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CLINICAL TRIAL PROTOCOL

Phase I Multicenter, Open-label, Clinical and Pharmacokinetic Study of PM01183 in Combination with Doxorubicin in Non-heavily Pretreated Patients with Selected Advanced Solid Tumors

INVESTIGATIONAL MEDICINAL PRODUCT: PM01183

Protocol Code: PM1183-A-003-10

EudraCT No: 2010-024291-25

NCT Code: 01970540

Protocol Version 4.0 (includes amendment #1 dated 21 November 2011, amendment #2 dated 10 July 2013, and amendment #3 dated 17 October 2014)

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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 I Multicenter, Open-label, Clinical and Pharmacokinetic Study of PM01183 in Combination with Doxorubicin in Non-Heavily Pretreated Patients with Selected Advanced Solid Tumors.
PROTOCOL CODE	PM1183-A-003-10
INVESTIGATORS / TRIAL LOCATION	A full list of investigators will be available as a separate document.
NUMBER OF SITES	Seven sites in Spain and the United Kingdom (UK) are expected to participate in this study.
STUDY OBJECTIVES	**Primary:** • To determine the maximum tolerated dose (MTD) and the recommended dose (RD) of PM01183 in combination with doxorubicin in patients with selected advanced solid tumors. **Secondary:** • To determine the MTD and the RD of PM01183 in combination with doxorubicin with primary prophylaxis with granulocyte-colony stimulating factor (G-CSF) in patients with selected advanced solid tumors [if dose-limiting toxicities (DLTs) of the combination without G-CSF prophylaxis are exclusively related to neutropenia]. • To characterize the safety profile and feasibility of this combination in patients with selected advanced solid tumors. • To characterize the pharmacokinetics (PK) of this combination and to detect major drug-drug PK interactions. • To obtain preliminary information on the clinical antitumor activity of this combination in non-heavily pretreated selected solid tumor patients. • Based on promising findings, to explore the feasibility, safety and efficacy of a potential improvable dose of this combination in selected tumor types [i.e. small cell lung cancer (SCLC) and endometrial cancer). • To evaluate the pharmacogenomics (PGx) in tumor samples of patients exposed to PM01183 and doxorubicin at the RD in order to assess potential markers of response and/or resistance.
STUDY DESIGN	Prospective, open-label, dose-ranging, uncontrolled phase I study with escalating doses of PM01183 in combination with doxorubicin. Patients will start receiving intravenous (i.v.) doxorubicin 50 mg/m^2 (fixed dose) as bolus followed by PM01183 3.5 mg, flat

	dose (FD), i.v. over one hour on Day 1 every three weeks (q3wk). A cycle is defined as an interval of three weeks. Cohorts of three to six patients will be included at each dose level (DL). If no dose-limiting toxicity (DLT) occurs in more than one patient in each cohort, escalation will proceed to the next dose level. The MTD will be the lowest dose level explored during the dose escalation at which more than one evaluable patient experience a DLT in Cycle 1. If one among the first three evaluable patients experiences a DLT, the dose level should be expanded up to six patients. Dose escalation will be terminated once the MTD or the last dose level (DL4) is reached, whichever occurs first, except if all DLTs occurring at a given dose level are related to neutropenia (e.g., febrile neutropenia, grade 4 neutropenia lasting more than 7 days or neutropenic sepsis) in which case dose escalation may be resumed, starting at the lowest dose level at which exclusively neutropenia-related DLTs were observed, and will follow the same original schedule but with compulsory primary G-CSF prophylaxis. An expansion cohort to complete a minimum of nine evaluable patients will be recruited at the immediate lower dose level, or at the last dose level (DL4) if the MTD is not defined yet. This level will be confirmed as the RD if less than one third of the first nine evaluable patients experience DLT during Cycle 1. Further to the finding of encouraging antitumor activity in the first 43 evaluable patients (13 responses, including four complete responses, with five partial responses in eight patients with small cell lung cancer, and one complete and one partial response in three patients with endometrial cancer), expansion of the cohort treated at the RD has been increased to include approximately 30 additional patients, for a total of around 39 patients. In addition, a new cohort of 20 evaluable patients with small cell lung cancer (SCLC) who failed after first-line standard cytotoxic-containing therapy and at least nine evaluable patients with endometrial cancer will be included to further define the efficacy, safety and feasibility of a doxorubicin dose adaptation (doxorubicin 40 mg/m^2 and PM01183 2.0 mg/m^2). In the event of DLTs occurring in the first patient at the first level, the second and third patients will be included at least two weeks apart. Otherwise and/or at subsequent dose levels, all patients within a dose level may be treated simultaneously. All evaluable patients within a dose level will be followed for at least one cycle (i.e., three weeks) before dose escalation may proceed. Intermediate dose levels could be tested on agreement between the Investigator and the Sponsor if deemed appropriate. The tumor type(s) that will be eligible to be included in the expansion cohort at the RD will be chosen according to the preliminary efficacy observed among those previously treated

	during the escalation phase, and will be discussed and agreed between the investigators and the Sponsor.
STUDY POPULATION **Inclusion criteria**	1) Voluntarily signed and dated written informed consent prior to any specific study procedure. 2) Age: between 18 and 75 years (both inclusive). For patients with SCLC and endometrial cancer included in the new cohort after implementation of Amendment #3: age ≥ 18 years. 3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1. For patients with SCLC and endometrial cancer included in the new cohort after implementation of Amendment #3: ECOG PS ≤ 2. 4) Life expectancy ≥ 3 months. 5) Patients not previously treated with anthracycline-containing therapy for advanced disease (Note: adjuvant therapy with anthracyclines is allowed provided not more than 300 mg/m^2 of doxorubicin or an equivalent total cumulative dose was administered and they did not have to discontinue treatment due to any anthracycline-related toxicity, and relapse occurred more than six months after the last drug administration). 6) No more than two prior lines of cytotoxic-containing chemotherapy regimens for advanced disease. For patients with SCLC included in the new cohort after implementation of Amendment #3: no more than one prior line of cytotoxic-containing chemotherapy regimens for advanced disease. 7) Patients with a histologically/cytologically confirmed diagnosis of advanced disease of any of the following tumors: a) Breast cancer (non-candidate for hormone therapy alone: i.e., hormone-sensitive patients with bone-limited disease). b) Soft-tissue sarcoma [excluding gastrointestinal stromal tumors (GIST)]. c) Primary bone sarcomas. d) Epithelial ovarian cancer (including primary peritoneal disease and/or fallopian tube carcinomas and/or endometrial adenocarcinomas). e) Hepatocellular carcinoma (HCC) (non-eligible for liver transplantation and Child-Pugh score A only). Elevated alpha-fetoprotein (AFP) levels in a patient with known risk factors and radiological findings compatible with HCC do not require pathological confirmation.

	f) Gastroenteropancreatic neuroendocrine tumors (GEP-NET). g) Small cell lung cancer (SCLC). h) Gastric cancer. i) Bladder cancer. j) Adenocarcinoma of unknown primary site (AUKPS). 8) **Expansion cohort at the RD:** All patients must have: a) Measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1; or b) Evaluable disease by serum markers in the case of ovarian cancer [Gynecologic Cancer Intergroup (GCIG) specific criteria]; and c) Documented disease progression during or immediately after last therapy according to any of the aforementioned criteria. 9) **New cohort after implementation of Amendment #3:** a) Measurable SCLC or endometrial cancer according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1; and b) Documented disease progression during or immediately after last therapy according to any of the aforementioned criteria. 10) At least three weeks since the last anticancer therapy, including radiotherapy, and at least six weeks since nitrosoureas and mitomycin C (systemic). In the case of hormone-sensitive breast cancer progressing while on hormone therapy, the latter must be either stopped up to one week before or continued without changes during the trial. 11) Adequate bone marrow, renal, hepatic, and metabolic function (assessed ≤ 7 days before inclusion in the study): a) Platelet count ≥ 100 x 10^9/l, hemoglobin ≥ 9.0 g/dl and absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l. b) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x the upper limit of normal (ULN), independently of the presence of liver metastases. c) Alkaline phosphatase (AP) ≤ 2.5 x ULN (≤ 5 x ULN if disease-related). d) Total bilirubin ≤ 1.5 x ULN or direct bilirubin ≤ ULN. e) International Normalized Ratio (INR) < 1.5 (except if patient is on oral anticoagulation therapy). f) Calculated creatinine clearance (CrCl) ≥ 30 ml/minute (using Cockcroft and Gault´s formula). g) Creatine phosphokinase (CPK) ≤ 2.5 x ULN. h) Albumin ≥ 2.5 g/dl.

	For patients with SCLC and endometrial cancer included in the new cohort after implementation of Amendment #3: albumin ≥ 3.0 g/dl. 12) Recovery to grade ≤ 1 or to baseline from any adverse event (AE) derived from previous treatment (excluding alopecia and/or cutaneous toxicity and/or peripheral sensory neuropathy and/or asthenia, all grade ≤ 2). 13) Left ventricular ejection fraction (LVEF) by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan within normal range (according to institutional standards). 14) Women of childbearing potential must have a negative serum pregnancy test before study entry. Both women and men must agree to use a medically acceptable method of contraception throughout the treatment period and for six weeks after discontinuation of treatment. Acceptable methods of contraception include intrauterine device (IUD), oral contraceptive, subdermal implant and/or double barrier.
Exclusion criteria	1) Concomitant diseases/conditions: a) History or presence of unstable angina, myocardial infarction, congestive heart failure, or clinically significant valvular heart disease within last year. b) Symptomatic arrhythmia or any uncontrolled arrhythmia requiring ongoing treatment. c) Ongoing chronic alcohol consumption, or cirrhosis with Child-Pugh score B or C. d) Active uncontrolled infection. e) Known human immunodeficiency virus (HIV) infection. f) Myopathy or any clinical situation that causes significant and persistent elevation of CPK (> 2.5 x ULN in two different determinations performed one week apart). g) Limitation of the patient's ability to comply with the treatment or follow-up 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) Symptomatic, progressive or corticosteroids-requiring documented brain metastases or leptomeningeal disease involvement. 3) Men or women of childbearing potential who are not using an effective method of contraception as previously described; women who are pregnant or breast feeding. 4) Patients who have had radiation therapy in more than 35% of the bone marrow. This criterion will **not** apply to patients with SCLC and endometrial cancer included in the new cohort after

<table>
<tr><td></td><td>implementation of Amendment #3.
5) History of previous bone marrow and/or stem cell transplantation.
6) Treatment with any investigational product in the period of ≥ 5 half-lives of the investigational compound prior to the first infusion.</td></tr>
<tr><td>STUDY POPULATION
Pharmacogenomic study criteria</td><td>The aim of the PGx component of this study is to identify and validate putative molecular markers associated with the clinical outcome of patients treated with PM01183 combined with doxorubicin. These molecular markers would help to select future patients who might preferentially benefit from PM01183 and doxorubicin treatment, thus contributing to improve health care through a more individualized medicine.
Eligibility criteria:
1) Patients with prior available tumor samples who are eligible for the trial will also be eligible for the PGx study.
2) Only patients who voluntarily sign the Informed Consent for the PGx study will participate. Refusal to participate in the PGx study will not affect patient participation in the clinical study PM1183-A-003-10.</td></tr>
<tr><td>Expected number of patients</td><td>The number of patients may vary depending both on the tolerability to PM01183 combined with doxorubicin and the number of dose levels required to identify the MTD. Approximately, 100 evaluable patients will participate in this study.</td></tr>
<tr><td>STUDY DRUG
Formulation</td><td><u>PM01183:</u>
PM01183 drug product (DP) will be presented as a lyophilized powder for concentrate for solution for infusion, with two strengths: 1 mg/vial and 4 mg/vial.
Before use, the 1-mg vial and 4-mg vial should be reconstituted with 2 ml and 8 ml of sterile water for injection, respectively, to give a solution containing 0.5 mg/ml of PM01183. For administration to patients as i.v. infusion, reconstituted vials will be diluted with glucose 50 mg/ml (5%) or sodium chloride 9 mg/ml (0.9%) solution for infusion.
The full composition of the PM01183 1-mg and 4-mg vials and the reconstituted solution per ml are as follows:
<table>
<tr><th>Component</th><th>PM01183 1 mg</th><th>PM01183 4 mg</th><th>Concentration per vial after reconstitution</th></tr>
<tr><td>PM01183</td><td>1.0 mg</td><td>4.0 mg</td><td>0.5 mg/ml</td></tr>
<tr><td>Sucrose</td><td>200 mg</td><td>800 mg</td><td>100 mg/ml</td></tr>
<tr><td>Lactic acid</td><td>5.52 mg</td><td>22.08 mg</td><td>2.76 mg/ml</td></tr>
<tr><td>Sodium hydroxide</td><td>1.28 mg</td><td>5.12 mg</td><td>0.64 mg/ml</td></tr>
</table></td></tr>
</table>

	Doxorubicin: Commercially available presentations of vials containing doxorubicin will be provided as appropriate.
Treatment schedule	Doxorubicin at a fixed dose of 50 mg/m^2 administered as an i.v. bolus followed by escalating doses of PM01183 as a 1-hour i.v. infusion on Day 1 q3wk. **New cohort after implementation of Amendment #3:** Patients with SCLC and endometrial cancer will be treated with doxorubicin at 40 mg/m^2 administered as an i.v. bolus/short infusion followed by PM01183 at 2.0 mg/m^2 as a 1-hour i.v. infusion on Day 1 q3wk.
Administration route and dose	Patients will consecutively receive the following on Day 1 q3wk (three weeks = one treatment cycle): • Doxorubicin: i.v. infusion of a total volume of 20 ml dilution on 0.9% saline or 5% dextrose, on a short i.v. bolus at a dose of 50 mg/m^2 (fixed dose), via a central or peripheral venous catheter after appropriate visual confirmation of effective venous blood return through the line, immediately followed by: • PM01183: i.v. infusion over one hour at a starting dose of 3.5 mg FD, over a minimum of 100 ml dilution on 5% glucose or 0.9% sodium chloride (at a fixed rate) via a central line (or a minimum of 250 ml dilution if a peripheral line will be used) through a pump device. Then PM01183 will be escalated as planned according to the respective dose levels. **New cohort after implementation of Amendment #3:** Patients with SCLC and endometrial cancer will consecutively receive the following on Day 1 q3wk (three weeks = one treatment cycle): • Doxorubicin: i.v. bolus/short infusion at a dose of 40 mg/m^2, administered as described above, immediately followed by: • PM01183: i.v. infusion over one hour at a dose of 2.0 mg/m^2, administered as described above. Both doxorubicin and PM01183 doses will be capped at 2.0 m^2 of BSA for individuals exceeding this BSA value. Doses will have to be recalculated for patients showing a ≥ 10% change in total body weight value compared to previous cycle. Doses will be rounded to the first decimal.

Prophylactic medication	All patients must receive the following prophylactic medication 20-30 minutes before infusion of any study drug:
	• Dexamethasone 8 mg i.v. or equivalent,
	• Ondansetron 8 mg i.v. or equivalent, with or without:
	  – Metoclopramide 10 mg i.v. or equivalent, and/or
	• Extended oral dexamethasone not exceeding 20 mg/days and/or oral ondansetron 4 to 8 mg or equivalent, at the investigator's criteria if required.
	• Additional antiemetics might be used, if required.
	• If primary G-CSF prophylaxis is required in specific cohorts of patients, it will consist of:
	  – G-CSF (non-pegylated filgrastim) at 300 μg/day subcutaneously for five consecutive days, starting on Day +3.

