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CLINICAL TRIAL PROTOCOL

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

INVESTIGATIONAL MEDICINAL PRODUCTS: Lurbinectedin (PM01183), pegylated liposomal doxorubicin (PLD) and topotecan.

Protocol Code: PM1183-C-004-14

EudraCT No: 2014-005251-39

Final Version 1.0 – 4 December 2014

NCT Code: NCT02421588

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

Confidentiality statement

PRINCIPAL INVESTIGATORS

A full list of Investigators will be available as a separate document.

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SYNOPSIS

TITLE	Phase III Randomized Clinical Trial of Lurbinectedin (PM01183) *versus* Pegylated Liposomal Doxorubicin or Topotecan in Patients with Platinum-resistant Ovarian Cancer (CORAIL Trial)
PROTOCOL CODE	PM1183-C-004-14
NUMBER OF SITES / TRIAL LOCATION	This is a multicenter study. A full list of investigators will be available as a separate document.
STUDY OBJECTIVES	**Primary:** • To determine a difference in progression-free-survival (PFS) between lurbinectedin (PM01183) and pegylated liposomal doxorubicin (PLD) or topotecan in platinum-resistant ovarian cancer patients according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1. **Secondary:** 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 *versus* PLD or topotecan. • To conduct an exploratory pharmacogenetic and pharmacogenomic (PGx) sub-study.
STUDY DESIGN	Multicenter, open-label, randomized, controlled phase III clinical trial to evaluate the activity and safety of PM01183 *versus* PLD or topotecan as control arm in patients with platinum-resistant ovarian cancer. PM01183 will be explored as single agent in the experimental arm (Arm A) *versus* PLD or topotecan in the control arm (Arm B). Central randomization will be implemented in all patients that 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 one 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, then the patient will not be eligible for this trial if this agent is the only possible option (e.g., the patient has been previously treated with topotecan, then PLD is the only possible option in case the patient is randomized to the Arm B despite the fact that 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), and prior chemotherapy (1-2 *vs.* 3 lines). Up to 420 patients 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 RECIST v.1.1. Operational details for the IRC and 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 (Arm A) only 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 (CSF) 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 (i.e., ~105 patients enrolled in each arm). 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 superiority in efficacy *vs.* the control arm is foreseen at that time. Crossover after treatment discontinuation from control Arm B to experimental Arm A is not allowed.
STUDY POPULATION	Patients with platinum-resistant [disease relapse or progression within one to six months after last platinum-containing chemotherapy; platinum-free interval (PFI=time between completion of the last platinum-containing regimen and the subsequent relapse or progression)] epithelial ovarian, fallopian tube or primary peritoneal cancer who have received no more than three prior systemic chemotherapy regimens.

STUDY POPULATION **Inclusion criteria**	1) Voluntary written informed consent (IC) of the patient obtained before any study-specific procedure. 2) Age ≥ 18 years. 3) Histologically or cytologically confirmed diagnosis of unresectable epithelial ovarian, fallopian tube or primary peritoneal cancer. 4) Platinum-resistant disease (PFI: 1-6 months after last platinum-containing chemotherapy). 5) Radiologically measurable and/or non-measurable progressive disease according to RECIST v 1.1. 6) No more than three prior systemic chemotherapy regimens. Note: in case that a patient had started a new systemic chemotherapy without disease progression to the prior chemotherapy line (e.g., treatment discontinuations due to toxicity; neoadjuvant followed by adjuvant chemotherapy regimens), these two chemotherapy regimens will considered as one. 7) ECOG PS ≤ 2. 8) Adequate hematological, renal, metabolic and hepatic function: a) Hemoglobin ≥ 9 g/dl [patients may have received prior red blood cell (RBC) transfusion]; absolute neutrophil count (ANC) ≥ 2.0 x 10^9/l, and platelet count ≥ 100 x 10^9/l. b) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 x upper limit of normal (ULN). c) Alkaline phosphatase (AP) < 5.0 x ULN. d) Total bilirubin ≤ ULN or direct bilirubin ≤ ULN if total bilirubin is > ULN. e) Albumin ≥ 3.0 g/dl. f) Calculated creatinine clearance (CrCL) ≥ 30 ml/min (using Cockcroft and Gault's formula). g) Creatine phosphokinase (CPK) ≤ 2.5 x ULN. 9) At least three weeks since last prior therapy, and grade ≤ 1 from any adverse event (AE) derived from previous treatment (excluding grade ≤ 2 alopecia or peripheral neuropathy) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v. 4). 10) Women of childbearing potential must have pregnancy excluded by appropriate testing before study entry. A medically acceptable method of contraception must be maintained throughout the treatment period and for at least six months after treatment discontinuation.

Exclusion criteria	1) Concomitant diseases/conditions: a) History of cardiac disease: myocardial infarction or symptomatic/uncontrolled angina within the year prior to enrollment; or congestive heart failure defined as abnormal left ventricular ejection fraction (LVEF) < 50% assessed by multiple-gated acquisition scan (MUGA) or equivalent by ultrasound (US); or symptomatic arrhythmia. b) Patients with any immunodeficiency, including those known to be infected by human immunodeficiency virus (HIV). c) Chronic active hepatitis or cirrhosis. For Hepatitis B, this includes positive tests for both Hepatitis B surface antigen and quantitative Hepatitis B polymerase chain reaction (PCR). For Hepatitis C, this includes positive tests for both Hepatitis C antibody and quantitative Hepatitis C PCR. d) Active uncontrolled infection. e) Bowel obstruction. f) Requirement of permanent or frequent (i.e., once per week) external drainages within two weeks prior to randomization. g) Limitation of the patient's ability to comply with the treatment or to follow-up the protocol. h) Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the patient's participation in this study. 2) Platinum-refractory or platinum-sensitive disease (PFI <1 or > 6 months). 3) Prior treatment with PM01183, trabectedin, or with both PLD and topotecan. **Note:** if 60% of recruitment is reached in one of the control treatment options (i.e., PLD or topotecan), patients could only be eligible if they did not previously receive the other control treatment option available (the Sponsor will inform the sites, if this occurs). 4) Known brain metastases or leptomeningeal disease involvement. 5) History of another neoplastic disease (except for curatively treated basal cell carcinoma, squamous cell carcinoma of the skin, or properly treated carcinoma *in situ* of the uterine cervix or breast) within three years prior to randomization. 6) Pregnant or breast feeding women.

<table>
<tr><td>INCLUSION CRITERIA FOR THE PHARMACOGENOMIC AND PHARMACOGENETIC SUB-STUDY</td><td>Only patients who voluntarily sign the informed consent (IC) for the PGx and pharmacogenetic sub-study will participate. Refusal to participate in the PGx and pharmacogenetic sub-study will not affect patient participation in the clinical study PM1183-C-004-14.</td></tr>
<tr><td>EXPECTED NUMBER OF PATIENTS</td><td>Up to 420 patients will be randomized at a 1:1 ratio over 18 months (~23 patients/month as mean estimate).
A futility analysis is planned after the recruitment of 210 patients.</td></tr>
<tr><td>REPLACEMENT OF PATIENTS</td><td>Randomized patients will not be replaced.</td></tr>
<tr><td>STUDY DRUGS FORMULATION</td><td><u>EXPERIMENTAL ARM (Arm A):</u>
• <u>PM01183:</u>
PM01183 drug product (DP) presented as a lyophilized powder for concentrate for solution for infusion in 4-mg vials will be supplied by the Sponsor for the purposes of this study.
Before use, the 4-mg vials should be reconstituted with 8 ml of water for injection to give a solution containing 0.5 mg/ml of PM01183. For administration to patients as an i.v. infusion, reconstituted vials are diluted with glucose 50 mg/ml (5%) solution for infusion or sodium chloride 9 mg/ml (0.9%) solution for infusion.
The full composition of the PM01183 4-mg vials and the reconstituted solution per ml is as shown in Table 1.

Table 1. Composition of lurbinectedin (PM01183) vials.
<table><tr><th>Component</th><th>Concentration/vial</th><th>Concentration/vial after reconstitution</th></tr><tr><td>PM01183</td><td>4.0 mg</td><td>0.5 mg/ml</td></tr><tr><td>Sucrose</td><td>800 mg</td><td>100 mg/ml</td></tr><tr><td>Lactic acid</td><td>22.08 mg</td><td>2.76 mg/ml</td></tr><tr><td>Sodium hydroxide</td><td>5.12 mg</td><td>0.64 mg/ml</td></tr></table>
<u>CONTROL ARM (Arm B):</u>
• <u>PLD:</u>
Commercially available intravenous (i.v.) presentations of vials containing PLD will be provided as appropriate.
• <u>Topotecan:</u>
Commercially available i.v. presentations of vials containing topotecan will be provided as appropriate.</td></tr>
</table>

ROUTE OF ADMINISTRATION	**EXPERIMENTAL ARM (Arm A):** • **PM01183:** Intravenously as a 1-hour infusion through peripheral or central lines. A minimum total volume of 100 ml, diluted in 5% glucose or 0.9% sodium chloride, to be infused over about one hour, must be used for administration through a central venous catheter, or a minimum 250-ml dilution if a peripheral venous catheter is used. **CONTROL ARM (Arm B):** • **PLD:** Intravenously at an initial rate of 1 mg/min through peripheral or central lines. If no infusion reactions are observed, the rate of infusion can be increased to complete the administration of the drug over 1 hour. Total PLD doses > 90 mg and ≤ 90 mg should be diluted in 500 and 250 ml of 5% glucose solution for infusion, respectively. • **Topotecan:** Intravenously as a 30-min infusion through peripheral or central lines. Topotecan will be diluted in a minimum of 50 ml of 0.9% sodium chloride or 5% glucose solution for infusion.
STARTING DOSES AND SCHEDULE	**EXPERIMENTAL ARM (Arm A):** • **PM01183 starting dose and schedule:** • 3.2 mg/m^2 on Day 1 q3wk (three weeks = one treatment cycle) Dose will be rounded to the first decimal. **CONTROL ARM (Arm B):** • **PLD starting dose and schedule:** 50 mg/m^2 on Day 1 q4wk (four weeks = one treatment cycle). Dose will be rounded to the first decimal. Patients previously treated with PLD will be assigned to receive topotecan if they are randomized to the control arm. • **Topotecan starting dose and schedule:** • 1.50 mg/m^2 daily on Days 1-5 q3wk (three weeks = one treatment cycle) for patients with calculated CrCL ≥ 60 ml/min. • 1.25 mg/m^2 daily on Days 1-5 q3wk for patients with calculated CrCL between 40 and 59 ml/min. • 0.75 mg/m^2 daily on Days 1-5 q3wk for patients with calculated CrCL between 30 and 39 ml/min. Dose will be rounded to the first decimal.

<table>
<tr><td></td><td>Skipped doses of topotecan will not be replaced.
Patients previously treated with topotecan will be assigned to receive PLD if they are randomized to the control arm.
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.
The dose for all three agents (PM01183, PLD or topotecan) will be capped at a body surface area (BSA) of 2.0 m^2 in those patients who have a greater BSA. BSA will be calculated according to the standard nomogram used at each center.</td></tr>
<tr><td>PROPHYLACTIC MEDICATION</td><td>All patients will receive standard antiemetic prophylaxis before each treatment infusion, as follows:
• Corticosteroids (dexamethasone i.v. at least 8 mg or equivalent, or at institutional standard antiemetic doses).
• Serotonin (5-HT_3) antagonists (ondansetron at least 8 mg i.v. or equivalent).
If necessary, in addition to the above, the duration of treatment with 5-HT_3 antagonists and/or dexamethasone could be extended. Additional antiemetic agents can be administered as appropriate.
Aprepitant and equivalent agents (e.g., fosaprepitant) are forbidden in patients treated with PM01183.
For the purpose of safety evaluations, an optimal prophylaxis is defined as all the aforementioned allowed medications at their respectively maximum dose.</td></tr>
<tr><td>CRITERIA FOR TREATMENT CONTINUATION</td><td>Further treatment cycles (i.e., Cycle 2 or subsequent) will be administered every three weeks (PM01183 or topotecan) or every four weeks (PLD) (with a window of ± 48 hours in all of them) if the patient fulfills all the re-treatment criteria defined in Table 2 (PM01183), Table 3 (PLD) or Table 4 (topotecan).
Table 2. Criteria for treatment continuation with PM01183 (Arm A).
<table>
<tr><th>Variable</th><th>Day 1</th></tr>
<tr><td>ECOG PS</td><td>≤ 2</td></tr>
<tr><td>ANC</td><td>≥ 1.5 x 10^9/l</td></tr>
<tr><td>Platelets</td><td>≥ 100 x 10^9/l</td></tr>
<tr><td>Hemoglobin [a]</td><td>≥ 8 g/dl</td></tr>
<tr><td>Total bilirubin</td><td>≤ 1.5 x ULN or direct bilirubin ≤ ULN if total bilirubin > ULN</td></tr>
<tr><td>Albumin</td><td>≥ 2.7 g/dl</td></tr>
<tr><td>AST/ALT</td><td>≤ 3.0 x ULN</td></tr>
<tr><td>CPK</td><td>≤ 2.5 x ULN</td></tr>
<tr><td>Calculated CrCl
(Cockcroft and Gault’s formula)</td><td>≥ 30 ml/min</td></tr>
</table></td></tr>
</table>

Other non-hematological drug-related AEs (except isolated increased GGT and/or AP; grade 2 alopecia, constipation, fatigue, neuropathy, and not optimally treated nausea)	Grade ≤ 1

[a] Patients may receive PRBC transfusion and/or EPO treatment if clinically indicated to increase/maintain adequate hemoglobin levels.
AEs, adverse events; ANC, absolute neutrophil count; AP, alkaline phosphatase; AST/ALT, aspartate aminotransferase/alanine aminotransferase; CPK, creatine phosphokinase; CrCL, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; EPO, erythropoietin; PRBC, packed red blood cells; ULN, upper limit of normal.

Table 3. Criteria for treatment continuation with PLD (Arm B).

Variable	**Day 1**
ECOG PS	≤ 2
ANC	≥ 1.5 x 10^9/l
Platelets	≥ 75 x 10^9/l
Hemoglobin [a]	≥ 8 g/dl
Total bilirubin	≤ 1.5 x ULN or direct bilirubin ≤ ULN if total bilirubin > ULN
Mucositis or hand-foot syndrome	Grade < 2
Calculated CrCl (Cockcroft and Gault's formula)	≥ 30 ml/min
Other non-hematological drug-related AEs (except isolated increased GGT and/or AP; grade 2 alopecia, constipation, fatigue, neuropathy, and not optimally treated nausea)	Grade ≤ 1

[a] Patients may receive PRBC transfusion and/or EPO treatment if clinically indicated to increase/maintain adequate hemoglobin levels.
AEs, adverse event(s); ANC, absolute neutrophil count; AP, alkaline phosphatase; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; EPO, erythropoietin; GGT, gamma-glutamyltransferase; PPE, palmar-plantar erythrodysesthesia; PRBC, packed red blood cells; ULN, upper limit of normal.

Table 4. Criteria for treatment continuation with topotecan (Arm B).

Variable	**Day 1**
ECOG PS	≤ 2
ANC	≥ 1.5 x 10^9/l
Platelets	≥ 100 x 10^9/l
Hemoglobin [a]	≥ 8 g/dl
Total bilirubin	≤ 1.5 x ULN or direct bilirubin ≤ ULN if total bilirubin > ULN
AST/ALT	≤ 3.0 x ULN
Calculated CrCl (Cockcroft and Gault's formula)	≥ 30 ml/min [b]
Other non-hematological drug-related AEs (except isolated increased GGT and/or AP, grade 2 alopecia, constipation, fatigue, neuropathy, and not optimally treated nausea)	Grade ≤ 1

	[a] Patients may receive PRBC transfusion and/or EPO treatment if clinically indicated to increase/maintain adequate hemoglobin levels. [b] Patients with CrCL between 40 and 59 ml/min must be re-treated with no more than 1.25 mg/m^2 of topotecan daily, and patients with CrCL between 30 and 39 ml/min must receive no more than 0.75 mg/m^2 of topotecan daily. AEs, adverse events; ANC, absolute neutrophil count; AP, alkaline phosphatase; AST/ALT, aspartate aminotransferase/alanine aminotransferase; CPK, creatine phosphokinase; CrCL, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; EPO, erythropoietin; PRBC, packed red blood cells; ULN, upper limit of normal. If a patient does not meet the requirements for treatment continuation on Day 1 of any cycle after Cycle 1, re-assessments should be performed within one week, and treatment will be withheld until appropriate recovery, for a maximum of two weeks after the treatment due date. If there is no recovery after a 2-week delay, treatment must be discontinued, except if objective clinical benefit is adequately documented by the Investigator, and upon agreement with the Sponsor. Then, treatment may continue after appropriate dose reduction.
DOSE REDUCTION	Patients who experience any grade ≥ 3 treatment-related non-hematological toxicity (according to the NCI-CTCAE v. 4) and/or grade 3 thrombocytopenia associated with bleeding or persistent at the time of re-treatment or grade 4, or frequent or prolonged treatment-related dose delays (> 1 week) (or skipped infusions if on topotecan) will continue treatment after appropriate dose reduction (see Table 5 for dose reduction in Arm A, PM01183; see Table 6 for dose reduction in Arm B, PLD or topotecan). Patients experiencing grade 4 neutropenia or any grade febrile neutropenia, or neutropenic infection during the preceding cycle or frequent treatment-related dose delays exclusively due to neutropenia may continue treatment without any dose reduction, but the patient must receive secondary prophylaxis with CSF starting at least 24 hours after the last infusion of the cycle. If despite appropriate CSF secondary prophylaxis, grade 4 neutropenia or febrile neutropenia, neutropenic infection or the dose delay re-occurs, then dose reduction should be implemented. Exceptions for dose reduction are: grade 3 nausea and/or vomiting not optimally prevented, grade 3 fatigue lasting ≤ 2 days, grade 3 diarrhea lasting ≤ 1 day or not optimally treated, isolated grade 3 ALT or AST elevations not leading to dose delays and/or non-clinically relevant isolated biochemical abnormalities (e.g., GGT).

Table 5. Levels of dose reduction in Arm A (PM01183).

	Arm A PM01183 dose (q3wk) (mg/m^2) [a]
1 (starting dose)	3.2
-1	2.6
-2	2.0

[a] PM01183 dose will be capped at a body surface area (BSA) of 2.0 m^2 in those patients who have a greater BSA.
q3wk, every three weeks.

Table 6. Levels of dose reduction in Arm B (PLD or topotecan).

	Arm B			
	PLD [e] (q4wk) (mg/m^2)	**Topotecan [e] daily dose (q3wk) (mg/m^2)**		
1 (starting dose)	50	1.50 [a]	1.25 [b]	0.75 [c, d]
-1	37.5	1.25	1.00	-
-2	28 [d]	1.00	0.75 [d]	-

[a] Starting dose for patients treated with topotecan with calculated CrCL ≥ 60 ml/min.
[b] Starting dose for patients treated with topotecan with calculated CrCL of 40-59 ml/min.
[c] Starting dose for patients treated with topotecan with calculated CrCL of 30-39 ml/min.
[d] No dose reduction below 28 mg/m^2 of PLD or 0.75 mg/m^2/day of topotecan will be implemented under any circumstances.
[e] PLD and topotecan dose will be capped at a body surface area (BSA) of 2.0 m^2 in those patients who have a greater BSA.
CrCL, creatinine clearance; PLD, pegylated liposomal doxorubicin; q3wk, every three weeks; q4wk, every four weeks.

In case of grade ≥ 2 hand-foot syndrome (HFS) or stomatitis secondary to PLD treatment, the PLD treatment administration will be delayed until resolved to grade ≤1 or discontinued if not resolved within two weeks. In addition, subsequent doses will be reduced if the HFS or stomatitis is ≥ grade 3 (Table 7).

Table 7. PLD dose modification guidelines according to hand-foot syndrome and stomatitis (Arm B).

Toxicity grade	**Hand-foot syndrome (HFS)**	**Stomatitis**	**Dose adjustment**
1	Mild erythema, swelling, or desquamation not interfering with daily activities.	Painless ulcers, erythema, or mild soreness.	**Re-treat unless patient has experienced previous grade 3 or 4 HFS/mucositis**. If so, delay up to two weeks and decrease dose one level. Return to original dose interval.

	2	Erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter.	Painful erythema, edema, or ulcers, but can eat.	**Delay dosing up to two weeks or until resolved to grade 0-1.** If after two weeks there is no resolution, PLD should be discontinued. If resolved to grade 0-1 within two weeks, and there are no prior grade 3-4 HFS/mucositis, continue treatment at previous dose and return to original dose interval. If patient experienced previous grade 3-4 toxicity, continue treatment with one dose level reduction and return to original dose interval.
	3	Blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing.	Painful erythema, edema, or ulcers, and cannot eat.	**Delay dosing up to two weeks or until resolved to grade 0-1.** Decrease dose one level and return to original dose interval. If after two weeks there is no resolution, PLD should be discontinued.
	4	Diffuse or local process causing infectious complications, or a bed ridden state or hospitalization.	Requires parenteral or enteral support.	**Delay dosing up to 2 weeks or until resolved to grade 0-1.** Decrease dose one level and return to original interval. If after two weeks there is no resolution, PLD should be discontinued.

