PD)				
Patient refusal to treatment				
Death				
Investigator's decision				
Study drug-related AE				
Non study drug-related AE				
Symptomatic deterioration				
Other				
Total				

When reason for discontinuation is study drug-related AE or study drug-related death, identify patients and describe them in depth here.

Listing 10.2.2 Reasons for treatment discontinuation other than progressive disease

Treatment arm*	Patient id.	Reason	Last cycle	Date	Specify (if applicable)

*PM01183/PLD/Topotecan

Listing 10.2.3 AEs with reported 'treatment withdrawn'

Treatment arm*	Patient id.	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	SAE	Onset date	Resolved date	Outcome

*PM01183/PLD/Topotecan

Table 10.2.4 Reasons for off study

Reason	PM01183		Control	
	N	%	N	%
Study termination (clinical cut-off)				
Withdrawal of consent				
Death				
Lost to follow-up				
Other				
Total				

10.3 Protocol Deviations

Classification will follow the definitions of the Protocol Deviation and Non-Compliance Management Plan.

Listing 10.3.1 Protocol deviations

Treatment arm*	Patient	Classification	Deviation Category	Deviation

*PM01183/PLD/Topotecan

11 Efficacy Evaluation

11.1 Demographic and other Baseline Characteristics

Baseline/screening characteristics will be carried out on the ITT population.

11.1.1 Patient Characteristics at Baseline

Table 11.1.1.1 Baseline characteristics

	PM01183		Control					
			Total		PLD		Topotecan	
	N	%	N	%	N	%	N	%
Number of patients								
Age Median (range) Mean (std)								
Age group 18-49 50-65 ≥65								
Childbearing potential? Yes No								
Race American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander White Other (specify) Not applicable								
ECOG PS 0 1 2 …								
Time from first diagnosis to randomization Median (range) Mean (std)								
Primary site Ovarian Fallopian Peritoneal								
Histology type Serous/Papillary Endometrioid Clear cell Mucinous Other (specify)								
Histology grade Well differentiated Moderately differentiated Poorly differentiated Undifferentiated UK								

	PM01183		Control					
			Total		PLD		Topotecan	
	N	%	N	%	N	%	N	%
FIGO stage at diagnosis I IA IB …								
FIGO stage at study entry I IA IB …								
BRCA status UK BRCA1 BRCA2 Not mutated								
Clinical/radiological signs of Intestinal subocclusion Yes No								
Clinical evidence of ascites at baseline Yes No								
Sites of current disease Peritoneal Lymph node …								
Number of sites involved 1 2 … Median (range) Mean (std)								
Physical examination by Body System examined Abnormalities found Yes No Clinically significant Not Clinically significant								
Weight Median (range) Mean (std)								
Height Median (range) Mean (std)								
Body surface area Median (range) Mean (std)								

	PM01183		Control					
			Total		PLD		Topotecan	
	N	%	N	%	N	%	N	%
BMI Median (range) Mean (std)								
BMI categories ≤ 20 20-25 25-30 > 30								
ECG Normal Significant abnormalities Non significant abnormalities								
LVEF Normal Significant abnormalities Non significant abnormalities								
ECG results **PR interval** Median (range) Mean (std) **Heart Rate** Median (range) Mean (std) **QT interval (raw)** Median (range) Mean (std) **QRS complex duration** Median (range) Mean (std) **Fridericia corrected QT** Median (range) Mean (std)								
LVEF results Median (range) Mean (std)								
Vital signs **Heart rate** Median (range) Mean (std) **Systolic blood pressure** Median (range) Mean (std) **Diastolic blood pressure** Median (range) Mean (std) **Temperature** Median (range) Mean (std)								

N(%) for categorical variables; Median (range)/Mean (std) for continuous variables

Table 11.1.1.2 Grade for hematological tests at baseline

	Total	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4		Grade 1-4	
	N	N	%	N	%	N	%	N	%	N	%	N	%
PM01183													
Leukopenia													
Anemia													
Thrombocytopenia													
Neutropenia													
Lymphopenia													
Control													
Leukopenia													
Anemia													
Thrombocytopenia													
Neutropenia													
Lymphopenia													

Table 11.1.1.3 Hematology values at baseline

	PM01183	Control
	n Median (range) Mean (std)	n Median (range) Mean (std)
WBC		
Neutrophils		
Hemoglobin		
Platelets		
Lymphocytes		
Monocytes		

Listing 11.1.1.4 Hematological tests not assessed at baseline

Treatment arm	Patient id.	Lab. test
	…	
	…	

Listing 11.1.1.5 Hematological abnormalities grade≥1 at baseline

Treatment arm	Patient id.	Test	Grade
	…		
	…		

Table 11.1.1.6 Grade for biochemical tests at baseline

	Total	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4		Grade 1-4	
	N	N	%	N	%	N	%	N	%	N	%	N	%
PM01183													
Creatinine increase													
CPK increase													
Bilirubin increase													
AP increase													
GGT increase													
AST increase													
ALT increase													
Control													
Creatinine increase													
CPK increase													
Bilirubin increase													
AP increase													
GGT increase													
AST increase													
ALT increase													

Table 11.1.1.7 Biochemistry values at baseline

	PM01183	Control
	n Median (range) Mean (std)	n Median (range) Mean (std)
Creatinine		
Creatinine clearance		
CPK		
Total bilirubin		
AP		
GGT		
AST		
ALT		

Listing 11.1.1.8 Biochemical tests not assessed at baseline

Treatment arm	Patient id.	Lab. test
	…	
	…	

Listing 11.1.1.9 Biochemical abnormalities grade≥1 at baseline

Treatment arm	Patient id.	Test	Grade
	…		
	…		

Table 11.1.1.10 Grade for other metabolic tests at baseline

	Total	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4		Grade 1-4	
	N	N	%	N	%	N	%	N	%	N	%	N	%
PM01183													
Hyperglycemia													
Hypernatremia													
Hyperkalemia													
Hypoglycemia													
Hyponatremia													
Hypokalemia													
Hypoalbuminemia													
Control													
Hyperglycemia													
Hypernatremia													
Hyperkalemia													
Hypoglycemia													
Hyponatremia													
Hypokalemia													
Hypoalbuminemia													

Table 11.1.1.11 Other metabolic values at baseline

	PM01183	Control
	n Median (range) Mean (std)	n Median (range) Mean (std)
Glucose		
Sodium		
Potassium		
Albumin		

Listing 11.1.1.12 Metabolic tests not assessed at baseline

Treatment arm	Patient id.	Lab. test
	…	
	…	

Listing 11.1.1.13 Other metabolic abnormalities grade≥1 at baseline

Treatment arm	Patient id.	Test	Grade
	…		
	…		

11.1.2 Prior Anticancer Therapy

Table 11.1.2.1 Prior therapy

	PM01183		Control					
			Total		PLD		Topotecan	
	N	%	N	%	N	%	N	%
Radiotherapy (Y/N)								
Type								
External								
Brachytherapy								
IORT								
Intention								
Curative								
Palliative								
Cytoredutive surgery (Y/N)								
Primary cytoreduction (Y/N)								
-Optimal								
-Suboptimal								
Interval cytoreduction (Y/N)								
-Optimal								
-Suboptimal								
Secondary cytoreduction (Y/N)								
-Optimal								
-Suboptimal								
Other surgical procedures (Y/N)								
Intention								
-Diagnostic/exploratory								
-Radical								
-Palliative								

Table 11.1.2.2 Prior anticancer medical therapy

	PM01183		Control					
			Total		PLD		Topotecan	
	N	%	N	%	N	%	N	%
Number of prior regimens								
1								
2								
…								
Median (range)								
Mean (std)								
Setting								
Adjuvant								
Neoadjuvant								
Advanced/Metastatic								
Number of prior chemotherapy lines								
1								
2								
…								
Median (range)								
Mean (std)								
Number of prior chemotherapy agents								
1								
2								
…								
Median (range)								
Mean (std)								
Prior agents of chemotherapy (ATC coded)								
Carboplatin								
Cisplatin								
…								
Prior biological agents (ATC coded)								
Bevacizumab								
…								
Prior investigational agents								
Prior hormonal agents								
Others								
Platinum-free Interval (calculated from dates reported and as reported in screening form)								
Median (range)								
Mean (std)								
1-3 months (calculated)								
>3 months (calculated)								
1-3 months (screening form)								
>3 months (screening form)								
Time from prior last progression to randomization								
Median (range)								
Mean (std)								
PFS to last prior therapy								
Median (range)								
Mean (std)								
Best response to last prior therapy								
CR								
PR								
SD								
PD								
NE/UK/NA								

11.1.3 Prior Relevant Medical History

A table with the description of the more relevant abnormalities found at baseline will be provided in this section.

Table 11.1.3.1 Medical history

SOC	Preferred term	PM01183		Control	
		N	%	N	%
Gastrointestinal disorders	Constipation				
	Diarrhoea NOS				
	…				
…	…				
	…				

11.1.4 Signs and Symptoms at Baseline

Signs and symptoms refer to any AE with onset date before the first treatment dose.

Table 11.1.4.1 Patients with signs and symptoms at baseline

	PM01183		Control					
			Total		PLD		Topotecan	
	N	%	N	%	N	%	N	%
No. of signs and symptoms per patient 0 1 2 ≥ 3 **Median (range)** **Mean (std)**								

Table 11.1.4.2 Signs and symptoms at baseline (MedDRA coded)

SOC	Preferred term	Total	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1-4	
		N	N	%	N	%	N	%	N	%	N	%
PM01183												
Gastrointestinal disorders	Constipation											
	Diarrhoea NOS											
	…											
Control												
Gastrointestinal disorders	Constipation											
	Diarrhoea NOS											
	…											

Listing 11.1.4.3 Signs and symptoms at baseline

Treatment arm*	Patient id.	Sign/symptom	Grade	Onset date

*PM01183/PLD/Topotecan

11.1.5 *Concomitant Medication at Baseline*

Concomitant medication at baseline according to the ATC classification.

Table 11.1.5.1 Concomitant medication at baseline (ATC1/ATC2/ATC4)

Concomitant medication at baseline	PM01183		Control	
	N	%	N	%
Alimentary tract and metabolism Antiacids Magnesium compounds ….				
Blood and blood forming organs Antithrombotic agents Vitamin K antagonists …				

11.1.6 PRO Analyses

Table 11.1.6.1 PRO scores at baseline

Item	PM01183			Control								
				Total			PLD			Topotecan		
	N	Median (range)	Mean (std)	N	Median (range)	Mean (std)	N	Median (range)	Mean (std)	N	Median (range)	Mean (std)
EORTC QLQ-C30												
Item 1												
Item 2												
…												
Item 30												
EORTC QLQ-OV28												
Item 31												
…												
Item 58												

11.2 Measurements of Treatment Compliance

Compliance of individual patients with the treatment regimen under study will be measured and tabulated in section 12.1 and listed in appendix 16.2.5 (ICH listings).