Allowed medications/ therapies	• Therapies for preexisting and treatment-emergent medical conditions, including pain management. • Blood products and transfusions, as clinically indicated. • Bisphosphonates. • In case of nausea or vomiting, secondary prophylaxis and/or symptomatic treatment for emesis according to American Society of Clinical Oncology (ASCO) guidelines will be allowed. • Erythropoietin use according to ASCO guidelines will be allowed. • Hormone-responsive breast cancer patients [i.e., those whose tumors express estrogen receptor (ER) and/or progestogen receptor (PrR)] may continue receiving their same prior hormonal therapy without interruption throughout their study participation. • Luteinizing hormone-releasing hormone (LHRH) agonists in women of reproductive age. • Palliative local radiation (excluding thorax and mediastinum) may be applied if needed after the first cycle of study treatment is completed. Any lesion within the irradiated area will then not be considered an area of measurable/evaluable disease. Thorax and mediastinum may be irradiated, if required, after a minimum of three weeks of doxorubicin discontinuation. • Megestrol acetate for appetite stimulation is also allowed.
Prohibited medications/ therapies	• Concomitant administration of any other antineoplastic therapy is prohibited, other than the aforementioned hormonal therapy for breast cancer. • Other investigational agents. • Aprepitant or directly related substances (e.g., fosaprepitant). • Immunosuppressive therapies, other than corticosteroids • Primary prophylaxis and/or treatment with colony-stimulating factors such as granulocyte colony-stimulating factor (G-CSF) and granulocyte/macrophage colony-

	stimulating factor (GM-CSF) during Cycle 1, (except if patient(s) is/are treated within an specific cohort resuming dose escalation with primary G-CSF prophylaxis, in which case use is not only allowed but compulsory). Secondary prophylaxis might be allowed, if required, during the following cycles, instead of a dose reduction due to exclusively hematological reasons and upon Sponsor agreement. **Note:** G-CSF treatment for non-febrile uncomplicated neutropenia during Cycle 1 and primary G-CSF or GM-CSF prophylaxis will not be allowed in patients with SCLC and endometrial cancer included in the new cohort after implementation of Amendment #3. • Thoracic and/or mediastinal irradiation concomitant with doxorubicin therapy.
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.
EVALUABILITY OF PATIENTS	An evaluable patient for the main objective of the study (determination of the MTD and RD) should have received at least one complete cycle (including observation period), except if early discontinuations or missed doses and/or assessments were the consequence of drug-related toxicity (excluding

	hypersensitivity reactions and/or extravasations). In the new cohort of patients with SCLC and endometrial cancer after implementation of Amendment #3, a patient evaluable for efficacy should have received at least one complete cycle (including observation period) and be evaluable as per RECIST, except if non-evaluability is due to treatment failure such as drug-related toxicity, death or early unequivocal PD outside the central nervous system.
EVALUATION CRITERIA **Primary endpoint**	• **<u>Determination of MTD and RD</u>**. o The MTD will be the lowest dose level explored during the dose escalation at which more than one evaluable patient experience a DLT in Cycle 1. o The RD will be the highest dose level explored in which less than one third of evaluable patients experience a DLT during Cycle 1. If the DLTs of the doxorubicin and PM01183 combination without G-CSF prophylaxis are exclusively related to neutropenia, <u>the MTD and RD will also be determined with primary G-CSF prophylaxis.</u>
DOSE-LIMITING TOXICITIES	DLTs are defined as AEs and laboratory abnormalities related to the study treatment during the first cycle of treatment and fulfilling at least one of the criteria outlined below. • Grade 4 neutropenia (ANC < 0.5 x 10^9/l) lasting > 7 days. • Grade ≥ 3 febrile neutropenia of any duration or neutropenic sepsis. • Grade 4 thrombocytopenia (platelet count < 25 x 10^9/l) or grade 3 with any major bleeding episode requiring a platelet transfusion. • Grade 4 ALT and/or AST increase, or grade 3 lasting > 14 days. • Treatment-related grade ≥ 2 ALT or AST increase concomitantly with ≥ 2 times ULN total bilirubin increase and normal AP. • Grade ≥ 3 CPK increase. • Any other grade 3/4 non-hematological AE that is suspected to be related to study drug(s), except nausea/vomiting (unless the patient is receiving an optimal anti-emetic regimen), hypersensitivity reactions, extravasations, grade 3 asthenia lasting less than one week, and non-clinically relevant isolated biochemical abnormalities [e.g., isolated increase in gamma-glutamyltransferase (GGT)]. In any case, the clinical relevance should be discussed between the Investigators and Sponsor's representatives. • Delay in the administration of Cycle 2 of the combination exceeding 15 days of the theoretical date (i.e., Day 22), due to any AEs related to the study drug(s).

	• The following circumstances will be discussed between the Principal Investigator and the Sponsor, and the final consensus will be documented: o DLTs with delayed onset (i.e., that occur after Cycle 1).
Secondary endpoints	• **Safety:** patients will be evaluable for safety if they have received at least one partial or complete infusion of PM01183. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4. • **Pharmacokinetics:** PK parameters will be evaluated in plasma by standard non-compartmental methods (compartmental modeling may be performed if appropriate). • **Efficacy:** although it is not the main objective of this study, antitumor activity will be measured according to the RECIST version 1.1 at least six weeks after treatment initiation in all patients with measurable disease, or by evaluation of tumor markers if applicable (e.g., ovarian cancer). Patients included at the RD in the expansion cohort must be evaluable per RECIST version 1.1 or by evaluation of tumor markers. In the new cohort after the implementation of Amendment #3, exploratory assessment for progression-free survival (PFS) and overall survival (OS) will be performed. • **Pharmacogenomics:** pharmacogenomics will be evaluated from available tumor samples previously obtained at diagnosis in order to determine predictive/prognostic markers of response and/or resistance to PM01183 and doxorubicin in those patients that signed the Informed Consent for the PGx study. The expression of XPG RNA will be evaluated in paraffin-embedded tumor tissues by real-time quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) and XPG, topoisomerase IIa (TopoIIa) and P-glycoprotein (Pgp) by immunohistochemistry (IHC) and associated with clinical outcome in patients treated with PM01183 and doxorubicin.
REPLACEMENT OF PATIENTS	Patients must be replaced if they are not evaluable for the assessment of the primary endpoint, i.e. if: • They are withdrawn from the study before receiving at least the infusion of both drugs on the first day (Day 1) of the first cycle of the scheduled treatment ("evaluable cycle"). An evaluable cycle is defined as: doxorubicin followed by PM01183 on Day 1 with the corresponding follow-up period of three weeks. • They require radiotherapy (RT) or other therapeutic procedure within three weeks after the first dose, unless they previously had another drug-related AE included in the definition of DLT. • There is a protocol violation resulting in an impossibility of concluding anything regarding the safety of the study

	therapy. In addition, patients with SCLC and endometrial cancer included in the new cohort after implementation of Amendment #3 must be replaced if: • They are not evaluable for efficacy as per RECIST for reasons other than treatment failure such as drug-related toxicity, death or early unequivocal PD outside the central nervous system. All replaced patients will be included in the general safety analysis and in the efficacy analysis (if appropriate).
DOSE ESCALATION SCHEDULE	Doxorubicin will be given at 50 mg/m^2 as an i.v. bolus, which corresponds to 100% of its actual RD when combined with other myelosuppressive agents; therefore, the doxorubicin dose will not be escalated in this study. The starting dose (DL1) for PM01183 will be 3.5 mg given as FD on Day 1 q3wk, which corresponds to 50% of the RD for this schedule when given as single agent. The dose escalation schedule is summarized in the following table: **DL** / **No. of patients** / **Relative DI (%) of doxorubicin / PM01183** / **Dose of doxorubicin (mg/m^2) / PM01183 (mg FD) on Day 1 q3wk** DL-1 / 0-6 / 100 / 42.85 / 50 / 3.0 DL1 / 3-6 / 100 / 50 / 50 / 3.5 DL2 / 3-6 / 100 / 71.4 / 50 / 5.0 DL3 / 3-6 / 100 / 85.7 / 50 / 6.0 DL4 / 3-6 / 100 / 100 / 50 / 7.0 The DL-1 level is to be explored only if DL1 is defined as the MTD. DI, dose intensity; DL, dose level; FD, flat dose. As shown in the table below, a minimum of three patients will be included at each DL. If no patients experience a DLT during the first cycle, the dose will be escalated. If one of three patients experiences a DLT, three additional patients will be included at that level. If >1 evaluable patient during dose escalation at a given DL experience a DLT during the first cycle, that level will be considered the MTD and dose escalation will be terminated except if all DLTs occurring at a given dose level are related to neutropenia (e.g., febrile neutropenia, grade 4 neutropenia lasting more than 7 days or neutropenic sepsis) in which case dose escalation may be resumed, starting at the lowest dose level where exclusively neutropenia-related DLTs have occurred, and will follow the same original schedule but with compulsory primary G-CSF prophylaxis. The DL immediately below the MTD, or DL4 if the MTD is not reached during dose escalation and the last dose level (DL4) is reached, was to be

<table>
<tr><td></td><td>initially expanded up to a minimum of nine evaluable patients. If less than three among the first nine evaluable patients treated within the expansion cohort experience a DLT during Cycle 1 this DL will be the RD.

Further to the finding of encouraging antitumor activity in the first 43 evaluable patients (13 responses, including four complete responses, with five partial responses in eight patients with small cell lung cancer, and one complete and one partial response in three patients with endometrial cancer), expansion of the cohort treated at the RD has been increased to include approximately 30 additional patients, for a total of around 39 patients.

<table>
<tr><th>No. of patients evaluable* for DLT</th><th>No. of patients with DLTs in first cycle</th><th>Action</th></tr>
<tr><td rowspan="3">3</td><td>0</td><td>Escalate DL until DL4 is reached</td></tr>
<tr><td>1</td><td>Add 3 patients</td></tr>
<tr><td>>1</td><td>MTD</td></tr>
<tr><td rowspan="2">6</td><td>1</td><td>Escalate DL until DL4 is reached</td></tr>
<tr><td>>1</td><td>MTD</td></tr>
</table>
DL, dose level; DLT: dose-limiting toxicities; MTD, maximum tolerated dose.
* Patients not evaluable for DLT during dose optimization must be replaced.

According to the toxicity observed, intermediate dose levels may be explored if considered appropriate by the investigators and the Sponsor.

Intra-patient dose escalation will not be allowed under any circumstances.</td></tr>
<tr><td>Criteria for treatment continuation</td><td>Patients will be treated with additional cycles of PM01183 combined with doxorubicin as long as no unacceptable toxicity and/or progression of the disease and/or withdrawal of consent occurs.

The administration of a new cycle should be delayed if the criteria in the table below are not met on the corresponding Day 1 of the next administration. Parameters will be reevaluated at minimum intervals of 48 hours. The new cycle will be started upon recovery of these parameters. A maximum delay of 15 days will be allowed for recovery from drug-related adverse events. If recovery has not occurred after a 15-day delay, the patient should discontinue the treatment, except in case of obvious patient benefit at the criteria of the Investigator and upon agreement with the Sponsor.

After delaying doses due to drug-related toxicity (except for neutropenia exclusively) exceeding the 15-day delay, or in</td></tr>
</table>

patients who experience a DLT, treatment may continue after appropriate dose reduction of PM01183, appropriate secondary prophylaxis with G-CSF (when due to neutropenia exclusively), or doxorubicin interruption (i.e., due to cardiac toxicity or maximal cumulative dose reached).

Criteria for Treatment Continuation

	PM01183	**Doxorubicin**
	Day 1	**Day 1**
ANC	≥ 1.5 x 10^9/l	≥ 1.5 x 10^9/l
Platelets	≥ 100 x 10^9/l	≥ 100 x 10^9/l
Hemoglobin	≥ 9 g/dl	≥ 9 g/dl
Total bilirubin (or direct bilirubin)	≤ 1.5 x ULN (≤ ULN)	≤ 1.5 x ULN (≤ ULN)
AST/ALT	≤ 3.0 x ULN	≤ 3.0 x ULN
Albumin	≥ 3.0 g/dl.	≥ 3.0 g/dl.
ECOG PS	0-2	0-2
Calculated CrCl (Cockcroft and Gault's formula)	≥ 30 ml/min	≥ 30 ml/min
Muscular toxicity (myalgia, muscular weakness, CPK increase)	Grade ≤ 1	Grade ≤ 1
Other non-hematological drug-related AEs (except increased GGT, not optimally treated nausea and vomiting , alopecia, asthenia and/or neuropathy) [a]	Grade ≤ 1	Grade ≤ 1
Mucositis	Grade ≤ 1	Grade ≤ 1
Signs and/or symptoms of CHF	-	No
Current cumulative doxorubicin-equivalent dose < 400 mg/m^2 [b]	-	Yes

If a patient does not meet the requirements for treatment continuation (excluding cardiac toxicity and/or maximal doxorubicin cumulative dose) on Day 1 of further cycles, both drugs (PM01183 and doxorubicin) infusions will be withheld until recovery for a maximum of 15 days after the theoretical treatment date. If recovery has not occurred after a delay of > 15 days, the patient must be withdrawn from the trial, except in case of perceived clinical benefit from the Investigator and upon agreement with the Sponsor.
If a patient does not meet the requirements for treatment continuation due to cardiac toxicity and/or maximal doxorubicin cumulative dose, doxorubicin will be permanently discontinued and treatment may continue with PM01183 alone at its single-agent RD, 7.0 mg FD q3wk, without any delay if clinically appropriate.

a Any grade accepted for increased GGT. Up to grade 2 for alopecia, nausea, vomiting, neuropathy and asthenia.

b The total doxorubicin cumulative dose received by each patient must never reach > 450 mg/m^2.

AEs, adverse event(s); ALT, alanine aminotransferase; ANC, absolute neutrophil count; AP, alkaline phosphatase; AST, aspartate aminotransferase; CHF, congestive heart failure; CPK, creatine phosphokinase; CrCl, creatinine clearance; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; FD, flat dose; GGT, gamma-glutamyltransferase; q3wk, every three weeks; ULN, upper limit of normal.

Dose reduction

Treatment after DLT, a treatment-related infusion delay greater than 15 days, or toxicity considered as unacceptable by the investigators may continue, after appropriate dose reduction, only if there is clear evidence of objective patient benefit. This will always be discussed with the Sponsor. Under this circumstance, and following recovery to pre-specified re-treatment criteria, patients will be re-treated at the immediately lowest dose level. If

	dose reduction beyond DL-1 is required, the dose of PM01183 may be reduced by an additional 0.5 mg (FD). Up to two individual dose reductions will be allowed per patient; any patients requiring more than two dose reductions will be withdrawn from the study. Once the dose has been reduced for an individual patient, it will not be re-escalated again under any circumstances. Patients requiring dose reduction exclusively due to grade 4 neutropenia or any grade febrile neutropenia that occurred during the preceding cycle may receive secondary prophylaxis with G-CSF instead of a dose reduction. If toxicity re-occurs despite G-CSF use, dose reduction will then be implemented. Patients who reach a maximal cumulative dose of 450 mg/m^2 of doxorubicin or have to discontinue doxorubicin due to a cardiac AE may continue receiving treatment with PM01183 (after Cycle 1) at the single-agent RD (7 mg FD q3wk) if patient benefit is perceived. These patients do not need to be replaced. **New cohort after implementation of Amendment #3:** Patients with SCLC and endometrial cancer included in the new cohort after implementation of Amendment #3 who require dose reduction due to the reasons described above will be re-treated at the following dose levels: • DL-1: Doxorubicin 40 mg/m^2 + PM01183 1.5 mg/m^2. • DL-2: Doxorubicin 30 mg/m^2 + PM01183 1.5 mg/m^2. Up to two sequential dose reductions will be allowed per patient; any patients requiring more than two dose reductions will be withdrawn from the study, except if there is objective clinical benefit or upon the Sponsor's agreement. Once the dose has been reduced for an individual patient, it will not be re-escalated again under any circumstances. Patients included in this cohort who have received ten cycles of the doxorubicin/PM01183 combination or have to discontinue doxorubicin due to a cardiac AE may continue receiving treatment with single-agent PM01183 at 4.0 mg/m^2 q3wk if patient benefit is perceived. These patients do not need to be replaced. Patients treated with single-agent PM01183 who require dose reduction due to the reasons described above will have their dose reduced by 25%. Up to two sequential dose reductions will be allowed per patient; any patients requiring more than two dose reductions will be withdrawn from the study, except if there is objective clinical benefit or upon the Sponsor's agreement.
PHARMACOKINETICS	The plasma PK of doxorubicin and PM01183 will be evaluated during Cycle 1 with a schedule of 16 samples. The sampling schedule will be as follows, taking as reference the doxorubicin administration:

	• Sample #1: before administration. • Sample #2: 5 minutes after administration; sample for doxorubicin determination only. • Sample #3: 30 minutes after administration. • Sample #4: 55 minutes after administration [i.e., 5 minutes before PM01183 end of infusion (EOI)]. • Sample #5: 1.5 hours after administration. • Sample #6: 2 hours after administration. • Sample #7: 2.5 hours after administration. • Sample #8: 3 hours after administration. • Sample #9: 4 hours after administration. • Sample #10: 5 hours after administration. • Sample #11: 6 hours after administration. • Sample #12: 8 hours after administration. • Sample #13: 24 hours after administration. • Sample #14: 48 hours after administration. • Sample #15: 96 hours after administration. • Sample #16: 168 hours after administration; sample for PM01183 determination only. PK parameters will be calculated using non-compartmental analysis and population methods if appropriate, after pooling data from this study with data obtained during phase I studies to check any PK interaction.
PHARMACOGENOMIC EVALUATIONS	The aim of this investigation is to identify molecular markers whose expression may be associated with the clinical outcome of patients. These molecular markers might allow the identification of those patients who will benefit from PM01183 and doxorubicin treatment, thus improving the health care by an individualized medicine. The following analyses will be done on paraffin-embedded tumor tissue samples from consenting patients treated with PM01183 and doxorubicin: • Quantitation of XPG mRNA expression by real-time qRT-PCR and other genes related to the mechanism of action of PM01183 and doxorubicin. • Quantitation of XPG, TopoIIa and Pgp expression and other proteins related to the mechanism of action of PM01183 and doxorubicin by IHC in tumor tissue microarrays constructed from the patient's paraffin-embedded tumor tissue blocks. In those patients responding to treatment, Myriads Genetics Homologous Recombination Deficiency (HRD) assay, including analysis of BRCA1 mutation status, will be performed, if considered relevant.
STATISTICAL METHODS	**<u>Demographics:</u>** Descriptive statistics (mean, median, standard deviation and 95% confidence interval, range of value, frequencies and percentages) will be used. Tables will be displayed by dose level.