HFS, hand-foot syndrome; PLD, pegylated liposomal doxorubicin.

Patients treated with PLD who have LVEF decreased to < 45% or with a 20% decrease from the baseline value have to permanently discontinue PLD treatment.

Control and experimental arms:

Patients who experience any treatment-related grade 3 or 4 hypersensitivity and/or extravasations will permanently discontinue treatment irrespectively of arm allocation.

Up to two dose reductions are allowed per patient. Patients who continue to experience treatment-related toxicity and/or frequent dose delays after two dose reductions must be withdrawn from the study. Once the dose has been reduced for an individual patient, it will not be re-escalated under any circumstances irrespectively of arm allocation.

ALLOWED MEDICATIONS/ THERAPIES

- Therapies for pre-existing and treatment-emergent medical conditions, including pain management.
- Blood products and transfusions, as clinically indicated.
- Bisphosphonates.
- In case of nausea or vomiting, extended symptomatic treatment for emesis will be allowed.
- Colony-stimulating factors (CSFs) or erythropoietin treatment according to the American Society of Clinical Oncology (ASCO) guidelines.
- Anticoagulants.

PROHIBITED MEDICATIONS/ THERAPIES	• Concomitant administration of any antineoplastic therapy (other than those specifically allowed). • Any radiotherapy other than limited field irradiation for cancer pain control exclusively. • Immunosuppressive therapies other than corticosteroids for antiemetic prophylaxis and/or pain control. • Aprepitant and equivalent agents (e.g., fosaprepitant) for patients allocated to the PM01183 arm (Arm A). • Primary CSF prophylaxis for patients allocated to the PM01183 arm (Arm A), unless recommended by the IDMC after the interim safety analysis. • Any other investigational agent/s.
DRUG-DRUG INTERACTIONS	*In vitro* studies using human liver microsomes have shown that PM01183 has the potential to inhibit cytochrome CYP2B6, CYP2C8 and CYP3A4. Moreover, the Ki values compared with the achieved maximum plasma concentration (C_{max}) values at relevant doses indicate that the likelihood of a clinically relevant inhibition of PM01183 is possible for CYP2B6 and CYP2C8 ([I]/Ki>0.1) and likely for CYP3A4 ([I]/Ki>1). Additional *in* vitro studies have demonstrated no time dependent inhibition or irreversible inhibition for cytochrome CYP3A4. The magnitude of the interaction is unknown at present. Therefore, caution should be exercised when PM01183 is administered concomitantly with CYP2B6, CYP2C8 and CYP3A4 substrates. Additionally, *in vitro* studies with human microsomes have shown that CYP3A4 is the major CYP isoform involved in the metabolism of PM01183, followed by CYP2E1, CYP2D6 and CYP2C9. The estimated contribution of the other CYP isoenzymes to the PM01183 metabolism is considered to be negligible. Therefore, concomitant drugs which induce or inhibit any of these cytochromes, especially CYP3A4, should be carefully monitored or avoided, whenever is possible. A potentially significant interaction with aprepitant is suggested by available phase II data from ovarian cancer patients. Four patients treated with aprepitant in Cycle 2 with available PK data had their PM01183 clearance reduced by 50%, approximately, compared to their Cycle 1 exposure. Aprepitant use was forbidden in Cycle 1 in all patients. Clinically, some of these patients had unusually long-lasting neutropenia and/or severe thrombocytopenia during Cycle 2 as well. Although all patients eventually recovered, the use of aprepitant is currently forbidden in all phase II/III PM01183 studies.

EFFICACY EVALUATIONS	Antitumor activity will be assessed using the RECIST v. 1.1 and followed until disease progression (PD) by the appropriate method [computed tomography (CT) scan or magnetic resonance imaging (MRI) of the pelvis, abdomen and chest]. 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 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 cutoff), whichever occurs first. After radiological PD is documented or a new antitumor therapy is started, patients will be followed for survival 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 a 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. A futility analysis is planned when 210 patients are recruited. The IDMC will review the efficacy and safety data available at that time and, based on the observed results, might recommend stopping the trial; no claim for superiority in efficacy *vs.* the control arm is foreseen at that time.
SAFETY EVALUATIONS	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 treatment-related AEs will be followed until recovery to at least grade 1 or stabilization of symptoms, whichever occurs first.

<table>
<tr><td></td><td>An interim safety analysis will be performed by the IDMC after the recruitment of the first 40 patients in the PM01183 arm (Arm A) to assess if the addition of primary CSF prophylaxis might be necessary. Although febrile neutropenia did not occur in the first-in-human PM01183 single-agent study, according to pooled data available from all ongoing phase II studies at 7.0 mg flat dose (FD), it occurred in about 16% of patients. In this clinical trial, the expected percentage of febrile neutropenia is lower, as the PM01183 dose will be administered based on BSA and with a dose (3.2 mg/m^2) below the RD found in the first-in-human PM01183 trial (4.0 mg/m^2 = 7.0 mg FD).
Furthermore, PM01183, PLD and topotecan dose will be capped at a BSA of 2.0 m^2 in those patients who have a greater BSA.
At the time of the interim safety analysis, recruitment in the control arm (Arm B, PLD and topotecan) is also expected to be 40 patients.
Safety evaluations will be also performed by the IDMC during the futility analysis to be conducted in the two treatment arms once 210 patients are recruited (i.e., ~105 patients enrolled in each arm).</td></tr>
<tr><td>PATIENT-REPORTED OUTCOMES (PRO)</td><td>PRO will be assessed every eight weeks from randomization and while on treatment to determine if efficacy and side effects are accompanied by measurable changes in the quality of life of patients. EORTC QLQ-C30 and EORTC QLQ-OV28 questionnaires will be used.</td></tr>
<tr><td>PHARMACOKINETIC EVALUATIONS</td><td>Sparse samples (detailed in Table 8) will be collected in all patients enrolled in the PM01183 arm (Arm A). The samples will be obtained in two cycles (in Cycle 1 and in a second cycle between Cycle 2 and 4). The selection of the second cycle with sample collection for the measurement of PM01183 will be assigned once the patient is randomized into Arm A.

Table 8. Blood samples for pharmacokinetic evaluations.
<table>
<tr><th>Sample No.</th><th>Sampling time</th><th>PK window</th></tr>
<tr><td>#1</td><td>Before PM01183 treatment start</td><td>1 to 5 min before treatment start</td></tr>
<tr><td>#2</td><td>5 min before PM01183 EOI</td><td>+/- 2 min</td></tr>
<tr><td>#3</td><td>1 hour after PM01183 EOI</td><td>+/- 10 min</td></tr>
<tr><td>#4</td><td>168 hours after PM01183 EOI</td><td>+/- 24 hours</td></tr>
</table>
EOI, end of infusion; PK, pharmacokinetics.</td></tr>
</table>

PHARMACOGENETIC EVALUATIONS	To explore factors that may help to explain individual variability in main pharmacokinetic (PK) parameters, the presence or absence of germline mutations or polymorphisms will be analyzed in leukocyte DNA extracted from a blood sample obtained before treatment start in the PM01183 arm (Arm A).
PHARMACOGENOMIC EVALUATIONS	The analysis of potential predictive factors to PM01183 treatment will be analyzed on prior available paraffin-embedded tumor tissue samples from consenting patients. Samples from Arm B will be also analyzed and used as controls in order to differentiate between the prognostic or predictive value of any obtained finding. The potential predictive factors will include genes involved in DNA repair mechanisms (such as nucleotide excision repair, homologous recombination repair or mismatch repair) and other factors related to the mechanism of action of PM01183 or to the pathogenesis of the disease, and their expression will be analyzed at the mRNA or protein level by quantitative polymerase chain reaction (PCR) and immunohistochemistry, respectively; their polymorphisms and mutations might be also analyzed, if relevant.
STUDY 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:** o **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. o **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 RECIST v.1.1. 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 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 cutoff), 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 Gynecologic Cancer Intergroup (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 analyzed 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 *versus* PLD or topotecan will be performed. Details of these analyses will be provided in the Statistical Analysis Plan. • **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 be also analyzed. Their correlation with the clinical response and outcome after treatment will be assessed.
STATISTICAL METHODS	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. The primary study endpoint (PFS by IRC) will be calculated by means of the stratified log-rank test on the intention-to-treat (ITT) population, defined as all randomized patients analyzed in the group where they were allocated. An IDMC will oversee the conduct of the study. **Sample size calculation:** Patients will be randomized to receive PM01183 given as 3.2 mg/m^2 (experimental Arm A) or either topotecan or PLD (control arm, Arm B). The prospective assumptions are a 30% reduction in the relative risk of progression or death [hazard ratio (HR)=0.70) 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. 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 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 RECIST v.1.1. A futility analysis with no claim for efficacy when 210 patients are recruited (i.e., ~105 patients enrolled in each arm) and the final analysis to reject the null hypothesis (HR=1) are planned; the significance level will be determined by the actual observed number of events, and to maintain scientific integrity spending function will be defined by O'Brien-Fleming boundaries. Following the prospective assumptions, the futility analysis will occur before 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. **Randomization:** Central randomization will be implemented in all patients that fulfill the inclusion 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 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 one 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. **Stratification:** Stratification will be performed according to ECOG PS (0 *vs.* ≥1), prior PFI (1-3 months *vs.* >3 months) and prior chemotherapy (1-2 *vs.* 3 lines). **Statistical analysis:** Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. The study protocol contains a general description; specific details will be provided in the Statistical Analysis Plan. Frequency tables will be prepared for categorical variables, and continuous variables will be described by means of summary tables, which will include the median, mean, standard deviation, minimum, and maximum of each variable. **Efficacy analyses:** 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 on the ITT population will be primarily used to compare the time-to-event variables. Unstratified log-rank tests will be also calculated as supportive analyses. The symmetry of tumor evaluations between the different arms will be examined. Sensitivity analyses for different PFS censoring (e.g. date of progression based on scheduled time instead of registered date) will be performed, these analyses will be detailed in the SAP. 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. Continuous variables that would have been categorized as discrete variables will also be investigated in the continuum range, and if the adjustment is better, then the continual variable will be chosen. 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 of the experimental arm (PM01183) and the control arm (PLD and topotecan). Waterfall plots will be used to describe the best variation of the sum of target lesions during the treatment.

	Safety analyses: AEs, SAEs, deaths, laboratory evaluations, dose delays/skipped/reductions and study drug discontinuations due to AEs will be tabulated in a descriptive way. Counts and percentages will be used for categorical variables, and summary tables will be used for continuous variables. Exploratory Fisher's exact tests will be performed to compare grade 4 or grade 3/4 between treatment arms. An interim safety analysis, performed when 40 patients are enrolled in the PM01183 arm (Arm A), will test if the addition of primary CSF prophylaxis might be necessary. 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% *versus* 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 would be considered necessary. At the time of the interim safety analysis, recruitment in the control arm (Arm B, PLD and topotecan) is also expected to be 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. A safety evaluation will also be performed by the IDMC as part of the futility analysis, when a total of 210 patients are included. **Patient-reported outcome (PRO) analyses:** PRO will be analyzed 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. **Pharmacokinetic analyses:** Sparse PK data will be listed in the population PK-report for all patients with available concentrations in the PM01183 treatment arm (Arm A). Patients will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (e.g., improper handling of PK samples; incomplete administration of the study agent; missing time or dosing information). All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. All patients and samples excluded from the analysis will be retained in the dataset, but they will be flagged out and the criteria for exclusion documented. Population PK analysis of plasma concentration-time data of PM01183 will be performed using non-linear mixed-effects modeling. Data may be combined with those of a selection of phase I or II studies to support a relevant structural model. Available patient characteristics (demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting PK parameters. 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. **Pharmacogenetic analyses:** The influence of known polymorphisms on main PK parameters will be assessed by Student's test or Mann-Whitney's U test as appropriate. **Pharmacogenomic analyses:** Analysis of RNA/protein expression, polymorphisms and mutations will be performed blind and with clinical data compiled only after all analyses are completed. A Fisher´s exact test/logistic regression for categorical variables and log rank test/Cox regression for time to event variables will be used to test whether a specific profile is associated with clinical outcome. The prognostic value of markers will be explored for objective response, PFS and OS. In each case, if applicable, a multivariate model will be developed by stepwise selection. All tests of statistical significance will be two-sided, and significance will be set at 0.05.
DURATION OF STUDY PERIOD (per patient)	Patients will be evaluated at scheduled visits during three study periods: • **Pre-treatment:** from signature of IC to the first infusion of the study treatment. • **Treatment:** from the first infusion of the study treatment to the end of treatment (EOT). • **Follow-up:** after EOT, patients will be followed every four weeks until resolution or stabilization of all toxicities, if any. Patients who finish treatment without radiological disease progression will be followed every eight weeks (± two weeks) from randomization until disease progression or start of a new antitumor therapy, death or until the date of study termination (clinical cutoff), whichever occurs first. After radiological disease progression is documented or a new antitumor therapy is started, patients will be followed at least every three months (± two weeks) 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 disease progression will be performed according to a calendar time. Patients will be considered to be **on-study** from the signature of the informed consent form (ICF) until death or study termination. Patients will be considered to be **on-treatment** from Day 1 of Cycle 1 until the day of EOT. This EOT is defined as 30 days after the day of the last study treatment infusion, unless the patient starts a new antitumor therapy or dies (whichever occurs first). An end-of-treatment visit (EOT visit) will be performed within 30 days (± 7 days) after the last study treatment administration, unless the patient starts any subsequent antitumor therapy, in which case the end-of-treatment visit should be performed immediately before the start of the new therapy.

	Patients will receive the study treatment(s) 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. • Requirement of > two dose reductions.
PLANNED TRIAL PERIODS (for the whole study)	The total duration of the study will be approximately 42 months, including approximately a 18-month enrolment period. **Planned start date** (first patient on study): approximately first quarter 2015. **Planned enrolment period**: approximately 18 months. **Planned end-of-study date** (clinical cutoff): 24 months after randomization of the last patient.

SCHEDULE OF ASSESSMENTS AND PROCEDURES

Assessments and procedures	Screening* (days before first drug infusion)	Treatment						End of treatment (EOT) ‡	Follow-up
		Cycle 1		Cycle 2**		Further cycles**			
		D1	D8	D1	D8	D1	D8		
Written informed consents (general and for pharmacogenetic and PGx sub-study)	Before any study procedure	-	-	-	-	-	-	-	-
Demographic data	-28 to 0	-	-	-	-	-	-	-	-
Medical and cancer history/baseline conditions	-14 to 0 (+1 week)	-	-	-	-	-	-	-	-
Assessment of disease-related signs and symptoms	-14 to 0 (+1 day)	-	-	-	-	-	-	-	-
Complete physical examination, including weight, height and calculation of BSA (1)	-14 to 0 (+1 day)	-	-	•	-	•	-	-	-
ECOG PS	-7 to 0 (+1 day)	-	-	•	-	•	-	•	-
Vital signs (heart rate, blood pressure, temperature)	-7 to 0 (+1 day)	-	-	•	-	•	-	-	-
Laboratory tests (2)	-7 to 0 (+3 days)	-	•	•	•	•	-	•	-
Pregnancy test (if applicable) (3)	-7 to 0 (+3 days)	Repeat if applicable							-
ECG (4)	-7 to 0 (+3 days)	Repeat if clinically indicated							-
LVEF by ECHO or MUGA	-14 to 0 (+2 weeks)	Repeat if clinically indicated In patients treated with PLD (Arm B), to be repeated every four cycles (or more frequently, if clinically indicated). After exceeding a cumulative anthracycline dose of 450 mg/m^2, LVEF will be assessed before each PLD infusion							-
Pharmacokinetics (PM01183 treatment arm only, in Cycle 1 and in a second cycle between Cycle 2 and Cycle 4)	-	• **(5)**	• **(5)**	• **(6)**	• **(6)**	• **(6)**	• **(6)**	-	-
Pharmacogenetics (polymorphisms), in Cycle 1 only if written informed consent given	-	• **(7)**	-	-	-	-	-	-	-
Pharmacogenomics (PGX), if written informed consent given	Available stored paraffin-embedded tumor tissue samples	-							-
Radiological tumor assessment (contrast enhanced helical CT-scan or MRI, as clinically relevant)	-14 to 0 (+2 weeks)	Every eight weeks from randomization until evidence of PD							• **(8)**
Tumor marker evaluation (CA-125)	-7 to 0 (+3 days)	Every eight weeks from randomization until evidence of PD (**9**)							• (9,**10**)
Patient-reported outcomes (EORTC QLQ-C30 and EORTC QLQ-OV28 questionnaires)	-7 to 0 (+1 day)	Every eight weeks from randomization						•	-

Assessments and procedures	Screening* (days before first drug infusion)	Treatment						End of treatment (EOT) ‡	Follow-up
		Cycle 1		Cycle 2**		Further cycles**			
		D1	D8	D1	D8	D1	D8		
Concomitant therapies	-14 to 0	Throughout the "on-treatment period"***							-
Adverse events	- §	Throughout the "on-treatment period"***							**• (11)**

Regardless of the treatment administered, the same schedule of assessments will apply.

* Screening procedures will have to be repeated in case that the first infusion of the study treatment is given out of the established windows. **Note: Randomization of patients should occur as close in time as possible to the administration of the first dose of study drug.**

**Further treatment cycles will be administered every three weeks (± 48 hours) for PM01183 (Arm A) and topotecan (Arm B), or every four weeks (± 48 hours) for PLD (Arm B) if the patient fulfills all re-treatment criteria.

***"On treatment period" = from first infusion of the study treatment (PM01183, PLD or topotecan) to EOT [30 days after the day of the last dose administration, unless the patient starts a new antitumor therapy or dies (whichever occurs first), in which case the date of administration of this new therapy or the date of death will be considered the date of end of treatment].

‡ At 30 ±7 days after the last treatment infusion, an EOT should be performed. The listed assessments will have to be done if no recent data are available (i.e. within last 10 days prior to the EOT visit) or if the last data available show a grade ≥ 2 treatment-related alteration whenever the medical condition of the patient may allow these evaluations.

§ Only information on SAEs that occur after signature of informed consent form is required. Grading should be as per NCI-CTCAE v. 4.

Time windows for Cycle 2 and further: a 3-day window will be allowed for laboratory tests and ECG, a 1-week window for tumor assessments as per RECIST v.1.1, tumor marker evaluation and patient-reported outcomes, a 1-day window for clinical assessments (ECOG PS, vital signs, weight, BSA, etc.), a 7-day window for the assessments at EOT, and a 2-week window for the follow-up period.

1. Height to be measured at baseline only.
2. **Any patient presenting grade 4 treatment-related AEs should have any relevant tests re-assessed at least within 72 hours until recovery to at least grade 3.**
3. Beta subunit-human chorionic gonadotropin (ß-hCG) (urine or serum).
4. Cardiac rhythm will be identified in ECG intervals of at least 30 seconds of duration, PR interval, QT interval (raw), heart rate and QRS complex
5. A total of four blood samples (before PM01183 treatment start, 5 min before the end of PM01183 infusion, and 1 hour and 168 hours after the end of PM01183 infusion) will be collected for pharmacokinetic PM01183 analyses in Cycle 1 in patients treated in Arm A.
6. A total of four blood samples (before PM01183 treatment start, 5 min before the end of PM01183 infusion, and 1 hour and 168 hours after the end of PM01183 infusion) will be collected in a second cycle (between Cycle 2 and 4) in patients treated in Arm A. The second cycle with blood sample collection for PK will be assigned once the patient is randomized into the PM01183 arm.
7. One blood sample will be collected before treatment start in patients treated in Arm A (if informed written consent given) for the pharmacogenetic sub-study.
8. 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 cutoff), 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 a calendar time.
9. To be repeated only if baseline levels were higher than normal.
10. To be measured every eight weeks (at the same time than radiological tumor assessments) in case of discontinuation without disease progression or until start of a new antitumor therapy, death or date of study termination (clinical cutoff), whichever occurs first.
11. Patients withdrawn from the study with a drug-related AE should be followed every four weeks until recovery to at least grade 1 or stabilization.

Laboratory tests include:

- **Hematology:** Differential WBC counts, including neutrophil, lymphocyte and monocyte counts, platelet count and hemoglobin.
- **Biochemistry**: Liver function test (ALT, AST, AP, GGT, total bilirubin; direct bilirubin only if total bilirubin is abnormally high); total proteins, albumin, creatinine, CPK, glucose, calculated CrCL (as per Cockcroft and Gault's formula), and serum electrolytes (Na^+, K^+, Cl^-).

AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BSA, body surface area; CPK, creatine phosphokinase; CrCL, creatinine clearance; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group Performance Status; EOT, end of treatment; GGT, gamma-glutamyl transferase; hCG, human chorionic gonadotropin; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition scan; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, progressive disease; PLD, pegylated liposomal doxorubicin; PS, performance status; RECIST, Response Evaluation Criteria In Solid Tumors; SAE, serious adverse event; ULN, upper limit of normal; WBC, white blood cells.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

5-HT$_3$	Serotonin
AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
β-hCGs	Beta Subunit of Human Chorionic Gonadotropins
BSA	Body Surface Area
C_{max}	Maximum Plasma Concentration
CI	Confidence Interval
CPK	Creatine Phosphokinase
CR	Complete Response
CrCL	Creatinine Clearance
CRF	Case Report Form
CSF	Colony-stimulating Factors
CT	Computed Tomography
d/D	Day(s)
DNA	Deoxyribonucleic Acid
DP	Drug Product
DR	Duration of Response
DSB	Double-strand Breaks
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EOI	End of Infusion
EOT	End of Treatment
EPO	Erythropoietin
FD	Flat Dose
FIGO	International Federation of Gynecology and Obstetrics
FiM	First-in-human (study)
FUP	Follow-up
GCIG	Gynecologic Cancer Intergroup
Gem	Gemcitabine
GCP	Good Clinical Practice
GGT	Gamma Glutamyltransferase

GMT	Greenwich Meridian Time
hCG	Human Chorionic Gonadotropin
HFS	Hand-foot Syndrome
HNPCC	Hereditary Non-polyposis Colorectal Cancer
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio/Homologous Recombination
IA	Investigator's Assessment
IB	Investigator's Brochure
IC	Informed Consent
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committees
IG_{50}	Concentration that Results in 50% of Cell Growth Inhibition
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	Intention-to-treat
IUD	Intrauterine Device
i.v.	Intravenous
LC-MS/MS	Liquid Chromatography/Mass Spectrometry/Mass Spectrometry
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mo	Months
MRI	Magnetic Resonance Imaging
MUGA	Multiple-gated Acquisition Scan
NA	Not Available
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NER	Nucleotide Excision Repair
NSCLC	Non-small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PFI	Platinum-free Interval
PFS	Progression-free Survival

PGx	Pharmacogenomics
PhV	Pharmacovigilance
PK	Pharmacokinetic
PLD	Pegylated Liposomal Doxorubicin
PPE	Palmar-plantar Erythrodysesthesia
PR	Partial Response
PRBC	Packed Red Blood Cells
PRE TT	Pre-treatment
PRO	Patient-reported Outcomes
PS	Performance Status
q3wk	Every Three Weeks
q4wk	Every Four Weeks
Qdx5x2	Two cycles of Five Daily Doses
Q7dx3	Three Consecutive Weekly Doses (D-0, 7, 14)
RBC(s)	Red Blood Cell(s)
RD	Recommended Dose
RNA	Ribonucleic Acid
RECIST	Response Evaluation Criteria In Solid Tumors
SAE(s)	Serious Adverse Event(s)
SCLC	Small Cell Lung Cancer
SD	Stable Disease
TT	Treatment
TTP	Time to Progression
ULN	Upper Limit of Normal
US	Ultrasound
USA	United States of America
WBC	White Blood Cells
wk/wks	Week/weeks
WMA	World Medical Association

1. INTRODUCTION

1.1 OVARIAN CANCER

Epithelial ovarian carcinoma is one of the most common gynecological malignancies and has the highest rate of cancer-related mortality among gynecological cancers in developed countries. It is the seventh most frequent cause of cancer death in women worldwide [1] and the fifth in the USA [2]. Half of the cases occur in women over 65 years.

Most ovarian cancers are sporadic; hereditary syndromes account for 10-15% of cases. Approximately 90% of hereditary ovarian cancer cases are associated with mutations in BRCA1 (chromosome 17) and BRCA2 (chromosome 13). Women with mutations in BRCA1 have a 40-50% chance of developing ovarian cancer and those with BRCA2 mutations have a 15-25% risk [3-5]. Hereditary non-polyposis colorectal cancer (HNPCC, Lynch II syndrome) carries an ovarian cancer risk of 12% [6]. Hereditary syndromes have to be distinguished from familiar syndromes. Women who have a single family member with epithelial ovarian cancer have a 4-5% risk, and those with two affected relatives have a 7% risk of developing ovarian cancer [7].

Due to the absence of specific clinical symptoms and the lack of standard screening tests for early diagnosis, nearly 75% of the patients have advanced stage at diagnosis. The International Federation of Gynecology and Obstetrics (FIGO) classification is the most extended staging system used. Survival rates at 5 years do correlate with the FIGO stage at diagnosis: 5-year survival exceeds 90% in early stages (IA, IB), but decreases to 40% and 20% in advanced stages (III and IV, respectively) [8].

Maximal surgical cytoreduction, followed by platinum-based combination chemotherapy are the standard of care for patients with advanced ovarian cancer. Combinations of platinum salts (carboplatin or cisplatin) with paclitaxel are highly active and induce objective response in 75% of patients, including nearly 40% of clinical complete responses [9, 10]. Complete response (CR) rate is higher in patients with early FIGO stage at diagnosis and in those with optimal debulking surgery. Platinum/paclitaxel combinations have also shown a significant improvement in progression-free survival (PFS) (18 *vs.* 13 months) and overall survival (OS) (38 *vs.* 24 months) compared to platinum combinations with older alkylant agents (cyclophosphamide), and therefore have become the standard frontline chemotherapy for advanced disease.

Despite this highly effective treatment, three quarters of the patients relapse and die due to progressive disease. The goal of treatment of relapsed ovarian cancer is palliative, as there is no realistic chance of curing patients whose disease has relapsed. On this basis, quality of life, prolongation of survival and control of cancer related symptoms are the primary goals of treatment of recurrent disease [11].

Given its therapeutic and prognostic relevance [12, 13], recurrent ovarian cancer is usually classified according to the length of platinum-free interval (PFI), defined as the time between completion of the last platinum-containing regimen and the subsequent relapse or progression. Ovarian cancer with a PFI longer than six months (i.e., the time between completion of the last platinum-containing chemotherapy and the date of relapse is longer than 6 months), is classified as platinum-sensitive. Patients with platinum-sensitive ovarian cancer have high likelihood of responding to a subsequent platinum-based chemotherapy and generally respond to non-platinum-based therapies as well. They have an overall better survival prognosis. Several therapeutic options are

available for platinum-sensitive disease, including platinum combinations with paclitaxel, gemcitabine or pegylated liposomal doxorubicin (PLD) [14-16], and non-platinum agents either alone or in combination (e.g., trabectedin plus PLD) [17-23].

In contrast, patients with platinum-resistant disease (PFI: 1-6 months) and those progressing or failing to achieve a response to a platinum-containing combination (platinum-refractory; PFI < 1 month) are less likely to respond to any subsequent therapy and have the worst prognosis in survival expectancy. Therapeutic options for these patients are very limited, and response rates rarely exceed 15%. Combination chemotherapy has not proven superior to monotherapy and it is usually more toxic.

The preferred chemotherapy for patients with platinum-resistant ovarian cancer is a single non-platinum agent. None of the approved chemotherapy agents (topotecan, PLD or paclitaxel) has been proved superior in OS in platinum-resistant ovarian cancer patients. Indeed, to date no approval of any available chemotherapies was granted on the basis of results in this specific disease setting; rather, results available for the relapsed ovarian cancer population in general were extrapolated. Response rates with single agents in platinum resistant disease are usually within the 10-15% range; PFS ranges 3 to 4 months, and OS is usually below one year with some exceptions (Table 1). Combination of chemotherapy with bevacizumab has not shown a statistically significant OS advantage over chemotherapy alone.

Table 1. Efficacy results of non-platinum chemotherapy in clinical trials conducted in platinum-resistant/platinum-refractory ovarian cancer patients.

Study (reference)	No of patients *	Treatment arms (n)	Refractory (%)	ORR (%)	PFS (mo)	OS (mo)
Ten Bokkel Huinink *et al.* (1997) [24]	119	Topotecan (60)	57	13.3	NA	NA
		Paclitaxel (59)	56	6.7	NA	NA
Gordon *et al.* (2001) [25]	254	Topotecan (124)	NA	6.5	3.4	10.3
		PLD (130)	NA	12.3	2.3	8.9
Gore *et al.* (2001) [26]	152	Oral topotecan (77)	52	8.0	NA	NA
		i.v. topotecan (75)	52	8.0	NA	NA
Mutch *et al.* (2007) [27]	195	Gemcitabine (99)	NA	6.1	3.6	Gem/PLD 12.7
		PLD (96)	NA	8.3	3.1	PLD/Gem 13.5
Vergote et al. (2009) [28]	461	Canfosfamide (231)	41	4.3	2.3	8.5
		PLD (130)	15	10.9	4.3	14.2
		Topotecan (87)				10.8
Vergote *et al.* (2010) [29]	125	Canfosfamide plus PLD (65)	20	12.3	5.6	11.8
		PLD (62)	13	8.3	3.7	7.8
Sehouli *et al.* (2011) [30]	194	Topotecan standard (97)	NA	19.0	4.4	9.3
		Topotecan weekly (97)	NA	9.0	3.0	9.6
Colombo *et al.* (2012) [31]	829	Patupilone (412)	20.1	15.5	3.7	13.2
		PLD (419)	18.8	7.9	3.7	12.7
Pujade-Lauraine *et al.* 2012 [32] Witteveen *et al.* 2013 [33] (AURELIA trial)	361	Chemotherapy ** (182)	Not allowed	12.6	3.4	13.3
		Chemotherapy** plus bevacizumab (179)		30.9	6.7	16.6

*Including both platinum-resistant and platinum-refractory ovarian cancer.
**Chemotherapy=topotecan (daily or weekly), weekly paclitaxel or PLD.
Gem, gemcitabine; mo, months; NA, data not available; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin.

The treatment of patients with platinum-resistant ovarian cancer is usually chosen based on the individual safety profile, since all these agents show very similar and limited efficacy, and the therapy aim is mainly to delay disease progression and palliate symptoms. These patients are usually candidates for clinical trials testing new treatment options.

1.2 INFORMATION ON THE STUDY DRUGS

1.2.1 Lurbinectedin (PM01183)

Please refer to the Investigator's Brochure (IB) for full information on PM01183.

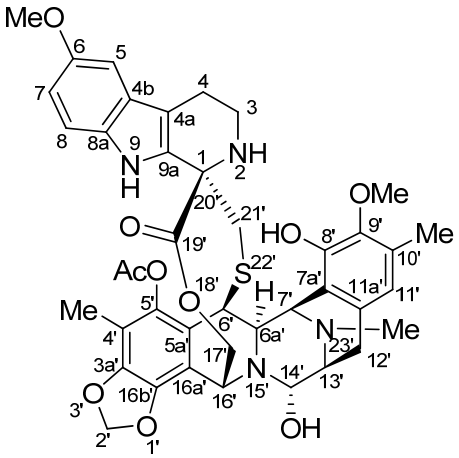
1.2.1.1 *Name and Chemical Information*

PM01183 is produced by synthesis and has the following chemical properties:

Chemical Name	(1R,6'R,6a'R,7'R,13'S,14'S,16'R)-8',14'-dihydroxy-6,9'-dimethoxy-4',10',23'-trimethyl-19'-oxo-2,3,4,6',7',9,12',13', 14',16'-decahydro-6a'H-spiro[ß-carboline-1,20'-[7,13]epimino[6,16](epithiopropanooxymethano)[1,3]dioxolo[7,8]isoquino[3,2-b][3]benzazocin]-5'-yl acetate
Molecular Formula	$C_{41}H_{44}N_4O_{10}S$
Molecular Weight	784.874

The structural and molecular formula of PM01183 are shown in Figure 1.

Figure 1. Molecular formula of lurbinectedin (PM01183).



1.2.1.2 *Non-clinical Data*

PM01183 is a new synthetic tetrahydroisoquinoline alkaloid which binds the deoxyribonucleic acid (DNA) minor groove, causing spatial distortion of DNA and protein complexes and leading to the formation of DNA double-strand breaks (DSBs), thus inducing apoptosis and delaying progression through the cell cycle S/G2 phase.

PM01183 has a negative COMPARE analysis when compared against other 98 standard anticancer agents in the standard National Cancer Institute (NCI) panel of 36 cell lines. Thus, its mechanism of action is likely to differ significantly from all the other drugs. It only showed a positive correlation (S-rank > 0.8) with trabectedin [34].

In vitro, PM01183 demonstrated cytotoxic effects against a broad selection of tumor-derived cell lines with half maximal inhibitory concentration (IC_{50}) values in the low to

very low nanomolar range (approximately median IC_{50} of 1^{-10} M). PM01183 also has *in vivo* antitumor activity against different murine models of xenografted human-derived tumor types.

The antineoplastic *in vitro* activity of PM01183 was evaluated in a panel of solid tumor cell lines (some of which are shown in Table 2), which were exposed to a range of PM01183 concentrations for 72 hours and then assayed for viability by a MTT short-term assay [35].

Table 2. Selected *in vitro* activity of PM01183.

Tumor	Cell line	IG_{50} (M)
Breast	BT-474	$1.3 \cdot 10^{-9}$
	MDA-MB-231	$3.5 \cdot 10^{-9}$
	MCF-7	$1.7 \cdot 10^{-9}$
Colon	LoVo	$2.0 \cdot 10^{-9}$
	HCT 116	$6.5 \cdot 10^{-8}$
	HT-29	$2.4 \cdot 10^{-9}$
Lung	A-549	$1.3 \cdot 10^{-9}$
	NCI-H460	$1.6 \cdot 10^{-9}$
	NCI-H23	$5.4 \cdot 10^{-10}$
Ovarian	A2780	$1.6 \cdot 10^{-9}$
	IGROV-1	$9.8 \cdot 10^{-9}$
Pancreas	MiaPaca-2	$1.1 \cdot 10^{-9}$
	PANC-1	$2.9 \cdot 10^{-9}$

IG_{50}, concentration that results in 50% of cell growth inhibition.

The antineoplastic *in vivo* activity of PM01183 was demonstrated in a panel of several different human-derived tumor types, i.e., breast, colon, lung, ovarian and prostate (Table 3). The resulting tumor susceptibility was analyzed in xenografts grown in athymic mice, when unformulated PM01183 was administered at the rodent maximum tolerated dose [0.3 mg/kg (0.9 mg/m^2)] as single bolus intravenous (i.v.) injection. PM01183 demonstrated statistically significant antitumor activity ($p<0.05$) against breast, lung and ovarian xenografts at different time points during the experiment, but had a more moderate antitumor profile against bladder, pancreas and prostate [36].

Table 3. Selected *in vivo* activity of PM01183.

Tumor	Cell line	Schedule	Dose level mg/kg/day (mg/m^2/day)	T/C %	Optimal day
Lung	LXFL 529	Q7dx3	0.18 (0.54)	5	D-28
Bladder	UM-UC-3	Qdx5x2	0.06 (0.18)	58	D-23
Breast	MDA-MB-231	Q7dx3	0.18 (0.54)	40	D-34
	MX-1	Q7dx3	0.18 (0.54)	0	D-21
Ovary	A2780	Q7dx3	0.18 (0.54)	34	D-17
Pancreas	Capan-1	Q7dx3	0.18 (0.54)	61	D-61
Prostate	PC-3	Q7dx3	0.18 (0.54)	65	D-27

D, day; Qdx5x2, two cycles of five daily doses; Q7dx3, three consecutive weekly doses (D-0, 7, 14); T/C, treatment/control.

Toxicology studies in rats and dogs showed that the main target organs were the bone marrow and the liver. The effect of a single bolus injection of PM01183 on cardiovascular parameters [arterial blood pressure, heart rate and lead II electrocardiogram (ECG)] was evaluated in dogs for six hours [37]. This study showed no effects on heart, blood pressure, lead II ECG variables (PR, QT, QTcF and QTcV intervals, and QRS duration), ECG gross morphology or rhythm in dogs treated with PM01183 at doses up to 0.01 mg/kg (0.2 mg/m^2). Additionally, two different studies

found no electrophysiological alterations in the heart rate and ECGs of dogs following single or repeated PM01183 administration at doses up to 0.05 mg/kg (1 mg/m^2) [38, 39].

The antineoplastic *in vitro* activity of PM01183 was also evaluated in combination with other antineoplastic agents in solid and non-solid tumor cell lines [40, 41]. In solid tumor models, two combinations were strongly synergistic: PM01183 combined with topotecan (colon HT29, pancreas PANC-1 and glioblastoma U87MG cell lines) and PM01183 combined with erlotinib (lung A-549, gastric HGC-27 and prostate PC-3 cell lines). Some other standard agents, including platinum agents like oxaliplatin and cisplatin, showed synergistic activity in combination with PM01183 in different cell lines.

Part of the *in vivo* antitumor activity of lurbinectedin (PM01183) could be related to host-mediated effects that occur *in vivo* but not *in vitro*. Recent studies have highlighted the ability of trabectedin to modify the tumor microenvironment; particularly the drug seems to induce a decrease in the tumor-associated macrophages with significant down-regulation of cytokines, chemokines and angiogenic factors [42-46]. Although these effects have been demonstrated for trabectedin, initial data suggest that some of these effects are shared by lurbinectedin (PM01183) (P.Allavena, unpublished data) [47].

1.2.1.3 *Clinical Data*

Based on the positive preclinical results described above, the clinical development program of PM01183 was started in March 2009. Currently, this program comprises three phase I single-agent studies (two in solid tumors and one in acute adult leukemia patients), five phase Ib combination studies with gemcitabine, capecitabine, doxorubicin, cisplatin, or paclitaxel with or without bevacizumab, in patients with selected advanced solid tumors, and four phase II studies: one trial as single agent or in combination with gemcitabine as second-line therapy in advanced non-small cell lung cancer (NSCLC), and three studies as single agent in second-line pancreatic cancer, in BRCA-mutated or in BRCA-unselected metastatic breast cancer patients and in platinum-resistant/refractory ovarian cancer. As of 15 January 2014, 366 patients (331 with solid tumors and 35 with advanced acute leukemia) had been treated with PM01183 in clinical trials within the clinical development program of this compound: 198 patients in phase I trials (35 with advanced acute leukemia) and 168 patients in phase II trials.

The two phase I trials which were exploring single-agent PM01183 schedules in solid tumor patients finished recruitment and a recommended dose (RD) was selected for further study in phase II trials. The first-in-human study (FiM) (PM1183-A-001-08) explored PM01183 administered as a 1-hour i.v. infusion every three weeks (q3wk) in patients with solid tumors. The RD was established at 4.0 mg/m^2/q3wk [48]; since PM01183 clearance was found to be unrelated to body surface area (BSA), all patients in the RD expansion cohort were treated at an equivalent flat dose (FD) of 7.0 mg q3wk. In this and subsequent studies, the median terminal plasma half-life was around 60 hours, though inter-individual variability was high. No evidence of drug accumulation was found. Non-hematological toxicity was generally mild and reversible. Standard antiemetic prophylaxis was used at the RD to control grade 2 nausea and/or vomiting. Hematological toxicity, particularly grade 4 non-febrile neutropenia, was the most relevant toxicity and occurred in 40% of patients at the RD in the single-agent phase I studies. Neutropenia was generally predictable and short-lasting, and rarely caused treatment delays. In the FiM study (Day 1, q3wk) nadir usually occurred during the

second week. One of 15 patients treated at the RD had a dose-limiting toxicity (grade 4 thrombocytopenia). No cases of febrile neutropenia occurred in this study, although patient selection might have played a role.

To explore the feasibility of an alternative schedule (Day 1 and 8, q3wk), a second phase I trial (PM1183-A-005-11) was started in advanced non-colorectal cancer patients following a prospective FD escalation. The RD was 5 mg FD on Day 1 and 8 q3wk; myelosuppression limited further dose escalation (around 40% of patients developed grade 4 neutropenia). Severe neutropenia was reversible in all cases, but two patients at the RD had grade 4 neutropenia lasting for more than one week. No unexpected toxicities were found. The safety profile of this schedule seems similar to that of the Day 1 q3wk trial, although neutropenia appeared more prolonged and may require additional dose adjustment.

Based on the results from single-agent phase I clinical trials, the Day 1 q3wk schedule has a good compliance and is more convenient. Therefore, the Day 1 q3wk schedule was selected for further clinical trials.

Antitumor activity has been observed with PM01183 either as single agent or in combination with other cytotoxics. Objective responses have been observed in patients with the following solid tumors (other than platinum-resistant ovarian cancer): pancreatic cancer, breast cancer, NSCLC, small cell lung cancer (SCLC), and other tumor types (neuroendocrine tumors, endometrial adenocarcinomas, bladder cancer, and soft tissue sarcoma). Results of the phase II trial in patients with platinum refractory/resistant ovarian cancer are summarized in the study rationale (Section 1.3.1).

1.2.2 Pegylated Liposomal Doxorubicin

Pegylated liposomal doxorubicin (PLD) is the anthracycline anticancer agent doxorubicin encapsulated within pegylated liposomes. This formulation has specific pharmacokinetic (PK) properties, including a smaller distribution volume, a higher area under the curve (AUC) value, a slower clearance and a longer elimination half-life [49]. Moreover, as much as 90-95% of circulating doxorubicin in the plasma of treated patients is encapsulated within liposomes, which significantly attenuates doxorubicin plasma peak concentration and likely reduces its associated toxicity (particularly nausea, vomiting and cardiotoxicity) compared to the standard doxorubicin formulation [50]. For this same reason, other toxicities than are rather unusual with the standard formulation are more frequent with PLD and sometimes even dose-limiting although usually not life-threatening, such as mucositis and palmar-plantar erythrodysesthesia (PPE).