11.3 Efficacy Analysis

Efficacy analysis will be carried out on the ITT population.

Table 11.3.1.1 PFS by IRC (primary analysis)

Variable	Stratification factors	p-value*
Treatment arm (main analysis)	Actual values	
Treatment arm (sensitivity)	Values reported for randomization	

*Stratified log rank test.

Progression-free survival by IRC

Table 11.3.1.2 Median FU for PFS by IRC

	Total (PM01183 and Control)	
Follow-up (descriptive way)	Median (range)	
Follow-up (reverse censoring method)	Median (95%CI)	

Table 11.3.1.3 PFS by IRC

	PM01183	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.3) will be shown too.

Table 11.3.1.4 Multivariate analysis of PFS by IRC (Stratification factors and treatment arm)

Analysis of maximum likelihood estimates								
Variable label	Variable values	DF	Parameter estimate	Standard error	Chi-square	Pr > ChiSq	Hazard ratio	95% Hazard ratio confidence limits

Table 11.3.1.5 Multivariate analysis of PFS by IRC

Analysis of maximum likelihood estimates								
Variable label	Variable values	DF	Parameter estimate	Standard error	Chi-square	Pr > ChiSq	Hazard ratio	95% Hazard ratio confidence limits

(see list of covariates in section 6.2).

Table 11.3.1.6 Proportional hazard assumption and restricted mean survival for PFS by IRC

Variable	PM01183	Control	Interaction p-value
Restricted mean survival*			

*It will be calculated if proportional hazard assumption is not met.

A forest plot (Figure 11.3.1.7) summarizing main results, stratification factors and covariates in terms of PFS by IRC will be plotted.

Progression-free survival by IA

Table 11.3.1.8 PFS by IA (Stratified log rank test)

Variable	Stratification factors	p-value*
Treatment arm (main analysis)	Actual values	
Treatment arm (sensitivity)	Values reported for randomization	

*Stratified log rank test.

Table 11.3.1.9 Median FU for PFS by IA

	Total (PM01183 and Control)	
Follow-up (descriptive way)	Median (range)	
Follow-up (reverse censoring method)	Median (95%CI)	

Table 11.3.1.10 PFS by IA

	PM01183	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.10) will be shown too.

Table 11.3.1.11 Multivariate analysis of PFS by IA (Stratification factors and treatment arm)

Analysis of Maximum Likelihood Estimates								
Variable label	Variable values	DF	Parameter estimate	Standard error	Chi-square	Pr > ChiSq	Hazard ratio	95% Hazard ratio confidence limits

Table 11.3.1.12 Multivariate analysis of PFS by IA

Analysis of Maximum Likelihood Estimates								
Variable label	Variable values	DF	Parameter estimate	Standard error	Chi-square	Pr > ChiSq	Hazard ratio	95% Hazard ratio confidence limits

(see list of covariates in section 6.2).

Table 11.3.1.13 Proportional hazard assumption and restricted mean survival for PFS by IA

Variable	PM01183	Control	Interaction p-value
Restricted mean survival*			

*It will be calculated if proportional hazard assumption is not met.

A forest plot (Figure 11.3.1.14) summarizing main results, stratification factors and covariates in terms of PFS by IA will be plotted.

Table 11.3.1.15 Time to disease assessments

Disease assessment	Treatment arm	n	Median (days)	Wilcoxon p-value
1	PM01183			
	Control			
2	PM01183			
	Control			
…	PM01183			
	Control			

-ITT population, Kaplan Meier plot (Figure 11.3.1.15) will be shown too.

Concordance PFS IRC and PFS IA

Table 11.3.1.16 Concordance PFS

	PM01183 (IRC)	PM01183 (IA)	Control (IRC)	Control (IA)	Parameter	p-value
N						
Events						
Censored						
Median PFS (95% CI)					Log-Rank:	LR:
PFS at 6 months (95% CI)						
PFS at 12 months (95% CI)						

Kaplan Meier plot (Figure 11.3.1.16) will be shown too.

Sensitivity PFS analyses

-Date of progression based on scheduled time instead of recorded date.

Table 11.3.1.17 PFS based on scheduled time by IRC

	PM01183	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.17) will be shown too.

Table 11.3.1.18 PFS based on scheduled time by IA

	PM01183	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.18) will be shown too.

-First date of progression combining IRC and IA assessments

Table 11.3.1.19 PFS based on first date of progression

	PM01183	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.19) will be shown too.

- Date of progression moved to the prior tumor assessment.

Table 11.3.1.20 PFS moved to the prior tumor assessment by IRC

	PM01183	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.20) will be shown too.

Table 11.3.1.21 PFS moved to the prior tumor assessment by IA

	PM01183	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.21) will be shown too.

Overall survival

Table 11.3.1.22 OS (Stratified log rank test)

Variable	Stratification factors	p-value*
Treatment arm (main analysis)	Actual values	
Treatment arm (sensitivity)	Values reported for randomization	

*Stratified log rank test.

Table 11.3.1.23 Median FU for OS

	Total (PM01183 and Control)	
Follow-up (descriptive way)	Median (range)	
Follow-up (reverse censoring method)	Median (95%CI)	

Table 11.3.1.24 OS

	PM01183	Control	Parameter	p-value
N				
Events				
Censored				
Median OS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
OS at 12 months (95% CI)			Diff:	
OS at 24 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.24) will be shown too.

Table 11.3.1.25 Multivariate analysis of OS (Stratification factors and treatment arm)

Analysis of Maximum Likelihood Estimates								
Variable label	Variable values	DF	Parameter estimate	Standard error	Chi-square	Pr > ChiSq	Hazard ratio	95% Hazard ratio confidence limits

Table 11.3.1.26 Multivariate analysis of OS

Analysis of Maximum Likelihood Estimates								
Variable label	Variable values	DF	Parameter estimate	Standard error	Chi-square	Pr > ChiSq	Hazard ratio	95% Hazard ratio confidence limits

(see list of covariates in section 6.2).

Table 11.3.1.27 Proportional hazard assumption and restricted mean survival for OS

Variable	PM01183	Control	Interaction p-value
Restricted mean survival*			

*It will be calculated if proportional hazard assumption is not met.

A forest plot (Figure 11.3.1.28) summarizing main results, stratification factors and covariates in terms of OS will be plotted.

Objective response and duration of response by IRC

Table 11.3.1.29 Response rate by IRC

Response	PM01183		Control		p-value
	N	%	N	%	
CR PR SD PD Unknown*					
CR+PR; n (%) and binomial exact 95% confidence interval					

(*) Including NE, non-responders and insufficient data available.

Table 11.3.1.30 Multivariate analysis of response rate by IRC (Stratification factors and treatment arm)

Analysis of Maximum Likelihood Estimates								
Variable label	Variable values	DF	Estimate	Standard error	Wald chi-square	Pr > ChiSq	Odds ratio estimate	95% Wald confidence limits

Table 11.3.1.31 Multivariate analysis of response rate by IRC

Analysis of Maximum Likelihood Estimates								
Variable label	Variable values	DF	Estimate	Standard error	Wald chi-square	Pr > ChiSq	Odds ratio estimate	95% Wald confidence limits

(See list of covariates in section 6.2).

A forest plot (Figure 11.3.1.32) summarizing main results, stratification factors and covariates in terms of response by IRC will be plotted.

A waterfall plot (Figure 11.3.1.33) describing the best variation of the sum of target lesions during the treatment will be plotted.

Table 11.3.1.34 DR by IRC

	PM01183	Control	Parameter	p-value
N				
Events				
Censored				
Median DR (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:

Objective response and duration of response by IA

Table 11.3.1.35 Response rate by IA

Response	PM01183		Control		p-value
	N	%	N	%	
CR PR SD PD Unknown*					
CR+PR; n (%) and binomial exact 95% confidence interval					

(*) Including NE, non-responders and insufficient data available.

Table 11.3.1.36 Multivariate analysis of response rate by IA (Stratification factors and treatment arm)

Analysis of maximum likelihood estimates								
Variable label	Variable values	DF	Estimate	Standard error	Wald chi-square	Pr > ChiSq	Odds ratio estimate	95% Wald confidence limits

Table 11.3.1.37 Multivariate analysis of response rate by IA

Analysis of maximum likelihood estimates								
Variable label	Variable values	DF	Estimate	Standard error	Wald chi-square	Pr > ChiSq	Odds ratio estimate	95% Wald confidence limits

(See list of covariates in section 6.2).

A forest plot (Figure 11.3.1.38) summarizing main results, stratification factors and covariates in terms of response by IA will be plotted.

A waterfall plot (Figure 11.3.1.39) describing the best variation of the sum of target lesions during the treatment will be plotted.

Table 11.3.1.40 DR by IA

	PM01183	Control	Parameter	p-value
N				
Events				
Censored				
Median DR (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:

CA-125 Objective response

Table 11.3.1.41 CA-125 response rate

Response	PM01183		Control		p-value
	N	%	N	%	
CR PR SD PD Unknown*					
CR+PR; n (%) and binomial exact 95% confidence interval					

(*) Including NE, non-responders and insufficient data available.

Table 11.3.1.42 CA-125 response rate (excluding UK category)

Response	PM01183		Control		p-value
	N	%	N	%	
CR PR SD PD					
CR+PR; n (%) and binomial exact 95% confidence interval					

Progression and censoring reasons by IRC/IA

Table 11.3.1.43 Progression type by IRC/IA

Reason	IRC				IA			
	PM01183		Control		PM01183		Control	
	N	%	N	%	N	%	N	%
Target lesion Non-target lesion Death due to malignant disease Other*								

(*)Please specify.

Table 11.3.1.44 Censoring reason by IRC/IA

Reason	IRC				IA			
	PM01183		Control		PM01183		Control	
	N	%	N	%	N	%	N	%
Free of progression last tumor assessment Subsequent therapy before documented progression Not treated Other*								

(*)Please specify.

Subgroup analyses

Forest plots summarizing main results, stratification factors and covariates for the comparison between PM01183 and PLD will be plotted.

- Figure 11.3.1.45 PFS by IRC (PM01183 *vs* PLD)
- Figure 11.3.1.46 PFS by IA (PM01183 *vs* PLD)
- Figure 11.3.1.47 OS (PM01183 *vs* PLD)
- Figure 11.3.1.48 RR by IRC (PM01183 *vs* PLD)
- Figure 11.3.1.49 RR by IA (PM01183 *vs* PLD)
- Figure 11.3.1.50 DR by IRC (PM01183 *vs* PLD)
- Figure 11.3.1.51 DR by IA (PM01183 *vs* PLD)
- Figure 11.3.1.52 CA125 by IRC (PM01183 *vs* PLD)

Forest plots summarizing main results, stratification factors and covariates for the comparison between PM01183 and Topotecan will be plotted.