	Safety: Descriptive statistics will be used to characterize the profiles of drug-related AEs, drug-related deaths, serious adverse events (SAEs), drug-related delays, dose reductions, and/or treatment discontinuations. Tables will be displayed by dose level. **Efficacy analysis:** Response rates (percentage of patients with any response [partial response (PR) or complete response (CR): overall response rate], percentages for PR and CR separately, as well as percentage of patients with prolonged stable disease (SD) ≥ 4 months) will be characterized using descriptive statistics (95% exact binomial confidence interval). If any particular tumor type is adequately represented, time-related parameters (i.e., progression-free survival, overall survival) will be analyzed according to the Kaplan-Meier method, if appropriate. The characteristics of the patients achieving an objective response or SD ≥ 4 months by RECIST version 1.1., or a clinically significant improvement as measured by tumor markers, if applicable, will be displayed. In addition, patients with SCLC and endometrial cancer included in the new cohort after the implementation of Amendment #3 will be followed for survival for up to 18 months after the first study dose. **Pharmacokinetics:** The PK parameters will be tabulated and selected parameters will be graphically displayed per dose level. The dose-exposure relationships for maximum plasma concentration (C_{max}) and area under the curve (AUC) will be evaluated. The potential influence on selected PK parameters of selected demographic and clinical dichotomous variables (gender, laboratory test results above/below selected cutoff values, etc.) will be evaluated by Student`s t test or Mann-Whitney's U test as appropriate. For multinomial variables, analysis of variance will be used. For selected continuous demographic and clinical variables, relationship with selected PK parameters will be graphically explored and assessed using correlation and regression methods. **Pharmacogenomics:** RNA expression and IHC scoring will be performed blind, and clinical data compiled only after all analyses are completed. Fisher's exact test will be used to test whether a specific protein-expression profile is associated with the clinical outcome after treatment with PM01183 and doxorubicin. The prognosis value of markers will be explored for objective clinical response, progression-free survival and overall survival. In each case, if applicable, a multivariate model will be developed by backwards elimination, starting with all markers with a p-value lower than 0.10 in the univariate analysis. If applicable, hazard ratios will be calculated with the univariate Cox model, and comparison between Kaplan-Meier survival (whenever available) and progression-free survival curves will be performed with the log-

	rank test. All tests of statistical significance will be two-sided, and significance will be set at 0.05 except in multiple comparisons, where it will be set at 0.017 in accordance with the Bonferroni correction of type I error.
DURATION OF STUDY PERIOD (per patient)	Patients will be evaluated at scheduled visits in three study periods: • **Pre-treatment:** from signature of informed consent to first infusion of study drugs. • **Treatment:** from first infusion of study drugs to end of treatment. • **Follow-up**: after end of treatment, patients will be followed every four weeks until resolution to at least grade 1 or stabilization of all toxicities, if any. Patients who finish treatment without disease progression will be followed every two months until disease progression, other antitumor therapy, death or until the date of study termination (clinical cutoff), whichever occurs first. In the new cohort after the implementation of Amendment #3, patients with SCLC and endometrial cancer will be followed every three months until death or the date of study termination, whichever occurs first. Patients will be considered to be **on-study** from the signature of the informed consent to the end of the follow-up period. Patients will be considered to be **on-treatment** for the duration of their treatment and until the day of end of treatment. **End of treatment** is defined as 30 days after the treatment discontinuation, unless the patient starts a new antitumor therapy or dies (whichever occurs first). An end-of-treatment visit will be performed within 30 days (± 7 days) after last dose administration, unless the patient dies or 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 medications 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 fulfillment of appropriate re-treatment criteria and/or safety continuation of the study. • Patient refusal and/or non compliance with study requirements. • Treatment delay > 15 days due to toxicity (except clear clinical benefit, with the Sponsor's approval). • Requirement of > 2 dose reductions. • Specifically, doxorubicin will be continued before a maximal total cumulative dose of 450 mg/m^2 has been reached. Thus, a maximum of ten cycles of the combination will be administered to patients with SCLC and endometrial cancer

	included in the new cohort after implementation of Amendment #3), in absence of disease progression and/or unacceptable toxicity. Patients discontinuing doxorubicin at any time after Cycle 1 will remain on study as long as they continue receiving PM01183.
PLANNED TRIAL PERIODS	The total duration of the study will be approximately 72 months, including approximately a 54-month enrolment period. Consenting patients will be followed until disease progression, other antitumor therapy, death or until the date of study termination (clinical cutoff), whichever occurs first. In the new cohort after the implementation of Amendment #3, consenting patients with SCLC and endometrial cancer will be followed until death or the date of study termination (clinical cutoff), whichever occurs first. **Planned start date** (first patient on study): Second quarter (Q2) 2011. **Planned enrolment period**: 54 months. **Planned end-of-study date** (clinical cutoff): 18 months after the first study dose of the last patient or when follow-up of all SCLC and endometrial cancer patients included in the cohort after implementation of Amendment #3 has been completed, whichever occurs first.

SCHEDULE OF ASSESSMENTS AND PROCEDURES

Assessments and procedures	Screening	Treatment						Follow-up
		Cycle 1			Further cycles *		End of treatment	
		D1	D8	D15	D22	D10 †		
Written informed consent	Before any study procedures	-	-	-	-	-	-	-
PGx study informed consent	Before any study procedures	-	-	-	-	-	-	-
Demographic data	-14 to 0	-	-	-	-	-	-	-
Medical and cancer history / Baseline condition	-14 to 0	-	-	-	-	-	-	-
Assessment of signs and symptoms (1)	-14 to 0	-	-	-	•	-	• **(3)**	-
Complete physical examination, including weight and BSA (1,2)	-14 to 0	-	-	-	•	-	• **(3)**	-
Performance status (ECOG) (2)	-14 to 0	•	-	-	•	-	• **(3)**	-
Vital signs (heart rate, blood pressure, temperature) (2)	-14 to 0	•	-	-	•	-	• **(3)**	-
Hematology (1,2,4)	-7 to 0	-	•	•	•	•	• **(3)**	-
Biochemistry-A (1,2,4)	-7 to 0	-	•	•	•	•	• **(3)**	-
Biochemistry-B and coagulation (1,2)	-7 to 0	-	-	-	•	-	• **(3)**	-
Pregnancy test (if applicable) (2,5)	-14 to 0	Repeat if applicable					-	
ECG (2,6)	-7 to 0	Repeat at the time of doxorubicin discontinuation and whenever is clinically indicated **(7)**					• **(8)**	-
LVEF by ECHO or MUGA (2)	-14 to 0	Repeat at the time of doxorubicin discontinuation and whenever is clinically indicated **(7)**					• **(8)**	-
Clinical and radiological tumor assessment as per RECIST (2,9)	-28 to 0	Every 6 weeks (±2 weeks) (or every 2 cycles prior to infusion)					-	• **(10)**
Pharmacokinetics	-	Immediately before treatment and during Cycle 1 only					-	
Pharmacogenomics, if PGx consented (11)	If tumor samples are available	-					-	
Concomitant therapies (2)	-14 to 0	← Throughout the "on-treatment" phase →						-
Adverse events	NA	← Throughout the "on-treatment" phase →						• **(12)**

* Day 1 = day of treatment start. Day 22 = Day 1 of the next cycle.
† A ±3-day window will be allowed for Day 10 of any further cycle.

1. Repeat prior to first infusion, if treatment will be administered after more than the pre-specified screening period plus the allowed window.
2. A +3-day window will be allowed for laboratory procedures, a ±2-week window for radiological procedures, a +24-hour window for clinical assessments (ECOG, vital signs, ECG, weight, BSA, etc.), a +2-week window for LVEF assessments, and a ±7-day window for the assessments at end of treatment.
3. To be repeated only for those parameters for which no measurement is available at one week + 3 days before the end-of-treatment visit, or for those parameters with values that are out of range in the last assessment (grade > 1 according to NCI-CTCAE version 4).
4. If any suspected or possible treatment-related NCI-CTCAE grade ≥ 3 toxicity occurs, the abnormal test(s) should be re-assessed at least every 2-3 days until recovery to at least grade 1. In the event of febrile neutropenia of any grade, grade 4 neutropenia and/or grade 4 thrombocytopenia, re-assessment should be performed daily until recovery to at least grade 3 and/or until 24 hours after fever resolution, if applicable, and then every 2-3 days thereafter until recovery to at least grade 1.
5. Beta serum hCG.

6. It should allow rhythm definition (at least 30 seconds of duration).
    - PR interval.
    - RR interval.
    - QT interval (raw).
    - QRS complex duration.
7. To be repeated in patients in no acute distress within three weeks of the last doxorubicin dose ± 1 week.
8. To be repeated at end of treatment only in patients who did not receive single-agent PM01183 after discontinuing doxorubicin.
9. Helical contrast-enhanced CT-scan or gadolinium enhanced MRI as appropriate every six weeks (method should be always the same throughout the study for each individual patient). In case of objective tumor response, a copy of CT-scans or MRIs can be requested by the Sponsor.
10. Patients who discontinued treatment without progression will be followed every two months until disease progression, other antitumor therapy, death or until the date of study termination, whichever occurs first.

    In the new cohort after the implementation of Amendment #3, consenting patients with SCLC and endometrial cancer will be followed every three months until death or the date of study termination, whichever occurs first.
11. Tumor samples from patients treated with PM01183 and doxorubicin will be used to analyze the expression of putative markers of response/resistance to treatment. Paraffin-embedded tumor tissue samples obtained at diagnosis of the disease can be collected at any time during treatment.
12. Patients withdrawn with a drug-related AE should be followed until recovery to baseline or stabilization. Beyond 30 days after the last administration of study drug, only those procedures that are relevant to any remaining toxicities adverse event need to be performed.

    Study termination date is defined as 18 months after the first study dose of the last patient or when follow-up of all SCLC and endometrial cancer patients included in the cohort after implementation of Amendment #3 has been completed, whichever occurs first.

Hematology: Differential WBC, hemoglobin and platelets.

Biochemistry A: AST, ALT, total bilirubin (and direct, if total is abnormally elevated), AP, LDH, creatinine, glucose, CPK (and CPK-MB fraction if total CPK is abnormally high), serum electrolytes (Na^+, K^+, Cl^-).

Biochemistry B and coagulation: total proteins, albumin, Ca^{++}, CRP, coagulation tests (PT/INR, PTT). Only at baseline and to be repeated if clinically indicated: alpha-1 acid glycoprotein (AAGP), total cholesterol, LDL, triglycerides, Mg^{++} and amylase. Exploratory/validated serum tumor marker as clinically indicated [CA-125 (ovarian cancer), CEA and/or CA19-9 (gastric cancer), AFP (HCC), NSE (NET) and/or CA15-3 (breast cancer)]. Repeat serum tumor marker assessment only in patients with abnormally elevated values at baseline. **No serum markers will be evaluated in patients with SCLC and endometrial cancer included in the new cohort after implementation of Amendment #3.**

AE, adverse event; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BSA, body surface area; CA19-9 and 15-3, carbohydrate antigen 19-9 and 15-3, respectively; CEA, carcinoembryonic antigen; CPK, creatine phosphokinase; CRP, C-reactive protein; CrCl, creatinine clearance; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; GGT, gamma-glutamyltransferase; HCC, hepatocarcinoma; hCG, human chorionic gonadotropin; INR, international normalized ratio; LDH, lactate dehydrogenase; LDL, low density lipoprotein; LVEF, left vascular ejection fraction; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition scan; NA, not applicable; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NET, neuroendocrine tumor; NSE, neuron-specific enolase; PGx, pharmacogenomics; PT, prothrombin time; PTT, partial thromboplastin time; RECIST, Response Evaluation Criteria in Solid Tumors; SCLC, small cell lung cancer; WBC, white blood cell.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AAGP	Alpha-1 Acid Glycoprotein
ABP	Arterial Blood Pressure
ADR	Adverse Drug Reaction
AE(s)	Adverse Event(s)
AFP	Alpha-fetoprotein
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under The Curve
AUKPS	Adenocarcinoma of Unknown Primary Site
β-hCGs	Beta Subunit of Human Chorionic Gonadotropins
BSA	Body Surface Area
CA-125	Carbohydrate Antigen-125
CA15-3	Carbohydrate Antigen 15-3
CA19-9	Carbohydrate Antigen 19-9
CEA	Carcinoembryonic Antigen
CHF	Congestive Heart Failure
CI	Combination Index
CL	Clearance
C_{max}	Maximum Plasma Concentration
CPK	Creatine Phosphokinase
CR	Complete Response/Complete Regression
CrCl	Creatinine Clearance
CRF	Case Report Form
CRP	C-reactive Protein
CT-scan	Computed Tomography Scan
d/D	Day(s)
DI	Dose Intensity
DL	Dose Level
DLT	Dose-limiting Toxicity
DNA	Deoxyribonucleic Acid
DSB	Double-strand Breaks
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group

EOA	End of Administration
EOI	End of Infusion
ER	Estrogen Receptor
FD	Flat Dose
FUP	Follow-up
G-CSF	Granulocyte Colony-stimulating Factor
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
GEP	Gene Expression Profiling
GEP-NET	Gastroenteropancreatic Neuroendocrine Tumors
GGT	Gamma-glutamyltransferase
GIST	Gastrointestinal Stromal Tumors
GM-CSF	Granulocyte/Macrophage Colony-stimulating Factor
GMT	Greenwich Meridian Time
HCC	Hepatocellular Carcinoma
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HRD	Homologous Recombination Deficiency
HR	Heart Rate; Homologous Recombination
IB	Investigator's Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committees
IG_{50}	Concentration that Result in 50% of Cell Growth Inhibition
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IUD	Intrauterine Contraceptive Device
i.v.	Intravenous (intravenously)
k	Terminal Rate Constant
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LHRH	Luteinizing Hormone-releasing Hormone
LVEF	Left Ventricular Ejection Fraction
ml	Milliliter
MMR	Mismatch Repair
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose

MUGA	Multiple-gated Acquisition Scan
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NER	Nucleotide Excision Repair
NET	Neuroendocrine Tumor
NSE	Non-specific Enolase
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
Pgp	P-glycoprotein
PGx	Pharmacogenomic(s)
PhV	Pharmacovigilance
PK	Pharmacokinetic(s)
PR	Partial Response
PRE TT	Pre-treatment
PrP	Progesterone Receptor
PS	Performance Status
Pt/Pts	Patient/Patients
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
q3wk	Every 3 Weeks
qRT-PCR	Quantitative Reverse Transcriptase Polymerase Chain Reaction
RD	Recommended Dose
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic Acid
RT	Radiotherapy
SAE(s)	Serious Adverse Event(s)
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Half-life
TGD	Tumor Growth Delay
TopoIIa	Topoisomerase IIa
TT	Treatment
Uk	Unknown
UK	United Kingdom
ULN	Upper Limit of Normal
V_{ss}	Volume of Distribution at Steady State
V_z	Volume of Distribution Based on the Terminal Half-life

WBC	White Blood Cells
WMA	World Medical Association

1. INTRODUCTION

1.1 BACKGROUND

Despite recent advances in the treatment of cancer, advanced (metastatic) disease remains mostly incurable and there is an urgent need for developing new therapeutic options for these patients, particularly including investigational drugs with novel mechanism of action. The introduction of new combination regimens of non-cross-resistant chemotherapy agents with acceptable toxicity profiles is a major way to improve the outcome of patients with advanced solid tumors.

1.2 INFORMATION ON STUDY DRUG: PM01183

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

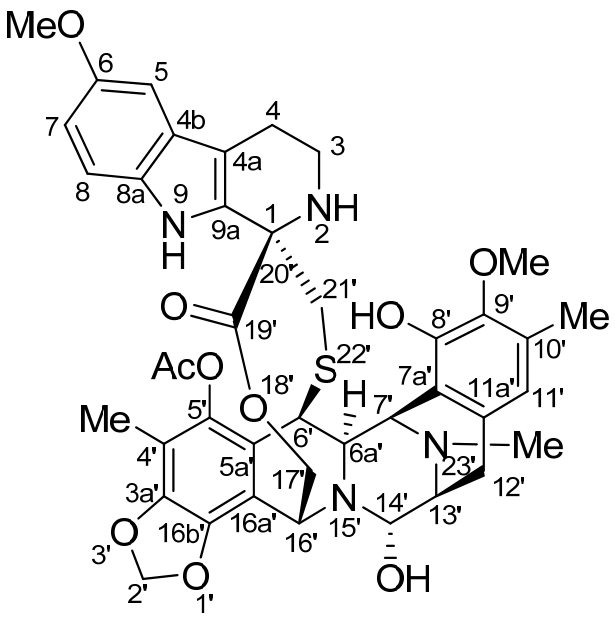
1.2.1 Name and Chemical Information

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 PM01183: $C_{41}H_{44}N_4O_{10}$ S



1.2.2 Non-clinical Data

PM01183 is a new chemical entity, structurally related to trabectedin that binds the DNA, leading to the formation of DNA double-strand breaks (DSBs), thus inducing apoptosis and delaying progression through the cell cycle S/G2 phase. The binding to DNA likely occurs in the minor groove region.

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 the other drugs. It only showed a positive correlation (S-rank > 0.8) with trabectedin (1).

In vitro, PM01183 demonstrated cytotoxic effects against a broad selection of tumor types with half maximal inhibitory concentration (IC_{50}) values in the low to very low nanomolar range (approximately median IC_{50} of 1^{-10} M). These PM01183 concentrations are far achievable, by two or three logarithms, in the plasma of patients in the clinical setting at the single-agent recommended dose (RD). Although some selectivity was also seen, a clustering of sensitive tumors has not been identified yet. PM01183 also exhibits *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 (Table 1), which were exposed to a range of PM01183 concentrations for 72 hours and then assayed for viability by a MTT short-term assay (2).

Table 1. Selected *in vitro* activity of PM01183.