Mechanistically, the antitumor activity of PLD is essentially the same as that of standard doxorubicin. It acts mainly by inhibiting topoisomerase II through covalent binding, and secondarily by the generation of free radicals that may damage the DNA and ribonucleic acid (RNA) and interfere with vital detoxifying intracellular processes. However, some studies have shown that liposome encapsulation favors higher intratumoral levels of doxorubicin than in healthy surrounding tissue due to the leaking properties of tumor microvessels.

PLD is currently approved in Western countries, alone or in combination, for treating several cancer types, including ovarian cancer, breast cancer, Kaposi's sarcoma and multiple myeloma.

When used alone, starting PLD doses of 50 mg/m^2 every 4 weeks (q4wk) have been widely used, although a dose reduction of approximately 20% is sometimes required

according to individual tolerance. Besides the mucositis and PPE, other common toxicities associated with PLD are alopecia (which is reversible after treatment discontinuation), flushing, headache, dyspnea, hypotension and mild myelosuppression.

PLD activity was identified in early phase II studies in relapsed ovarian cancer. This led to the design of a phase III study by Gordon *et al*. [25] where the efficacy of PLD was compared to that of standard topotecan in recurrent ovarian cancer. In this trial, no clinical or statistically significant difference was found between PLD and topotecan in a pre-planned subgroup analysis of platinum-refractory or resistant patients with respect to response rate (6.5% *vs.* 12.3%), time to tumor progression (9.1 weeks *vs.* 13.6 weeks), and OS (36 weeks *vs.* 41 weeks), respectively [25].

PLD has been subsequently compared to gemcitabine in a phase II trial in patients with platinum-resistant ovarian cancer. There were no statistical differences between the two arms for median OS (13.5 vs 12.7 months) or PFS (3.1 months versus 3.6 months) [27].

More recently, PLD has been used as the comparator arm in other phase III trials testing new single-agent chemotherapeutics, such as canfosfamide and patupilone in women with recurrent ovarian cancer [28, 29, 31].

1.2.3 Topotecan

Topotecan is a camptothecin analogue approved for treating relapsed ovarian carcinoma, lung cancer, cervical cancer and some hematological malignancies.

Camptothecins, like other epipodophyllotoxins (etoposide, teniposide), exert their cytotoxic effect through covalent binding to the DNA-topoisomerase I complex, thus preventing the repair of single-strand DNA breaks.

Topotecan has a large distribution volume in humans; only 20-40% of plasma concentration is bound to albumin. Hence, extensive peripheral tissue binding is most likely responsible for this large steady-state distribution volume. Mild to moderate hepatic dysfunction seems not to alter topotecan pharmacokinetics [51], but patients with moderate to severe renal dysfunction (creatinine clearance < 40 ml/min) need to have a dose adjustment [52].

The most remarkable and dose-limiting toxicity of topotecan is myelosuppression, in particular grade 4 neutropenia, which occurs in more than half of the patients at the RD. Other toxicities are usually less severe and include diarrhea, nausea and vomiting, alopecia, rash, urticaria, fever, fatigue, weight loss, and hepatic enzymes elevation that in some cases is concomitant with hyperbilirubinemia.

The conventional dose and schedule of topotecan (standard regimen) is 1.5 mg/m^2/daily times x 5 q3wk [53]. A weekly regimen (Days 1, 8 and 15 every four weeks) has also been used in order to minimize the hematological toxicity. Both regimens were prospectively compared in a randomized phase II study in patients with platinum-resistant ovarian cancer [54]. Although the trial design had several limitations to draw conclusions regarding efficacy, both schedules reached similar OS rates. The weekly schedule showed a lower incidence of hematological toxicity, but objective responses were doubled (19% *vs.* 9%) and PFS values were better with the conventional schedule than with the weekly schedule. Therefore, it appears that the conventional schedule must be preferred as a standard of care.

Topotecan activity in recurrent ovarian cancer was compared to paclitaxel in a randomized phase III study in paclitaxel and topotecan-naïve pretreated patients [24]. Response rates, PFS and OS data slightly favored the topotecan arm, but the differences

were not statistically significant except for time to progression. These results were further supported in a phase II study in patients who had failed a prior paclitaxel/platinum containing regimen, with a consistent 12.4% response rate in platinum-resistant patients [55]. Patient selection remains critical to try to minimize the impact of topotecan-associated toxicity in these patients. As mentioned in the above, section, topotecan was also compared to PLD in a randomized trial of 474 patients with recurrent ovarian cancer (combined platinum-resistant and platinum-sensitive disease) [25]. There was no clinical or statistical difference between PLD and topotecan in the platinum-refractory or resistant subpopulation in objective response, time to tumor progression and OS.

1.3 STUDY RATIONALE

Patients with platinum-resistant ovarian cancer have poor prognosis among relapsed ovarian cancer. New treatment options are needed, 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. As per COMPARE analysis, it does not have an overlapping mechanism of action with other 98 standard cytotoxic agents.

PM01183 has *in vitro* and *in vivo* anticancer activity in several platinum sensitive and resistant ovarian cancer-derived cell lines (IGROV-1, OVA9, A2780 and IGROV-1/CDDP, OVA9-RT, A2780/CDDP) and in mice-bearing tumor xenografts (both platinum-sensitive and resistant).

On the basis of preclinical results, a controlled, phase II exploratory clinical trial to evaluate the activity and safety of PM01183 as a single agent in platinum-resistant/refractory advanced ovarian cancer was conducted (PM1183-B-002-11) [56, 57].

The study consisted of two stages:

- In the first stage, 18 patients were to receive PM01183 as a 7.0 mg FD 1-hour i.v. infusion q3wk. If the minimum threshold of antitumor activity was met (at least two confirmed tumor responses), then:
- In the second stage, 60 patients were to be stratified according to platinum-resistance or refractoriness and randomized 1:1 to receive PM01183 at the same dose and schedule as in the first stage or to the control arm. The control arm initially consisted of standard PLD q4wk for patients not previously treated with PLD, or standard i.v. topotecan daily times five q3wk for patients previously treated with PLD or with any contraindication to receive PLD. However, due to the worldwide shortage of PLD, the protocol was amended replacing the PLD treatment option with a weekly topotecan schedule. Therefore, the control arm consisted of i.v. topotecan on Days 1-5 q3wk (standard regimen) or on Days 1, 8 and 15 q4wk (weekly regimen), according to the Investigators' preference. During the second stage, crossover from control arm to the experimental arm was allowed in patients with disease progression. If ≥8 patients of the total of 48 evaluable PM01183 patients achieved the primary endpoint, PM01183 was to be considered for further clinical development in this setting.

The primary efficacy endpoint of the study was the ORR, defined as the percentage of patients with a response, CR or partial response (PR), according to the Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 or by Gynecologic Cancer

Intergroup (GCIG) criteria (in patients with disease not measurable as per RECIST). Secondary endpoints included time-to-event variables (PFS and OS) and safety profile of PM01183.

1.3.1 Preliminary Results of Study PM1183-B-002-11

A total of 81 patients were recruited; all of them were evaluable for analysis at cutoff (May 2014). In the first stage, six of 22 patients treated with PM01183 responded to treatment; therefore, the trial proceeded to the second stage.

In the second stage, 59 patients were included: 30 were treated with PM01183 and 29 with topotecan (eight with standard treatment and 21 with weekly treatment).

In the total population, 49 patients (61%) had platinum-resistant disease: 33 (65%) were treated with PM01183 and 16 (55%) with topotecan.

Preliminary efficacy results are summarized in Table 4.

Table 4. Preliminary efficacy data of study PM1183-B-002-11 (May 2014).

	PM01183 (n=52)	**Topotecan (n=29)**	**p-value**
Best response, overall (RECIST/GCIG)			
Confirmed (RECIST/GCIG), n (%) (95% CI)	11 (9/2*) (21%) (11-35%)	0 (0%) (0-12%)	0.006
CR	1 (2%)	0 (0%)	
PR	10 (19%)	0 (0%)	
SD	26 (50%)	15 (52%)	
PD	14 (27%)	14 (48%)	
Treatment failure	1 (2%)	0 (0%)	
Confirmed+unconfirmed (RECIST/GCIG), n (%)	15 (12/3) (29%)	0 (0%)	
Response according to platinum status			
Platinum-resistant (PM01183 n=33/Topotecan n=16)	10 (30%) (95% CI: 16-49)	-	
Platinum-refractory (PM01183 n=18/Topotecan n=13)	1 (5%) (95% CI: 0-26)	-	
Duration of confirmed responses (months)	4.6 (95% CI: 2.5-5.9)	-	
Disease control rate (%)	71	52	
Progression-free survival (median and 95% CI) (months)	3.5 (95% CI, 2.5-5.0)	2.0 (95% CI, 1.4-2.8)	HR=0.48; log-rank p=0.005
Overall survival (median and 95% CI) (months)	11.1 (95% CI, 9.5-21.8)	7.3 (95% CI, 3.3-14.9)	HR=0.52; log-rank p=0.016

*Nine responses according to RECIST and two responses according to GCIG criteria.
CI, confidence interval; CR, complete response; GCIG, Gynecologic Cancer Intergroup; HR, hazard ratio; PD, disease progression; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors (v.1.1); SD, stable disease.

ORR was significantly better for PM01183: 21% *vs.* no responses in the topotecan arm. Ten of the 11 confirmed responses were obtained in patients with platinum-resistant disease (response rate=30% in this subpopulation).

In all patients, median PFS was significantly longer with PM01183 (3.5 months) than that of topotecan (2.0 months). The difference in median PFS between the two treatment arms was higher in patients with platinum-resistant disease: 5.0 months (95% CI, 2.7-6.9 months) in the PM01183 arm *vs.* 1.7 months (95% CI, 1.3-3.2 months) in topotecan

arm (HR: 0.34; log-rank test p=0.002). Median PFS was 5.7 months in this subpopulation in the PM01183 arm for the second stage. At the time of the analysis of the OS data, 32% of cases were censored. Data showed a median OS of 11.1 months in PM01183 arm *vs.* 7.3 months in topotecan arm. In the subset of patients with platinum-resistant disease, median OS was 13.5 months in PM01183 treated patients *vs.* 8.3 months in the control arm (HR: 0.44; log-rank test p=0.023). The median OS in the PM01183 platinum-resistant population during the second stage had not been reached yet.

Preliminary safety results showed that most frequent grade 3/4 adverse events were fatigue (36.5% of patients), nausea (15.4%) and febrile neutropenia (21.2%) in PM01183-treated patients, and febrile neutropenia (10.3%) in topotecan-treated patients.

The most frequent grade 3/4 laboratory abnormality irrespective of their relationship with the study treatment was neutropenia in both PM01183-treated patients (84.6%) and topotecan-treated patients (41.4%)

In summary, the primary endpoint of this phase II study was met. PM01183 showed statistically significant superiority in ORR/PFS/OS over topotecan in platinum-resistant/refractory ovarian cancer and, particularly, in the platinum-resistant population. Therefore, further studies with PM01183 in platinum-resistant ovarian cancer are warranted.

1.4 RATIONALE FOR THE PM01183 DOSE

The recommended dose (RD) originally found in the first-in-human trial was 4.0 mg/m^2 administered i.v. (1-hour infusion) on day 1 q3wk. Since no relationship was observed between BSA and PM01183 clearance, a 7.0 mg FD q3wk was implemented in the expansion cohort of this phase I trial and finally adopted as RD for phase II trials [48].

To date, grade 3/4 neutropenia and thrombocytopenia have been reported in 71% and 27%, respectively, of treated patients in all single-agent phase II trials at this flat dose; in addition, febrile neutropenia has been reported in 16% of these patients. A recent pooled data logistic regression analysis suggested that grade 3/4 neutropenia and thrombocytopenia could be related to BSA. Other parameters evaluated during the logistic regression (e.g. fatigue, vomiting, nausea or ALT level) have shown a similar trend (i.e. increased probability of severe events with low BSA values), but relationship was not as strong. Owing to these findings, and being conservative, a BSA-based dosing strategy will be used in the present phase III study to limit severe toxicity.

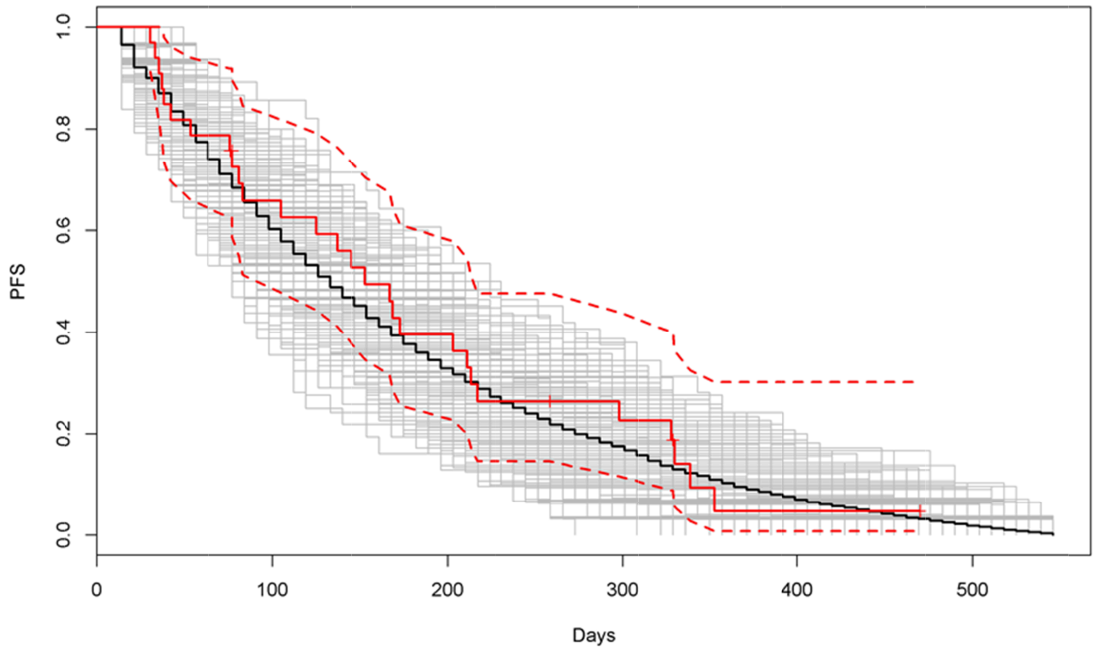
Furthermore, in order to improve tolerability, a PM01183 dose level 20% lower than the original RD of 4.0 mg/m^2 will be implemented in the current phase III clinical trial. Hence, the PM01183 dose level will be 3.2 mg/m^2.

A retrospective analysis of patients treated with PM01183 as flat dose in phase II trials showed that, when the PM01183 dose was transformed according to the patients' BSA value, grade 4 neutropenia was found in 9% of patients receiving a dose $\leq$ 3.2 mg/m^2 at any time during the treatment period (i.e. taking into account dose reductions) (n=23) *vs.* 47% of those receiving a dose > 3.2 mg/m^2 (n=172). Febrile neutropenia was observed in 4% of patients treated at $\leq$ 3.2 mg/m^2 *vs.* 16% of those treated at > 3.2 mg/m^2. Furthermore, no grade 4 thrombocytopenia or PM01183-related grade 3 nausea or vomiting was observed at or below the starting dose for this phase III trial.

In the PM1183-B-002-11 phase II trial, objective responses and prolonged tumor stabilizations were observed in platinum-resistant ovarian cancer patients who received a BSA-based PM01183 dose close to 3.2 mg/m^2 or even lower.

Simulations were performed using a PKPD model that linked PM01183 doses, PM01183 exposure, changes in tumor size and CA-125 levels, and PFS. Figure 2 shows in a solid red line the PFS observed in platinum-resistant ovarian cancer patients treated with PM01183 in the PM1183-B-002-11 trial (slash red lines are the upper and lower 95% CI limits). The gray lines are the PFS simulated for 300 replicated trials using the doses and times reported in the trial, and the central solid black line represents the central trend of the simulations.

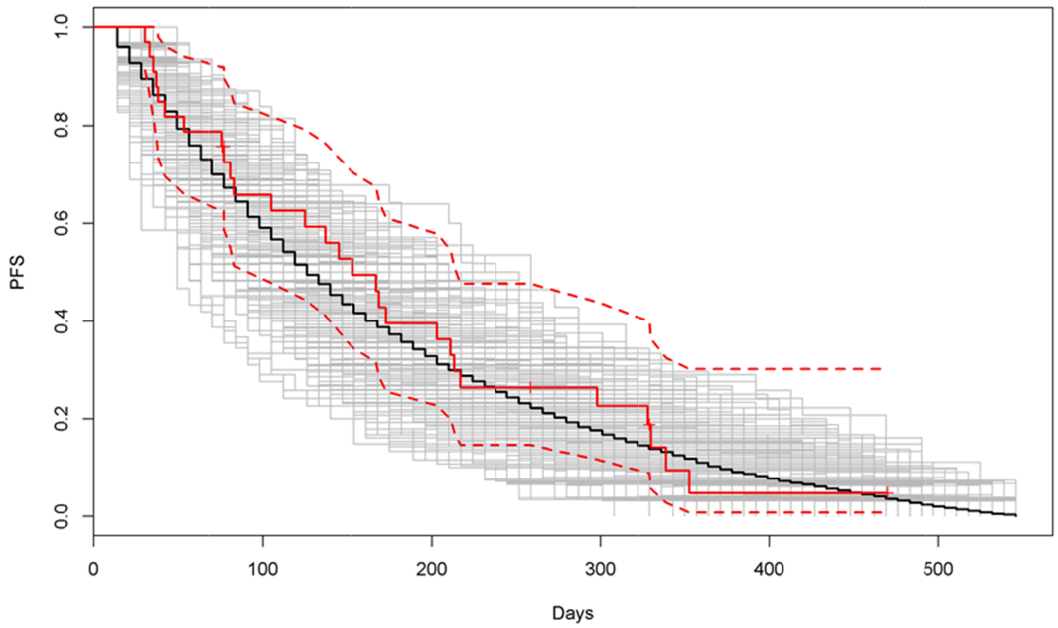
Figure 2. Progression-free survival in real and simulated data for patients with platinum-resistant ovarian cancer in the PM1183-B-002-11 trial.



PFS, progression-free survival.

Using the same PKPD model for efficacy, 300 trials were simulated for patients with platinum-resistant disease at the dose level of 3.2 mg/m^2 and using the schedule used in the PM1183-B-002-11 trial. The PFS curves in the simulations were similar (Figure 3); hence, efficacy was not affected.

Figure 3. Progression-free survival in real and simulated data for patients with platinum-resistant ovarian cancer in the PM1183-B-002-11 trial at the dose level of 3.2 mg/m^2.



PFS, progression-free survival.

A futility analysis will be performed when 210 patients are recruited (i.e., ~105 patients enrolled in each arm). Based on the observed results, a recommendation to stop the trial might be issued; no claim for superiority in efficacy *vs*. the control arm is foreseen at that time.

1.5 Rationale for the Interim Safety Analysis

Data from the phase II study in ovarian cancer population (PM1183-B-002-11) showed an incidence of febrile neutropenia slightly over 20%. An interim safety analysis is planned when 40 patients are enrolled in the PM01183 arm (Arm A); this interim analysis will be done to evaluate the requirement of primary prophylactic use of colony-stimulating factors (CSFs) in this arm.

Although febrile neutropenia did not occur in the first-in-human PM01183 single-agent study, according to pooled data available from all ongoing phase II studies at 7.0 mg FD, it occurred in about 16% of patients. In this clinical trial, the expected percentage of febrile neutropenia is lower, as the PM01183 dose will be administered based on BSA (with a capped dose at a BSA of 2.0 m^2) and at a dose (3.2 mg/m^2) below the RD found in the first-in-human PM01183 trial (4.0 mg/m^2 = 7.0 mg FD).

1.6 Rationale for the Control Arm

PLD and topotecan, the two agents included in the control arm of this phase III clinical trial, are widely accepted standard treatment options for its use in patients with ovarian cancer whose disease has progressed or relapsed after platinum-based chemotherapy. A confirmatory phase III trial comparing topotecan *versus* PLD did not find clinical or statistically significant difference between both drugs in the platinum-refractory or resistant subpopulation in ORR, TTP and OS [25]. Furthermore, no statistically

significant difference in OS has been observed between PLD and topotecan in a phase III trial where canfosfamide was explored *versus* a control arm using PLD or topotecan [28].

1.7 RATIONALE FOR THE PHARMACOGENETIC SUB-STUDY

Germline mutations or polymorphisms may be involved in the metabolism and/or transport of PM01183. Then, to explore factors that may help to explain individual variability in the main pharmacokinetic parameters, the presence or absence of germline mutations or polymorphisms will be analyzed in leukocyte DNA extracted from one blood sample obtained before PM01183 treatment.