- Figure 11.3.1.53 PFS by IRC (PM01183 *vs* Topotecan)
- Figure 11.3.1.54 PFS by IA (PM01183 *vs* Topotecan)
- Figure 11.3.1.55 OS (PM01183 *vs* Topotecan)
- Figure 11.3.1.56 RR by IRC (PM01183 *vs* Topotecan)
- Figure 11.3.1.57 RR by IA (PM01183 *vs* Topotecan)
- Figure 11.3.1.58 DR by IRC (PM01183 *vs* Topotecan)
- Figure 11.3.1.59 DR by IA (PM01183 *vs* Topotecan)
- Figure 11.3.1.60 CA125 by IRC (PM01183 *vs* Topotecan)

Forest plots summarizing main results, stratification factors and covariates for the comparison between PM01183 and Control arm selecting patients who received as first subsequent therapy a platinum line will be plotted.

- Figure 11.3.1.61 PFS by IRC (PM01183 *vs* Control)
- Figure 11.3.1.62 PFS by IA (PM01183 *vs* Control)
- Figure 11.3.1.63 OS (PM01183 *vs* Control)

- Figure 11.3.1.64 RR by IRC (PM01183 *vs* Control)
- Figure 11.3.1.65 RR by IA (PM01183 *vs* Control)
- Figure 11.3.1.66 DR by IRC (PM01183 *vs* Control)
- Figure 11.3.1.67 DR by IA (PM01183 *vs* Control)
- Figure 11.3.1.68 CA125 by IRC (PM01183 *vs* Control)

In the forest plots continuous variables not categorized in the definition will be coded into two categories taking as reference the median value, below or equal the median value and above the median value.

Characteristics of responders

A summary of the main characteristics of patients showing clinical benefit, defined as patients with response or PFS≥4 months by IRC/IA will be shown.

Listing 11.3.1.69 Characteristics of patients with clinical benefit

Treatment arm*	Patient id.	Age	Strata	Prior therapy**	Cycles received	RR by IRC/IA	PFS by IRC/IA	DR by IRC/IA	OS

*PM01183/PLD/Topotecan

**Last prior therapy data; Setting, Best response and prior PFS.

12 Safety Analysis

Safety analysis will be carried out on the safety population.

12.1 Extent of Exposure

12.1.1 Treatment Administration

Table 12.1.1.1 Number of cycles administered and dose intensity

	PM01183		PLD		Topotecan	
No. of cycles administered per patient	N	%	N	%	N	%
1 2 3 …						
Median (range) / Mean (std)						
Time on treatment (weeks) Median (range) / Mean (std)						
Cumulative dose (mg/m²) Median (range) / Mean (std)						
Dose intensity (mg/m²/wk) Median (range) / Mean (std)						
Relative dose intensity (%) Median (range) / Mean (std)						

12.1.2 Cycle Delays

12.1.2.1 Number of Patients and Cycles with Dosing Delay, any Relationship

Table 12.1.2.1.1 Number of patients and cycles with dosing delay, any relationship

	PM01183		Control					
			Total		PLD		Topotecan	
	N	%	N	%	N	%	N	%
No. of patients treated								
No. of patients susceptible to be delayed*								
No. of patients with any dose delay								
No. of patients with any drug related dose delay								
Hematological reason								
Non-hematological reason								
Both reason								
No. of cycles administered								
No. of cycles susceptible to be delayed**								
No. of cycles with dosing delay***								
No. of patients with No cycle delayed 1 cycle delayed 2 cycles delayed ≥ 3 cycles delayed								

* Excluding patients who received only the first cycle.
** All cycles excluding first cycle.
*** Denominator= Number of cycles susceptible to be delayed.

Table 12.1.2.1.2 Number of patients and cycles with dosing delay according to the relationship

	PM01183				Control											
					Total				PLD				Topotecan			
	Rel**		No		Rel**		No		Rel**		No		Rel**		No	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
No. of patients with																
No delayed																
1 cycle																
2 cycles																
≥ 3 cycles																
No. of cycles with dosing delay*																

* Denominator= Number of cycles susceptible to be delayed.

**Related: Hematological reason, non-hematological reason or both. If the cause is related and not related the most conservative approach will be used (i.e. counted only once as related).

Table 12.1.2.1.3 Duration of dosing delay

Length of delay	PM01183						Control																	
							Total						PLD						Topotecan					
	Rel*		No		Total		Rel*		No		Total		Rel*		No		Total		Rel*		No		Total	
Median (range) Mean (std)																								
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
<=7 days																								
(7,14] days																								
>14 days																								

*Related: Hematological reason, non-hematological reason or both. If the cause is related and not related the most conservative approach will be used (i.e. counted only once as related).

12.1.2.2 Number of Delays According to Cycle Number

Table 12.1.2.2.1 Number and reasons of delays according to cycle number

	PM01183						Control																	
							Total						PLD						Topotecan					
	Cycle 2		Cycle n^{th}		Total		Cycle 2		Cycle n^{th}		Total		Cycle 2		Cycle n^{th}		Total		Cycle 2		Cycle n^{th}		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Number of delays																								
Treatment-related*																								
Hematological																								
Non-hematological																								
Both																								
Non related*																								

* Denominator= Number of cycles susceptible to be delayed.

The distribution of delays according to the cycle administered will be studied by means of counts and percentages. The reasons for cycle delay will be detailed, specifying how many were due to treatment and how many were not.

Listing 12.1.2.2.2 Patients and cycles with dosing delays

Treatment arm	Patient id.	Cycle	Reason of delay	Delay (days)

Listing 12.1.2.2.3 AEs associated with a cycle delay as action taken

Treatment arm	Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Outcome

12.1.3 Dose Reductions

Table 12.1.3.1 Number of patients and cycles with dose reduction, any relationship

	PM01183		Control					
			Total		PLD		Topotecan	
	N	%	N	%	N	%	N	%
No. of patients treated								
No. of patients susceptible to be dose reduced*								
No. of patients with dose reductions								
No. of patients with any drug related dose reduction								
Hematological reason								
Non-hematological reason								
Both reason								
No. of cycles administered								
No. of cycles susceptible to be dose reduced**								
No. of cycles with dose reduction***								
No. of patients with No reduction 1 reduction 2 reductions ≥ 3 reductions								

* Excluding patients who received only the first cycle.
** All cycles excluding the first cycle.
*** Denominator= Number of cycles susceptible to be reduced.

Table 12.1.3.2 Number of patients and cycles with dose reduction according to relationship

	PM01183				Control											
					Total				PLD				Topotecan			
	Rel**		No		Rel**		No		Rel**		No		Rel**		No	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
No. of patients with																
No reduction																
1 reduction																
2 reductions																
≥ 3 reductions																
No. of cycles with dose reduction*																

* Denominator= Number of cycles susceptible to be reduced.

**Hematological reason, non-hematological reason or both. If the cause is related and not related the most conservative approach will be used (i.e. counted only once as related).

Table 12.1.3.3 Number and reasons of reductions according to cycle number

	PM01183						Control																	
							Total						PLD						Topotecan					
	Cycle 2		Cycle n^{th}		Total		Cycle 2		Cycle n^{th}		Total		Cycle 2		Cycle n^{th}		Total		Cycle 2		Cycle n^{th}		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Number of reductions																								
Treatment-related*																								
Hematological																								
Non-hematological																								
Both																								
Non related*																								

* Denominator= Number of cycles susceptible to be reduced.

Listing 12.1.3.4 Dose reductions

Treatment arm	Patient id.	Cycle	Dose	Reason

Listing 12.1.3.5AEs associated with a dose reduction as action taken

Treatment arm	Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Serious Outcome

12.2 Adverse Events (AEs)

12.2.1 Adverse Events

Treatment emergent AEs will be described irrespective of their relationship to the drug and as drug-related events stated as Related to Study Drug or Unknown. Safety will be described according to the NCI-CTCAE v4. AEs consisting of laboratory abnormalities (e.g., neutropenia) may be under-reported as AEs. Since these events are better evaluated using objective laboratory results, laboratory abnormalities will be discussed in Section 12.4.

The type of toxicity and worst grade or severity by cycle and by patient will be summarized according to System Organ Class (SOC) and Preferred Term (PT) as per the MedDRA dictionary. Subsequent grouping of similar or clinically related items might be appropriate at the time of the analysis. Tables will be organized by category of events using SOC and in descending frequencies (e.g. higher to lower).

12.2.2 Display of Adverse Events

Table 12.2.2.1 Summary of adverse events

Category	PM01183	Control
	N (%)	N (%)
Number of patients with any AE		
Number of patients with any drug-related AE		
Number of patients with any grade 3/4 AE		
Number of patients with any grade 4 AE		
Number of patients with any grade 3/4 drug-related AE		
Number of patients with any grade 4 drug-related AE		
Number of patients with any SAE in DB		
Number of patients with any drug-related SAE in DB		

Category	PM01183	Control
	N (%)	N (%)
Number of patients with any grade 3/4 SAE in DB		
Number of patients with any grade 4 SAE in DB		
Number of patients with any grade 3/4 drug-related SAE in DB		
Number of patients with any grade 4 drug-related SAE in DB		
Number of patients with death associated with AEs		
Number of patients with death associated with drug-related AEs		
Number of patients with treatment discontinuations associated with AEs		
Number of patients with treatment discontinuations associated with drug-related AEs		
Number of patients with delays associated with AEs		
Number of patients with delays associated with drug-related AEs		
Number of patients with reductions associated with AEs		
Number of patients with reductions associated with drug-related AEs		

Table 12.2.2.2 Drug-related adverse events. Worst grade by patient

Category/MedDRA Code		**Grade**																			
		PM01183										**Control**									
		1		**2**		**…**		**G≥1**		**G≥3**		**1**		**2**		**…**		**G≥1**		**G≥3**	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Blood and lymphatic system disorders																					
	Anaemia NOS																				
	…																				
Cardiac disorders																					
	Arrhythmia NOS																				
	…																				
...																					

Table 12.2.2.3 Drug-related adverse events. Worst grade by cycle

Category/MedDRA Code		**Grade**																			
		PM01183										**Control**									
		1		**2**		**…**		**G≥1**		**G≥3**		**1**		**2**		**…**		**G≥1**		**G≥3**	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Blood and lymphatic system disorders																					
	Anaemia NOS																				
	…																				
Cardiac disorders																					
	Arrhythmia NOS																				
	…																				
...																					

Table 12.2.2.4 Adverse Events regardless of relationship. Worst grade by patient

Category/MedDRA Code		**Grade**																			
		PM01183										**Control**									
		1		**2**		**…**		**G≥1**		**G≥3**		**1**		**2**		**…**		**G≥1**		**G≥3**	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Blood and lymphatic system disorders																					
	Anaemia NOS																				
	…																				
Cardiac disorders																					
	Arrhythmia NOS																				
	…																				
...																					