Type	Tumor	Cell line	IG_{50} (M)
Solid	Breast	BT-474	$1.3 \cdot 10^{-9}$
		MDA-MB-231	$3.5 \cdot 10^{-9}$
		MCF-7	$1.7 \cdot 10^{-9}$
	Kidney	Caki-1	$1.7 \cdot 10^{-9}$
		RXF 393	$8.6 \cdot 10^{-10}$
	Liver	HepG2	$3.1 \cdot 10^{-9}$
		SK-HEP-1	$3.1 \cdot 10^{-9}$
	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	$2.9 \cdot 10^{-9}$
Non-solid	Leukemia	K-562	$1.6 \cdot 10^{-9}$
		MOLT-4	$1.1 \cdot 10^{-9}$

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

The *in vivo* "Proof of Concept" for PM01183 was first accomplished by using a panel of six human tumor types, i.e., breast, colon, gastric, ovarian, prostate, and renal. The resulting tumor susceptibility was analyzed in xenografts grown in athymic mice, when unformulated PM01183 was administered at the 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, colon, gastric and kidney xenografts at different time points during the experiment (3).

PM01183 was further evaluated for *in vivo* activity in bladder, breast, kidney, lung, ovary, pancreas and prostate xenografted models (4-11). In summary, PM01183 demonstrated antitumor activity in breast, kidney, ovary and lung, but had moderate antitumor activity against bladder, pancreas and prostate xenografted models.

Finally, PM01183 was also evaluated for *in vivo* activity, by using the M5076 sarcoma model that spontaneously metastasizes in the liver of tumor-bearing female C57Bl/6 mice (12). PM01183 was administered i.v. at a dose of 0.2 mg/kg/day (0.6 mg/m^2/day) for three consecutive weeks. Results showed marginal activity as evaluated by tumor growth inhibition. However, PM01183 statistically significantly reduced the number of liver metastasis compared to placebo-treated animals.

Toxicology studies in rats and dogs showed that the main target organs were the bone marrow and the liver. In particular, the effect of a single bolus injection of PM01183 on cardiovascular parameters [arterial blood pressure (ABP), heart rate (HR) and lead II electrocardiogram (ECG)] was evaluated in conscious, telemetered dogs for six hours (13). 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). When the dogs received an actual dose of 0.023 mg/kg (0.46 mg/m^2), they showed a short-lasting tachycardia during the first 30 minutes after administration (mean increase of 89% after one minute, followed by rapid normalization). Although a direct pharmacological effect of PM01183 cannot be ruled out, other factors contributing to an increase in HR should be considered, such as vomiting episodes (in three of four animals) and/or increasing pain related to PM01183, especially in the sequential, dose-increase design of this study. Moreover, two different toxicity studies found no electrophysiological alterations in the HR and the ECGs of dogs following single or repeated PM01183 administration at doses up to 0.05 mg/kg (1 mg/m^2) (14, 15).

1.2.3 Clinical Data

Based on the promising preclinical results described above, the first-in-human phase I clinical study with PM01183 was started in March 2009. Accrual was closed in September 2010, after 31 relapsed/refractory cancer patients with no available standard therapy had been treated. The primary endpoint was to find a safe RD for phase II studies of single-agent PM01183 when administered as a 1-hour i.v. infusion on Day 1 every three weeks (q3wk). The RD was established at 4.0 mg/m^2/q3wk; however, PM01183 clearance was found to be unrelated to body surface area (BSA), and therefore all patients treated at the RD in this study's expansion cohort were treated at a flat dose (FD) of 7.0 mg as a 1-hour i.v. infusion q3wk (16). The median terminal plasma half-life at the RD was 62 hours and interindividual variability was high.

One of the 15 patients treated at the RD experienced a dose-limiting toxicity (DLT) during their first cycle (grade 4 thrombocytopenia). Toxicity was generally mild and reversible. Standard antiemetic prophylaxis was required at the RD in order to avoid grade 2 nausea and vomiting. Myelosuppression, particularly non-complicated short-duration grade 4 neutropenia, was the most relevant toxicity (in up to 40% of the patients treated at the RD). It was also predictable and easily manageable; it caused no delays and all patients recovered by Day +22. Neutropenia nadir occurred during the second week (median on Day +13) and lasted a median of 3 days without granulocyte colony-stimulating factor (G-CSF) treatment. The severity of the neutropenia correlated better with the observed area under the curve (AUC) concentration than with the dose

administered. Other drug-related toxicities found at the RD were transient and reversible mild transaminase increases, asthenia, diarrhea, mild nausea and anemia. Neither treatment-related deaths nor signs of potential cardiac toxicity were observed in this population of pretreated patients (a median of 2 prior lines per patient, range, 1-7). In conclusion, treatment with PM01183 was very well tolerated by most patients.

Regarding the antitumor clinical activity of PM01183, ten of the 15 patients treated at the RD were evaluable for efficacy at the time of the latest clinical cutoff (September 2010). The majority of these patients had advanced colorectal cancer, and no hints of clinical activity were seen in this particular subgroup. Nevertheless, one patient with a pancreatic adenocarcinoma showed a confirmed partial response (PR) as per Response Evaluation Criteria In Solid Tumors (RECIST) after only three cycles of PM01183; in addition, this patient showed normalization of serum tumor marker [carbohydrate antigen 19-9 (CA19-9)] levels after the fourth cycle, and was still ongoing at the clinical cutoff. Three other patients with progressing tumors (one melanoma and two soft tissue sarcomas) at study entry had clinically meaningful disease stabilizations with tumor shrinkage lasting more than three months and were still on treatment at the clinical cutoff, having received 13+, 6+ and 4+ cycles, respectively. This further reinforces the finding that clinically active PM01183 concentrations are achieved at a safe and tolerable dose and schedule.

1.3 INFORMATION ON STUDY DRUG: DOXORUBICIN

Doxorubicin (hydroxyldaunorubicin) is one of the anthracyclines most widely used in onco-hematology worldwide. Alone or, more frequently, in combinations, anthracyclines are commonly used to treat a variety of advanced malignancies, from acute leukemias (17) or lymphomas (18, 19), to solid tumors such as breast cancer (20), soft-tissue and bone sarcomas (21, 22), ovarian cancer (23), small cell lung cancer (24), hepatocellular carcinoma (25), gastric cancer (26), neuroendocrine tumors (27) and adenocarcinoma of unknown primary site (AUKPS) (28).

Doxorubicin primarily acts by inhibiting DNA synthesis through intercalation between DNA base pairs and forming a complex with topoisomerase II (topoII), one of the enzymes responsible for uncoiling the double helix at the early beginning of the S-phase of the cell cycle. It also generates free radicals (similarly to ionizing radiation), which can also generate direct or indirect DNA damage (29). Several mechanisms of primary or acquired tumor resistance have been described for anthracyclines, such as overexpression of P-glycoprotein (which also confers resistance to many other widely used drugs), increased intracellular radicals scavengers such as gluthathione synthesis, mutations and/or post-transcriptional changes in its main target (topoII), and also loss of other important proteins involved in DNA repair and apoptosis signals such as mismatch repair (MMR) deficiency (30); however, the relative clinical relevance of each one is difficult to determine.

The main DLT of doxorubicin is neutropenia, with the nadir occurring between Days 10-14 and usually recovering by Day 21. To a slight degree, it also induces anemia and thrombocytopenia. However, the most characteristic toxicity of anthracyclines is a dose cumulative and schedule-dependent cardiac toxicity. In effect, the risk of developing a congestive cardiac failure starts to rise steeply, over 10%, after a total cumulative dose of over 450 mg/m^2 (31). Thus, the strategy to not exceed this dose in a patient during his/her lifetime does not remove the risk completely, but it keeps it acceptably low.

Alternatively, co-administration with dexrazoxane (a chelating agent), and/or special formulations such as liposomal encapsulated has shown some advantages and allows to increase (although marginally) the maximal deliverable dose. Other cardiotoxics such as ionizing radiation or trastuzumab have been shown to increase doxorubicin cardiotoxicity as well, and therefore they are not used concomitantly (32). Other common adverse events related to doxorubicin include nausea and vomiting, diarrhea, reversible alopecia and mucositis; in addition, it is a highly vesicant agent if extravasation occurs.

A dose-response relationship has been shown for anthracyclines in breast cancer patients (33); however, no consistent advantage has been observed in the use of doxorubicin at doses over 50 mg/m^2 per cycle (34) when combined with other agents, and doses over 60 mg/m^2 in combination usually require G-CSF support (35).

1.4 INFORMATION ON THE COMBINATION OF PM01183 AND DOXORUBICIN

The *in vivo* antitumor activity of PM01183 administered alone and in combination with doxorubicin was investigated in mice bearing A2780 xenografted tumors (36). Treatments administered were: i) placebo; ii) PM01183 at four different dose levels, i.e. the maximum tolerated dose (MTD) (0.180 mg/kg), 0.75·MTD, 0.5·MTD and 0.25·MTD; iii) doxorubicin at four different dose levels, MTD (8 mg/kg), 0.75·MTD, 0.5·MTD and 0.25·MTD; and, iv) PM01183 plus doxorubicin, administered with the combination at (1+1), (0.75+0.75), (0.50+0.50) and (0.25+0.25) of their respective MTDs. Doxorubicin was found to induce modest and dose-dependent antitumor activity in A2780-bearing animals; tumors were significantly ($P < 0.05$) smaller with doxorubicin than with placebo in all groups, except at the lowest dose level. The highest-dosed cohort also showed modest tumor growth delay (TGD), which was calculated as 90.0%. Single therapy of PM01183 in mice bearing A2780 xenografts resulted in very modest antitumor activity: only animals dosed at the two highest levels had tumors significantly ($P < 0.05$) smaller than placebo-treated mice. However, the combination of PM01183 and doxorubicin showed strong and dose-dependent antitumor activity: all groups of animals treated with the combination (except the lower) showed a highly significant ($P < 0.01$) reduction of tumor volume compared to placebo-treated animals. Of note, the group treated at (1+1)·MTD experienced a TGD of 184.0%. The antitumor effect induced by any treatment (single-agent or combination) was analyzed using the median-effect principle (37). The results suggested a synergistic combination index (CI), with values ≤ 1, in mice bearing ovarian (A2780) xenografted tumors.

1.5 STUDY RATIONALE

PM01183 is a new chemical entity with promising *in vitro* and *in vivo* cytotoxic activity at clinically achievable concentrations. Its mechanism of action and main target is likely different to that of doxorubicin. Evidence of synergistic antitumor activity has been observed *in vivo* with the combination. Preclinically, a pattern of cytotoxic activity overlaps significantly for both compounds, whereas the clinical toxicity of each compound does not seem to overlap completely, according to currently available data. Therefore, it is feasible to evaluate the safety and efficacy of a combination of PM01183 and doxorubicin in non-heavily pretreated candidate patients with advanced cancer.

The first phase I clinical study revealed that a RD of 7.0 mg for PM01183 when given as single-agent as a 1-hour i.v. infusion q3wk (16) was safe, tolerable and mostly induced a predictable, manageable and reversible myelosuppression that correlated to the drug's AUC. Based on these results, a dose equivalent to 50% of this RD was chosen as a safe starting dose of PM01183 for its combination with doxorubicin. Moreover, the targeted non-heavily pretreated patient population (with no more than two prior lines of chemotherapy per patient) will adequately represent the median treatment lines of those patients already treated in the first study with PM01183 for whom tolerance has been excellent.

The doxorubicin dose of 50 mg/m^2/cycle, which is the standard dose for the drug when used in combination schedules, will be fixed throughout the study so as to prevent undertreatment of patients at potentially inadequate doses. The decision to not escalate doxorubicin is well justified in the literature, as higher doses are unlikely to provide additional clinical benefit.

The tumor type selection in this study is based on the standard clinical use of doxorubicin in solid tumor patients as well as on preclinical evidence of potential activity of PM01183. The higher likelihood of clinical benefit in these patients will provide a chance for assessing the tolerability and feasibility of the combination regimen both in the short and the median term.

1.5.1 Pharmacogenomics Rationale

The antitumor activity of PM01183 is associated with the following cell events, as described in Leal *et al.* (38):

- 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 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 5,000 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 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 to PM01183, in order to implement a customized therapy in the future.

Initially the mRNA expression of XPG will be determined in paraffin-embedded tumor tissue blocks from consenting patients treated with PM01183 and doxorubicin. Depending on the availability and quality of the samples, the RNA expression analysis could be extended to other genes involved in the mechanism of action of PM01183 and/or doxorubicin. In addition, a tissue microarray containing representative sections of the patients' paraffin-embedded tumor tissue blocks will be constructed and analyzed for protein expression of the key suppressor gene Topoisomerase II (TopoIIa) and P-glycoprotein (Pgp) by immunohistochemistry (IHC) using specific antibodies. As for RNA, protein expression analyses could be extended to other proteins involved in the mechanism of action of PM01183 and/or doxorubicin.

2. STUDY OBJECTIVES

2.1 PRIMARY

- To determine the MTD and the RD of PM01183 in combination with doxorubicin in patients with selected advanced solid tumors.

2.2 SECONDARY

- To determine the MTD and the RD of PM01183 in combination with doxorubicin and primary prophylaxis with G-CSF in patients with selected advanced solid tumors (if DLTs of the combination without G-CSF prophylaxis are exclusively related to neutropenia).
- To characterize the safety profile and feasibility of this combination in patients with selected advanced solid tumors.
- To characterize the pharmacokinetics (PK) of this combination and to detect major drug-drug PK interactions.
- To obtain preliminary information on the clinical antitumor activity of this combination in non-heavily pretreated selected solid tumor patients.
- Based on promising findings, to explore the feasibility, safety and efficacy of a potential improvable dose of this combination in selected tumor types [i.e. small cell lung cancer (SCLC) and endometrial cancer).
- To evaluate the pharmacogenomics (PGx) in tumor samples of patients exposed to PM01183 and doxorubicin at the RD in order to assess potential markers of response and/or resistance.

3. OVERALL STUDY DESIGN

Prospective, open-label, dose-ranging, uncontrolled phase I study with escalating doses of PM01183 in combination with fixed doses of doxorubicin (see escalation dose scheme in Section 3.3).

Patients will start receiving i.v. doxorubicin 50 mg/m^2 (fixed dose) as bolus followed by PM01183 3.5 mg FD i.v. over one hour on Day 1 q3wk. A cycle is defined as an interval of three weeks.

Cohorts of three to six patients will be included at each dose level (DL). If no DLT occurs in more than one patient within each cohort, escalation will proceed to the following dose level. If one of the first three evaluable patients experiences a DLT, the dose level should be expanded up to six patients. The MTD will be the lowest dose level explored during the dose escalation at which more than one evaluable patient experience a DLT in Cycle 1. All evaluable patients within a dose level will be followed for at least one cycle (i.e., three weeks) before dose escalation may proceed. Dose escalation will be terminated once the MTD or the last dose level (DL4) is reached, whichever occurs first, except if all DLTs occurring at a given dose level are related to neutropenia (e.g., febrile neutropenia, grade 4 neutropenia lasting more than 7 days or neutropenic sepsis) in which case dose escalation may be resumed, starting at the lowest dose level where exclusively neutropenia-related DLTs have occurred, and will follow the same original schedule but with compulsory primary G-CSF prophylaxis. An expansion cohort to complete a minimum of nine evaluable patients will be recruited at the immediate lower dose level, or at the last dose level (DL4) if the MTD is not defined yet. This level will be confirmed as the RD if less than one third of the first nine evaluable patients experience DLT during Cycle 1.

Further to the finding of encouraging antitumor activity in the first 43 evaluable patients (13 responses, including four complete responses, with five partial responses in eight patients with small cell lung cancer, and one complete and one partial response in three patients with endometrial cancer), expansion of the cohort treated at the RD has been increased to include approximately 30 additional patients, for a total of around 39 patients.

In the event of DLTs occurring in the first patient at the first level, the second and third patients will be included at least two weeks apart. Otherwise and/or at subsequent dose levels, all patients within a dose level may be treated simultaneously.

Patients treated at the expansion cohort must be evaluable by the RECIST version 1.1 and/or by serum markers (carbohydrate antigen-125, CA-125) in the case of ovarian cancer, as appropriate [according to the Gynecologic Cancer Intergroup (GCIG) specific criteria] (see Section 9.7), and must have documented disease progression according to any of these criteria. The tumor type(s) that will be eligible to be included in the expansion cohort at the RD will be chosen according to the preliminary efficacy observed among those previously treated during the escalation phase, and will be discussed and agreed between the investigators and the Sponsor.

Intermediate dose levels could be tested on agreement between the Investigator and the Sponsor, if deemed appropriate.

Patients will receive PM01183 and doxorubicin until progression, unacceptable toxicity, consent withdrawal or while it is considered to be in their best interest. More specifically, doxorubicin will be administered in the absence of disease progression or unacceptable toxicity until a maximal total cumulative dose of 450 mg/m^2 is reached; once this dose has been reached, the patients may continue treatment with PM01183 alone at the established single-agent RD, 7.0 mg FD q3wk. Tumor assessments will be done every six weeks while on treatment. After treatment discontinuation, patients will be followed every four weeks until resolution or stabilization of all toxicities, if any.

Patients discontinuing treatment without progression will be followed every two months until disease progression, other antitumor therapy, death or the date of study termination, whichever occurs first (see Section 5.9).

Antitumor response will be assessed using the RECIST version 1.1 and/or serum tumor markers as appropriate (e.g., ovarian cancer markers).

Patients will be evaluated at scheduled visits on three study periods: Pre-treatment, Treatment and Follow-up (see Section 5.2).