1.8 RATIONALE FOR THE PHARMACOGENOMICS SUB-STUDY

The antitumor activity of PM01183 is associated with the following cell events, as described in Leal *et al*. [58]:

- PM01183 binds to the minor groove of DNA. This binding occurs in preferred GC-rich trinucleotide sequences, preferably AGC. The binding of PM01183 to the DNA produces a stabilization of the DNA duplex. This could account for the need of the same DNA repair machinery that usually deals with inter-strand cross-links and involves proteins from both homologous recombination (HR) and nucleotide excision repair (NER) machineries.
- PM01183 induces DNA double-strand breaks (DSBs). In fact, treatment of cells with the drug induces the formation of foci of γ-H2AX, which is indicative of the formation of DSBs. In addition, treatment of cells with PM01183 leads to cell cycle delay in the S phase, activation of the DNA damage checkpoint, and cell death by apoptosis.
- PM01183 interferes with DNA repair. Experimental data reveal that the NER system is essential to overcome PM01183-induced DNA damage. When the pattern of sensitivity to PM01183 was analyzed in a collection of 5000 haploid deletion mutants of the yeast *Saccharomyces cerevisiae*, Rad13Δ (orthologue of human XPG) haploid deletion mutants were found to be more resistant to PM01183 than wild-type cells, therefore indicating the dependence of the cytotoxic effect of this compound to a functional NER system. XPG is a member of the NER system.

Objective of the Pharmacogenomic Sub-study

- The experimental data indicate that PM01183 binds to DNA and interferes with NER pathway, inducing DSBs and cell death by apoptosis. Thus, it seems of interest to conduct studies correlating the tumor/patient and genes/proteins determinant in the efficiency/deficiency of the DNA repair pathways and the outcome of patients exposed to PM01183. The ultimate goal is the characterization of such patients who shall be prone to respond or show resistance to PM01183, in order to implement a customized therapy in the future.
- Initially, the mRNA and/or protein expression levels of genes involved in DNA repair mechanisms (such as nucleotide excision repair, homologous recombination repair or mismatch repair) and other factors related to the mechanism of action of lurbinectedin or to the pathogenesis of the disease will be determined in paraffin-embedded tumor tissue blocks from consenting patients. Their polymorphisms and mutations might be also analyzed, if relevant.

2. STUDY OBJECTIVES

2.1 PRIMARY

- 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.

2.2 SECONDARY

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 *versus* PLD or topotecan.
- To conduct an exploratory pharmacogenetic and pharmacogenomic (PGx) sub-study.

3. OVERALL STUDY DESIGN

Multicenter, open-label, randomized, controlled phase III clinical trial to evaluate the activity and safety of PM01183 *versus* 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) *versus* PLD or topotecan in the control arm (Arm B).

Central randomization will be implemented in all patients that 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 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 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, then the patient will not be eligible for this trial if this agent is the only possible option (e.g., the patient has been previously treated with topotecan, then PLD is the only possible option in case the patient is randomized to the Arm B despite the fact that 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), and prior chemotherapy (1-2 *vs.* 3 lines).

Up to 420 patients 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 RECIST

v.1.1. Operational details for the IRC and the algorithm and its validation by an expert panel is described in detail in the IRC charter.

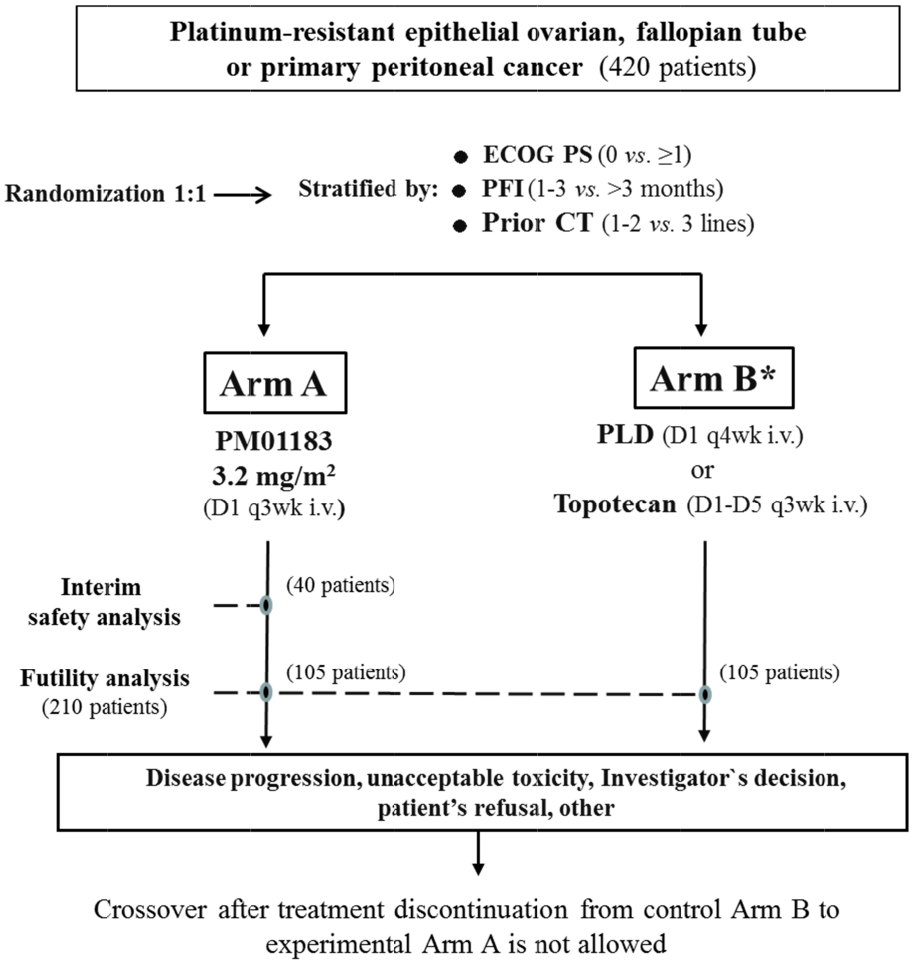
An interim safety analysis will be performed in the PM01183 arm only (Arm A) when 40 patients are enrolled in this arm. Based on the results of this analysis, the IDMC may provide recommendations on the primary prophylactic use of CSFs as part of the therapy in the experimental Arm A. The recruitment 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, but 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 Figure 4.

Figure 4. Study design.



*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 (see Section 5.2). This clinical trial will finish (clinical cutoff) when all required OS events have occurred according to statistical assumptions.

3.1 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.

3.2 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 RECIST v.1.1. 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 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 cutoff), 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 analyzed 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 *versus* PLD or topotecan will be performed. Details of these analyses will be provided in the Statistical Analysis Plan.
- **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 be also analyzed. Their correlation with the clinical response and outcome after treatment will be assessed.

4. SELECTION OF PATIENTS

Patients must fulfill all the following inclusion/exclusion criteria to be eligible to participate in the study.

4.1 INCLUSION CRITERIA

1) Voluntary written informed consent (IC) of the patient obtained before any study-specific procedure.
2) Age ≥ 18 years.
3) Histologically or cytologically confirmed diagnosis of unresectable epithelial ovarian, fallopian tube or primary peritoneal cancer

4) Platinum-resistant disease (PFI: 1-6 months after last platinum-containing chemotherapy).
5) Radiologically measurable and/or non-measurable progressive disease according to RECIST v 1.1.
6) No more than three prior systemic chemotherapy regimens. Note: in case that a patient had started a new systemic chemotherapy without disease progression to the prior chemotherapy line (e.g., treatment discontinuations due to toxicity; neoadjuvant followed by adjuvant chemotherapy regimens), these two chemotherapy regimens will considered as one.
7) ECOG PS ≤ 2 (see APPENDIX 1).
8) Adequate hematological, renal, metabolic and hepatic function:
   a) Hemoglobin ≥ 9 g/dl [patients may have received prior red blood cell (RBC) transfusion]; absolute neutrophil count (ANC) ≥ 2.0 x 10^9/l, and platelet count ≥ 100 x 10^9/l.
   b) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 x upper limit of normal (ULN).
   c) Alkaline phosphatase (AP) < 5.0 x ULN.
   d) Total bilirubin ≤ ULN or direct bilirubin ≤ ULN if total bilirubin is > ULN.
   e) Albumin ≥ 3.0 g/dl.
   f) Calculated creatinine clearance (CrCL) ≥ 30 ml/min (using Cockcroft and Gault's formula).
   g) Creatine phosphokinase (CPK) ≤ 2.5 x ULN.
9) At least three weeks since last prior therapy, and grade ≤ 1 from any AE derived from previous treatment (excluding grade ≤ 2 alopecia or peripheral neuropathy) according to the NCI-CTCAE v. 4.
10) Women of childbearing potential must have pregnancy excluded by appropriate testing before study entry. A medically acceptable method of contraception* must be maintained throughout the treatment period and for at least six months after treatment discontinuation.

    * Acceptable methods of contraception include intrauterine device (IUD), complete abstinence (non-periodic), oral contraceptive, subdermal implant, or double barrier.

4.2 EXCLUSION CRITERIA

1) Concomitant diseases/conditions:
   a) History of cardiac disease: myocardial infarction or symptomatic/uncontrolled angina within the year prior to enrollment; or congestive heart failure defined as abnormal left ventricular ejection fraction (LVEF) < 50% assessed by multiple-gated acquisition scan (MUGA) or equivalent by ultrasound (US); or symptomatic arrhythmia.
   b) Patients with any immunodeficiency, including those known to be infected by human immunodeficiency virus (HIV).
   c) Chronic active hepatitis or cirrhosis. For Hepatitis B, this includes positive tests for both Hepatitis B surface antigen and quantitative Hepatitis B polymerase chain reaction (PCR). For Hepatitis C, this includes positive tests for both Hepatitis C antibody and quantitative Hepatitis C PCR.

d) Active uncontrolled infection.
e) Bowel obstruction.
f) Requirement of permanent or frequent (i.e., once per week) external drainages within two weeks prior to randomization.
g) Limitation of the patient's ability to comply with the treatment or to follow-up the protocol.
h) Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the patient's participation in this study.

2) Platinum-refractory or platinum-sensitive disease (PFI <1 or >6 months).
3) Prior treatment with PM01183, trabectedin, or with both PLD and topotecan.
4) Known brain metastases or leptomeningeal disease involvement.
5) History of another neoplastic disease (except for curatively treated basal cell carcinoma, squamous cell carcinoma of the skin, or properly treated carcinoma *in situ* of the uterine cervix or breast) within three years prior to randomization.
6) Pregnant or breast feeding women.

4.3 PATIENTS FOR THE PHARMACOGENOMIC (PGX) AND PHARMACOGENETIC EVALUATIONS

Only patients who voluntarily sign the IC for the PGx and pharmacogenetic sub-study will participate. Refusal to participate in the PGx and pharmacogenetic sub-study will not affect patient participation in the clinical study PM1183-C-004-14.

5. PLAN OF THE STUDY

5.1 PLANNED TRIAL PERIODS (FOR THE WHOLE STUDY)

The total duration of the study will be approximately 42 months, including approximately a 18-month enrolment period.

Planned start date (first patient on study): approximately first quarter 2015.

Planned enrolment period: approximately 18 months.

Planned end-of-study date (clinical cutoff): 24 months after randomization of the last patient.

5.2 PLANNED TRIAL PERIODS (INDIVIDUALLY PER PATIENT)

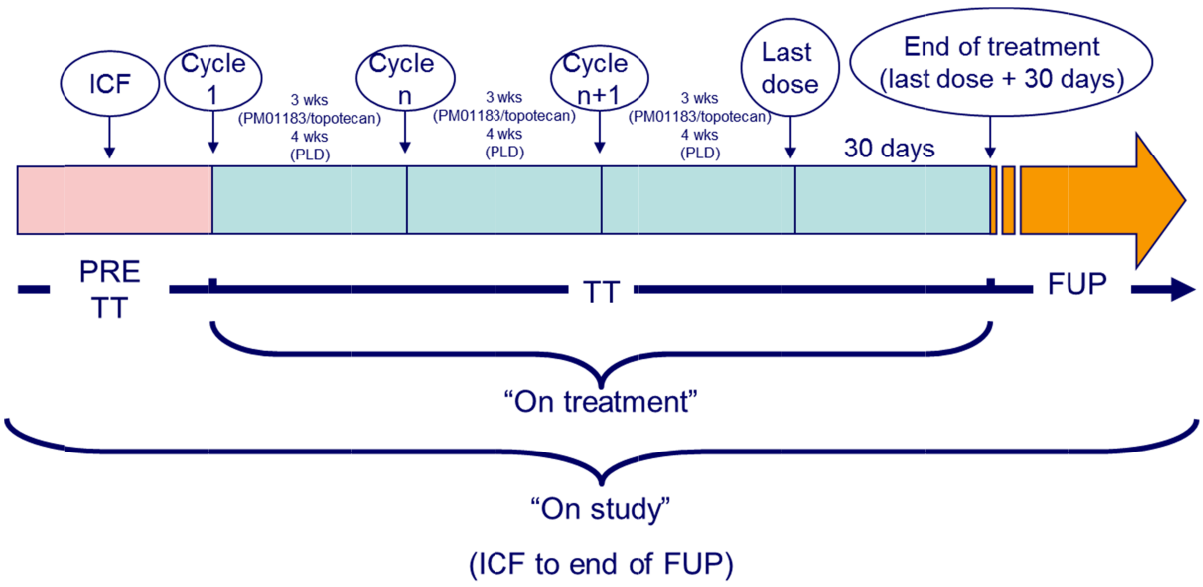
Patients will be evaluated at scheduled visits during three study periods:

- **Pre-treatment:** from signature of IC to the first infusion of the study treatment.
- **Treatment:** from the first infusion of the study treatment to the *end of treatment* (EOT) (see Section 5.2.1.1).
- **Follow-up**: after EOT, patients will be followed every four weeks until resolution or stabilization of all toxicities, if any. Patients who finish treatment without radiological disease progression will be followed every eight weeks from randomization until disease progression or start of a new antitumor therapy, death or until the date of study termination (clinical cutoff), whichever occurs first. After radiological disease progression is documented or a new antitumor therapy is started, patients will be followed at least every three months (± two weeks) 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 disease progression will be performed according to a calendar time.

Patients will be considered to be **on-study** from the signature of the informed consent form (ICF) until death or study termination. Patients will be considered to be **on-treatment** from Day 1 of Cycle 1 until the day of EOT. This EOT is defined as 30 days after the day of the last study treatment infusion (see Figure 5), unless the patient starts a new antitumor therapy or dies (whichever occurs first). An end-of-treatment visit (EOT visit) will be performed within 30 days (± 7 days) after the last study treatment administration, unless the patient starts any subsequent antitumor therapy, in which case the end-of-treatment visit should be performed immediately before the start of the new therapy.

Figure 5. Study periods.



FUP, follow-up; ICF, informed consent form; PRE TT, pre-treatment; TT, treatment; wks, weeks.

5.2.1 Discontinuations

5.2.1.1 *Treatment Discontinuation*

Treatment discontinuation occurs when an enrolled patient ceases to receive the study treatment (PM01183, PLD or topotecan) regardless of the circumstances. By convention, the date of end of treatment is defined as 30 days after the day of the day of last dose of the study treatment (treatment discontinuation), start of a new antitumor therapy or death, whichever occurs first, in which case the date of administration of this new therapy or the date of death will be considered the date of EOT.

The primary reason for any treatment discontinuation will be recorded on the patient's Case Report Form (CRF).

Should a patient decide to prematurely discontinue the study treatment (refuses treatment), all efforts will be made to complete and report the observations as thoroughly as possible. She should be asked if she can still be contacted for further information. The outcome of that discussion should be documented in the medical records.

5.2.1.2 *Reasons for Treatment Discontinuation*

Patients will receive the study treatment(s) 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 study requirements.
- A major protocol deviation that may affect the risk/benefit ratio for the participating patient.
- Requirement of > two dose reductions.

Patients who are withdrawn for any reasons must not be re-treated in the context of this study at any time. For follow-up activities, please refer to Section 5.9.

5.2.1.3 *Study Discontinuation*

Study discontinuation occurs when an enrolled patient ceases to participate in the study, regardless of the reason (as detailed under "Follow-up" in Section 5.2). The date and reason for study discontinuation will be clearly documented in the medical records of the patient.

5.2.2 Protocol Deviations

A protocol deviation is defined as any departure from what is described in the protocol of a clinical trial approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and Competent Authorities. Therefore, it applies to deviations related to patient inclusion and clinical procedures (e.g., assessments to be conducted or parameters to be determined), and also to other procedures described in the protocol that concern the Good Clinical Practice (GCP) guidelines or ethical issues (e.g., issues related to obtaining the patients' Informed Consent, data reporting, the responsibilities of the Investigator, etc.).

Deviations with no effects on the risk/benefit ratio of the clinical trial (such as minimal delays in assessments or visits) will be distinguished from those that might have an effect on this risk/benefit ratio, such as:

- Deviations that might affect the clinical trial objectives, such as those involving the inclusion/exclusion criteria (which could mean that the patient is not eligible for the trial) and those having an effect on patient evaluability.
- Deviations that might affect the patient's well-being and/or safety, such as an incorrect dosing of the study treatment due to not following dose adjustment specifications or an incorrect preparation of the medication.
- Deviations related to the following of GCP guidelines as described in the protocol and regulations in force, such as deviations when obtaining the Informed Consent or not following the terms established for reporting SAEs, etc.

No deviations that may have an effect on the risk/benefit ratio of the clinical trial will be authorized. All protocol deviations detected during the study will be appropriately

documented, and those considered particularly relevant (i.e., those related to ethical issues, to fulfillment of GCP guidelines and with an effect on the risk/benefit ratio) will be notified, if applicable, to the pertinent IEC/IRB and to the Competent Authorities as established by local regulations.

5.3 REPLACEMENT OF PATIENTS

Randomized patients will not be replaced.

5.4 PRE-TREATMENT ASSESSMENTS

During the pre-treatment period, following signature of the ICF, the Investigator will confirm the patient's eligibility for the study by conducting the assessments summarized in Table 5.

Table 5. Screening period: pre-treatment assessments.

	ASSESSMENT	TIME
1. Written informed consent (general and pharmacogenetic and PGx sub-study)		Before any study procedures.
2. Medical and cancer history/ clinical examination	◆ Demographic data.	Within 28 days prior to first infusion.
	◆ Medical and cancer history/baseline condition: o Primary diagnosis. o Prior treatments (with best response and TTP, when available). o Documented date of relapse. ◆ Disease-related signs and symptoms. ◆ Complete physical examination, including weight, height and calculation of BSA. ◆ Concomitant therapies.	Within 14 days prior to first infusion.*/**
	◆ Performance status (ECOG PS). ◆ Vital signs: heart rate, blood pressure and body temperature.	Within 7 days prior to first infusion.*
3. Laboratory tests	◆ **Hematology:** differential WBC counts (including neutrophil, lymphocyte and monocyte counts), platelet count and hemoglobin. ◆ **Biochemistry:** Liver function test (ALT, AST, AP, GGT, total bilirubin; direct bilirubin only if total bilirubin is abnormally high); total proteins, albumin, creatinine, CPK, glucose, calculated CrCL (as per Cockcroft and Gault's formula), and serum electrolytes (Na^+, K^+, Cl^-).	Within 7 days prior to first infusion.***
4. Pregnancy test (if women of childbearing potential)	Assessment of β-hCG (urine or serum).	Within 7 days prior to first infusion, if applicable.***
5. ECG	Cardiac rhythm will be identified in ECG intervals of at least 30 seconds of duration, PR interval, QT interval (raw), heart rate and QRS complex.	Within 7 days prior to first infusion.***
6. LVEF	ECHO or MUGA.	Within 14 days prior to first infusion.****
7. PGx	Available stored paraffin-embedded tumor tissue samples; only in those patients that give their written informed consent for the PGx sub-study.	-

	ASSESSMENT	TIME
8. Radiological tumor assessment	Contrast enhanced helical CT-scan or MRI, as clinically relevant.	Within 14 days prior to first infusion.****
9. Tumor marker evaluation	CA-125.	Within 7 days prior to first infusion.***
10. Patient-reported outcomes	EORTC QLQ-C30 and EORTC QLQ-OV28 questionnaires.	Within 7 days prior to first infusion.*
11. Adverse events	Only information on SAEs that occurred after signature of the informed consent is required before treatment start. Grading should be as per the NCI-CTCAE v.4.	-

Regardless of the treatment administered, the same schedule of assessments will apply.
*A 1-day window is allowed for assessment of disease-related signs and symptoms, complete physical examination, ECOG PS, vital signs, and patient-reported outcomes at screening.
**A +1-week window is allowed for medical and cancer history/baseline conditions at screening.
***A +3-day window is allowed for laboratory tests, CA-125 assessment, pregnancy tests and ECG at screening.
****A +2-week window is allowed for LVEF and tumor assessments as per RECIST v.1.1.
ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; β-hCG, beta subunit of human chorionic gonadotropin; BSA, body surface area; CPK, creatine phosphokinase; CrCL, creatinine clearance; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; GGT, gamma glutamyltransferase; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition scan; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PGx, pharmacogenomics; PS, performance status; RECIST, Response Evaluation Criteria In Solid Tumors, SAE, serious adverse event; TTP, time to progression; WBC, white blood cells.

Screening procedures will have to be repeated in case that the first infusion of the study treatment is given out of the established windows.

5.5 PATIENT REGISTRATION

After the patient has signed the ICF, the patient will be registered into the trial and a patient number will be provided. This patient number should be used in all future documentation and correspondence referring to this patient.