Table 12.2.2.5 Adverse Events regardless of relationship. Worst grade by cycle

Category/MedDRA Code		**Grade**																			
		PM01183										**Control**									
		1		**2**		**…**		**G≥1**		**G≥3**		**1**		**2**		**…**		**G≥1**		**G≥3**	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Blood and lymphatic system disorders																					
	Anaemia NOS																				
	…																				
Cardiac disorders																					
	Arrhythmia NOS																				
	…																				
...																					

Listing 12.2.2.6 Drug-related grade 3/4 adverse events. Worst grade by cycle

Treatment arm*	Patient id.	Cycle	SOC Name	PTCode	Grade

*PM01183, PLD or Topotecan

Listing 12.2.2.7 Grade 3/4 adverse events regardless of relationship. Worst grade by cycle

Treatment arm*	Patient id.	Cycle	SOC Name	PTCode	Grade

*PM01183, PLD or Topotecan

12.2.3 Evolution of Signs and Symptoms during the Treatment

Worst grade of signs and symptoms present at baseline in a percentage≥10% or grade ≥3 and their evolution during treatment will be shown regardless of relationship.

Table 12.2.3.1 Shift of signs and symptoms during treatment

MedDRA PT	Baseline grade	Worst grade per patient during treatment							
		Grade 1		Grade 2		Grade 3		Grade 4	
		N	%	N	%	N	%	N	%
PM01183									
Constipation	1								
	2								
	…								
...	1								
	…								
Control									
Constipation	1								
	…								
Diarrhea	1								
	…								

12.3 Serious Adverse Events and Deaths.

12.3.1 Serious Adverse Events

Table 12.3.1.1 Drug-related serious adverse events. Worst grade by patient

Category/MedDRA Code		**Grade**																			
		PM01183										**Control**									
		1		**2**		**…**		**G≥1**		**G≥3**		**1**		**2**		**…**		**G≥1**		**G≥3**	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Blood and lymphatic system disorders																					
	Anaemia NOS																				
	…																				
Cardiac disorders																					
	Arrhythmia NOS																				
	…																				

Table 12.3.1.2 Drug-related serious adverse events. Worst grade by cycle

Category/MedDRA Code		**Grade**																			
		PM01183										**Control**									
		1		**2**		**…**		**G≥1**		**G≥3**		**1**		**2**		**…**		**G≥1**		**G≥3**	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Blood and lymphatic system disorders																					
	Anaemia NOS																				
	…																				
Cardiac disorders																					
	…																				
	...																				

Table 12.3.1.3 Serious adverse events regardless of relationship. Worst grade by patient

Category/MedDRA Code		Grade																			
		PM01183										Control									
		1		2		…		G≥1		G≥3		1		2		…		G≥1		G≥3	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Blood and lymphatic system disorders																					
	Anaemia NOS																				
	…																				
Cardiac disorders																					
	Arrhythmia NOS																				
	…																				
...																					
	...																				

Table 12.3.1.4 Serious adverse events regardless of relationship. Worst grade by cycle

Category/MedDRA Code		Grade																			
		PM01183										Control									
		1		2		…		G≥1		G≥3		1		2		…		G≥1		G≥3	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Blood and lymphatic system disorders																					
	Anaemia NOS																				
	…																				
Cardiac disorders																					
	Arrhythmia NOS																				
	…																				
...																					

Listing 12.3.1.5 Drug-related grade 3/4 serious adverse events. Worst grade by cycle

Treatment arm*	Patient id.	Cycle	SOC Name	PTCode	Grade

*PM01183, PLD or Topotecan

Listing 12.3.1.6 Grade 3/4 serious adverse events regardless of relationship. Worst grade by cycle

Treatment arm*	Patient id.	Cycle	SOC Name	PTCode	Grade

*PM01183, PLD or Topotecan

12.3.2 Interim Bayesian Safety Analysis

For PM01183 a bayesian test assuming non-informative prior distribution will be done to assess the null hypothesis of febrile neutropenia < 20% *versus* the alternative hypothesis of febrile neutropenia ≥20%. If the probability associated with the alternative hypothesis is higher than 50%, at the interim analysis with the first 40 patients treated in arm A, the addition of primary CSF prophylaxis will be considered necessary.

Table 12.3.2.1 Bayesian test

	Probability of being under null hypothesis	Probability of being under alternative hypothesis
Observed Proportion		

12.3.3 Deaths

Table 12.3.3.1 Cause of death

Reason[#]	PM01183		Control					
			Total		PLD		Topotecan	
	N	%	N	%	N	%	N	%
Malignant disease								
Study drug-related AE								
Non study drug-related AE								
Other								
Total								

(#) Denominator=Number of patients who died

Listing 12.3.3.2 Deaths

Treatment arm[*]	Patient id.	Death date	Cause	Number of cycles administered	Last infusion date	Time on treatment[**]	Time from Last dose[***]

*PM01183, PLD or Topotecan

**Time on treatment: defined as the date of the last infusion minus the first infusion date plus 30 days; or the date of death minus the first infusion date; or the date of start of new antitumor therapy minus the first infusion date (whichever comes first).

***Time from the last dose: defined as the date of death minus the last infusion date.

Listing 12.3.3.3 AEs reported as Fatal

Treatment arm[*]	Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date

*PM01183, PLD or Topotecan

12.4 Clinical Laboratory Evaluation

12.4.1 Hematological Abnormalities

Hematological toxicities classified according to NCI-CTCAE v4 will be calculated for all cycles. The worst grade reached by each patient during treatment will also be calculated.

Table 12.4.1.1 Hematological abnormalities, worst grade per patient

	Grade																			
	PM01183										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Leukopenia																				
Anemia																				
Thrombocytopenia																				
Neutropenia																				
Lymphopenia																				

Listing 12.4.1.2 Hematological tests not assessed at any treatment visit by patient

Treatment arm*	Patient id.	Lab. test
	…	
	…	

*PM01183, PLD or Topotecan

Table 12.4.1.3 Hematological abnormalities, worst grade per cycle

	Grade																			
	PM01183										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Leukopenia																				
Anemia																				
Thrombocytopenia																				
Neutropenia																				
Lymphopenia																				

Table 12.4.1.4 Hematological abnormalities, worst grade per cycle by cycle

	Grade																			
	PM01183										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Cycle 1																				
Leukopenia																				
Anemia																				
Thrombocytopenia																				
Neutropenia																				
Lymphopenia																				
Cycle ...																				

Listing 12.4.1.5 Hematological tests not assessed by patient and cycle

Treatment arm*	Patient id.	Cycle	Lab. test
	…		
	…		

*PM01183, PLD or Topotecan

Listing 12.4.1.6 Grade 3/4 hematological abnormalities. Worst grade by cycle

Treatment arm*	Patient id.	Cycle	Test	Grade

*PM01183, PLD or Topotecan

12.4.2 Biochemical Abnormalities

Table 12.4.2.1 Biochemical abnormalities, worst grade per patient

	Grade																			
	PM01183										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Creatinine increase																				
CPK increase																				
Bilirubin increase																				
AP increase																				
GGT increase																				
AST increase																				
ALT increase																				

Listing 12.4.2.2 Biochemical tests not assessed at any treatment visit by patient

Treatment arm*	Patient id.	Lab. test
	…	
	…	

*PM01183, PLD or Topotecan

Table 12.4.2.3 Biochemical abnormalities, worst grade per cycle

	Grade																			
	PM01183										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Creatinine increase																				
CPK increase																				
Bilirubin increase																				
AP increase																				
GGT increase																				
AST increase																				
ALT increase																				

Table 12.4.2.4 Biochemical abnormalities, worst grade per cycle by cycle

	Grade																			
	PM01183										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Cycle 1																				
Creatinine increase																				
CPK increase																				
Bilirubin increase																				
AP increase																				
GGT increase																				
AST increase																				
ALT increase																				
Cycle ...																				

Listing 12.4.2.5 Biochemical tests not assessed by patient and cycle

Treatment arm*	Patient id.	Cycle	Lab. test
	…		
	…		

*PM01183, PLD or Topotecan

Listing 12.4.2.6 Grade 3/4 biochemical abnormalities. Worst grade by cycle

Treatment arm*	Patient id.	Cycle	Test	Grade

*PM01183, PLD or Topotecan

12.4.3 Other Metabolic Parameters

Table 12.4.3.1 Metabolic abnormalities, worst grade per patient

	Grade																			
	PM01183										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Hyperglycemia																				
Hypernatremia																				
Hyperkalemia																				
Hypoglycemia																				
Hyponatremia																				
Hypokalemia																				
Hypoalbuminemia																				

Listing 12.4.3.2 Metabolic tests not assessed at any treatment visit by patient

Treatment arm*	Patient id.	Lab. test
	…	

*PM01183, PLD or Topotecan

Table 12.4.3.3 Metabolic abnormalities, worst grade per cycle

	Grade																			
	PM01183										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Hyperglycemia																				
Hypernatremia																				
Hyperkalemia																				
Hypoglycemia																				
Hyponatremia																				
Hypokalemia																				
Hypoalbuminemia																				

Table 12.4.3.4 Metabolic abnormalities, worst grade per cycle by cycle

	Grade																			
	PM01183										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Cycle 1																				
Hyperglycemia																				
Hypernatremia																				
Hyperkalemia																				
Hypoglycemia																				
Hyponatremia																				
Hypokalemia																				
Hypoalbuminemia																				
Cycle ...																				

Listing 12.4.3.5 Metabolic tests not assessed by patient and cycle

Treatment arm*	Patient id.	Cycle	Lab. test
	…		
	…		

*PM01183, PLD or Topotecan

Listing 12.4.3.6 Grade 3/4 metabolic abnormalities. Worst grade by cycle

Treatment arm*	Patient id.	Cycle	Test	Grade

*PM01183, PLD or Topotecan

12.4.4 Laboratory Values over Time

A summary of the laboratory values found in all patients will be shown.

Laboratory abnormality categories will be defined as:

-Hematological abnormalities, including leukopenia, neutropenia, anemia, thrombocytopenia and lymphopenia.

-Biochemical abnormalities, including creatinine increase, CPK increase, total bilirubin increase, AP increase, GGT increase, AST increase and ALT increase.

-Other metabolic abnormalities, including hyperglycemia, hypernatremia, hyperkalemia, hypoglycemia, hyponatremia, hypokalemia and hypoalbuminemia.

Table 12.4.4.1 Summary of laboratory values

Category	PM01183	Control
	N (%)	N (%)
Any abnormality (G1/4) in laboratory value (hema, bio or metabolic)		
Any abnormality (G3/4) in laboratory value (hema, bio or metabolic)		
Any abnormality (G4) in laboratory value (hema, bio or metabolic)		
Any abnormality (G1/4) in hematological value		
Any abnormality (G3/4) in hematological value		
Any abnormality (G4) in hematological value		

Category	PM01183	Control
	N (%)	N (%)
Any abnormality (G1/4) in biochemical value		
Any abnormality (G3/4) in biochemical value		
Any abnormality (G4) in biochemical value		
Any abnormality (G1/4) in other metabolic value		
Any abnormality (G3/4) in other metabolic value		
Any abnormality (G4) in other metabolic value		

The worst grade during treatment and in the first cycle compared to baseline will be shown for hematological and biochemical parameters.