In addition, a new cohort of 20 evaluable patients with small cell lung cancer (SCLC) who failed after first-line standard cytotoxic-containing therapy and at least nine evaluable patients with endometrial cancer will be included to further define the efficacy, safety and feasibility of a doxorubicin dose adaptation. These patients will be treated with doxorubicin at 40 mg/m^2 administered as an i.v. bolus/short infusion followed by PM01183 at 2.0 mg/m^2 as a 1-hour i.v. infusion on Day 1 q3wk. The administered doses of both PM01183 and doxorubicin will be capped at 2.0 m^2 of body surface area (BSA) for any patients exceeding this BSA value. Patients in this cohort who have received ten cycles of the doxorubicin/PM01183 combination or have to discontinue doxorubicin due to a cardiac AE may continue receiving treatment with single-agent PM01183 at 2.0 mg/m^2 q3wk if patient benefit is perceived according to the Investigator. These patients will be followed every three months until death or the date of study termination, whichever occurs first.

3.1 PRIMARY ENDPOINT

3.1.1 Determination of MTD and RD

An evaluable patient for the main objective of the study (i.e., the determination of the MTD and RD) should have received at least one complete cycle (including observation period), except if early discontinuations or missed doses and/or assessments were the consequence of drug-related toxicity (excluding hypersensitivity reactions and/or extravasations).

As shown in Table 2, a minimum of three patients will be included at each DL. If no patients experience a DLT during Cycle 1, the dose will be escalated. If one of three patients experiences a DLT, three additional patients will be included at that level. If >1 evaluable patient during dose escalation at a given DL experience a DLT during Cycle 1, that DL will be considered the MTD and dose escalation will be terminated, except if all DLTs are related to neutropenia exclusively, in which case dose escalation may be resumed as originally planned in a new cohort of patients but with compulsory primary G-CSF prophylaxis. The DL immediately below the MTD, or DL4 if the MTD is not yet defined during dose escalation before the last DL (i.e., DL4) is reached, was to be initially expanded up to a minimum of nine evaluable patients. If less than three among the first nine evaluable patients treated within the expansion cohort experience a DLT during Cycle 1, this DL will be the RD.

Further to the finding of encouraging antitumor activity in the first 43 evaluable patients (13 responses, including four complete responses, with five partial responses in eight patients with small cell lung cancer, and one complete and one partial response in three patients with endometrial cancer), expansion of the cohort treated at the RD has been

increased to include approximately 30 additional patients, for a total of around 39 patients.

Table 2. Determination of the maximum tolerated dose.

No. of patients evaluable* for DLT	No. of patients with DLTs in first cycle	Action
3	0	Escalate DL until DL4 is reached
	1	Add 3 patients
	>1	MTD
6	1	Escalate DL until DL4 is reached
	>1	MTD

DL, dose level; DLT, dose-limiting toxicities; MTD, maximum tolerated dose.
* Patients not evaluable for DLT during dose optimization must be replaced.

Decisions on delayed-onset DLTs (i.e., those DLTs occurring after Cycle 1) will be individually discussed between the Investigators and Sponsor, and might end affecting the definition of the proposed RD for phase II clinical trials.

In the new cohort of patients with SCLC and endometrial cancer after implementation of Amendment #3, a patient evaluable for efficacy should have received at least one complete cycle (including observation period) and be evaluable as per RECIST, except if non-evaluability is due to treatment failure such as drug-related toxicity, death or early unequivocal PD outside the central nervous system.

Definition of Dose-limiting Toxicities

DLTs are defined as adverse events (AEs) and laboratory abnormalities related to the study treatment during the first cycle of treatment and fulfilling at least one of the criteria outlined below.

- Grade 4 neutropenia [absolute neutrophil count (ANC) < 0.5 x 10^9/l] lasting > 7 days.
- Grade ≥ 3 febrile neutropenia of any duration or neutropenic sepsis.
- Grade 4 thrombocytopenia (platelet count < 25 x 10^9/l) or grade 3 with any major bleeding episode requiring a platelet transfusion.
- Grade 4 alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) increase, or grade 3 lasting > 14 days.
- Treatment-related grade ≥ 2 ALT or AST increase concomitantly with ≥ 2 times the upper limit of normal (ULN) total bilirubin increase and normal alkaline phosphatase (AP).
- Grade ≥ 3 creatine phosphokinase (CPK) increase.
- Any other grade 3/4 non-hematological AE that is suspected to be related to study drug(s), except nausea/vomiting (unless the patient is receiving an optimal anti-emetic regimen), hypersensitivity reactions, extravasations, grade 3 asthenia lasting less than one week, and non-clinically relevant isolated biochemical

abnormalities [e.g., isolated increase in gamma-glutamyltransferase (GGT)]. In any case, the clinical relevance should be discussed between the Investigators and Sponsor's representatives.

- Delay in the administration of Cycle 2 of the combination exceeding 15 days of the theoretical date (i.e., Day 22), due to any AEs related to study drug(s).
- The following circumstances will be discussed between the Principal Investigator and the Sponsor, and the final consensus will be documented:
  - DLTs with delayed onset (i.e., that occur after Cycle 1).

3.2 SECONDARY ENDPOINTS

3.2.1 Safety

Patients will be evaluable for safety if they have received at least one partial or complete infusion of PM01183. AEs will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4. For further details on safety evaluation see Section 9.2.

3.2.2 Pharmacokinetics

PK analyses will be evaluated in plasma by standard non-compartmental methods (population compartmental modeling may be performed if appropriate) (see Section 9.6 for PK evaluation).

3.2.3 Efficacy

Although it is not the main objective of this study, antitumor activity will be measured according to the RECIST version 1.1 at least six weeks after treatment initiation in all patients with measurable disease, or by evaluation of serum tumor markers if applicable (e.g., ovarian cancer markers). Patients included at the RD in the expansion cohort must be evaluable per RECIST version 1.1 or by evaluation of tumor markers (see Section 9.7 for efficacy evaluation).

In the new cohort after the implementation of Amendment #3, exploratory assessment for progression-free survival (PFS) and overall survival (OS) will be performed.

3.2.4 Pharmacogenomics

PGx will be evaluated from available tumor samples obtained at diagnosis in order to determine predictive/prognostic markers of response and/or resistance to PM01183 and doxorubicin in those patients that signed the Informed Consent for the PGx study (see Section 9.8 for evaluation of PGx).

3.3 DOSE ESCALATION SCHEDULE

Doxorubicin will be given at 50 mg/m² as an i.v. bolus on Day 1 q3wk, which corresponds to 100% of its actual RD when combined with other myelosuppressive agents. It will not be escalated in this study.

The starting dose (DL1) for PM01183 will be 3.5 mg given as FD on Day 1 q3wk, which corresponds to 50% of the RD for this schedule when given as single agent.

The dose escalation schedule is summarized in Table 3.

Table 3. Dose escalation schedule.

DL	No. of patients	Relative DI (%) of doxorubicin / PM01183	Dose of doxorubicin (mg/m^2) / PM01183 (mg FD) on Day 1 q3wk
DL-1	0-6	100 / 42.85	50 / 3.0
DL1	3-6	100 / 50	50 / 3.5
DL2	3-6	100 / 71.4	50 / 5.0
DL3	3-6	100 / 85.7	50 / 6.0
DL4	3-6	100 / 100	50 / 7.0

The DL-1 level is to be explored only if DL1 is defined as the MTD.
DI, dose intensity; DL, dose level; FD, flat dose.

According to the toxicity observed, intermediate dose levels may be explored if considered appropriate by the investigators and the Sponsor.

Intra-patient dose escalation will not be allowed under any circumstances.

3.3.1 Dose Escalation Meetings

The Sponsor will organize raw data review and discussion (e.g., a teleconference) with the phase I investigators on a regular basis as per protocol requirement (e.g., monthly or after first patient enrolled at a given dose level has completed the first cycle or when a dose level cohort has been completed). Prior to the meeting, all relevant safety and laboratory data must be collected and sent by the Investigators to the Sponsor's responsible. Investigators must guarantee the accuracy of the information provided against the source documents.

At the dose escalation discussion, the clinical course (safety information, including DLTs, all grade ≥ 2 toxicity data during Cycle 1, and available PK data) of each patient in the ongoing dose cohort will be described in detail. Updated safety data from other ongoing patients, including data collected in later treatment cycles, will be also discussed. The final decision to escalate dose will be based primarily, although not exclusively, on DLT information, but also on a clinical synthesis of all relevant toxicity observed (both DLT and non-DLT), treatment-related dose delays, PK and efficacy data, when available. The parties must reach a consensus on whether to further escalate the dose, or whether to de-escalate or expand recruitment into particular cohorts.

Finally, available slot assignment for the next cohort of patients to be included will also be updated during these discussions. The investigators will be responsible for informing the Sponsor of any potential candidate patients on screening at that time. The Sponsor will immediately update all investigators on slot availability as soon as a screening failure is notified.

The Sponsor will document the final agreement or decision adopted per dose level, irrespectively of the type of data review implemented in each particular case, and will keep the information and all support documents in the trial master file.

4. SELECTION OF PATIENTS

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

4.1 INCLUSION CRITERIA

1) Voluntarily signed and dated written informed consent prior to any specific study procedure.

2) Age: between 18 and 75 years (both inclusive).

   For patients with SCLC and endometrial cancer included in the new cohort after implementation of Amendment #3: age ≥ 18 years.

3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 1 (see APPENDIX 1).

   For patients with SCLC and endometrial cancer included in the new cohort after implementation of Amendment #3: ECOG PS ≤ 2.

4) Life expectancy ≥ 3 months.

5) Patients not previously treated with anthracycline-containing therapy for advanced disease (Note: adjuvant therapy with anthracyclines is allowed provided not more than 300 mg/m^2 of doxorubicin or an equivalent total cumulative dose was administered and they did not have to discontinue treatment due to any anthracycline-related toxicity, and relapse occurred more than six months after the last drug administration).

6) No more than two prior lines of cytotoxic-containing chemotherapy regimens for advanced disease.

   For patients with SCLC included in the new cohort after implementation of Amendment #3: no more than one prior line of cytotoxic-containing chemotherapy regimens for advanced disease.

7) Patients with a histologically/cytologically confirmed diagnosis of advanced disease of any of the following tumors:

   a) Breast cancer (non-candidate for hormone therapy alone: i.e., hormone-sensitive patients with bone-limited disease).

   b) Soft-tissue sarcoma [excluding gastrointestinal stromal tumors (GIST)].

   c) Primary bone sarcomas.

   d) Epithelial ovarian cancer (including primary peritoneal disease and/or fallopian tube carcinomas and/or endometrial adenocarcinomas).

   e) Hepatocellular carcinoma (HCC) (non-eligible for liver transplantation and Child-Pugh score A only). Elevated alpha-fetoprotein (AFP) levels in a patient with known risk factors and radiological findings compatible with HCC do not require pathological confirmation.

   f) Gastroenteropancreatic neuroendocrine tumors (GEP-NET).

g) Small cell lung cancer (SCLC).

h) Gastric cancer.

i) Bladder cancer.

j) Adenocarcinoma of unknown primary site (AUKPS).

8) **Expansion cohort at the RD:**

All patients must have:

a) Measurable disease according to RECIST version 1.1 (see APPENDIX 2); or

b) Evaluable disease by serum markers in the case of ovarian cancer (GCIG specific criteria) (see APPENDIX 3); and

c) Documented disease progression during or immediately after last therapy according to any of the aforementioned criteria.

9) **New cohort after implementation of Amendment #3:**

a) Measurable SCLC or endometrial cancer according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1; and

b) Documented disease progression during or immediately after last therapy according to any of the aforementioned criteria.

10) At least three weeks since the last anticancer therapy, including radiotherapy (RT), and at least six weeks since nitrosoureas and mitomycin C (systemic). In the case of hormone-sensitive breast cancer progressing while on hormone therapy, the latter must be either stopped up to one week before or continued during the trial.

11) Adequate bone marrow, renal, hepatic, and metabolic function (assessed ≤ 7 days before inclusion in the study):

a) Platelet count ≥ 100 x 10^9/l, hemoglobin ≥ 9.0 g/dl and ANC ≥ 1.5 x 10^9/l.

b) AST and ALT ≤ 3.0 x ULN, independently of the presence of liver metastases.

c) AP ≤ 2.5 x ULN (≤ 5 x ULN if disease-related).

d) Total bilirubin ≤ 1.5 x ULN or direct bilirubin ≤ ULN.

e) International Normalized Ratio (INR) < 1.5 (except if patient is on oral anticoagulation therapy).

f) Calculated creatinine clearance (CrCl) ≥ 30 ml/minute (using Cockcroft and Gault´s formula; see APPENDIX 4).

g) CPK ≤ 2.5 x ULN.

h) Albumin ≥ 2.5 g/dl.

For patients with SCLC and endometrial cancer included in the new cohort after implementation of Amendment #3: albumin ≥ 3.0 g/dl.

12) Recovery to grade ≤ 1 or to baseline from any AE derived from previous treatment (excluding alopecia and/or cutaneous toxicity and/or peripheral sensory neuropathy and/or asthenia, all grade ≤ 2).

13) Left ventricular ejection fraction (LVEF) by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan within normal range (according to institutional standards).

14) Women of childbearing potential must have a negative serum pregnancy test before study entry. Both women and men must agree to use a medically acceptable method of contraception throughout the treatment period and for six weeks after discontinuation of treatment. Acceptable methods of contraception include intrauterine device (IUD), oral contraceptive, subdermal implant and/or double barrier.

4.2 EXCLUSION CRITERIA

1) Concomitant diseases/conditions:
   a) History or presence of unstable angina, myocardial infarction, congestive heart failure, or clinically significant valvular heart disease within last year.
   b) Symptomatic arrhythmia or any uncontrolled arrhythmia requiring ongoing treatment.
   c) Ongoing chronic alcohol consumption, or cirrhosis with Child-Pugh score B or C.
   d) Active uncontrolled infection.
   e) Known human immunodeficiency virus (HIV) infection.
   f) Myopathy or any clinical situation that causes significant and persistent elevation of CPK (> 2.5 x ULN in two different determinations performed one week apart).
   g) Limitation of the patient's ability to comply with the treatment or follow-up 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) Symptomatic, progressive or corticosteroids-requiring documented brain metastases or leptomeningeal disease involvement.
3) Men or women of childbearing potential who are not using an effective method of contraception as previously described; women who are pregnant or breast feeding.
4) Patients who have had RT in more than 35% of the bone marrow.

   This criterion will **not** apply to patients with SCLC and endometrial cancer included in the new cohort after implementation of Amendment #3.
5) History of previous bone marrow and/or stem cell transplantation.
6) Treatment with any investigational product in the period of ≥ 5 half-lives of the investigational compound prior to the first infusion.

4.3 PATIENTS FOR THE PHARMACOGENOMIC STUDY

1) Patients with prior available tumor samples who are eligible for the trial will also be eligible for the PGx study.

2) Only patients who voluntarily sign the Informed Consent for the PGx study will participate. Refusal to participate in the PGx study will not affect patient participation in the clinical study PM1183-A-003-10.

5. PLAN OF THE STUDY

5.1 DURATION OF THE STUDY (WHOLE POPULATION)

The total duration of the study will be approximately 72 months, including approximately a 54-month enrolment period. Consenting patients will be followed until disease progression, other antitumor therapy, death, or until the date of study termination (clinical cutoff), whichever occurs first.

In the new cohort after the implementation of Amendment #3, consenting patients with SCLC and endometrial cancer will be followed until death or the date of study termination (clinical cutoff), whichever occurs first.

Planned start date (first patient on study): second quarter (Q2) 2011.

Planned enrolment period: 54 months.

Planned end-of-study date (clinical cutoff): 18 months after the first study dose of the last patient or when follow-up of all SCLC and endometrial cancer patients included in the cohort after implementation of Amendment #3 has been completed, whichever occurs first.

5.2 DURATION OF STUDY AND TREATMENT (PER PATIENT)

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

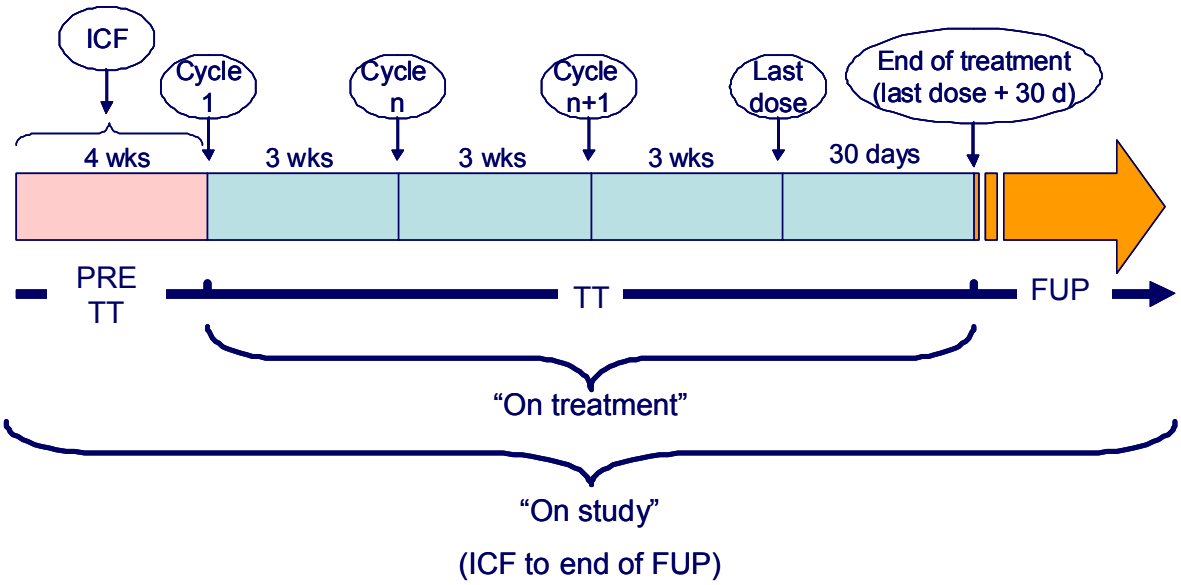
- **Pre-treatment:** from signature of informed consent to first infusion of study drugs.
- **Treatment:** from first infusion of study drugs to end of treatment (see Section 5.2.1).
- **Follow-up**: after end of treatment, patients will be followed every four weeks until resolution to at least grade 1 or stabilization of all toxicities, if any. Patients who finish treatment without disease progression will be followed every two months until disease progression, other antitumor therapy, death or until the date of study termination (clinical cutoff), whichever occurs first.