5.6 PATIENT RANDOMIZATION

Central randomization will be implemented in all patients that fulfill the inclusion 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 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 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 PFI (1-3 months *vs.* >3 months) and prior chemotherapy (1-2 *vs.* 3 lines).

5.7 EVALUATIONS DURING TREATMENT

The following assessments will be done while the patient is on treatment (Table 6).

Table 6. Evaluations during treatment.

	ASSESSMENT	TIME
1. Clinical examination	◆ Complete physical examination, including weight and calculation of BSA.	Cycle 2 and beyond: Day 1 of each cycle (always prior to treatment infusion).*
	◆ Performance status (ECOG PS). ◆ Vital signs: heart rate, blood pressure and body temperature.	Day 1 of each cycle (always prior to treatment infusion).*
	◆ Concomitant therapies.	Throughout the "on treatment" period.**
2. Laboratory tests	◆ **Hematology:** differential WBC counts (including neutrophil, lymphocyte and monocyte counts), platelet count and hemoglobin. ◆ **Biochemistry:** Liver function test (ALT, AST, AP, GGT, total bilirubin; direct bilirubin only if total bilirubin is abnormally high); total proteins, albumin, creatinine, CPK, glucose, calculated CrCL (as per Cockcroft and Gault's formula), and serum electrolytes (Na^+, K^+, Cl^-).	Cycle 1: Day 8.* Cycle 2: Day 1 (always prior to treatment infusion) and Day 8.* Cycle 3 and beyond: Day 1 of each cycle (always prior to treatment infusion). * Any patient presenting grade 4 treatment-related AEs should have any relevant tests re-assessed at least within 72 hours until recovery to at least grade 3.
3. Pregnancy test (if women of childbearing potential)	Assessment of β-hCG (urine or serum).	Repeat if applicable.
4. ECG	Cardiac rhythm will be identified in ECG intervals of at least 30 seconds of duration, PR interval, QT interval (raw), heart rate and QRS complex.	Repeat if clinically indicated.
5. LVEF	ECHO or MUGA.	Repeat if clinically indicated. In patients treated with PLD (Arm B), to be repeated every four cycles (or more frequently, if clinically indicated). After exceeding a cumulative anthracycline dose of 450 mg/m^2, LVEF will be assessed before each PLD infusion.
6. Pharmacokinetics (in the PM01183 treatment arm only)	-	A total of eight blood samples (before PM01183 treatment start, 5 min before the end of PM01183 infusion, and 1 hour and 168 hours after the end of PM01183 infusion) will be collected for pharmacokinetic PM01183 analyses in **Cycle 1** (four samples) and **in a second cycle** (**between Cycle 2 and 4**; four samples) in patients treated in Arm A. The second cycle with blood sample collection for PK will be assigned once the patient is randomized into Arm A (see details in Section 7.7.1).
7. Pharmacogenetics	Only in those patients that give their written informed consent for the pharmacogenetic sub-study	One blood sample will be collected before treatment start in patients treated in Arm A along with the first pharmacokinetic sample of **Cycle 1** for the pharmacogenetic sub-study.
8. Radiological tumor assessment	Contrast enhanced helical CT-scan or MRI, as clinically relevant.	Every eight weeks from randomization until evidence of PD.*

	ASSESSMENT	TIME
9. Tumor marker evaluation	CA-125.	Every eight weeks from randomization until evidence of PD, but only if baseline levels were higher than normal.*
10. Patient-reported outcomes	EORTC QLQ-C30 and EORTC QLQ-OV28 questionnaires.	Every eight weeks from randomization.*
11. Adverse events	As per NCI-CTCAE v.4.	Throughout the "on treatment" period.**

Regardless of the treatment administered, the same schedule of assessments will apply.
* A 3-day window will be allowed for laboratory tests and ECG, a 1-week window for tumor assessments as per RECIST v.1.1, tumor marker evaluation and patient-reported outcomes, and a 1-day window for clinical assessments (ECOG PS, vital signs, weight, BSA, etc.).
** "On treatment period" = from first infusion of the study treatment (PM01183, PLD or topotecan) to EOT [30 days after the day of the last dose administration, unless the patient starts a new antitumor therapy or dies (whichever occurs first), in which case the date of administration of this new therapy or the date of death will be considered the date of end of treatment].
AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; β-hCG, beta subunit of human chorionic gonadotropin; BSA, body surface area; CPK, creatine phosphokinase; CrCL, creatinine clearance; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; EORTC, European Organization for Research and Treatment of Cancer; GGT, gamma glutamyltransferase; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition scan; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PLD, pegylated liposomal doxorubicin; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors, WBC, white blood cells.

5.8 EVALUATIONS AT END OF TREATMENT

The *end-of-treatment visit* will be scheduled within 30 days (± 7 days) after the last treatment infusion, unless the patient starts any subsequent antitumor therapy, in which case the end-of-treatment visit should be performed immediately before the start of the new therapy (ideally the day before or the same day).

Patients, regardless of the reason for ending the treatment, will have to undergo at the end of treatment the following assessments:

- ECOG PS.
- Concomitant therapies.
- Laboratory tests (hematology and biochemistry).
- Pregnancy test (if applicable).
- ECG (if clinically indicated).
- LVEF by ECHO or MUGA (if clinically indicated).
- Radiological tumor assessment (only in those patients who discontinue treatment without radiological PD when the end-of-treatment visit coincides with the planned every-eight-weeks evaluation schedule).
- Tumor marker (CA-125) evaluation, if baseline levels were higher than normal.
- Patient-reported outcomes (EORTC QLQ-C30 and EORTC QLQ-OV28 questionnaires).
- Adverse events.

All these evaluations will only have to be repeated for those parameters for which no measurement is available within 10 days before the end-of-treatment visit, or for those parameters with values that were out of range in the last assessment (grade $\geq$ 2 according to NCI-CTCAE v.4) and considered as treatment-related whenever the medical condition of the patient may allow these evaluations.

Adverse events must be reported for 30 days after the last study treatment administration. All serious adverse events (SAEs) occurring within 30 days of the last study treatment administration or until the start of a new antitumor therapy, whichever occurs first, will be reported. Beyond this period of time, only those suspected to be treatment-related SAEs will be reported (Section 7.4.2).

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

5.9 FOLLOW-UP AFTER END-OF-TREATMENT VISIT

Patients who finish treatment without radiological disease progression will be followed every eight weeks (± two weeks) from randomization until disease progression or start of a new antitumor therapy, death or until the date of study termination (clinical cutoff), whichever occurs first. Radiological tumor assessments and a tumor marker (CA-125) evaluation (if baseline levels were higher than normal) will be conducted during each of these follow-up visits. After radiological disease progression is documented or a new antitumor therapy is started, patients will be followed at least every three months (± two weeks) 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 disease progression will be performed according to a calendar time. In this survival follow-up, for the purpose of collecting information, a documented telephone call would be acceptable.

The end-of-study date (clinical cutoff) is defined as 24 months after randomization of the last patient. The date and reason of the study discontinuation will be recorded on the patient's CRF (see Section 5.2.1.1).

All AEs suspected to be related to the study treatment must be followed after the end of treatment until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator.

Additional parameters and/or increased frequency of observations should be performed at the Investigator's discretion and according to the nature of the observed AEs. In case of death, autopsy data should be provided when available.

6. TREATMENT

6.1 DESCRIPTION OF TREATMENT

6.1.1 Drug Formulation and Supply

6.1.1.1 *Experimental Arm (PM01183): Arm A*

PM01183 drug product (DP) presented as a lyophilized powder for concentrate for solution for infusion in 4-mg vials will be supplied by the Sponsor for the purposes of this study.

Before use, the 4-mg vials should be reconstituted with 8 ml of water for injection to give a solution containing 0.5 mg/ml of PM01183. For administration to patients as an i.v. infusion, reconstituted vials are diluted with glucose 50 mg/ml (5%) solution for infusion or sodium chloride 9 mg/ml (0.9%) solution for infusion.

For details on reconstitution/dilution, please refer to the IB and Preparation Guide for Infusion. PM01183 reconstitution/dilution records will be kept by the site.

The full composition of the PM01183 4-mg vials and the reconstituted solution per ml is as shown in Table 7.

Table 7. Composition of lurbinectedin (PM01183) vials.

Component	Concentration/vial	Concentration/vial after reconstitution
PM01183	4.0 mg	0.5 mg/ml
Sucrose	800 mg	100 mg/ml
Lactic acid	22.08 mg	2.76 mg/ml
Sodium hydroxide	5.12 mg	0.64 mg/ml

6.1.1.2 *Control Arm (PLD and topotecan): Arm B*

- **PLD:**
  Commercially available i.v. presentations of vials containing PLD will be provided as appropriate.
- **Topotecan:**
  Commercially available i.v. presentations of vials containing topotecan will be provided as appropriate.

PLD and topotecan will be prepared in accordance with the applicable Summary of Product Characteristics. Medication preparation records will be kept by the site.

6.2 ADMINISTRATION OF STUDY MEDICATION

6.2.1.1 *Experimental Arm (PM01183): Arm A*

Intravenously as a 1-hour infusion through peripheral or central lines.

A minimum total volume of 100 ml, diluted in 5% glucose or 0.9% sodium chloride, to be infused over about one hour, must be used for administration through a central venous catheter, or a minimum 250-ml dilution if a peripheral venous catheter is used.

6.2.1.2 *Control Arm (PLD and topotecan): Arm B*

- **PLD:**
  Intravenously at an initial rate of 1 mg/min through peripheral or central lines. If no infusion reactions are observed, the rate of infusion can be increased to complete the administration of the drug over 1 hour.
  Total PLD doses > 90 mg and ≤ 90 mg should be diluted in 500 and 250 ml of 5% glucose solution for infusion, respectively.
- **Topotecan:**
  Intravenously as a 30-min infusion through peripheral or central lines.
  Topotecan will be diluted in a minimum of 50 ml of 0.9% sodium chloride or 5% glucose solution for infusion.

6.3 STARTING DOSES AND SCHEDULE

6.3.1.1 *Experimental Arm (PM01183): Arm A*

- 3.2 mg/m^2 on Day 1 q3wk (three weeks = one treatment cycle)

Dose will be rounded to the first decimal.

6.3.1.2 *Control Arm (PLD and topotecan): Arm B*

- **PLD starting dose and schedule:**

  50 mg/m^2 on Day 1 q4wk (four weeks = one treatment cycle).

  Dose will be rounded to the first decimal.

  Patients previously treated with PLD will be assigned to receive topotecan if they are randomized to the control arm.

- **Topotecan starting dose and schedule:**
  - 1.50 mg/m^2 daily on Days 1-5 q3wk (three weeks = one treatment cycle) for patients with calculated CrCL ≥ 60 ml/min.
  - 1.25 mg/m^2 daily on Days 1-5 q3wk for patients with calculated CrCL between 40 and 59 ml/min.
  - 0.75 mg/m^2 daily on Days 1-5 q3wk for patients with calculated CrCL between 30 and 39 ml/min.

  Dose will be rounded to the first decimal.

  Skipped doses of topotecan will not be replaced.

Patients previously treated with topotecan will be assigned to receive PLD if they are randomized to the control arm.

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 (see Section 5.6).

The dose for all three agents (PM01183, PLD or topotecan) will be capped at a body surface area (BSA) of 2.0 m^2 in those patients who have a greater BSA. BSA will be calculated according to the standard nomogram used at each center.

6.4 PROPHYLACTIC MEDICATION

All patients will receive standard antiemetic prophylaxis before each treatment infusion, as follows:

- Corticosteroids (dexamethasone i.v. at least 8 mg or equivalent, or at institutional standard antiemetic doses).
- Serotonin (5-HT$_3$) antagonists (ondansetron at least 8 mg i.v. or equivalent).

If necessary, in addition to the above, the duration of treatment with 5-HT$_3$ antagonists and/or dexamethasone could be extended. Additional antiemetic agents can be administered as appropriate.

Aprepitant and equivalent agents (e.g., fosaprepitant) are forbidden in patients treated with PM01183.

For the purpose of safety evaluations, an optimal prophylaxis is defined as all the aforementioned allowed medications at their respectively maximum dose.

6.5 CRITERIA FOR TREATMENT CONTINUATION

Further treatment cycles (i.e., Cycle 2 or subsequent) will be administered every three weeks (PM01183 or topotecan) or every four weeks (PLD) (with a window of ± 48

hours in all three treatment arms) if the patient fulfills all the re-treatment criteria defined in Table 8 (PM01183), Table 9 (PLD) or Table 10 (topotecan).

Table 8. Criteria for treatment continuation with PM01183 (Arm A).

Variable	**Day 1**
ECOG PS	≤ 2
ANC	≥ 1.5 x 10^9/l
Platelets	≥ 100 x 10^9/l
Hemoglobin [a]	≥ 8 g/dl
Total bilirubin	≤ 1.5 x ULN or direct bilirubin ≤ ULN if total bilirubin > ULN
Albumin	≥ 2.7 g/dl
AST/ALT	≤ 3.0 x ULN
CPK	≤ 2.5 x ULN
Calculated CrCl (Cockcroft and Gault's formula)	≥ 30 ml/min
Other non-hematological drug-related AEs (except isolated increased GGT and/or AP; grade 2 alopecia, constipation, fatigue, neuropathy, and not optimally treated nausea)	Grade ≤ 1

[a] Patients may receive PRBC transfusion and/or EPO treatment if clinically indicated to increase/maintain adequate hemoglobin levels.
AEs, adverse events; ANC, absolute neutrophil count; AP, alkaline phosphatase; AST/ALT, aspartate aminotransferase/alanine aminotransferase; CPK, creatine phosphokinase; CrCL, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; EPO, erythropoietin; PRBC, packed red blood cells; ULN, upper limit of normal.

Table 9. Criteria for treatment continuation with PLD (Arm B).

Variable	**Day 1**
ECOG PS	≤ 2
ANC	≥ 1.5 x 10^9/l
Platelets	≥ 75 x 10^9/l
Hemoglobin[a]	≥ 8 g/dl
Total bilirubin	≤ 1.5 x ULN or direct bilirubin ≤ ULN if total bilirubin > ULN
Mucositis or hand-foot syndrome	Grade < 2
Calculated CrCl (Cockcroft and Gault's formula)	≥ 30 ml/min
Other non-hematological drug-related AEs (except isolated increased GGT and/or AP; grade 2 alopecia, constipation, fatigue, neuropathy, and not optimally treated nausea)	Grade ≤ 1

Variable	Day 1

[a] Patients may receive PRBC transfusion and/or EPO treatment if clinically indicated to increase/maintain adequate hemoglobin levels.
AEs, adverse event(s); ANC, absolute neutrophil count; AP, alkaline phosphatase; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; EPO, erythropoietin; GGT, gamma-glutamyltransferase; PPE, palmar-plantar erythrodysesthesia; PRBC, packed red blood cells; ULN, upper limit of normal.

Table 10. Criteria for treatment continuation with topotecan (Arm B).

Variable	Day 1
ECOG PS	≤ 2
ANC	≥ 1.5 x 10^9/l
Platelets	≥ 100 x 10^9/l
Hemoglobin [a]	≥ 8 g/dl
Total bilirubin	≤ 1.5 x ULN or direct bilirubin ≤ ULN if total bilirubin > ULN
AST/ALT	≤ 3.0 x ULN
Calculated CrCl (Cockcroft and Gault's formula)	≥ 30 ml/min [b]
Other non-hematological drug-related AEs (except isolated increased GGT and/or AP, grade 2 alopecia, constipation, fatigue, neuropathy, and not optimally treated nausea)	Grade ≤ 1

[a] Patients may receive PRBC transfusion and/or EPO treatment if clinically indicated to increase/maintain adequate hemoglobin levels.
[b] Patients with CrCL between 40 and 59 ml/min must be re-treated with no more than 1.25 mg/m^2 of topotecan daily, and patients with CrCL between 30 and 39 ml/min must receive no more than 0.75 mg/m^2 of topotecan daily.
AEs, adverse events; ANC, absolute neutrophil count; AP, alkaline phosphatase; AST/ALT, aspartate aminotransferase/alanine aminotransferase; CPK, creatine phosphokinase; CrCL, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; EPO, erythropoietin; PRBC, packed red blood cells; ULN, upper limit of normal.

If a patient does not meet the requirements for treatment continuation on Day 1 of any cycle after Cycle 1, re-assessments should be performed within one week, and treatment will be withheld until appropriate recovery, for a maximum of two weeks after the treatment due date. If there is no recovery after a 2-week delay, treatment must be discontinued, except if objective clinical benefit is adequately documented by the Investigator, and upon agreement with the Sponsor. Then, treatment may continue after appropriate dose reduction.

6.6 DOSE REDUCTION

Patients who experience any grade ≥ 3 treatment-related non-hematological toxicity (according to the NCI-CTCAE v. 4) and/or grade 3 thrombocytopenia associated with bleeding or persistent at the time of re-treatment or grade 4, or frequent or prolonged treatment-related dose delays (> 1 week) (or skipped infusions if on topotecan) will continue treatment after appropriate dose reduction (see Table 11 for dose reduction in Arm A, PM01183; see Table 12 for dose reduction in Arm B, PLD or topotecan).

Patients experiencing grade 4 neutropenia or any grade febrile neutropenia, or neutropenic infection during the preceding cycle or frequent treatment-related dose delays exclusively due to neutropenia may continue treatment without any dose reduction, but the patient must receive secondary prophylaxis with CSF starting at least 24 hours after the last infusion of the cycle. If despite appropriate CSF secondary prophylaxis, grade 4 neutropenia or febrile neutropenia, neutropenic infection or the dose delay re-occurs, then dose reduction should be implemented.

Exceptions for dose reduction are: grade 3 nausea and/or vomiting not optimally prevented, grade 3 fatigue lasting ≤ 2 days, grade 3 diarrhea lasting ≤ 1 day or not optimally treated, isolated grade 3 ALT or AST elevations not leading to dose delays and/or non-clinically relevant isolated biochemical abnormalities (e.g., GGT).

Table 11. Levels of dose reduction in Arm A (PM01183).

	Arm A PM01183 dose (q3wk) (mg/m^2) [a]
1 (starting dose)	3.2
-1	2.6
-2	2.0

[a] PM01183 dose will be capped at a body surface area (BSA) of 2.0 m^2 in those patients who have a greater BSA.
q3wk, every three weeks.

Table 12. Levels of dose reduction in Arm B (PLD or topotecan).

	Arm B			
	PLD [e] (q4wk) (mg/m^2)	**Topotecan [e] daily dose (q3wk) (mg/m^2)**		
1 (starting dose)	50	1.50 [a]	1.25 [b]	0.75 [c, d]
-1	37.5	1.25	1.00	-
-2	28 [d]	1.00	0.75 [d]	-

[a] Starting dose for patients treated with topotecan with calculated CrCL ≥ 60 ml/min.
[b] Starting dose for patients treated with topotecan with calculated CrCL of 40-59 ml/min.
[c] Starting dose for patients treated with topotecan with calculated CrCL of 30-39 ml/min.
[d] No dose reduction below 28 mg/m^2 of PLD or 0.75 mg/m^2/day of topotecan will be implemented under any circumstances.
[e] PLD and topotecan dose will be capped at a body surface area (BSA) of 2.0 m^2 in those patients who have a greater BSA.
CrCL, creatinine clearance; PLD, pegylated liposomal doxorubicin; q3wk, every three weeks; q4wk, every four weeks.

In case of grade ≥ 2 hand-foot syndrome (HFS) or stomatitis secondary to PLD treatment, the PLD treatment administration will be delayed until resolved to grade ≤1 or discontinued if not resolved within two weeks. In addition, subsequent doses will be reduced if the HFS or stomatitis is ≥ grade 3 (Table 13).

Table 13. PLD dose modification guidelines according to hand-foot syndrome and stomatitis (Arm B).

Toxicity grade	Hand-foot syndrome (HFS)	Stomatitis	Dose adjustment
1	Mild erythema, swelling, or desquamation not interfering with daily activities.	Painless ulcers, erythema, or mild soreness.	**Re-treat unless patient has experienced previous grade 3 or 4 HFS/mucositis**. If so, delay up to two weeks and decrease dose one level. Return to original dose interval.
2	Erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter.	Painful erythema, edema, or ulcers, but can eat.	**Delay dosing up to two weeks or until resolved to grade 0-1.** If after two weeks there is no resolution, PLD should be discontinued. If resolved to grade 0-1 within two weeks, and there are no prior grade 3-4 HFS/mucositis, continue treatment at previous dose and return to original dose interval. If patient experienced previous grade 3-4 toxicity, continue treatment with one dose level reduction and return to original dose interval.
3	Blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing.	Painful erythema, edema, or ulcers, and cannot eat.	**Delay dosing up to two weeks or until resolved to grade 0-1.** Decrease dose one level and return to original dose interval. If after two weeks there is no resolution, PLD should be discontinued.
4	Diffuse or local process causing infectious complications, or a bed ridden state or hospitalization.	Requires parenteral or enteral support.	**Delay dosing up to 2 weeks or until resolved to grade 0-1.** Decrease dose one level and return to original dose interval. If after two weeks there is no resolution, PLD should be discontinued.