Table 12.4.4.2 Shift of hematological abnormalities, worst grade per patient *vs.* baseline

	Baseline grade*	Worst grade per patient during treatment							
		Grade 0		Grade 1		Grade …		Grade 4	
		N	%	N	%	N	%	N	%
PM01183									
Leukopenia	0								
	1								
	…								
Neutropenia	0								
	…								
…**	0								
	…								
Control									
Leukopenia	0								
	1								
	…								
Neutropenia	0								
	…								
…**	0								

*Defined as the last value recorded before or on the date of first infusion.
** Anemia, thrombocytopenia and lymphopenia.

Table 12.4.4.3 Shift of hematological abnormalities, worst grade during first cycle *vs.* baseline

	Baseline grade*	Worst grade per patient during first cycle							
		Grade 0		Grade 1		Grade …		Grade 4	
		N	%	N	%	N	%	N	%
PM01183									
Leukopenia	0								
	1								
	…								
Neutropenia	0								
	…								
…**	0								
	…								
Control									
Leukopenia	0								
	…								
Neutropenia	0								
…**	0								
	…								

*Defined as the last value recorded before or on the date of first infusion.
** Anemia, thrombocytopenia and lymphopenia.

Table 12.4.4.4 Shift of biochemical abnormalities, worst grade per patient *vs.* baseline

	Baseline grade*	Worst grade per patient during treatment							
		Grade 0		Grade 1		Grade …		Grade 4	
		N	%	N	%	N	%	N	%
PM01183									
ALT	0								
	1								
	…								
AST	0								
	…								
…**	0								
	…								
Control									
ALT	0								
	1								
	…								
AST	0								
	…								
…**	0								
	…								

*Defined as the last value recorded before or on the date of first infusion.
** Total bilirubin, AP, GGT, CPK, creatinine, hyperglycemia, hypernatremia, hyperkalemia, hypoglycemia, hyponatremia, hypokalemia and hypoalbuminemia.

Table 12.4.4.5 Shift of biochemical abnormalities, worst grade during first cycle *vs.* baseline

	Baseline grade*	Worst grade per patient during first cycle							
		Grade 0		Grade 1		Grade …		Grade 4	
		N	%	N	%	N	%	N	%
PM01183									
ALT	0								
	1								
	…								
AST	0								
	…								
…**	0								
	…								
Control									
ALT	0								
	1								
	…								
AST	0								
	…								
…**	0								
	…								

*Defined as the last value recorded before or on the date of first infusion.
** Total bilirubin, AP, GGT, CPK, creatinine, hyperglycemia, hypernatremia, hyperkalemia, hypoglycemia, hyponatremia, hypokalemia and hypoalbuminemia.

Median intercycle figures showing PM01183 and Control arms for laboratory values will be added.

- Figure 12.4.4.6 Median nadir values for platelets
- Figure 12.4.4.7 Median nadir values for neutrophils
- Figure 12.4.4.8 Median peak values for AST
- Figure 12.4.4.9 Median peak values for ALT

Example intercycle graph

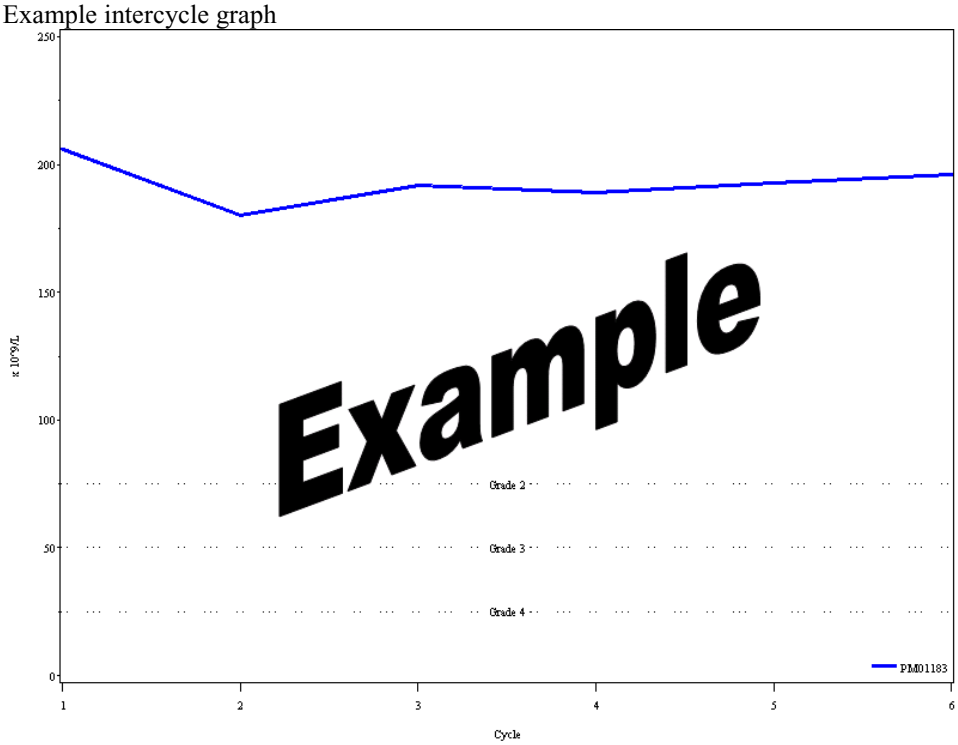


Table 12.4.4.10 Fisher exact test. Worst grade <3 *vs.* grade ≥3 by patient

	PM01183		Control		p-value
	Grade <3	Grade ≥3	Grade <3	Grade ≥3	
Thrombocytopenia					
Neutropenia					
ALKP					
Bilirubin					
SGOT-AST					
SGPT-ALT					
CPK					
Nausea					
Vomiting					
Fatigue					
Other*					

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.4.4.11 Fisher exact test. Worst grade <4 *vs.* grade ≥4 by patient

	PM01183		Control		p-value
	Grade <4	Grade ≥4	Grade <4	Grade ≥4	
Thrombocytopenia					
Neutropenia					
ALKP					
Bilirubin					
SGOT-AST					
SGPT-ALT					
CPK					
Nausea					
Vomiting					
Fatigue					
Other*					

*Any drug-related toxicity present in >=5% of patients in any group.

12.5 Subgroup Analyses Related to Safety

Information for laboratory abnormalities comes from hematology/biochemistry forms and not from AE form.

Table 12.5.1 Worst grade 3/4 by patient in special subgroups (Age)

Laboratory abnormalities/ drug-related AEs	<65 years-old			≥65 years-old		
	No. of patients evaluated	Grade 3/4	%	No. of patients evaluated	Grade 3/4	%
PM01183						
Thrombocytopenia						
Neutropenia						
ALKP						
Bilirubin						
SGOT-AST						
SGPT-ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						
Control						
Thrombocytopenia						
Neutropenia						
ALKP						
Bilirubin						
SGOT-AST						
SGPT-ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.5.2 Worst grade 3/4 by cycle in special subgroups (Age)

Laboratory abnormalities/ drug-related AEs	<65 years-old			≥65 years-old		
	No. of cycles evaluated	Grade 3/4	%	No. of cycles evaluated	Grade 3/4	%
PM01183						
Thrombocytopenia						
Neutropenia						
ALKP						
Bilirubin						
SGOT-AST						
SGPT-ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						
Control						
Thrombocytopenia						
Neutropenia						
ALKP						
Bilirubin						
SGOT-AST						
SGPT-ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

*Any drug-related toxicity present in >=3% of cycles in any group.

Table 12.5.3 Worst grade 3/4 by patient in special subgroups (Race)

Laboratory abnormalities/ drug-related AEs	White			Other		
	No. of patients evaluated	Grade 3/4	%	No. of patients evaluated	Grade 3/4	%
PM01183						
Thrombocytopenia						
Neutropenia						
ALKP						
Bilirubin						
SGOT-AST						
SGPT-ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						
Control						
Thrombocytopenia						
Neutropenia						
ALKP						
Bilirubin						
SGOT-AST						
SGPT-ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.5.4 Worst grade 3/4 by cycle in special subgroups (Race)

Laboratory abnormalities/ drug-related AEs	White			Other		
	No. of cycles evaluated	Grade 3/4	%	No. of cycles evaluated	Grade 3/4	%
PM01183						
Thrombocytopenia						
Neutropenia						
ALKP						
Bilirubin						
SGOT-AST						
SGPT-ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						
Control						
Thrombocytopenia						
Neutropenia						
ALKP						
Bilirubin						
SGOT-AST						
SGPT-ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

*Any drug-related toxicity present in >=3% of cycles in any group.

Table 12.5.5 Worst grade 3/4 by patient in special subgroups (Number of prior chemotherapy lines)

Laboratory abnormalities/ drug-related AEs	1-2			3		
	No. of cycles evaluated	Grade 3/4	%	No. of cycles evaluated	Grade 3/4	%
PM01183						
Thrombocytopenia						
Neutropenia						
ALKP						
Bilirubin						
SGOT-AST						
SGPT-ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						
Control						
Thrombocytopenia						
Neutropenia						
ALKP						
Bilirubin						
SGOT-AST						
SGPT-ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.5.6 Worst grade 3/4 by cycle in special subgroups (Number of prior chemotherapy lines)

Laboratory abnormalities/ drug-related AEs	1-2			3		
	No. of cycles evaluated	Grade 3/4	%	No. of cycles evaluated	Grade 3/4	%
PM01183						
Thrombocytopenia						
Neutropenia						
ALKP						
Bilirubin						
SGOT-AST						
SGPT-ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						
Control						
Thrombocytopenia						
Neutropenia						
ALKP						
Bilirubin						
SGOT-AST						
SGPT-ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

*Any drug-related toxicity present in >=3% of cycles in any group.