  In the new cohort after the implementation of Amendment #3, consenting patients with SCLC and endometrial cancer will be followed every three months until death or the date of study termination, whichever occurs first.

Patients will be considered to be **on-study** from the signature of the informed consent to the end of the follow-up period. Patients will be considered to be **on-treatment** for the duration of their treatment and until the day of end of treatment.

End of treatment is defined as 30 days after the day of last dose of study drug administration (see Figure 2), unless the patient starts a new antitumor therapy or dies (whichever occurs first).

Figure 2. Study periods.



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

Patients may withdraw their consent at any time; under this circumstance, no further study activities will be conducted on them.

5.2.1 Discontinuations

5.2.1.1 *End of Treatment*

Treatment discontinuation occurs when an enrolled patient ceases to receive PM01183 regardless of the circumstances. The primary reason for any treatment discontinuation will be recorded on the patient's Case Report Form (CRF). By convention, the date of end of treatment is defined as 30 days after the day of last dose of study drug administration (PM01183 treatment discontinuation), start of a new antitumor therapy or death (whichever occurs first).

An *end-of-treatment visit* will be performed within 30 days (± 7 days) after last dose 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 (ideally the day before or the same day).

If a patient discontinues treatment, every effort should be made to complete the scheduled assessments.

5.2.1.2 *Reasons for End of Treatment*

Patients will receive the study medications 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 fulfillment of appropriate re-treatment criteria and/or safety continuation of the study.

- Patient refusal and/or non compliance with study requirements.
- Treatment delay > 15 days due to toxicity (except clear clinical benefit, with the Sponsor's approval).
- Requirement of > 2 dose reductions.
- Specifically, doxorubicin will be continued before a maximal total cumulative dose of 450 mg/m^2 has been reached. Thus, a maximum of ten cycles of the combination will be administered to patients with SCLC and endometrial cancer included in the new cohort after implementation of Amendment #3), in absence of disease progression and/or unacceptable toxicity.

Patients discontinuing doxorubicin at any time after Cycle 1 will remain on study as long as they continue receiving PM01183. 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). Patients have the right to withdraw consent at any time; if this is the case, no further study procedures should be performed.

The date and reason for study discontinuation will be clearly documented on the patient's CRF.

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) 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 investigational medicinal product (PM01183) 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 Serious Adverse Events, etc.

The Investigators may suggest to the Sponsor the authorization of certain protocol deviations, especially if they are related to the inclusion/exclusion criteria or if they may have an effect on the evaluability of the patients. As a general rule, 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 to the pertinent IEC and, if applicable, to the Competent Authorities as established by local regulations.

5.3 REPLACEMENT OF PATIENTS

Patients must be replaced if they are not fully evaluable for the assessment of the primary endpoint, i.e. if:

- They are withdrawn from the study before receiving at least the infusion of both drugs on the first day (Day 1) of the first cycle of the scheduled treatment ("evaluable cycle"). An evaluable cycle is defined as: doxorubicin followed by PM01183 on Day 1 with the corresponding follow-up period of three weeks.
- They require RT or other therapeutic procedure within three weeks after the first dose, unless they previously had another drug-related AE included in the definition of DLT.
- There is a protocol violation resulting in an impossibility of concluding anything regarding the safety of the study therapy.

In addition, patients with SCLC and endometrial cancer included in the new cohort after implementation of Amendment #3 must be replaced if:

- They are not evaluable for efficacy as per RECIST for reasons other than treatment failure such as drug-related toxicity, death or early unequivocal PD outside the central nervous system.

All replaced patients will be included in the general safety analysis and in the efficacy analysis (if appropriate).

5.4 PRE-TREATMENT ASSESSMENTS

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

Table 4. Screening period: pre-treatment assessments.

	ASSESSMENT	TIME
1. Written informed consent		Prior to any specific study procedure
2. PGx study informed consent		Prior to any specific study procedure

	ASSESSMENT	TIME
3. Medical history and clinical examination	◆ Medical and cancer history: ○ Demographic data (race/ethnicity, age). ○ Date of diagnosis of the primary disease. ○ Prior treatments (surgery, radiotherapy, chemotherapy, immunotherapy), specifying best response and date of PD, when available. ○ Signs and symptoms. ◆ Complete physical examination, including weight and BSA. ◆ Performance status (ECOG PS; see APPENDIX 1). ◆ Vital signs: heart rate, blood pressure and body temperature ◆ Concomitant therapies.	Within 14 days prior to registration. *
4. Laboratory tests	◆ **Hematology:** differential WBC, hemoglobin and platelets. ◆ **Biochemistry-A:** AST, ALT, total bilirubin (and direct bilirubin, if total is abnormally elevated), AP, LDH, creatinine, glucose, CPK (and CPK-MB fraction if total CPK is abnormally high) and serum electrolytes (sodium, potassium, chloride). ◆ **Biochemistry-B and coagulation:** ○ Total proteins, albumin, AAGP, total cholesterol, LDL, triglycerides, magnesium, calcium, CRP, amylase (only at baseline). ○ Coagulation tests: PT/INR, PTT. ○ Exploratory/validated serum tumor marker as clinically indicated: CA-125 (ovarian cancer), CEA and/or CA19-9 (gastric cancer), AFP (HCC), NSE (NET) and/or CA15-3 (breast cancer). **	Within seven days prior to registration. *
5. Pregnancy test	Measurement of beta serum hCG.	Within 14 days prior to registration, if applicable.
6. Cardiac assessment	◆ ECG. ***	Within seven days prior to registration.
	◆ LVEF assessment by ECHO or MUGA.	Within 14 days prior to registration. *
7. Clinical and radiological tumor assessment	Helical contrast-enhanced CT-scan or gadolinium-enhanced MRI of all measurable/evaluable sites as per RECIST version 1.1 (see APPENDIX 2).	Within 28 days prior to registration. *
8. PGx	Available archived tissue samples will be taken to analyze potential markers of sensitivity or resistance to study treatment in consenting patients for the PGx study.	-

* A +3-day window will be allowed for laboratory procedures, a ±2-week window for radiological procedures, a +24-hour window for clinical assessments (ECOG, vital signs, ECG, weight, BSA, etc.), and a +2-week window for LVEF assessments.

** The analysis of these exploratory tumor markers will be only descriptive, and formal efficacy evaluation will be performed according only to RECIST version 1.1 criteria (see APPENDIX 2), and by GCIG criteria (patients with ovarian cancer) when applicable (see APPENDIX 3). The analysis will be repeated before starting a new cycle only in those patients with abnormally elevated values at baseline.

*** It should allow rhythm definition (at least 30 seconds of duration), and should include assessment of PR interval, RR interval, QT interval (raw) and QRS complex duration.

AAGP, alpha-1 acid glycoprotein; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BSA, body surface area; CA19-9 and 15-3, carbohydrate antigen 19-9 and 15-3 respectively; CEA, carcinoembryonic antigen; CPK, creatine phosphokinase; CRP, C-reactive protein; CrCl, creatinine clearance; CT-scan, computed tomography scan; ECG, electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; GCIG, Gynecologic Cancer Intergroup; GGT, gamma-glutamyltransferase; HCC, hepatocarcinoma; hCG, human chorionic gonadotropin; ß-hCG, beta subunit of human chorionic gonadotropin; INR, international normalized ratio; LDH, lactate dehydrogenase; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition scan; NET, neuroendocrine tumor; NSE, neuron-specific enolase; PD, progressive disease; PGx, pharmacogenomics; PS, performance status; PT, prothrombin time; PTT, partial thromboplastin time; RECIST, Response Evaluation Criteria In Solid Tumors; WBC, white blood cells.

Additional information on the collection and processing of PGx samples will be provided in a separate document ("Guide for identification, packaging and shipment of Pharmacogenomic samples").

5.5 PATIENT REGISTRATION

After ensuring that the patient meets all eligibility criteria and has given written informed consent, he/she can be registered into the study by contacting the designated trial monitor at the Sponsor location and faxing the completed Registration Form. The Registration form will be checked and eligibility confirmed by the Sponsor. A patient number will be provided to the site of enrolment within one working day. This patient number should be used on all future documentation and correspondence referring this patient. Regardless of circumstances, the investigators will not be allowed to treat any patient before appropriate receipt of the patient's registration number that confirms the Sponsor's agreement.

A patient who has been treated prior to registration without the Sponsor's agreement documentation will not be considered evaluable for the study and will need to be replaced.

Baseline and off-study visit should be completed for patients registered but never treated.

5.6 PATIENT RANDOMIZATION

Not applicable.

5.7 EVALUATIONS DURING TREATMENT

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

Table 5. Evaluations during treatment.

	ASSESSMENT	TIME
1. Clinical examination	◆ Complete physical examination, including weight and BSA.	Repeat on Day of 1 of Cycle 2 and subsequent cycles (always prior to treatment infusion). *
	◆ Signs and symptoms.	Repeat on Day 1 of Cycle 2 and subsequent cycles (always prior to treatment infusion). *
	◆ Performance status (ECOG PS; see APPENDIX 1).	Repeat on Day 1 of all cycles (always prior to treatment infusion). *
	◆ Vital signs**:** heart rate, blood pressure and body temperature.	Repeat on Day 1 of all cycles (always prior to treatment infusion). *
	◆ Concomitant therapies.	Throughout the "on treatment" period. **
2. Laboratory tests	◆ **Hematology:** differential WBC, hemoglobin and platelets. ◆ **Biochemistry-A:** AST, ALT, total bilirubin (and direct bilirubin, if total is abnormally elevated), AP, LDH, creatinine, glucose, CPK (and CPK-MB fraction if total CPK is abnormally high) and serum electrolytes (sodium, potassium, chloride).	Repeat on Days 8 and 15 of Cycle 1 and on Day 1 (always prior to treatment infusion) * and Day 10 (± 3 days) of all subsequent cycles If any suspected or possible treatment-related NCI-CTCAE grade ≥ 3 toxicity occurs, the abnormal test(s) should be re-assessed at least every 2-3 days until recovery to at least grade 1.

	ASSESSMENT	TIME
		In the event of febrile neutropenia of any grade, grade 4 neutropenia and/or grade 4 thrombocytopenia, re-assessment should be performed daily until recovery to at least grade 3 and/or until 24 hours after fever resolution, if applicable, and then every 2-3 days thereafter until recovery to at least grade 1.
	◆ **Biochemistry-B and coagulation:** ○ Total proteins, albumin, calcium, CRP. ○ AAGP, total cholesterol, LDL, triglycerides, magnesium, amylase (only if clinically indicated). ○ Coagulation tests: PT, PTT, INR. ○ Repeat only the same serum tumor marker that was abnormally elevated at baseline, if applicable: CA-125 (ovarian cancer), CEA and/or CA19-9 (gastric cancer), AFP (HCC), NSE (NET) and/or CA15-3 (breast cancer). ***	Repeat on Day 1 of Cycle 2 and subsequent cycles (always prior to treatment infusion). * If any suspected or possible treatment-related NCI-CTCAE grade ≥ 3 toxicity occurs, the abnormal test(s) should be re-assessed at least every 2-3 days until recovery to at least grade 1.
3. Pregnancy test	Measurement of beta serum hCG.	Repeat if applicable.
4. Cardiac assessment	◆ ECG. **** ◆ LVEF assessment by ECHO or MUGA.	Repeat at the time of doxorubicin discontinuation and whenever is clinically indicated. *****
5. Clinical and radiological tumor assessment	Helical contrast-enhanced CT-scan or gadolinium-enhanced MRI of all measurable/evaluable sites as per RECIST version 1.1 (see APPENDIX 2).	Every six weeks. *. The method should be always the same throughout the study for each individual patient.
6. PK sampling	As in Section 6.	Immediately before, during and after the infusions administered on Day 1 of Cycle 1.
7. Adverse events	As per NCI-CTCAE, version 4.	Throughout the "on treatment" period. **

* A +3-day window will be allowed for laboratory procedures, a ±2-week window for radiological procedures, a +24-hour window for clinical assessments (ECOG, vital signs, ECG, weight, BSA, etc.), and a +2-week window for LVEF assessments.
** "On treatment period" = from first infusion of study drugs to end of treatment [30 days after the day of last dose of study drug 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].
*** The analysis of these exploratory tumor markers will be only descriptive, and formal disease evaluation will be performed according only to RECIST version 1.1 criteria (see APPENDIX 2), and by GCIG criteria (patients with ovarian cancer) when applicable (see APPENDIX 3).
**** It should allow rhythm definition (at least 30 seconds of duration), and should include assessment of PR interval, RR interval, QT interval (raw) and QRS complex duration.
***** To be repeated in patients in no acute distress within three weeks of the last doxorubicin dose ± 1 week.
AAGP, alpha-1 acid glycoprotein; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BSA, body surface area; CA19-9 and 15-3, carbohydrate antigen 19-9 and 15-3 respectively; CEA, carcinoembryonic antigen; CPK, creatine phosphokinase; CRP, C-reactive protein; CrCl, creatinine clearance; CT-scan, computed tomography scan; ECG, electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; GCIG, Gynecologic Cancer Intergroup; GGT, gamma-glutamyltransferase; HCC, hepatocarcinoma; hCG, human chorionic gonadotropin; ß-hCG, beta subunit of human chorionic gonadotropin; INR, international normalized ratio; LDH, lactate dehydrogenase; LDL, low density lipoprotein; 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; NET, neuroendocrine tumor; NSE, neuron-specific enolase; PD, progressive disease; PGx, pharmacogenomics; PK, pharmacokinetics; PS, performance status; PT, prothrombin time; PTT, partial thromboplastin time; 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 after the day of last dose of study drug administration, unless the patient starts a new 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).

Evaluable patients, regardless of the reason for ending the treatment, will have to undergo at the end of treatment the same workup conducted before study entry; a ±7-day window will be allowed to conduct these assessments. These will include the following:

- Signs and symptoms.
- Complete physical examination (including weight and BSA).
- ECOG performance status.
- Vital signs (heart rate, blood pressure, body temperature).
- Concomitant therapies.
- Hematology.
- Biochemistry-A.
- Biochemistry-B and coagulation.
- Electrocardiogram (only in patients who did not receive single-agent PM01183 after discontinuing doxorubicin).
- LVEF assessment by ECHO or MUGA (only in patients who did not receive single-agent PM01183 after discontinuing doxorubicin).
- Adverse events.

These evaluations will only have to be repeated for those parameters for which no measurement is available at one week + 3 days before the end-of-treatment visit, or for those parameters with values that are out of range in the last assessment (grade > 1 according to NCI-CTCAE version 4).

Adverse events must be reported for 30 days after the last study drug administration. All serious adverse events (SAEs) occurring within 30 days of the last study drug administration will be reported. Beyond this period of time, only those suspected to be treatment-related SAEs will be reported (Section 9.3.2).

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

The date and reason of the study discontinuation will be recorded on the patient's CRF (see Section 5.2.1.1).

Patients who discontinue treatment without disease progression will be followed every two months until disease progression, other antitumor therapy, death or until the date of study termination, whichever occurs first.

In the new cohort after the implementation of Amendment #3, patients with SCLC and endometrial cancer will be followed every three months until death or the date of study termination, whichever occurs first.

The end-of-study date (clinical cutoff) is defined as 18 months after the first study dose of the last patient or when follow-up of all SCLC and endometrial cancer patients included in the cohort after implementation of Amendment #3 has been completed, whichever occurs first.

All AEs suspected to be related to study drugs must be followed after the end of treatment until the event or its sequel resolve or stabilize at a level acceptable to the Investigator and the clinical monitor or his/her designated representative. After the end of treatment, patients will be followed every four weeks until resolution or stabilization of toxicities, if any.

Patients who withdraw consent will not be followed with any study procedures.

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. When available, autopsy data should be provided in case of death.

6. PHARMACOKINETICS

All patients included in the study will be sampled for PK analysis. Before, during and after the infusion on Day 1 of the first cycle, 16 blood samples will be collected at the time points detailed in Table 6 for the determination in plasma of PM01183 and doxorubicin. A total volume of 120 ml of whole blood will be extracted.

Table 6. Sampling schedule for the determination of PM01183 and doxorubicin.