HFS, hand-foot syndrome; PLD, pegylated liposomal doxorubicin.

Patients treated with PLD who have LVEF decreased to < 45% or with a 20% decrease from the baseline value have to permanently discontinue PLD treatment.

Control and experimental arms:

Patients who experience any treatment-related grade 3 or 4 hypersensitivity and/or extravasations will permanently discontinue irrespectively of arm allocation.

Up to two dose reductions are allowed per patient. Patients who continue to experience treatment-related toxicity and/or frequent dose delays after two dose reductions must be withdrawn from the study. Once the dose has been reduced for an individual patient, it will not be re-escalated under any circumstances irrespectively of arm allocation.

6.7 CONCOMITANT MEDICATION

All treatments received by the patient during the "on-treatment" period of the trial must be documented in the CRF.

6.7.1 Allowed Medications/Therapies

- Therapies for pre-existing and treatment-emergent medical conditions, including pain management.
- Blood products and transfusions, as clinically indicated.
- Bisphosphonates.

- In case of nausea or vomiting, extended symptomatic treatment for emesis will be allowed.
- CSFs or erythropoietin treatment according to the American Society of Clinical Oncology (ASCO) guidelines.
- Anticoagulants.

6.7.2 Prohibited Medications/Therapies

- Concomitant administration of any antineoplastic therapy (other than those specifically allowed).
- Any radiotherapy other than limited field irradiation for cancer pain control exclusively.
- Immunosuppressive therapies other than corticosteroids for antiemetic prophylaxis and/or pain control.
- Aprepitant and equivalent agents (e.g., fosaprepitant) for patients allocated to the PM01183 arm (Arm A).
- Primary CSF prophylaxis for patients allocated to the PM01183 arm (Arm A), unless recommended by the IDMC after the interim safety analysis.
- Any other investigational agent/s.

6.7.3 Drug-drug Interactions

In vitro studies using human liver microsomes have shown that PM01183 has the potential to inhibit cytochrome CYP2B6, CYP2C8 and CYP3A4. Moreover, the Ki values compared with the achieved maximum plasma concentration (C_{max}) values at relevant doses indicate that the likelihood of a clinically relevant inhibition of PM01183 is possible for CYP2B6 and CYP2C8 ([I]/Ki>0.1) and likely for CYP3A4 ([I]/Ki>1). Additional *in vitro* studies have demonstrated no time dependent inhibition or irreversible inhibition for cytochrome CYP3A4. The magnitude of the interaction is unknown at present. Therefore, caution should be exercised when PM01183 is administered concomitantly with CYP2B6, CYP2C8 and CYP3A4 substrates.

Additionally, *in vitro* studies with human microsomes have shown that CYP3A4 is the major CYP isoform involved in the metabolism of PM01183, followed by CYP2E1, CYP2D6 and CYP2C9. The estimated contribution of the other CYP isoenzymes to the PM01183 metabolism is considered to be negligible. Therefore, concomitant drugs which induce or inhibit any of these cytochromes, especially CYP3A4, should be carefully monitored or avoided, whenever is possible (see *APPENDIX 3*).

A potentially significant interaction with aprepitant is suggested by available phase II data from ovarian cancer patients. Aprepitant use was forbidden in Cycle 1 in all patients. Four patients treated with aprepitant in Cycle 2 with available PK data had their PM01183 clearance reduced by 50%, approximately, compared to their Cycle 1 exposure. Clinically, some of these patients had unusually long-lasting neutropenia and/or severe thrombocytopenia during Cycle 2. Although all patients eventually recovered, the use of aprepitant is currently forbidden in the PM01183 treatment arms from all phase II/III PM01183 studies.

6.8 DRUG ACCOUNTABILITY

Proper drug accountability will be done by the appropriate trained study personnel. Each study site will keep records to allow a comparison of quantities of drug received and used at each site for monitoring purposes. The Investigator at each study site will be the person ultimately responsible for drug accountability at the site.

All unused drug supplied by the Sponsor will be properly destroyed at the study site. Documentation of this procedure must be provided to the clinical trial monitor. If the Sponsor agrees, unused drug supplies may be returned to the drug repository.

6.9 TREATMENT COMPLIANCE

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

7. STUDY EVALUATIONS

7.1 EFFICACY

The primary aim of this clinical trial is to determine a difference in PFS between PM01183 and PLD or topotecan in platinum-resistant ovarian cancer patients. Secondary endpoints of efficacy include antitumor activity according to RECIST v.1.1.

Antitumor activity will be assessed using the RECIST v. 1.1 (see APPENDIX 2) and followed until disease progression (PD) by the appropriate method [computed tomography (CT) scan or magnetic resonance imaging (MRI) of the pelvis, abdomen and chest].

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 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 cutoff), 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 a 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.

A futility analysis is planned when 210 patients are recruited (~105 patients enrolled in each arm). The IDMC will review the efficacy and safety data available at that time and, based on the observed results, might recommend stopping the trial; no claim for superiority in efficacy *vs.* the control arm is foreseen at that time.

7.2 SAFETY

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 treatment-related AEs will be followed until recovery to at least grade 1 or stabilization of symptoms, whichever occurs first.

An interim safety analysis will be performed by the IDMC after the recruitment of the first 40 patients in the PM01183 arm (Arm A) to assess if the addition of primary CSF prophylaxis might be necessary. Although febrile neutropenia did not occur in the first-in-human PM01183 single-agent study, based on pooled data available from all ongoing phase II studies at 7.0 mg FD, it occurred in about 16% of patients. In this clinical trial, the expected percentage of febrile neutropenia is lower, as the PM01183 dose will be administered based on BSA and at a dose (3.2 mg/m^2) below the RD found in the first-in-human PM01183 trial (4.0 mg/m^2 = 7.0 mg FD).

Furthermore, PM01183, PLD and topotecan dose will be capped at a BSA of 2.0 m^2 in those patients who have a greater BSA.

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

Safety evaluations will be also performed by the IDMC during the futility analysis to be conducted in all treatment arms once 210 patients are recruited.

7.3 ADVERSE EVENTS DEFINITIONS

7.3.1 Adverse Event (AE)

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

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

Illnesses with onset during the study or exacerbations of pre-existing illnesses, including but not limited to clinically significant changes in physical examination findings and abnormal objective tests/procedures findings (e.g., X-ray, ECG) should be recorded. The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

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

"Disease progression" will not be reported as an AE, as this information will be used for efficacy assessment.

7.3.2 Serious Adverse Event (SAE)

A SAE is any adverse experience occurring at any dose that:

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

Medical and scientific judgment should be exercised in deciding medically significant events; this criterion should be applied to AEs that may not be immediately life-threatening or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the above definition.

"Disease progression" as a term will not be reported as a SAE.

7.3.3 Death

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

Grade 5 should be used for events which lead immediately (within 24 hours) and directly to death, and grade 4 should be used with outcome death for events which lead to death after a longer time period, and that may also be linked to additional morbidities.

7.3.4 Life-threatening Event

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

7.3.5 Hospitalization or Prolongation of Hospitalization

Any AE requiring hospitalization (or prolongation of hospitalization) that occurs or worsens during the course of a patient's participation in a clinical trial must be reported as a SAE unless exempted from SAE reporting (see Section 7.4.2). Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the initial admission, as determined by the Investigator or treating physician.

Hospitalizations that do not meet criteria for SAE reporting are:

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

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

c. Pre-planned hospitalizations: any pre-planned surgery or procedure must be documented in the source documentation. Only if the pre-planned surgery needs to

be performed earlier due to a worsening of the condition, should this event (worsened condition) be reported as a SAE.

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

d. An emergency visit due to an accident where the patient is treated and discharged.
e. When the patient is held 24 hours for observation and finally is not admitted.
f. Planned treatments at sites not associated to a hospital and generally considered as minor surgical procedures (i.e., laser eye surgery, arthroscopy, etc.).

7.3.6 Unlisted/Unexpected Adverse Event

An AE, the nature or severity of which is not consistent with the applicable reference safety information.

The Sponsor will use as the reference safety information for the evaluation of listedness/expectedness the IB for lurbinectedin (PM01183) and the Reference Safety Information for PLD and topotecan.

7.3.7 Adverse Reactions

All untoward and unintended responses to an investigational medicinal product related to any dose administered. This definition covers also medication errors and uses outside what is foreseen in the protocol, including overdose, lack of efficacy, misuse and abuse of the product.

7.3.8 Adverse Events Related to the Study Drug

An AE is considered related to a study drug/IMP if the Investigator's assessment of causal relationship to the IMP(s) is "Y (yes)" (see Section 7.3.10).

The Investigator will assess the causal relationship of the IMP(s) to the SAE.

The Sponsor may also consider related to the study drug(s)/IMP(s) those events for which the Investigator assesses the causal relationship with the IMP(s) as "Uk (unknown)" when it cannot rule out a role of the IMP(s) in the event.

7.3.9 Expedited Reporting

The Sponsor is responsible for the appropriate expedited reporting according to the applicable legislation.

7.3.10 Assessment of Causal Relationship to the Study Drug

The Investigator must provide an assessment of the causal relationship of each SAE to the clinical trial IMP(s) according to the following scale:

Y There is a reasonable possibility that the IMP(s) caused the SAE.

N There is no reasonable possibility that the IMP(s) caused the SAE and other causes are more probable.

Uk (Unknown). Only to be used in special situations where the Investigator has insufficient information (i.e., the patient was not seen at his/her center) if none of the above can be used.

7.4 ADVERSE EVENTS REPORTING PROCEDURES

7.4.1 Reporting Adverse Events

The Sponsor will collect AEs until 30 days after administration of the last dose of study drug(s)/IMP(s) or until the start of a new antitumor therapy or until the date of death, whichever occurs first. All AEs suspected to be related to the study drug/IMP must be

followed-up after the time of therapy discontinuation until the event or its sequelae resolve or stabilize at an acceptable level to the Investigator and the Sponsor.

All AEs, including medication errors and uses outside what is foreseen in the protocol, must be recorded in English using medical terminology in the source document and the CRF. Whenever possible, the Investigator will record the main diagnosis instead of the signs and symptoms normally included in the diagnoses.

Investigators must assess severity (grade) of the event following the NCI-CTCAE v. 4 and assign a relationship to each study drug(s)/IMP(s); and pursue and obtain information adequate both to determine the outcome and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to Pharma Mar S.A. or its designated representative. The Investigator must provide any relevant information as requested by the Sponsor in addition to that on the CRF.

Abnormal laboratory tests occurring during the study should only be recorded in the AE section of the CRF if the disorder:

- Is associated with clinically significant symptoms, and/or
- Leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
- Leads to any of the outcomes included in the definition of a SAE.

Otherwise laboratory results should be reported in the corresponding section of the CRF (e.g. biochemistry, hematology).

All episodes of febrile neutropenia must always be reported within 24 hours following the same procedure for reporting SAEs (see Section 7.4.2), including episodes that occurred in patients without seriousness criteria. For these cases, the seriousness criterion should be reported as a medically significant event.

7.4.2 Reporting Serious Adverse Events

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

All SAEs (as defined above) occurred after patient registration regardless of relationship to the study drug(s)/IMP(s) must be reported immediately, and always within 24 hours to the Pharma Mar S.A. Pharmacovigilance Department, electronically by completing the applicable e-CRF section.

SAEs occurring during the screening phase (from ICF signature to randomization), SAEs that may occur off-study, or in case the electronic system fails or is not available, will be reported within 24 hours to the Pharmacovigilance Department using the paper SAE form by fax (+34 91 846 6004), e-mail (phv@pharmamar.com) or telephone (+34 91 823 4556).

Out of office hours [Greenwich Meridian Time (GMT)], assistance on SAE reporting can be obtained by calling the Pharmacovigilance Department at +34 91 823 4742. SAEs initially reported by alternative methods (not electronically), must be followed by a completed electronic SAE reporting on e-CRF from the investigational staff within one working day.

All SAEs suspected to be related to the IMP(s) must be followed until the event or its sequelae resolves or stabilizes at an acceptable level by the Investigator.

7.4.3 Reporting Pregnancy Cases Occurred within the Clinical Trial

National regulations require that clinical trial Sponsors collect information on pregnancies occurring during clinical trials, in which exposure to the IMP(s) at any time during pregnancy, via either maternal or paternal exposure, is suspected.

Therefore, pregnancy and suspected pregnancy (including a positive pregnancy test regardless of age or disease state) of a patient occurring while on study drug, or within 30 days after the administration of the last dose of the study drug(s)/IMP(s), are considered immediately reportable events. Beyond this timeframe, the investigator will report any pregnancy if there is any suspicion that the study drug(s)/IMP(s) might have an impact on the occurrence of the pregnancy.

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

- Any occurrence of a pregnancy where any kind of exposure to the IMP(s) is suspected.
- Possible exposure of a pregnant woman.
- All reports of elevated/questionable or indeterminate beta human chorionic gonadotropins (β-hCGs).

Immediately after detecting a case of suspected pregnancy in a patient, the decision on her continued participation in the clinical trial will be jointly taken by the patient, the Investigator and the Sponsor, with the patient's best interest in mind. A decision to continue the pregnancy will require immediate withdrawal from the trial.

Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Pharma Mar S.A. Pharmacovigilance immediately using the Pregnancy Report form.

The Investigator will follow the pregnancy until its outcome, and must notify Pharma Mar S.A. Pharmacovigilance the outcome of the pregnancy within 24 hours of first knowledge as a follow-up to the initial report.

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

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

7.5 ADVERSE EVENTS MONITORING

Safety review will be performed at Pharma Mar S.A. once SAE forms have been received and the CRFs electronically completed by the Investigator.

At every monitoring visit performed by the designed clinical research monitor in charge of the study, the consistency between the CRF/SAE data reported to the Pharmacovigilance Department and the patient's source data will be reviewed. When a discrepancy is found during the review, data will be amended/updated in the CRF and

the SAE form/information reported to the Pharmacovigilance department (when applicable), according to source data.

SAEs will be continuously collected, assessed and reported throughout all the study as per the applicable legislation by the Pharma Mar S.A. Pharmacovigilance Department. Periodic safety reviews of SAE reports including events of special interest (e.g., neutropenia and thrombocytopenia) are to be conducted and documented by the Pharmacovigilance Department.

Non-serious AEs will be verified during monitoring visits by the clinical trial monitor, who will discuss them with the Investigators, if applicable. AEs will be assessed by the Investigators and by the study team at Pharma Mar S.A. The personnel in charge of this process are defined in the section "*Study Contacts*" of this protocol. Pharma Mar S.A. Pharmacovigilance Department will review the safety data of this trial on an ongoing basis. Periodic safety review of safety data from the clinical database, i.e. AEs and laboratory data, will be performed along the study by the Pharma Mar S.A. Pharmacovigilance, Clinical Oncology and Data Management departments.

7.6 PATIENT-REPORTED OUTCOMES

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.

7.7 PHARMACOKINETICS

7.7.1 Blood Sampling

Sparse samples (detailed in Table 14) will be collected in all patients enrolled in the PM01183 arm (Arm A). The samples will be obtained in two cycles (in Cycle 1 and in a second cycle between Cycle 2 and 4). The selection of the second cycle with sample collection for the measurement of PM01183 will be assigned once the patient is randomized into Arm A.

Table 14. Blood samples for pharmacokinetic evaluations.

Sample No.	Sampling time	PK window
#1	Before PM01183 treatment start	1 to 5 min before treatment start
#2	5 min before PM01183 EOI	+/- 2 min
#3	1 hour after PM01183 EOI	+/- 10 min
#4	168 hours after PM01183 EOI	+/- 24 hours

EOI, end of infusion; PK, pharmacokinetics.

The infusion rate will be predetermined to ensure that the dose of PM01183 is infused in 60 min at a constant rate. In order to obtain reliable PK information, the infusion rate should not be modified once the infusion begins. If a variation in the infusion time eventually occurs, it is very important this to be reflected in the CRF. The accurate recording of actual dosing and sampling times is much more important than the strict adherence to the scheduled times

Blood samples will be obtained into a vacutainer tube by using a peripheral catheter placed in a vein of the arm opposite to the side used for drug infusion. Even the last sample must never be collected from the catheter used for drug infusion.

A total of eight samples of about 4 ml each will be collected for the determination of plasma concentrations of PM01183 on Cycle 1 and in a second cycle between Cycle 2

and 4 (about 32 ml of whole blood) at the predefined times depicted in the above table. A Laboratory Manual will be provided with details on collection and storage of PK samples. Please read it carefully before PK sampling. In short, after collection, each sample will be centrifuged and the resulting plasma layer transferred into a new tube for the determination of PM01183 concentration. The plasma-containing tubes will be stored frozen until their shipment to the Central Laboratory for PK Samples (see details in the Study Contacts). All the material for PK procedures will be provided by the Sponsor(s).

7.7.2 Analytical Procedures

Plasma samples will be analyzed to determine concentrations of PM01183 using a validated, specific, and sensitive liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) method by or under the supervision of the Sponsor.

7.7.3 Pharmacokinetic Parameters

Pharmacokinetic analysis will be the responsibility of the Sponsor in accordance with the current Clinical Pharmacokinetics guidelines on population pharmacokinetic analyses [59, 60]. Clearance and volume of distribution will be the primary parameters of interest for the population PK analysis. Additional PK parameters will be calculated, if deemed appropriate.

7.8 PHARMACOGENETIC EVALUATIONS

To explore factors that may help to explain individual variability in the main PK parameters, the presence or absence of germline mutations or polymorphisms that may be involved in the metabolism and/or transport of PM01183 will be analyzed in leukocyte DNA extracted from one blood sample (10 ml) obtained before PM01183 treatment in Cycle 1 in patients treated with PM01183 (Arm A). The collection and management of the polymorphisms samples are quite different than those for PK assessment (please, refer to the Laboratory Manual for details). The assessment of polymorphisms is not affected by treatment. Therefore, the Sponsor may require the collection of additional polymorphisms samples later on, if the first assessment has not been performed accurately. Only patients who voluntarily sign the IC for this pharmacogenetic sub-study will participate in the pharmacogenetic evaluation. Refusal to participate in this sub-study will not affect patient participation in the clinical study PM1183-C-004-14.

7.9 PHARMACOGENOMIC (PGX) EVALUATIONS

Provision of samples for PGx analyses will be optional and performed upon patient consent by signing the PGx IC. For those patients who consent to participate in the PGx study, available tumor tissue blocks obtained at diagnosis of the disease will be collected during his/her participation in the associated clinical trial. Samples from Arm B will be used as controls in order to differentiate between the prognostic or predictive value of any obtained finding.

The following analyses will be done in paraffin-embedded tumor tissue from consenting patients:

- Quantitation of mRNA expression of selected genes involved in DNA repair mechanisms and/or related to the mechanism of action of PM01183 or to the pathogenesis of the disease by real-time qRT-PCR.
- Quantitation of protein expression of selected genes involved in DNA repair mechanisms and/or related to the mechanism of action of PM01183 or to the pathogenesis of the disease by IHC in tumor tissue microarrays constructed.
- Analysis of polymorphisms and mutations of the above mentioned selected genes will be analyzed, if relevant, by qRT-PCR and/or DNA sequencing.

Expression levels of the different markers will be correlated with the patient's clinical outcome.

8. STATISTICAL METHODS

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.

The primary study endpoint (PFS by IRC) will be calculated by means of the stratified log-rank test on the intention-to-treat (ITT) population, defined as all randomized patients analyzed in the group where they were allocated.

An IDMC will oversee the conduct of the study.

8.1 SAMPLE SIZE

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

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.

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 RECIST v.1.1.

A futility analysis with no claim for efficacy when 210 patients are recruited and the final analysis to reject the null hypothesis (HR=1) are planned; the significance level will be determined by the actual observed number of events, and to maintain scientific integrity spending function will be defined by O'Brien-Fleming boundaries. Following the prospective assumptions, the futility analysis will occur before 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.

8.2 STATISTICAL ANALYSIS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. The study protocol contains a general description; specific details will be provided in the Statistical Analysis Plan.

Frequency tables will be prepared for categorical variables, and continuous variables will be described by means of summary tables, which will include the median, mean, standard deviation, minimum, and maximum of each variable.

8.2.1 Efficacy Analyses

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 on the ITT population will be primarily used to compare the time-to-event variables.

Unstratified log-rank tests will also be calculated as supportive analyses. The symmetry of tumor evaluations between the different arms will be examined. Sensitivity analyses for different PFS censoring (e.g. date of progression based on scheduled time instead of registered date) will be performed, these analyses will be detailed in the SAP.

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. Continuous variables that would have been categorized as discrete variables will also be investigated in the continuum range, and if the adjustment is better, then the continual variable will be chosen.

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 of the experimental arm (PM01183) and the control arm (PLD and topotecan).

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

8.2.2 Safety Analyses

AEs, SAEs, deaths, laboratory evaluations, dose delays/skipped/reductions and study drug discontinuations due to AEs will be tabulated in a descriptive way. Counts and percentages will be used for categorical variables, and summary tables will be used for continuous variables. Exploratory Fisher's exact tests will be performed to compare grade 4 or grade 3/4 between treatment arms.

An interim safety analysis, performed when 40 patients are enrolled in the PM01183 arm (Arm A), will test if the addition of primary CSF prophylaxis might be necessary. 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% *versus* 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 would be considered necessary.