Table 12.5.7 Worst grade 3/4 by patient in special subgroups (Geographical area)

Laboratory abnormalities/ drug-related AEs	USA			Europe			Rest of the world		
	No. of patients evaluated	Grade 3/4	%	No. of patients evaluated	Grade 3/4	%	No. of patients evaluated	Grade 3/4	%
PM01183									
Thrombocytopenia									
Neutropenia									
ALKP									
Bilirubin									
SGOT-AST									
SGPT-ALT									
CPK									
Nausea									
Vomiting									
Fatigue									
Other*									
Control									
Thrombocytopenia									
Neutropenia									
ALKP									
Bilirubin									
SGOT-AST									
SGPT-ALT									
CPK									
Nausea									
Vomiting									
Fatigue									
Other*									

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.5.8 Worst grade 3/4 by cycle in special subgroups (Geographical area)

Laboratory abnormalities/ drug-related AEs	USA			Europe			Rest of the world		
	No. of patients evaluated	Grade 3/4	%	No. of patients evaluated	Grade 3/4	%	No. of patients evaluated	Grade 3/4	%
PM01183									
Thrombocytopenia									
Neutropenia									
ALKP									
Bilirubin									
SGOT-AST									
SGPT-ALT									
CPK									
Nausea									
Vomiting									
Fatigue									
Other*									
Control									
Thrombocytopenia									
Neutropenia									
ALKP									
Bilirubin									
SGOT-AST									
SGPT-ALT									
CPK									
Nausea									
Vomiting									
Fatigue									
Other*									

*Any drug-related toxicity present in >=3% of cycles in any group.

Table 12.5.9 Worst grade by patient comparison *vs.* PLD

Laboratory abnormalities/ drug-related AEs	Grade																			
	PM01183										PLD									
	0		1		…		G≥1		G≥3		0		1		…		G≥1		G≥3	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Thrombocytopenia																				
Neutropenia																				
ALKP																				
Bilirubin																				
SGOT-AST																				
SGPT-ALT																				
CPK																				
Nausea																				
Vomiting																				
Fatigue																				
Other*																				

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.5.10 Worst grade by cycle comparison *vs.* PLD

Laboratory abnormalities/ drug-related AEs	Grade																			
	PM01183										PLD									
	0		1		…		G≥1		G≥3		0		1		…		G≥1		G≥3	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Thrombocytopenia																				
Neutropenia																				
ALKP																				
Bilirubin																				
SGOT-AST																				
SGPT-ALT																				
CPK																				
Nausea																				
Vomiting																				
Fatigue																				
Other*																				

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.5.11 Worst grade by patient comparison *vs.* topotecan

Laboratory abnormalities/ drug-related AEs	**Grade**																			
	PM01183										Topotecan									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Thrombocytopenia																				
Neutropenia																				
ALKP																				
Bilirubin																				
SGOT-AST																				
SGPT-ALT																				
CPK																				
Nausea																				
Vomiting																				
Fatigue																				
Other*																				

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.5.12 Worst grade by cycle comparison *vs.* topotecan

Laboratory abnormalities/ drug-related AEs	**Grade**																			
	PM01183										Topotecan									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Thrombocytopenia																				
Neutropenia																				
ALKP																				
Bilirubin																				
SGOT-AST																				
SGPT-ALT																				
CPK																				
Nausea																				
Vomiting																				
Fatigue																				
Other*																				

*Any drug-related toxicity present in >=5% of patients in any group.

12.6 Concomitant Medication during Treatment

Table 12.6.1 Concomitant medication during treatment (ATC1/ATC2/ATC4)

Concomitant medication	PM01183		Control	
	N	%	N	%
Alimentary tract and metabolism Antiacids Magnesium compounds ….				
Blood and blood forming organs Antithrombotic agents Vitamin K antagonists …				

Table 12.6.2 CSF, transfusions or EPO

	PM01183		Control					
			Total		PLD		Topotecan	
	N	%	N	%	N	%	N	%
CSF CSF (prophylactic) CSF (therapeutic) Platelets transfusions RBC transfusions EPO								

Listing 12.6.3 Patients who have been treated with CSF, transfusions or EPO

Treatment arm*	Patient id.	Type	Agent	Route	Dose	Unit	Start date	Stop date	Reason	Indication

*PM01183, PLD or Topotecan

Table 12.6.4 Neutropenia by CSF, worst grade in the first cycle

	Grade																			
	CSF=YES										**CSF=NO**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
PM01183																				
PLD																				
Topotecan																				

12.7 Subsequent Therapy

Table 12.7.1 Subsequent therapy

	PM01183		Control					
			Total		PLD		Topotecan	
	N	%	N	%	N	%	N	%
Type Chemotherapy Surgery …								
Subsequent chemotherapy Platinum Taxanes …								

12.8 PRO at treatment

Completion rate is defined as the number of patients with answer to item X in the numerator and the number of patients on treatment in each time point as denominator.

Missing data will not be taken into account in the analyses; anyway, if the quantity is considered relevant then supportive analyses will be performed applying a conservative approach of assuming missing data as failures.

Table 12.8.1 Completion rate

Item	**Cycle**	PM01183		Control	
		Missing (%)	Completed (%)	Missing (%)	Completed (%)
EORTC QLQ-C30					
Item 1	Baseline				
	Week 6				
	…				
….	Baseline				
	…				
Any item	Baseline				
	Week 6				
	…				
EORTC QLQ-OV28					
Item 31	Baseline				
	Week 6				
	…				
….	Baseline				
	…				
Any item	Baseline				
	Week 6				
	…				
EORTC QLQ-C30 and QLQ-OV28					
Any item	Baseline				
	…				

Table 12.8.2 T-test change *vs.* baseline

Item	**Cycle**	PM01183		Control*		p-value
		N	Mean (std)	N	Mean (std)	
*Control refers to PLD and/or topotecan						
Item 1	Week 6					
	Week 12					
	…					
….	Week 6					
	Week 12					
	…					
Item 58	Week 6					
	Week 12					
	…					
*Control refers to PLD						
Item 1	Week 6					
	Week 12					
	…					
….	Week 6					
	Week 12					
	…					
Item 58	Week 6					
	Week 12					
	…					
*Control refers to topotecan						
Item 1	Week 6					
	Week 12					
	…					
….	Week 6					
	Week 12					
	…					
Item 58	Week 6					
	Week 12					
	…					

Table 12.8.3 Percentage of patients with an improvement ≥10% *vs.* baseline

Item	**Cycle**	PM01183		Control*		p-value
		N	%	N	%	
*Control refers to PLD and/or topotecan						
Item 1	Week 6					
	Week 12					
	…					
….	Week 6					
	Week 12					
	…					

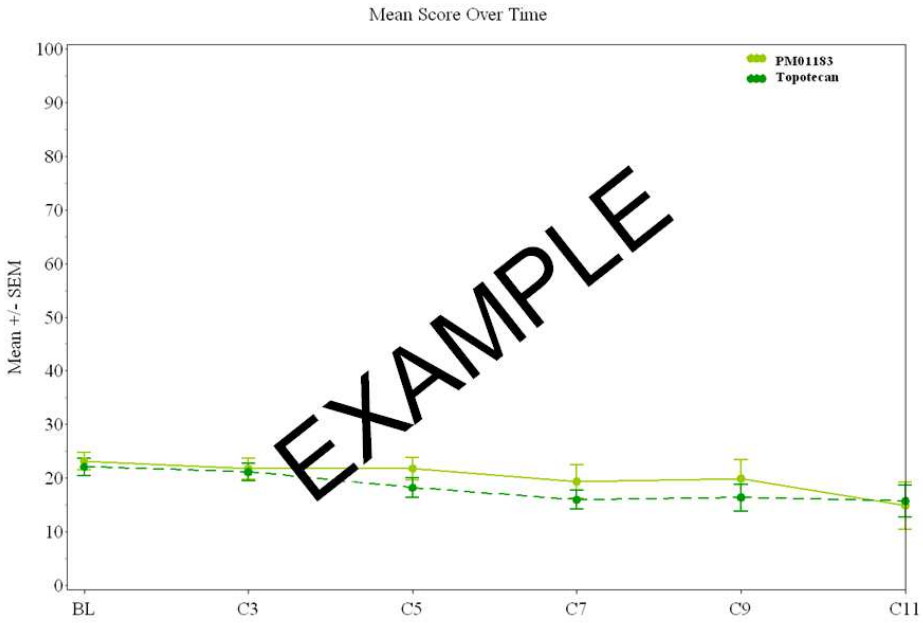
Item	Cycle	PM01183		Control*		p-value
		N	%	N	%	
Item 58	Week 6					
	Week 12					
	…					
*Control refers to PLD						
Item 1	Week 6					
	Week 12					
	…					
….	Week 6					
	Week 12					
	…					
Item 58	Week 6					
	Week 12					
	…					
*Control refers to topotecan						
Item 1	Week 6					
	Week 12					
	…					
….	Week 6					
	Week 12					
	…					
Item 58	Week 6					
	Week 12					
	…					

Longitudinal analyses will be performed assuming a mixed-effect model with treatment (Y), time effect (days after baseline), and a time-treatment interaction as covariates, using a covariance structure of autoregressive order 1.

Table 12.8.4 Mixed effect model

Item	Estimated point change per day	p-value	Mean change during treatment
*Control refers to PLD and/or topotecan			
Item 1			
….			
Item 58			
*Control refers to PLD			
Item 1			
….			
Item 58			
*Control refers to topotecan			
Item 1			
….			
Item 58			

Figures 12.8.5-12.8.62 Means plot by each item



APPENDIX II

13 DB Listings

Database listings including key variables showing all the recorded information following CRF's Form name will be shown.

-Listing 13.1.1: Subject

Treatment arm	Patient id.	Country / Site number	Country	Investigator first name	Investigator last name	Institution	Address

-Listing 13.1.2: Visit Date

Treatment arm	Patient id.	Date of visit

-Listing 13.1.3: Screening

Treatment arm	Patient id.	Protocol version	Date of birth	Informed consent date	Planned date of treatment initiation	Histology	PFI	PS	#Regimens	Prior agents (Preference)	RECIST (Measurable)	ANC (10^9/L)	BSA	Subject met all eligibility requirements (If not, specify)	Is patient a screening failure	Screen failure date

-Listing 13.1.4: Randomization Details

Treatment arm	Patient id.	Ready to randomization?	Randomization ID	Date and time of randomization	Date of patient randomization in the study	Stratum name	PFI	PS	Prior chemotherapy	Actual treatment to be given	Now

-Listing 13.1.5: Study Registration

Treatment arm	Patient id.	Informed consent date	PGt/PGx consent	Date of PGt/PGx sample	Date of blood sample	Adequate contraception (If NA, specify)

-Listing 13.1.6: Demographics

Treatment arm	Patient id.	Date of birth	Age (years)	Is the patient of childbearing potential?	Race (Other, specify)	Estimated DOB

-Listing 13.1.7: Pregnancy Test

Treatment arm	Patient id.	Visit	Not done	Which type of test was performed?	Date of sample	Reason for clinically indicated repeat	Result

-Listing 13.1.8: Medical History

Treatment arm	Patient id.	Medical history	Description	Verbatim	Onset date	Resolved date	Ongoing?

MedDRA codes will be also added.