Sample number	Day	Absolute time (h) from the doxorubicin administration	Sampling time for doxorubicin	Sampling time for PM01183
#1	1	0	Preinfusion	Preinfusion
#2	1	0.0833	5 min after EOA	-
#3	1	0.5	30 min after EOA	30 min before EOI
#4	1	1	55 min after EOA	5 min before EOI
#5	1	1.5	1.5 h after EOA	30 min after EOI
#6	1	2	2 h after EOA	1 h after EOI
#7	1	2.5	2.5 h after EOA	1.5 h after EOI
#8	1	3	3 h after EOA	2 h after EOI
#9	1	4	4 h after EOA	3 h after EOI
#10	1	5	5 h after EOA	4 h after EOI
#11	1	6	6 h after EOA	5 h after EOI
#12	1	8	8 h after EOA	7 h after EOI
#13	2	24*	24 h after EOA	23 h after EOI
#14	3	48*	48 h after EOA	47 h after EOI
#15	5	96**	96 h after EOA	95 h after EOI
#16	8	168**	-	167 h after EOI

EOA: End of administration. EOI: End of infusion.

* There is a ±3 hour flexibility in sampling times.

** There is a ±24 hour flexibility in sampling times to avoid weekends and sampling on holidays, but the sample should be obtained with a difference of at least 24 hours *vs.* the previous and the next samples.

The sampling times may be changed while maintaining or decreasing the total number and volume of samples, if information obtained during evaluation allows improvement of the schedule.

The accurate recording of actual dosing and sampling times is much more important than strict adherence to the scheduled times.

Samples intended for the measurement of doxorubicin will have a volume of 4 ml, those intended for PM01183 will have a volume of 4 ml, while those intended for both drugs will have a volume of 8 ml. All vacuum tubes will have a total volume of 9 ml, furthermore they will need to be filled with 4 or 8 ml of blood depending on the drugs to be measured.

The exact recording of the time of drug administration and sampling times during infusions is crucial. Patients will start receiving i.v. doxorubicin as bolus followed by PM01183, i.v. over one hour on Day 1 q3wk. Drugs will be infused at a constant rate throughout the corresponding period. In order to obtain reliable PK information, the infusion rate should not be modified once infusion begins. If a variation in the infusion time eventually occurs, it is very important to record this on the CRF, writing clearly the time of the beginning and the end of the infusion. If the infusion needs to be stopped, the reason and relationship to study product should be documented on the CRF, as well as the time of stopping and re-initiation of infusion if applicable. PK sampling will then be modified according to current end of infusion (EOI) time and not to the one originally scheduled. The infusion rate should not be changed to maintain the scheduled duration of infusion. It is enough to simply record the actual duration on the CRF and on the PK sampling sheet.

Blood samples for PK analysis will be obtained through a peripheral vein located in the contralateral side to that of the infusion. In any case, the sampling vein has to be different to that in which drugs are infused. Even the last sample **must never be collected from the catheter used for drug infusion**.

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

The Instruction Manual for the Collection, Labeling, Storage and Shipment of Pharmacokinetic Samples describes in detail the procedures. Please, read carefully all the procedures before PK days. In summary, after the collection of each sample, the sample will be centrifuged and the plasma layer transferred into a single tube for the determination of doxorubicin or PM01183, or split into two tubes for the determination of PM01183 and doxorubicin. The plasma tubes will be stored under frozen conditions until shipment to the analysis laboratory. All the PK material will be provided by Pharma Mar S.A.

Once all samples from a patient have been collected, they should be shipped to the central laboratory for PK analysis as soon as possible, ideally on the next shipping day. If the same center has samples from several patients, the samples can be sent in the same shipment. However, the time span between the moment the last PK sample for a patient has been collected and the shipment of all the samples from this patient to the central laboratories should not exceed one month.

Sampling PK sheets should be sent at the same time, but never in contact with dry ice. Samples will be identified with the following data: study reference, drug, patient number, sample number, date and time of collection. The confidentiality of patients' data will be maintained at all times. Samples will be destroyed following the appropriate laboratory procedures, after the approval of the final analytical study report by the Sponsor.

7. PHARMACOGENOMICS

The objective of this pharmacogenomic study is to evaluate the role of potential markers of sensitivity to treatment in a population of advanced cancer patients treated with PM01183 combined with doxorubicin.

For those patients who consent to participate in the PGx study, response to therapy will be correlated with the RNA/protein expression levels of the selected genes. Tumor tissue blocks used for the initial diagnosis of the disease will be collected during his/her participation in the associated clinical trial. Provision of samples for such PGx analyses will be optional and performed upon patient consent by signing the PGx informed consent form (ICF).

These analyses will include the use of transcriptional profiling technologies and other molecular biology techniques to identify and validate PGx markers from pre-treatment tumor samples. The basal expression levels of these markers will be correlated with the patient's response outcome data. In addition, the experimental data will be analyzed with respect to duration of response and time to disease progression.

Experimental Methods

The experimental data indicate that PM01183 binds to DNA and interferes with the NER pathway, therefore inducing DSBs and cell death by apoptosis. It seems thus 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 to PM01183 in order to implement a customized therapy in the future.

This PGx substudy will be focused on the expression of XPG mRNA (a key gene in the NER pathway), which has previously been correlated to the sensitivity/resistance to other DNA binders, such as trabectedin and platinum compounds. In addition, a tissue microarray containing representative sections of the patients' paraffin-embedded tumor tissue blocks will be constructed and analyzed for protein expression of TopoIIa (a gene directly related with the mechanism of action of doxorubicin) and Pgp (MDR1, a detoxifying pump responsible for resistance to multiple antitumor drugs).

The mRNA expression of XPG in the patients' paraffin-embedded tumor tissue will be determined by quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR), and the p53 protein expression by IHC using the corresponding antibodies.

The analytical methods required for this molecular characterization analysis are described in a separate document. Briefly, the required tumor tissue samples are 5-µm slices of paraffin-embedded tumor tissue from patients treated with PM01183 and

doxorubicin and mounted on laser microdissection microscopy slides. The tumor tissue will be microdissected, the total RNA will be extracted and the mRNA expression of the selected genes will be quantitated by qRT-PCR using gene-specific primers.

In addition, the same samples used in the mRNA expression analysis will be studied at the protein level in tissue microarrays for determining the protein expression of TopoIIa and Pgp. Briefly, cylinders from the paraffin-embedded tissue blocks will be cut and arrayed in a new paraffin block to allow the simultaneous determination of the expression of proteins by IHC using adequate antibodies. Hence, the expression of several proteins and their histological location may be analyzed and correlated in a technical setting more familiar for the Pathology departments.

Both analyses will be done at the Central Laboratories for PGx samples (see Study Contacts). The gene expression profiling (GEP) and IHC analysis will be done at baseline conditions, i.e. using the tumor tissue obtained at the diagnosis of the disease.

The level of mRNA expression of these genes and their corresponding protein products will be used to evaluate their utility in making clinical predictions. Genes which expression is most highly correlated to clinical outcome will be considered candidate markers. Candidate markers must be validated in at least one independent technology and in an independent population in order to be considered potentially useful in making clinical decisions.

In those patients responding to treatment, Myriads Genetics Homologous Recombination Deficiency (HRD) assay, including analysis of BRCA1 mutation status, will be performed, if considered relevant.

The Sponsor will provide a Charter document detailing the procedures to be followed for sample collection, labeling and shipment.

8. TREATMENT

8.1 DESCRIPTION OF TREATMENT

8.1.1 Drug Formulation and Supply

8.1.1.1 *PM01183*

PM01183 is presented as a lyophilized powder for concentrate for solution for infusion with two strengths: 1 mg/vial and 4 mg/vial.

Before use, the 1-mg vial and 4-mg vial should be reconstituted with 2 ml and 8 ml of sterile water for injection, respectively, to give a solution containing 0.5 mg/ml of PM01183. For administration to patients as i.v. infusion, reconstituted vials will be 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 1-mg and 4-mg vials and the reconstituted solution per ml are summarized in Table 7.

Table 7. Composition of PM01183 vials and the reconstituted solution.

Component	PM01183 1 mg	PM01183 4 mg	Concentration per vial after reconstitution
PM01183	1.0 mg	4.0 mg	0.5 mg/ml
Sucrose	200 mg	800 mg	100 mg/ml
Lactic acid	5.52 mg	22.08 mg	2.76 mg/ml
Sodium hydroxide	1.28 mg	5.12 mg	0.64 mg/ml

For instructions regarding drug inventory, handling, reconstitution, dilution, storage, accountability and disposal, please refer to the Preparation Guide for PM01183 and the PM01183 Investigator's Brochure (IB), both provided as separate documents.

8.1.1.2 *Doxorubicin*

Commercially available presentations of vials containing doxorubicin will be provided as appropriate.

8.2 ADMINISTRATION OF STUDY MEDICATION

Patients will consecutively receive the following on Day 1 q3wk (three weeks = one treatment cycle):

- Doxorubicin: i.v. infusion of a total volume of 20 ml dilution on 0.9% saline or 5% dextrose, on a short i.v. bolus at a dose of 50 mg/m^2 (fixed dose), via a central or peripheral venous catheter after appropriate visual confirmation of effective venous blood return through the line, immediately followed by:
- PM01183: i.v. infusion over one hour at a starting dose of 3.5 mg (FD), over a minimum of 100 ml dilution on 5% glucose or 0.9% sodium chloride via a central line (or a minimum of 250 ml dilution if a peripheral line will be used), through a pump device.

Information on dose escalation may be found in Section 3.3.

New cohort after implementation of Amendment #3:

Patients with SCLC and endometrial cancer will consecutively receive the following on Day 1 q3wk (three weeks = one treatment cycle):

- Doxorubicin: i.v. bolus/short infusion at a dose of 40 mg/m^2, administered as described above, immediately followed by:
- PM01183: i.v. infusion over one hour at a dose of 2.0 mg/m^2, administered as described above.

Both doxorubicin and PM01183 doses will be capped at 2.0 m^2 of BSA for individuals exceeding this BSA value. Doses will have to be recalculated for patients showing a ≥ 10% change in total body weight value compared to previous cycle.

Doses will be rounded to the first decimal.

8.3 CRITERIA FOR TREATMENT CONTINUATION

Patients will be treated with additional cycles of PM01183 combined with doxorubicin as long as no unacceptable toxicity and/or progression of the disease and/or withdrawal of consent occurs (see Section 5.2.1).

Complete blood counts, blood chemistries and other tests will be done prior to starting the next infusion (please refer to Section 5.4 and Section 5.7 for the full list of tests to be done before first study drug administration and/or further treatment cycles).

Table 8 lists the minimum requirements needed to re-expose the patient to the treatment schedule. Other factors might be considered critical by the Investigator. In this case, these factors should be appropriately documented in the patient's record and on the CRF, and discussed with the Sponsor.

The administration of a new cycle should be delayed if the criteria shown in Table 8 are not met on the corresponding Day 1 of the next administration, with parameters being reevaluated at minimum intervals of 48 hours. The new cycle will start upon recovery of these parameters.

A maximum delay of 15 days will be allowed for recovery from drug-related AEs. If recovery has not occurred after a 15-day delay, the patient should discontinue the treatment, except in case of obvious patient benefit at the criteria of the Investigator and upon agreement with the Sponsor.

After delaying doses due to drug-related toxicity (except for neutropenia exclusively) exceeding the 15-day delay, or in patients who experience a DLT, treatment may only continue after appropriate dose reduction of PM01183, appropriate secondary prophylaxis with G-CSF (when due to neutropenia exclusively), or doxorubicin interruption (i.e., due to cardiac toxicity or maximal cumulative dose reached) (see Section 8.4).

In order to avoid unnecessary administrative delays, patients who undergo radiological tumor assessment but the results of which are still pending on the due date of retreatment may exceptionally receive their scheduled infusions without any delays, in the absence of clinical PD and provided all retreatment criteria are otherwise met. However, if PD is observed radiologically once the results are available, treatment will be immediately discontinued and the date of PD will be the day when the radiological assessment was originally performed.

Table 8. Criteria for continuation of treatment.

Variable	PM01183	Doxorubicin
	Day 1	Day 1
ANC	≥ 1.5 x 10^9/l	≥ 1.5 x 10^9/l
Platelets	≥ 100 x 10^9/l	≥ 100 x 10^9/l
Hemoglobin	≥ 9 g/dl	≥ 9 g/dl
Total bilirubin (or direct bilirubin)	≤ 1.5 x ULN (≤ ULN)	≤ 1.5 x ULN (≤ ULN)
AST/ALT	≤ 3.0 x ULN	≤ 3.0 x ULN
Albumin	≥ 3.0 g/dl.	≥ 3.0 g/dl.
ECOG PS	0-2	0-2

Variable	PM01183	Doxorubicin
	Day 1	Day 1
Calculated CrCl (Cockcroft and Gault's formula)	≥ 30 ml/min	≥ 30 ml/min
Muscular toxicity (myalgia, muscular weakness, CPK increase)	Grade ≤ 1	Grade ≤ 1
Other non-hematological drug-related AEs (except increased GGT, not optimally treated nausea and vomiting, alopecia, asthenia and/or neuropathy) [a]	Grade ≤ 1	Grade ≤ 1
Mucositis	Grade ≤ 1	Grade ≤ 1
Signs and/or symptoms of CHF	-	No
Current cumulative doxorubicin-equivalent dose < 400 mg/m^2 [b]	-	Yes

If a patient does not meet the requirements for treatment continuation (excluding cardiac toxicity and/or maximal doxorubicin cumulative dose) on Day 1 of further cycles, both drugs (PM01183 and doxorubicin) infusions will be withheld until recovery for a maximum of 15 days after the theoretical treatment date. If recovery has not occurred after a delay of > 15 days, the patient must be withdrawn from the trial, except in case of perceived clinical benefit from the Investigator and upon agreement with the Sponsor.

If a patient does not meet the requirements for treatment continuation due to cardiac toxicity and/or maximal doxorubicin cumulative dose, doxorubicin will be permanently discontinued and treatment may continue with PM01183 alone at its single-agent RD, 7.0 mg FD q3wk, without any delay if clinically appropriate.

a Any grade accepted for increased GGT. Up to grade 2 for alopecia, nausea, vomiting, neuropathy and asthenia.

b The total doxorubicin cumulative dose received by each patient must never reach > 450 mg/m^2.

AEs, adverse event(s); ALT, alanine aminotransferase; ANC, absolute neutrophil count; AP, alkaline phosphatase; AST, aspartate aminotransferase; CHF, congestive heart failure; CPK, creatine phosphokinase; CrCl, creatinine clearance; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; FD, flat dose; GGT, gamma-glutamyltransferase; RD, recommended dose; ULN, upper limit of normal; q3wk, every three weeks.

8.4 DOSE REDUCTION

Patients will continue treatment at the same dose level as long as they did not experience a DLT(s) and/or infusion delays due to toxicity during the preceding cycle and they continue to meet the criteria for re-treatment.

Treatment after DLT, a treatment-related infusion delay greater than 15 days, or a toxicity considered as unacceptable by the investigators may continue, after appropriate dose reduction, only if there is clear evidence of objective patient benefit. This will always be discussed with the Sponsor. Under this circumstance, and following recovery to pre-specified re-treatment criteria, patients will be re-treated at the immediately lowest dose level. If dose reduction beyond DL-1 is required, the dose of PM01183 may be reduced by an additional 0.5 mg (FD).

Up to two individual dose reductions will be allowed per patient; any patients requiring more than two dose reductions will be withdrawn from the study. Once the dose has been reduced for an individual patient, it will not be re-escalated again under any circumstances.

Patients requiring dose reduction exclusively due to grade 4 neutropenia or any grade febrile neutropenia that occurred during the preceding cycle may receive secondary prophylaxis with G-CSF instead of a dose reduction. If toxicity re-occurs despite G-CSF use, dose reduction will then be implemented.

Patients who reach a maximal cumulative dose of 450 mg/m^2 of doxorubicin or have to discontinue doxorubicin due to a cardiac AE may continue receiving treatment with PM01183 (after Cycle 1) at the single-agent RD (7 mg FD q3wk) if patient benefit is perceived. These patients do not need to be replaced.

Patients who may require thoracic RT for pain palliation after Cycle 1 may continue treatment with PM01183 alone at its single-agent RD (7.0 mg FD q3wk), after a minimum doxorubicin washout period of three weeks and without any dose adjustments if patient benefit is perceived; these patients do not need to be replaced.

New cohort after implementation of Amendment #3:

Patients with SCLC and endometrial cancer included in the new cohort after implementation of Amendment #3 who require dose reduction due to the reasons described above will be re-treated at the following dose levels:

- DL-1: Doxorubicin 40 mg/m^2 + PM01183 1.5 mg/m^2.
- DL-2: Doxorubicin 30 mg/m^2 + PM01183 1.5 mg/m^2.

Up to two sequential dose reductions will be allowed per patient; any patients requiring more than two dose reductions will be withdrawn from the study, except if there is objective clinical benefit or upon the Sponsor's agreement. Once the dose has been reduced for an individual patient, it will not be re-escalated again under any circumstances.

Patients included in this cohort who have received ten cycles of the doxorubicin/PM01183 combination or have to discontinue doxorubicin due to a cardiac AE may continue receiving treatment with single-agent PM01183 at 4.0 mg/m^2 q3wk if patient benefit is perceived. These patients do not need to be replaced.

Patients treated with single-agent PM01183 who require dose reduction due to the reasons described above will have their dose reduced by 25%. Up to two sequential dose reductions will be allowed per patient; any patients requiring more than two dose reductions will be withdrawn from the study, except if there is objective clinical benefit or upon the Sponsor's agreement.

8.5 CONCOMITANT MEDICATION

All tumor-specific prior chemotherapy, radiation therapy and all relevant information must be recorded on the patient's CRF.