At the time of the interim safety analysis, recruitment in the control arm (Arm B, PLD and topotecan) is also expected to be 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.

A safety evaluation will also be performed by the IDMC as part of the futility analysis, when a total of 210 patients are included.

8.2.3 Patient-reported Outcomes (PRO) Analyses

PRO will be analyzed 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.

8.2.4 Pharmacokinetic Analyses

Sparse PK data will be listed in the population PK-report for all patients with available concentrations in the PM01183 treatment arm (Arm A). Patients will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (e.g., improper handling of PK samples; incomplete administration of the study agent; missing time or dosing information). All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. All patients and samples excluded from the analysis will be retained in the dataset, but they will be flagged out and the criteria for exclusion documented.

Population PK analysis of plasma concentration-time data of PM01183 will be performed using non-linear mixed-effects modeling. Data may be combined with those of a selection of phase I or II studies to support a relevant structural model. Available patient characteristics (demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting PK parameters. 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.

8.2.5 Pharmacogenetic Analyses

The influence of known polymorphisms on main PK parameters will be assessed by Student's test or Mann-Whitney's U test as appropriate.

8.2.6 Pharmacogenomic (PGx) Analyses

Analysis of RNA/protein expression, polymorphisms and mutations will be performed blind and with clinical data compiled only after all analyses are completed. A Fisher´s exact test/logistic regression for categorical variables and log rank test/Cox regression for time to event variables will be used to test whether a specific profile is associated with clinical outcome. The prognostic value of markers will be explored for objective response, PFS and OS. In each case, if applicable, a multivariate model will be developed by stepwise selection. All tests of statistical significance will be two-sided, and significance will be set at 0.05.

8.3 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. The IDMC will review efficacy and safety data available at that time and, based on the observed results, might recommend stopping the trial.

Following the prospective assumptions, this futility analysis will occur before one year after start of recruitment. The significance level will be determined by the actual observed number of events, and type II error will be controlled by O'Brien-Fleming boundaries.

8.4 INTERIM SAFETY ANALYSIS

An interim safety analysis, performed when 40 patients are enrolled in the PM01183 arm (Arm A), will test if the addition of primary CSF prophylaxis might be necessary. 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 $\leq 20\%$ versus 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 would be considered necessary.

At the time of the interim safety analysis, recruitment in the control arm (Arm B, PLD and topotecan) is also expected to be 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.

9. ADMINISTRATIVE SECTION

9.1 ETHICS

This clinical trial will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki (see APPENDIX 4) and will be consistent with GCP guidelines and pertinent regulatory requirements.

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

The study will be conducted in compliance with the protocol. The protocol, any amendments and the patient informed consent will receive IEC/IRB approval/favorable opinion prior to initiation, according to pertinent regulations.

The decision of the IEC/IRB concerning the conduct of the study will be made in writing to the Investigator, and a copy of this decision will be provided to the Sponsor before the beginning of the study.

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

All protocol amendments will be agreed upon by the Sponsor and the Investigator.

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

9.2 MONITORING, AUDITING AND INSPECTING

The study will be monitored by regular site visits and telephone calls to the Investigator by the clinical trial monitor designated by Pharma Mar S.A.

During site visits, the trial monitor should revise original patient records, drug records and document retention (study file). Additionally, the trial monitor should observe study procedures and will discuss any problems with the Investigator.

Adequate time for these visits should be allocated by the Investigator. The Investigator should also ensure that the monitor is given direct access [as per International Conference on Harmonization (ICH) Topic E6 (R1) Guideline for Good Clinical Practice, Sections 4.9.7 and 6.10] to source documents (i.e., hospital or private charts, original laboratory records, appointment books, etc.) of the patient which support data entered in the case report forms, as defined in the ICH Topic E6 (R1) Guideline for Good Clinical Practice, Sections 1.51 and 1.52.

Systems and procedures will be implemented to ensure the quality of every aspect of the trial.

During the course of the trial, the Clinical Quality Assurance Department of Pharma Mar S.A. or external auditors contracted by the Sponsor may conduct an onsite audit visit (ICH Topic E6 (R1) Guideline for GCP, Section 1.6).

Participation in this trial implies acceptance of potential inspection by national or foreign Competent Authorities.

9.3 PATIENT INFORMED CONSENT

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

The ICFs will include all elements required by ICH, GCP and applicable regulatory requirements.

Prior to inclusion into the trial, the Investigator or a person designated by the Investigator, must provide the patient with one copy of the Informed Consent Forms (ICFs). This copy must provide written full information about the clinical trial, in a language that is non-technical and easily understood, as well as on the sub-study (PGx and pharmacogenetic). The Investigator should allow the necessary time for the patient or his/her legally acceptable representative to inquire about the details of the clinical trial; then, the ICFs must be freely signed and personally dated by the patient and by the person who conducted the Informed Consent discussion before the beginning of the study. The patient should receive a copy of the signed ICFs and any other written information provided to study patients prior to participation in the trial.

During a patient's participation in the trial, any updates to the consent forms and any updates to the written information will be provided to him/her.

If there is a need to obtain new consent from the patients, the Investigator or a person designated by the Investigator should inform the patients of any new information relevant to the patients' willingness to continue participation in the study, before obtaining the written consent.

9.4 CONFIDENTIALITY/ PATIENTS IDENTIFICATION

The collection and processing of personal data from the patients enrolled in this clinical trial will be limited to those data that are necessary to investigate the efficacy, safety, quality and usefulness of the study drug used in this trial.

It is the Investigator's responsibility that sufficient information on the identity of the patients will be retained.

The trial monitor, the Sponsor's auditor, the IECs/IRBs and the Competent Authorities should have direct access to all requested trial-related records, and agree to keep the identity of study patients confidential.

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

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

Pharma Mar S.A. shall comply with the Directive 95/46/EEC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

9.5 CASE REPORT FORMS

Electronic CRFs will be used to record all data for each patient. It is the responsibility of the Investigator to ensure that the CRFs are properly and completely filled in, in English. CRFs must be completed for all patients who have given their informed consent.

A patient's source documentation is the patient's records (including but not limited to physician/hospital notes, nurses notes, IMP preparation records including reconstitution and dilution, IMP administration records, patient-reported outcomes, etc.) and any original document, and as such they should be maintained at the study site.

The data collected in the CRF will be entered into databases, which comply with the Spanish Act implementing the Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data.

9.6 INSURANCE

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

9.7 RETENTION OF RECORDS

The Investigator/Institution should maintain trial documents according to Section 8 of the ICH Topic E6 (R1) Guideline for Good Clinical Practice and as required by applicable regulatory requirements.

Essential documents should be retained as per the aforementioned ICH guideline or for a longer period of time, if required by the applicable regulations.

9.8 USE OF INFORMATION AND PUBLICATION

Before the investigators of this study submit a paper or abstract for publication or otherwise publicly disclose information concerning the study drug or products, Pharma Mar S.A. must be provided with at least 60 days to revise and approve the proposed publication or disclosure to ensure that confidential and proprietary data are protected.

If Pharma Mar S.A. determines that patentable patient matter is disclosed in the proposed publication or disclosure, the publication or disclosure will be withheld for a period of time considered convenient. If the study is part of a multicenter study, the first publication of the study shall be made in conjunction with the presentation of a joint, multicenter publication of the study results with the investigators and the institutions from all appropriate sites that are contributing data, analysis and comments. However, if such a multicenter publication is not submitted within 12 months after conclusion, abandonment or termination of the study at all sites, the present study may be published individually in accordance with the procedure established above.

The order of the coauthors will reflect the relative contribution of each one to study development and analysis. In general, the first author will be the investigator who recruits the highest number of patients with information finally available for data analysis. Relevant Pharma Mar S.A. personnel who have fully participated in the study must be considered for co-authorship of the publication.

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11. APPENDICES

APPENDIX 1: ECOG PERFORMANCE STATUS ASSESSMENT SCALE

Grade	ECOG PS*
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

*As published in Am. J. Clin. Oncol *5:649-655, 1982*: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group.*

APPENDIX 2: EVALUATION OF RESPONSE. THE RECIST.

This document summarizes the main information contained in RECIST version 1.1.

Further details can be found in the original article: Eisenhauer EA, Therasse P, Bogaerts J, et al.: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2): 228-247.[2]

LIST OF ABBREVIATIONS

CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
MRI	Magnetic Resonance Imaging
NE	Not Evaluable
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-free Survival
PR	Partial Response
PSA	Prostate-specific Antigen
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable Disease
TTP	Time to Progression

LIST OF TABLES

[2] A summary of major changes from RECIST 1.0 to RECIST 1.1 can be found at the beginning of this document (**Table 1**).

[3] This table is named Appendix I in the original RECIST 1.1 article.

The main changes from RECIST 1.0 to RECIST 1.1 are shown in the following table.

Table 1. Summary of major changes from RECIST 1.0 to RECIST 1.1.

RECIST 1.0		**RECIST 1.1**	**Rationale**
Minimum size measurable lesions	CT: 10 mm spiral 20 mm non-spiral	CT 10 mm; delete reference to spiral scan	Most scans used have 5 mm or less slice thickness. Clearer to give instruction based on slice interval if it is greater than 5 mm
	Clinical: 20 mm	Clinical: 10 mm (must be measurable with calipers)	Caliper measurement will make this reliable
	Lymph node: not mentioned	CT: ≥ 15 mm short axis for target ≥ 10–<15 mm for non-target < 10 mm is non-pathological	Since nodes are normal structure need to define pathological enlargement. Short axis is most sensitive
Special considerations on lesion measurability	–	Notes included on bone lesions, cystic lesions	Clarify frequently asked questions
Overall tumor burden	10 lesions (5 per organ)	5 lesions (2 per organ)	Data warehouse analysis shows no loss of information if lesion number reduced from 10 to 5. A maximum of 2 lesions per organ yields sufficient representation per disease site
Response criteria target disease	CR lymph node not mentioned	CR lymph nodes must be <10 mm short axis	In keeping with normal size of nodes
	PD 20% increase over smallest sum on study or new lesions	PD 20% increase over smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions	Clarification that if baseline measurement is smaller than any on study measurement, it is reference against which PD is assessed 5 mm absolute increase to guard against over calling PD when total sum is very small and 20% increase is within measurement error
Response criteria non-target disease	'Unequivocal progression' considered as PD	More detailed description of 'unequivocal progression' to indicate that it should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase	Confusion with RECIST 1.0 where some were considering PD if 'increase' in any non-target lesion, even when target disease is stable or responding
New lesions	–	New section on New lesions	To provide guidance on when a lesion is considered new (and thus PD)

RECIST 1.0		RECIST 1.1	Rationale
Overall response	Table integrated target and non-target lesions	Two tables: one integrating target and non-target and the other of non-target only Special notes: How to assess and measure lymph nodes CR in face of residual tissue Discussion of 'equivocal' progression	To account for the fact that RECIST criteria are now being used in trials where PFS is the endpoint and not all patients have measurable (target) disease at baseline Frequently asked questions on these topics
Confirmatory measure	For CR and PR: criteria must be met again 4 weeks after initial documentation	Retain this requirement ONLY for non-randomized trials with primary endpoint of response	Data warehouse shows that response rates rise when confirmation is eliminated, but the only circumstance where this is important is in trials where there is no concurrent comparative control and where this measure is the primary endpoint
Progression-free survival	General comments only	More specific comments on use of PFS (or proportion progression-free) as phase II endpoint Greater detail on PFS assessment in phase III trials	Increasing use of PFS in phase III trials requires guidance on assessment of PD in patients with non-measurable disease
Reporting of response results	9 categories suggested for reporting phase II results	Divided into phase II and phase III 9 categories collapsed into 5 In phase III, guidance given about reporting response	Simplifies reporting and clarifies how to report phase II and III data consistently
Response in phase III trials	More relaxed guidelines possible if protocol specified	This section removed and referenced in section above: no need to have different criteria for phase II and III	Simplification of response assessment by reducing number of lesions and eliminating need for confirmation in randomized studies where response is not the primary endpoint makes separate 'rules' unnecessary
Imaging appendix	Appendix I	Appendix II: updated with detailed guidance on use of MRI, PET/CT Other practical guidance included	Evolving use of newer modalities addressed. Enhanced guidance in response to frequent questions and from radiology review experience
New appendices		Appendix I: comparison of RECIST 1.0 and 1.1 Appendix III: frequently asked questions	

RECIST 1.0	RECIST 1.1	Rationale

CR, complete response; CT, computed tomography; MRI, magnetic resonance imaging; RECIST, response evaluation criteria in solid tumors; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PR, partial response.

1. MEASURABILITY OF TUMOR LESIONS AT BASELINE

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

1.1.1 Measurable

Tumor Lesions:

Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by computed tomography (CT) scan (irrespective of scanner type) and magnetic resonance imaging (MRI) (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (when superficial).
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

Malignant Lymph Nodes:

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed (see Schwartz *et al.* Eur J Cancer. 2009; 45(2):261-267). See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as lesions considered truly non-measurable. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3 Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone Lesions:

- Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as

CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2. Specifications by Methods of Measurement

1.2.1 Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than four weeks before the beginning of the treatment.

1.2.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions:

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-Ray:

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. See original article, Appendix II, for more details.

Computed Tomography (CT), Magnetic Resonance Imaging (MRI):

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in original article (Appendix II), when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is

also acceptable in certain situations (e.g., for body scans). More details concerning the use of both CT and MRI for assessment of objective tumor response evaluation are provided in the original article, Appendix II.

Ultrasound:

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in the original article, Appendix II). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy:

The use of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

2. TUMOR RESPONSE EVALUATION

2.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall *tumor burden at baseline* and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 1. Measurability of tumor at baseline). In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

2.2 Baseline Documentation of "Target" and "Non-target" Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as ***target lesions*** and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved that a *maximum* of two and four lesions will be recorded, respectively). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts *et al.* Eur J Cancer 2009;45:248–260.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion which can be measured reproducibly should be selected. To illustrate this point see the example in the original article, Figure 3 of Appendix II.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted in the previous section, pathological nodes which are defined as measurable and may be identified as

target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement (see also the example in the original article, Figure 4 of Appendix II). All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3 Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

2.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum diameters while on study.

2.3.2 Special Notes on the Assessment of Target Lesions

Lymph Nodes:

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms (CRFs) or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target Lesions that Become 'Too Small to Measure':

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that Split or Coalesce on Treatment:

As noted in the original article, Appendix II, when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3 Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression (see comments below) of existing non-target lesions (Note: the appearance of one or more new lesions is also considered progression).

2.3.4 Special Notes on Assessment of Progression of Non-target Disease

The concept of progression of non-target disease requires additional explanation as follows:

When the Patient Also Has Measurable Disease:

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see examples in the original article, Appendix II and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has only Non-measurable Disease:

This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. Some illustrative examples are shown in the original article, Figures 5 and 6 of Appendix II. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

2.3.5 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change

in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement (see Section 2.6. Confirmatory Measurement/Duration of Response). Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

2.4.1 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. **Table 2** provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 2. Time point response: patients with target (+/–non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non- PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR, complete response; NE, inevaluable; PD, progressive disease; PR, partial response; SD, stable disease.

When patients have non-measurable (therefore non-target) disease only, **Table 3** is to be used.

Table 3. Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR, complete response, NE, inevaluable; PD, progressive disease.

[a] 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials; so, to assign this category when no lesions can be measured is not advised.

2.4.2 Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3 Best Overall Response: All Time Points

The best overall response is determined once all the data for the patient is known.

Best Response Determination in Trials Where Confirmation of Complete or Partial Response IS NOT Required:

Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best Response Determination in Trials Where Confirmation of Complete or Partial Response IS Required:

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally four weeks later). In this circumstance, the best overall response can be interpreted as in **Table 4**.

Table 4. Best overall response when confirmation of complete response (CR) and partial response (PR) is required.

Overall response. First time point	Overall response. Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR, complete response; NE, inevaluable; PD, progressive disease; PR, partial response; SD, stable disease.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

APPENDIX 3: LIST OF CYP1/CYP2/CYP3 INHIBITORS, INDUCERS AND SUBSTRATES

Table 1. Classification of In Vivo Inhibitors of CYP Enzymes (1)

CYP enzymes	Strong Inhibitors (2) ≥ 5-fold increase in AUC or > 80% decrease in CL	Moderate inhibitors (3) ≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL	Weak inhibitors (4) ≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL
CYP1A2	Ciprofloxacin, enoxacin, fluvoxamine	Methoxsalen, mexiletine, oral contraceptives, phenylpropanolamine, thiabendazole, zileuton	Acyclovir, allopurinol, caffeine, cimetidine, Daidzein, (5), disulfiram, Echinacea, (5) famotidine, norfloxacin, propafenone, propranolol, terbinafine, ticlopidine, verapamil
CYP2B6			Clopidogrel, ticlopidine prasugrel
CYP2C8	Gemfibrozil(6)		Fluvoxamine, ketoconazole, trimethoprim
CYP2C9		Amiodarone, fluconazole, miconazole, oxandrolone	Capecitabine, cotrimoxazole, etravirine, fluvastatin, fluvoxamine, metronidazole, sulfinpyrazone, tigecycline, voriconazole, zafirlukast
CYP2C19	Fluconazole, (7) Fluvoxamine, (8) ticlopidine (9)	Esomeprazole, fluoxetine, moclobemide, omeprazole, voriconazole	Allicin (garlic derivative), armodafinil, carbamazepine, cimetidine, etravirine, human growth hormone (rhGH), felbamate, ketoconazole, oral contraceptives (10)
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice, (11) indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, (12) nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, (11) imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, (5) goldenseal, (5) isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton
CYP2D6	Bupropion, fluoxetine, paroxetine, quinidine	Cinacalcet, duloxetine, terbinafine	Amiodarone, celecoxib, cimetidine, desvenlafaxine, diltiazem, diphenhydramine, Echinacea, (5) escitalopram, febuxostat, gefitinib, hydralazine, hydroxychloroquine, imatinib, methadone, oral contraceptives, propafenone, ranitidine, ritonavir, sertraline, telithromycin, verapamil

1. Please note the following: This is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.
2. A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.
3. A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.

4. A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 5-fold.
5. Herbal product.
6. Gemfibrozil also inhibits OATP1B1.
7. Fluconazole is listed as a strong CYP2C19 inhibitor based on the AUC ratio of omeprazole, which is also metabolized by CYP3A; fluconazole is a moderate CYP3A inhibitor.
8. Fluvoxamine strongly inhibits CYP1A2 and CYP2C19, but also inhibits CYP2C8/2C9 and CYP3A;
9. Ticlopidine strongly inhibits CYP2C19, but also inhibits CYP3A, CYP2B6, and CYP1A2.
10. Effect seems to be due to CYP2C19 inhibition by ethinyl estradiol.
11. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).
12. Withdrawn from the United States market because of safety reasons.

Table 2. Classification of In Vivo Inducers of CYP Enzymes (1)

CYP enzymes	Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
CYP1A2		Montelukast, phenytoin, smokers *versus* non-smokers (2)	Moricizine, omeprazole, phenobarbital,
CYP2B6		Efavirenz, rifampin	Nevirapine
CYP2C8		Rifampin	
CYP2C9		Carbamazepine, rifampin	Aprepitant, bosentan, phenobarbital, St. John's wort (3,4)
CYP2C19		Rifampin	Artemisinin
CYP3A	Avasimibe, (5) carbamazepine, phenytoin, rifampin, St. John's wort (3)	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea,(4) pioglitazone, prednisone, rufinamide
CYP2D6	None known	None known	None known

1. Please note the following: This is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.
2. For a drug that is a substrate of CYP1A2, the evaluation of the effect of induction of CYP1A2 can be carried out by comparative PK studies in smokers vs. non-smokers.
3. The effect of St. John's wort varies widely and is preparation-dependent.
4. Herbal product.
5. Not a marketed drug.

Table 3. Examples (1) of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range

CYP enzymes	Sensitive substrates (2)	Substrates with narrow therapeutic range (3)
CYP1A2	Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	Theophylline, tizanidine
CYP2B6 (4)	Bupropion, efavirenz	
CYP2C8	Repaglinide (5)	Paclitaxel
CYP2C9	Celecoxib	Warfarin, phenytoin
CYP2C19	Lansoprazole, omeprazole, S-mephenytoin	S-mephenytoin
CYP3A (6)	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole, (7) cisapride, (7) cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine (7)

CYP enzymes	Sensitive substrates (2)	Substrates with narrow therapeutic range (3)
CYP2D6	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine

1. Note that this is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.
2. Sensitive CYP substrates refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.
3. CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).
4. The AUC of these substrates were not increased by 5-fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.
5. Repaglinide is also a substrate for OATP1B1, and it is only suitable as a CYP2C8 substrate if the inhibition of OATP1B1 by the investigational drug has been ruled out.
6. Because a number of CYP3A substrates (e.g., darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.
7. Withdrawn from the United States market because of safety reasons.

APPENDIX 4: DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

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

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

5. Medical progress is based on research that ultimately must include studies involving human subjects.

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

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

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

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

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

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

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

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

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

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

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

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

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

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific

information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

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

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

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

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

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

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may

be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

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

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised

representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.