-Listing 13.1.9: Cancer History

Treatment arm	Patient id.	Date of diagnosis	Primary site	Histology type ovarian	Histology grade	FIGO stage at diagnosis	FIGO stage at study entry	BRCA Status	Radiological and/or clinical signs of intestinal subocclusion?	Clinically evident ascites	Date of last progression	Site (s) of current disease (If other, specify)

-Listing 13.1.10: Prior Anticancer Therapy: Cytoreductive surgeries

Treatment arm	Patient id.	None	Procedure	Specify	Date	Optimal/Suboptimal

-Listing 13.1.11: Prior AntiCancer Therapy: Other Surgical Procedures

Treatment arm	Patient id.	Prior surgery	Procedures	Date	Intention

-Listing 13.1.12: Prior AntiCancer Therapy: RadioTherapy

Treatment arm	Patient id.	Radiotherapy	Type	Intention	Site anatomic	Total dose (Gy)	First dose	Last dose

-Listing 13.1.13: Prior AntiCancer Medical Therapy for Study Disease

Treatment arm	Patient id.	Prior therapy	Regimen	Type	Agent	Route	Setting	Start date	Stop date	Best response	Progression date	Non PD	Prior anthracycline containing regimen?	If Yes, provide total doxorubicin cumulative dose (mg/m^2)

ATC codes will be also added.

-Listing 13.1.14: Hematology

Treatment arm	Patient id.	Visit	Not done	Date	WBC	Neutrophils	Lymphocytes	Monocytes	Platelets	Hemoglobin	Clinically indicated repeat

-Listing 13.1.15: Biochemistry

Treatment arm	Patient id.	Visit	Not done	Date	ALT	AST	AP	GGT	Total Bilirubin	Direct Bilirubin	Total Proteins	Albumin	Creatinine	Creatinine Clearance	CPK	Glucose	Na	K	Cl	Clinically indicated repeat

-Listing 13.1.16: Physical Examination

Treatment arm	Patient id.	Visit	Not done	Date	Abnormalities	Body system	Findings	Clinical significance	Weight	Height	BSA

-Listing 13.1.17: Performance Status

Treatment arm	Patient id.	Visit	Not done	Date	PS (ECOG)

-Listing 13.1.18: Vital Signs

Treatment arm	Patient id.	Visit	Not done	Date	Heart rate	BPS	BPD	Temperature

-Listing 13.1.19: Electrocardiogram

Treatment arm	Patient id.	Visit	Not done	Date	Reason for clinically indicated	Result	Abnormal, specify	PR	Heart rate	QT interval (raw)	QRS complex duration	QTcF

-Listing 13.1.20: Left Ventricular Ejection Fraction (LVEF)

Treatment arm	Patient id.	Visit	Not done	Date	Reason for clinically indicated	Method	LVEF (%)	Range (%)	Result	Abnormal, specify	LVEF (derived)

-Listing 13.1.21: Anti-emetic Prophylactic Medication (Per Protocol)

Treatment arm	Patient id.	Visit	Not done	Drug type	Specify	Route	Daily dose	Units	Start date	Stop date	Taken per protocol	Specify (not per protocol)

ATC codes will be also added.

-Listing 13.1.22: CSF Prophylactic Medication

Treatment arm	Patient id.	Visit	Not Done/Not Applicable	Drug	Route	Daily dose	Units	Start date	Stop date

ATC codes will be also added.

-Listing 13.1.23: PM01183 Administration

Treatment arm	Patient id.	Visit	Date	Route	Start time	End time	Intended dose level	Total intended dose	Total dose	Total volume given	Reduction	Reduction reason	Delay	Delay reason	Interruption	Interruption reason	Date end time derived	Cycle	Number of doses

-Listing 13.1.24: PM01183 Re-Administration

Treatment arm	Patient id.	Visit	Not done	Date	Route	Start time	End time	Total dose	Total volume given

-Listing 13.1.25: Topotecan Administration

Treatment arm	Patient id.	Visit	Not Done	Delay (reason)	Day	Date	Route	Start time	End time	Intended dose level	Total intended dose	Total dose	Omission (reason)	Reduction (reason)	Interruption (reason)	No. of doses	Cycle

-Listing 13.1.26: Topotecan Re-Administration

Treatment arm	Patient id.	Visit	Day	Not done	Date	Route	Start time	End time	Total dose

-Listing 13.1.27: PLD Administration

Treatment arm	Patient id.	Visit	Date	Route	Start time	End time	Intended dose level	Total intended dose	Total dose	Total volume given	Reduction (reason)	Delay (reason)	Interruption (reason)	Cycle

-Listing 13.1.28: PLD Re-Administration

Treatment arm	Patient id.	Visit	Not done	Date	Route	Start time	End time	Total dose	Total volume given

-Listing 13.1.29: Adverse Events YN?

Treatment arm	Patient id.	AEs

-Listing 13.1.30: Adverse Events

Treatment arm	Patient id.	Adverse event	Grade	Start date (Ongoing)	End date (Duration/ongoing)	Relationship (PM1183/Topotecan/PLD/Specify)	Action	Serious Event (Death/Life Threat./Hospi./Disa./Conge./Other Impor./Infectious.)	Outcome	SAE associated to QC?	Case ID	Derived subject number

MedDRA codes will be also added.

-Listing 13.1.31: SAE summary

Treatment arm	Patient id.	Adverse event	Outcome	Start date	Case ID	Death	Life Threat.	Hospi.	Admission date	Discharge date	Disa.	Conge.	Other Medi.	Infec.	Narrative	Nulli.	Related docs?	Serious event	#Submi. to PHV

-Listing 13.1.32: SAE Attachments

Treatment arm	Patient id.	Attachment

-Listing 13.1.33: Concomitant Medication YN?

Treatment arm	Patient id.	Concomitant medication?

-Listing 13.1.34: Concomitant Medication

Treatment arm	Patient id.	Type of therapy	Drug name	Route	Dose	Unit	Frequency	No. of doses	No. of time units	Time units	Start date	End date	Ongoing	Reason	Indication	AEs	MH	Other, specify

ATC codes will be also added.

-Listing 13.1.35: Concomitant Procedures

Treatment arm	Patient id.	Not Done	Procedure	Indication	Date of Procedure	AE	MH	Result / Comments

MedDRA codes will be also added.

-Listing 13.1.36: Other tests/procedures

Treatment arm	Patient id.	Not done	Test name	Test date	Test result	Test unit

MedDRA codes will be also added.

-Listing 13.1.37: Target Lesions

Treatment arm	Patient id.	Were target lesions assessed	Target lesions	Lesion number	Organ	Specify	Lesion description	Date	Method (specify)	Longest diameter	Sum of diameters

-Listing 13.1.38: Non Target Lesions

Treatment arm	Patient id.	Were non target lesions assessed.	Non target lesions	Organ	Specify	Lesion description	Date	Method (specify)	Response

-Listing 13.1.39: New Lesions

Treatment arm	Patient id.	New lesions	Organ	Specify	Lesion description	Date	Method (specify)

-Listing 13.1.40: Radiological Evaluation of Response

Treatment arm	Patient id.	Evaluation (Not done)	Date	Target lesions	Non-Target lesions	New lesion	Not done	Overall cycle response

-Listing 13.1.41: Tumor Markers

Treatment arm	Patient id.	Not done	Date	CA125	Clinically indicated repeat	Age (Hidden)

-Listing 13.1.42: End of Treatment

Treatment arm	Patient id.	Reason	Specify (Investigator's decision)	Specify (AE)	Specify (Other)	Symptomatic deterioration date	Symptomatic deterioration, please specify

-Listing 13.1.43: Follow Up

Treatment arm	Patient id.	Date	Survival	Disease status	PD or any further therapy	TA done	TA not done	Specify (not done)

-Listing 13.1.44: Surgery procedures for Study Disease (after End of Treatment)

Treatment arm	Patient id.	Further surgery	Procedure	Date	Surgery Result

-Listing 13.1.45: Radiotherapy/Brachytherapy (after End of Treatment)

Treatment arm	Patient id.	Further radiotherapy	Site	Start date	End date	Ongoing	Total dose (Gy)

-Listing 13.1.46: Medical Treatment (after End of Treatment)

Treatment arm	Patient id.	Further therapy	Agent	Route	Start date	End date	Ongoing	Best response

ATC codes will be also added.

-Listing 13.1.47: Death Report Form

Treatment arm	Patient id.	Date	Cause	Specify (Other)	Autopsy	Attachment

-Listing 13.1.48: Off Study

Treatment arm	Patient id.	Off study	Date	Primary reason

-Listing 13.1.49: Pharmacokinetics

Treatment arm	Patient id.	PK samples	Sample No.	Day	Sampling time	Not done	Date	Actual time	Derived DateTime	Comments	Cycle the next Pharmacokinetics is due at:

-Listing 13.1.50: EORTC Quality of Life Questionnaire

Treatment arm	Patient id.	Not done	Date	Q1 to Q5	Specify if not performed	Q6 to Q28	Specify if not performed	Q29-Q30	Specify if not performed	Q31-Q54	Specify if not performed	Q55-Q56	Specify if not performed	Q57-Q58	Specify if not performed

-Listing 13.1.51: Treatment Continuation

Treatment arm	Patient id.	Add next cycle?

-Listing 13.1.52: Investigator Comments

Treatment arm	Patient id.	Visit	Form	Date	Comment

-Listing 13.1.53: Unscheduled

Treatment arm	Patient id.	Visit	Pregnancy test	LVEF	ECG

APPENDIX III

14 ICH Listings

Following ICH E-3 guidelines, patient listings will be prepared as specified for section 16.2.

- 16.2.1 Discontinued Patients

Treatment arm	Patient id.	Country	Institution	Subject met all eligibility requirements (If not, specify)	Is patient a screening failure	Screen failure date	Randomization date	Treated (Yes/No)	Drug adm. Start date (First cycle)	Cycles received	End of treatment (specify)	Off study (reason)

- 16.2.2 Protocol Deviations

Treatment arm	Patient id.	Severity	Type	Deviation

- 16.2.3 Patients Not Included in the Efficacy Analysis

Treatment arm	Patient id.	Reason

- 16.2.4 Demographic Data

Treatment arm	Patient id.	Age (years)	Race (Other, specify)	ECOG PS	Histology type ovarian	FIGO stage at study entry	Radiological and/or clinical signs of intestinal subocclusion?	Clinically evident ascites	BRCA Status	Site (s) of current disease (If other, specify)	BSA (m^2)	Prior surgery	Prior radiotherapy	PFI (months)	#Prior chemotherapy	Prior Agents

- 16.2.5 Compliance and/or Drug Concentration Data

Treatment arm	Patient id.	Cycles received	Cumulative dose (mg/m^2)	Dose intensity ($mg/m^2/wk$)	Relative dose intensity (%)	Visit	Treatment	Date	Intended dose level	Reduction (reason)	Delay (reason)	Interruption (reason)	Omission (reason)

- 16.2.6 Individual Efficacy Response Data

Treatment arm	Patient id.	IRC					IA						OS (mo.)	Event /Censored
		Overall response	PFS (mo.)	Event /Censored	DR (mo.)	Event /Censored reason	Overall response	CA125 response	PFS (mo.)	Event /Censored	DR (mo.)	Event /Censored reason		

- 16.2.7 Adverse Event Listing (each patient)

Treatment arm	Patient id.	SOC	PT	Adverse event	Grade	Start date (Ongoing)	End date (Duration/ongoing)	Relationship (PM1183/Topotecan/PLD/Specify)	Action	Serious event (Death/Life Threat./Hospi./Disa./Conge./Other Impor./Infectious.)	Outcome

- 16.2.8 Listing of Individual Laboratory Measurements by Patient

Treatment arm	Patient id.	Visit	Date	Test	Standard value	Normal lab. range	Grade

15 History of Changes

Clarifications/modifications, highlighted in ***italic bold***, have been added to the SAP v1.0 dated on 30/April/2015.

- Company Logo has been updated
- Clarification of the way the stratification factors should be handled in the analyses. A listing of patients assigned to the wrong strata at the time of randomization will be also included.
- Modifications/clarifications of list of covariates.
- Clarification in the incomplete dates imputation rules.
- Inclusion of neutropenia summary in the first cycle in patients with or without GCSF.
- Inclusion of shell listings for section 13 DB Listings and for section 14 ICH Listings.
- Other not relevant minor comments/clarifications (not specified in the document to maintain the simplicity).

Original (Cover)

Changes to (Cover)

Original Text (Section 6.2 Efficacy Analysis Methods):

The stratified log-rank test, using all randomization strata variables, on the ITT population will be primarily used to compare the time-to-event variables.

Changes to (Section 6.2 Efficacy Analysis Methods):

The stratified log-rank test, using ***actual values for*** all randomization strata variables, on the ITT population will be primarily used to compare the time-to-event variables. ***If***

the actual value is not a pre-defined category the value will be added to the most similar category (e.g. patients with more than three prior chemotherapy lines will be included in the 3-lines category).

Original Text (Section 6.2 Efficacy Analysis Methods):
Multivariate models (main effects or including interaction terms, if appropriate) will include all stratification factors and/or prognostic factors/covariates widely reported and recognized by the scientific community: treatment (PM01183 *vs.* control), ECOG PS (0 *vs.* ≥1 or coded as 0 *vs.* 1 *vs.* 2) prior platinum-free interval (1-3 months *vs.* >3 months or used as continuous variable), prior chemotherapy (1-2 *vs.* 3 lines or coded as 1 *vs.* 2 *vs.* 3) , geographical area (USA *vs.* Europe *vs.* rest of the world), age, age at diagnosis, race (caucasian *vs.* other), histology type (serous/papillary *vs.* other), histology grade (poorly/undifferentiated *vs.* other), primary tumor site (ovarian *vs.* other), FIGO stage at diagnosis (metastatic/locally advanced [stage III] *vs.* other), FIGO stage at study entry (metastatic *vs.* locally advanced [stage III]/other), BRCA status (mutated *vs.* other), clinical/radiological signs of intestinal subocclusion at entry (yes *vs.* no), site of current disease: lung/liver (yes *vs.* no), liver metastases (yes *vs.* no), number of prior metastatic sites (1 *vs.* >1), body mass index (BMI), height, weight, body surface area (BSA), time from diagnosis to first infusion, prior radical surgery (yes [primary *vs.* interval *vs.* secondary cytoreduction] *vs.* no), prior radiotherapy (yes *vs.* no), platinum resistance (primary *vs.* secondary), clinically evidence of ascites at baseline (yes *vs.* no), time elapsed from last dose of last prior platinum-containing regimen to randomization, prior antiangiogenic agents (yes *vs.* no), presence of any bulky (< 50 mm *vs.* ≥ 50 mm) lesion at baseline, measurable (yes *vs.* no), sum of all target lesion diameters, baseline CA-125, PFS prior line and baseline global QoL. In addition, continuous variables categorized as discrete variables will also be investigated in the continuum range and if the adjustment is better then the continual variable will be selected in the model.

Changes to (Section 6.2 Efficacy Analysis Methods):
Multivariate models (main effects or including interaction terms, if appropriate) will include all stratification factors and/or prognostic factors/covariates widely reported and recognized by the scientific community: treatment (PM01183 *vs.* control), ECOG PS (0 *vs.* ≥1 or coded as 0 *vs.* 1 *vs.* 2) prior platinum-free interval (1-3 months *vs.* >3 months or used as continuous variable), prior chemotherapy (1-2 *vs.* 3 lines or coded as 1 *vs.* 2 *vs.* 3) , geographical area (USA *vs.* Europe *vs.* rest of the world), ***investigator's preference for the control arm (Topotecan vs. PLD),*** age, age at diagnosis, race (caucasian *vs.* other), histology type (serous/papillary *vs.* other), histology grade (poorly/undifferentiated *vs.* other), primary tumor site (ovarian *vs.* other), FIGO stage at diagnosis (metastatic/locally advanced [stage III] *vs.* other), FIGO stage at study entry (metastatic *vs.* locally advanced [stage III]/other), BRCA status (mutated *vs.* other), clinical/radiological signs of intestinal subocclusion at entry (yes *vs.* no), site of current disease: lung/liver (yes *vs.* no), liver metastases (yes *vs.* no), number of prior metastatic sites (***≤2*** *vs.* ***>2***), body mass index (BMI), height, weight, body surface area (BSA), time from diagnosis to first infusion, ~~***prior radical surgery (yes [primary vs. interval vs. secondary cytoreduction] vs. no)***~~, ***prior cytoreduction (optimal vs. suboptimal vs. no surgery)***, prior radiotherapy (yes *vs.* no), platinum resistance (primary *vs.* secondary), clinically evidence of ascites at baseline (yes *vs.* no), time elapsed from last dose of last prior platinum-containing regimen to randomization, prior antiangiogenic ***treatment with bevacizumab*** ~~***agents***~~ (yes *vs.* no), ***prior PARPi (yes vs. no)***, presence of any bulky (< 50 mm *vs.* ≥ 50 mm) lesion at baseline, measurable ***disease*** (yes *vs.* no), sum of all

target lesion diameters, baseline CA-125, ***albumin value at baseline,*** PFS prior line, ***response to last platinum therapy (yes vs. no)*** and baseline global QoL. In addition, continuous variables categorized as discrete variables will also be investigated in the continuum range and if the adjustment is better then the ***continuous*** variable will be selected in the model.

Original Text (Section 8.6 Imputation in Incomplete Dates):

Dates of certain historical or current clinical activities...

Before randomization

All variables needed to summarize...

After end of treatment

A conservative approach for the variables collecting information after end of treatment where partial information is available (e.g., main time-to-event variables; PFS and OS) will be imputed by means of SAS programming. The following rules will be implemented: if the day of a date is unknown then the imputed day will be 1; if the month is also unknown, then the imputed date will be 1/July. This assumption will be valid if the imputed date occurs later than the last drug administration date; otherwise, the imputed date will be the last drug administration date plus 1 day.

Changes to (Section 8.6 Imputation in Incomplete Dates):

Dates of certain historical or current clinical activities...

Before randomization

All variables needed to summarize...

Between treatment start and end of treatment

All date variables during treatment where information is needed and is not fully available, for example adverse events or concomitant medications, will be subject of imputation by means of SAS programming. If the day of a date is unknown then the imputed day will be 1, if the month and/or year is also unknown then the imputed date will 1/January (this assumption will be valid if the imputed date is earlier than the treatment start date; otherwise, the imputed date will be the treatment start date).

After end of treatment.

A conservative approach for the variables collecting information after end of treatment where partial information is available (e.g., main time-to-event variables; PFS and OS) will be imputed by means of SAS programming. The following rules will be implemented: if the day of a date is unknown then the imputed day will be 1; if the month is also unknown, then the imputed date will be 1/July. This assumption will be valid if the imputed date occurs later than the last drug administration date; otherwise, the imputed date will be the last drug administration date plus 1 day.

If the date of subsequent therapy is incomplete (day or month is missing) and the

patient had documented disease progression, the date of subsequent therapy will be imputed to the end of the month when the progression occurred. If the subsequent therapy is given before progression to the study treatment, the rules specified above will apply.

Table/listing added (Section 10.1 Patient Disposition):

Listing 10.1.8 Patients assigned to incorrect strata at the time of randomization

Treatment arm*	***Patient***	***Actual stratum (Screening form)***	***Strata reported at randomization (Randomization form)***

****PM01183/PLD/Topotecan***

Table 10.1.9 Investigator's preference for the control arm

	PM01183		***Topotecan***		***PLD***	
	N	***%***	***N***	***%***	***N***	***%***
Topotecan						
PLD						

Original Text (Section 11.3 Efficacy Analysis):

Table 11.3.1.1 PFS by IRC (primary analysis)

Variable	p-value*
Treatment arm	

*Stratified log rank test.

Changes to (Section 11.3 Efficacy Analysis):

Table 11.3.1.1 PFS by IRC (primary analysis)

Variable	***Stratification factors***	p-value*
Treatment arm ***(main analysis)***	***Actual values***	
Treatment arm (sensitivity)	***Values reported for randomization***	

*Stratified log rank test.

Original Text (Section 11.3 Efficacy Analysis):

Table 11.3.1.8 PFS by IA (Stratified log rank test)

Variable	p-value*
Treatment arm	

*Stratified log rank test.

Changes to (Section 11.3 Efficacy Analysis):

Table 11.3.1.8 PFS by IA (Stratified log rank test)

Variable	***Stratification factors***	p-value*
Treatment arm ***(main analysis)***	***Actual values***	
Treatment arm (sensitivity)	***Values reported for randomization***	

*Stratified log rank test.

Original Text (Section 11.3 Efficacy Analysis):

Table 11.3.1.22 OS (Stratified log rank test)

Variable	p-value*
Treatment arm	

*Stratified log rank test.

Changes to (Section 11.3 Efficacy Analysis):

Table 11.3.1.22 OS (Stratified log rank test)

Variable	***Stratification factors***	p-value*
Treatment arm ***(main analysis)***	***Actual values***	
Treatment arm (sensitivity)	***Values reported for randomization***	

*Stratified log rank test.

Adds to (12.6 Concomitant Medication during Treatment)

Table 12.6.4 Neutropenia by CSF, worst grade in the first cycle

	Grade																			
	CSF=YES										**CSF=NO**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
PM01183																				
PLD																				
Topotecan																				

Adds to (13 DB Listings)

Shell listings based on the unique forms for eCRF dated on 13MAY2015 have been added to the main body of the SAP where they were not present previously. To avoid unnecessary multiplicity, they have not been repeated in this summary section.

Adds to (14 ICH Listings)

Shell listings have been added to the main body of the SAP where they were not present previously. To avoid unnecessary multiplicity, they have not been repeated in this summary section.