In addition, reasonable efforts will be made to determine all treatments received by the patient during administration of the study drugs. This information must be documented in the concomitant therapy Section of the CRF.

8.5.1 Prophylactic Medication

All patients must receive the following prophylactic medication 20-30 minutes before infusion of any study drug:

- Dexamethasone 8 mg i.v. or equivalent,
- Ondansetron 8 mg i.v. or equivalent, with or without:
  - Metoclopramide 10 mg i.v. or equivalent, and/or

- Extended oral dexamethasone not exceeding 20 mg/days and/or oral ondansetron 4 to 8 mg or equivalent, at the investigator's criteria if required.
- Additional antiemetics might be used, if required.
- If primary G-CSF prophylaxis is required in specific cohorts of patients, it will consist of:
  - G-CSF (non-pegylated filgrastim) at 300 μg/day subcutaneously for five consecutive days, starting on Day +3.

8.5.2 Allowed Medications/Therapies

- Therapies for preexisting and treatment-emergent medical conditions, including pain management.
- Blood products and transfusions, as clinically indicated.
- Bisphosphonates.
- In case of nausea or vomiting, secondary prophylaxis and/or symptomatic treatment for emesis according to American Society of Clinical Oncology (ASCO) guidelines (39) will be allowed.
- Erythropoietin use according to ASCO guidelines (40) will be allowed.
- Hormone-responsive breast cancer patients [i.e., those whose tumors express estrogen receptor (ER) and/or progestogen receptor (PrR)] may continue receiving their same prior hormonal therapy without interruption throughout their study participation.
- Luteinizing hormone-releasing hormone (LHRH) agonists in women of reproductive age.
- Palliative local radiation (excluding thorax and mediastinum) may be applied if needed after the first cycle of study treatment is completed. Any lesion within the irradiated area will then not be considered an area of measurable/evaluable disease. Thorax and mediastinum may be irradiated, if required, after a minimum of three weeks of doxorubicin discontinuation.
- Megestrol acetate for appetite stimulation is also allowed.

8.5.3 Prohibited Medications/Therapies

- Concomitant administration of any other antineoplastic therapy is prohibited, other than the aforementioned hormonal therapy for breast cancer.
- Other investigational agents.
- Aprepitant or directly related substances (e.g., fosaprepitant).
- Immunosuppressive therapies, other than corticosteroids.
- Primary prophylaxis and/or treatment with colony-stimulating factors such as G-CSF and granulocyte/macrophage colony stimulating factor (GM-CSF) during Cycle 1, (except if patient(s) is/are treated within an specific cohort resuming dose escalation with primary G-CSF prophylaxis, in which case use is not only allowed but compulsory). Secondary prophylaxis might be allowed, if required, during the following cycles, instead of a dose reduction due to exclusively hematological reasons and upon Sponsor agreement.

Note: G-CSF treatment for non-febrile uncomplicated neutropenia during Cycle 1 and primary G-CSF or GM-CSF prophylaxis will not be allowed in patients with SCLC and endometrial cancer included in the new cohort after implementation of Amendment #3.

- Thoracic and/or mediastinal irradiation concomitant with doxorubicin therapy.

8.5.4 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.

A list of commonly prescribed drugs that are substrates for these enzymes is provided in APPENDIX 5.

8.5.5 Drug Accountability

Proper drug accountability will be done by the clinical trial monitor. Each study site will keep records to allow a comparison of quantities of drug received and used at each site. 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.

8.6 TREATMENT COMPLIANCE

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

9. STUDY EVALUATIONS

9.1 DETERMINATION OF MTD AND RD

The definition of the MTD and the RD may be found in Section 3.1.1.

9.2 SAFETY

Patients will be evaluable for safety if they have received at least one partial or complete infusion of PM01183. AEs will be graded according to the NCI-CTCAE version 4.

The evaluation period for individual patients should include observations since start of the treatment until 30 days after the last administration of study drug. Any previous drug-related AEs must be followed until recovery to at least grade 1 or stabilization, if present after end of treatment.

9.3 ADVERSE EVENTS DEFINITIONS

9.3.1 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 test 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 an AE by the Investigator.

9.3.2 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 whether expedited reporting is appropriate in other situations such an important medical events 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.

9.3.3 Death

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

9.3.4 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.

9.3.5 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 9.4.2). 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).

9.3.6 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 most updated IB for PM01183 and the Summary of Product Characteristics for doxorubicin.

9.3.7 Adverse Events Related to the Study Drugs

An AE is considered an adverse drug reaction (ADR) if it is related to a study drug/IMP, i.e., if the Investigator's assessment of causal relationship to the IMP(s) is "Y (yes)" (see Section 9.3.9).

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.

9.3.8 Expedited reporting

The Sponsor is responsible for the appropriate expedited reporting of serious unlisted/unexpected and related adverse events (SUSAR/SUAE) to the Competent Authorities. The Sponsor will also report all SAEs that are unlisted/unexpected and related to the study drug(s) [IMP(s)] to the Investigators and to the IECs according to the current legislation, unless otherwise required and documented by the IECs.

9.3.9 Assessment of Causal Relationship to the Study Drug

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

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

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

Uk. (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.

9.4 ADVERSE EVENTS REPORTING PROCEDURES

9.4.1 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, 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 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 version 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).

9.4.2 Reporting Serious Adverse Events

The Sponsor will collect SAEs from the signing of the ICF. If the patient is definitively included in the study, this information will also be recorded in the AE section of the CRF.

SAEs will be collected until 30 days after administration of the last dose of study drug(s)/IMP(s) or until the start of a new antitumor therapy, whichever occurs first. Beyond this period of time, only those SAEs suspected to be related to the IMP 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) 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 function by fax (+34 91 846 6004) 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 Service at +34 91 823 4742.

The preferred reporting method is by faxing the completed SAE form. An initial report by telephone must be followed by a completed “Serious Adverse Event Form” from the investigational staff within one working day.

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

9.4.3 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 female patient or the female partner of a male patient occurring while the patient is on study drug, or within 30 days of the patient’s discontinuation visit, are considered immediately reportable events.

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

- Any occurrence of a pregnancy where any kind of exposure to the IMP(s) is suspected.
- Possible exposure of a pregnant woman [this could involve a partner of a male patient or a pregnant female who came in contact with the clinical trial IMP(s)].
- All reports of elevated/questionable or indeterminate beta human chorionic gonadotropins (β-hCGs).

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

Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Pharma Mar S.A. Pharmacovigilance immediately by facsimile using the Pregnancy Report form. In the case of pregnancy of the female partner of a trial patient, the Investigator will obtain her informed consent to provide the information by using the applicable form provided by the Sponsor who will also advise the Investigator in these situations.

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 by facsimile within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death at any time thereafter that the Investigator suspects is related to the exposure to the study drug(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.

9.5 ADVERSE EVENTS MONITORING

Safety review will be performed at Pharma Mar S.A. once CRFs have been monitored, collected and shipped to the Sponsor.

Periodic safety review of clinical data will be performed; however, no formal Data Safety Monitoring Board has been appointed for this trial. AEs will be monitored 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. In general, a clinical oncologist, together with a member of the Pharma Mar S.A. Pharmacovigilance Department will review the safety data of this trial on an ongoing basis.

SAEs will be collected, assessed and reported as per the applicable Regulations by the Pharmacovigilance Department. Periodic safety reviews of SAE reports are to be conducted by the clinical oncologist every 3-6 months, depending on recruitment.

As per the applicable regulations, Pharma Mar S.A. will report to the IECs, Investigators and Competent Authorities:

- expeditedly: all serious, related, unlisted/unexpected AEs or critical safety findings from this and any other clinical trial with PM01183 and,
- periodically: all relevant safety information generated in all clinical trials with the IMP(s) within an Annual Safety Report.

Non-serious AEs will be assessed during monitoring visits by the monitor, who will discuss them with the Investigators.

Any protocol deviation will also be discussed with the Investigator during monitoring visits.

9.6 EVALUATION OF PHARMACOKINETICS

The PK will be elucidated using standard non-compartmental methods. The following parameters will be calculated: C_{max}, AUC, volume of distribution based on the terminal half-life (V_z), volume of distribution at steady state (V_{ss}), clearance (CL) and half-life ($t_{1/2}$).

The C_{max} will be derived directly from the experimental data. The terminal rate constant (k) will be estimated by log linear regression analysis of the terminal phase of the plasma concentration versus time curve. The area under the plasma concentration-time curve (AUC_{inf}) will be determined using the log-linear trapezoidal method with extrapolation to infinity using the terminal rate constant k (C_{last}/k, where C_{last} is the last measured analyte concentration). The $t_{1/2}$ will be calculated from the equation 0.693/k; total plasma clearance (CL) will be determined by dividing the total administered dose by the AUC_{inf}. If considered appropriate by the Sponsor, compartmental analysis on the study results will be also performed, and population kinetic analysis will be made in pooled results of the different studies.

9.7 EFFICACY

The evaluation of antitumor response is not a main objective in phase I trials. However, patients entered in this study at the expansion cohort of the RD must have either:

- Measurable disease according to the RECIST version 1.1 (41) (see details in APPENDIX 2), or
- Evaluable disease by serum tumor markers, in patients with ovarian cancer.

Response rates will be determined in patients with measurable or evaluable disease. If any tumor type is adequately represented, time-related parameters will be also analyzed.

In patients with measurable disease, tumor assessments will be done every six weeks, and tumor response will be evaluated by the RECIST version 1.1 (see details in APPENDIX 2). In case of patient objective tumor response, a copy of CT-scans or MRIs can be requested by the Sponsor.

If early progression occurs (i.e., before six weeks since treatment) or if treatment should be discontinued due to any treatment-related toxicity before appropriate tumor assessments have been performed, the patient's objective response will be considered as a treatment failure or progressive disease (PD); therefore, their data will be included in the analysis of objective response as per RECIST version 1.1.

In patients with ovarian cancer, serum tumor marker (CA-125) assessments will be obtained before every new cycle (i.e., three weeks) and tumor response will be evaluated by GCIG specific criteria (see details in APPENDIX 3).

Analysis of other clinically routinely employed serum markers will be performed for individual patients in an exploratory fashion, as clinically indicated. This will include baseline measurements of:

- Carcinoembryonic antigen (CEA) or carbohydrate antigen 19-9 (CA19-9): for patients diagnosed with gastric cancer.
- Alpha-fetoprotein (AFP): for patients diagnosed with HCC.
- Non-specific enolase (NSE): for patients diagnosed with neuroendocrine tumor (NET).
- Carbohydrate antigen 15-3 (CA15-3): for patients diagnosed with breast cancer.

Patients for whom disease diagnostic applies and are found to have elevated baseline values, according to the institution reference (which will be also provided), will be assessed before treatment on Day 1 of Cycle 2 and all subsequent cycles.

Since formal consensus on response criteria for these markers is lacking, the analysis of these markers will be only descriptive in nature. Moreover, no clinical decisions regarding treatment continuation or disease progression will be taken based solely on these parameters (except for CA-125).

Note: No serum markers will be evaluated in patients with SCLC and endometrial cancer included in the new cohort after implementation of Amendment #3.

9.7.1 Duration of Overall Response

The duration of overall response will be measured from the time measurement criteria are met for complete response (CR)/ PR, whichever is first recorded, until the first date in which progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started) or the date of death. In absence of disease progression or death, the duration of response will be censored on the date of last tumor evaluation.

9.7.2 Progression-free Survival

Progression-free survival (PFS) is defined as the time from the date of first infusion of study treatment to the date of progression or death (due to any cause). If progression or death has not occurred at the time of the analysis, the PFS will be censored on the date of last tumor evaluation.

9.7.3 Overall Survival

Overall survival (OS) is defined as the time from the date of first infusion of study treatment to the date of death (due to any cause). Patients with no documented death will be censored at the last date they are known to be alive.

9.8 EVALUATION OF PHARMACOGENOMICS

Provision of samples for PGx analyses will be optional and performed upon patient consent by signing the PGx ICF (see Section 4.3).

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 (see Section 5.4, Table 4).

The following analyses will be done on samples from consenting patients treated with PM01183 and doxorubicin:

- Quantitation of XPG mRNA expression in paraffin-embedded tumor tissue by real-time qRT-PCR and other genes related to the mechanism of action of PM01183 and doxorubicin.
- Quantitation of XPG, TopoIIa and Pgp expression and other proteins related to the mechanism of action of PM01183 and doxorubicin by IHC in tumor tissue microarrays constructed from the patient's paraffin-embedded tumor tissue blocks.

In those patients responding to treatment, Myriads Genetics Homologous Recombination Deficiency (HRD) assay, including analysis of BRCA1 mutation status, will be performed, if considered relevant.

If possible, expression levels of the different markers should be correlated with the patient's clinical outcome.

10. STATISTICAL METHODS

10.1 SAMPLE SIZE

The number of patients may vary depending both on the tolerability to PM01183 combined with doxorubicin and the number of dose levels required to identify the MTD. Approximately, 100 evaluable patients will participate in this study.

10.2 STATISTICAL ANALYSIS

10.2.1 Demographics

Descriptive statistics (mean, median, standard deviation and 95% confidence interval, range of value, frequencies and percentages) will be used. Tables will be displayed by dose level.

10.2.2 Safety

Descriptive statistics will be used to characterize the profiles of drug-related AEs, drug-related deaths, SAEs, drug-related delays, dose reductions and/or treatment discontinuations. Tables will be displayed by dose level.

10.2.3 Efficacy Analysis

Response rates [percentage of patients with any response (PR or CR: overall response rate), percentages for PR and CR separately, as well as percentage of patients with prolonged stable disease (SD) ≥ 4 months] will be characterized using descriptive statistics (95% exact binomial confidence interval).

If any particular tumor type is adequately represented, time-related parameters (i.e., progression-free survival, overall survival) will be analyzed according to the Kaplan-Meier method, if appropriate.

The characteristics of the patients achieving an objective response or SD ≥ 4 months by RECIST version 1.1, or a clinically significant improvement as measured by tumor markers, if applicable, will be displayed.

In addition, patients with SCLC and endometrial cancer included in the new cohort after the implementation of Amendment #3 will be followed for survival for up to 18 months after the first study dose.

10.2.4 Pharmacokinetics

The PK parameters will be tabulated and selected parameters will be graphically displayed per dose level. The dose-exposure relationships for C_{max} and AUC will be evaluated and any potential PK interaction between doxorubicin and PM01183 will be explored.

The potential influence on selected PK parameters of selected demographic and clinical dichotomous variables (gender, laboratory test results above/below selected cutoff values, etc.) will be evaluated by Student`s *t* test or Mann-Whitney's U test as appropriate.

For multinomial variables, analysis of variance will be used. For selected continuous demographic and clinical variables (age, laboratory test results…), relationship with selected pharmacokinetic parameters will be graphically explored and assessed using correlation and regression methods.

Other tests may be applied if the results of the above evaluations suggest that they may yield additional relevant information.

10.2.5 Pharmacogenomics

RNA expression and IHC scoring will be performed blind, and clinical data compiled only after all analyses are completed. Fisher's exact test will be used to test whether a specific protein-expression profile is associated with the clinical outcome after treatment with PM01183 and doxorubicin.

The prognosis value of markers will be explored for objective clinical response, progression-free survival and overall survival. In each case, if applicable, a multivariate

model will be developed by backwards elimination, starting with all markers with a p-value lower than 0.10 in the univariate analysis.

If applicable, hazard ratios will be calculated with the univariate Cox model, and comparison between Kaplan-Meier survival (whenever available) and progression-free survival curves will be performed with the log-rank test. All tests of statistical significance will be two-sided, and significance will be set at 0.05 except in multiple comparisons, where it will be set at 0.017 in accordance with the Bonferroni correction of type I error.

10.3 INTERIM ANALYSIS

The patient's safety will be assessed on a regular basis prior to each dose escalation upon completion of a cohort. No formal interim analyses are planned.

11. ADMINISTRATIVE SECTION

11.1 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 6) 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 approval/favorable opinion prior to initiation, according to pertinent regulations.

The decision of the IEC 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 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.

11.2 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 accountability 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 Good Clinical Practice, Section 1.6).

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

11.3 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 ICF for the clinical trial and one copy of the ICF for the PGx study, if applicable. Both copies must provide written full information about the clinical trial and the PGx study, in a language that is non-technical and easily understood. 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 and the PGx study; then, both 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 both 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.

11.4 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 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.

11.5 CASE REPORT FORMS

Case report forms (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 and have been enrolled into the study.

A patient's source documentation is the physician's patient records, and as such they should be maintained at the study site.

The data collected in the CRF will be entered into Pharma Mar S.A. 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.

11.6 INSURANCE

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

11.7 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.

11.8 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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13. 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

RECIST 1.0		RECIST 1.1	Rationale
New lesions	–	New section on New lesions	To provide guidance on when a lesion is considered new (and thus PD)
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

RECIST 1.0		RECIST 1.1	Rationale
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	

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 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.

Tumor Markers:

Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response (CR). Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) have been published (Rustin *et al.* J Natl Cancer Inst 2004; 96:487–488).

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, saggital 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: GCIG SPECIFIC CRITERIA

GCIC-Rustin-modified Criteria for CA-125 Response[4]

Patients will be scored as having attained a CA-125 response if they meet the GCIG-Rustin-modified criteria which require that there is at least a 50% reduction in CA-125 levels from a pre-treatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA-125 only if they have a pre-treatment sample that is at least twice the upper limit of normal and within two weeks prior to starting treatment. In addition, CA-125 levels in samples obtained after administration of mouse antibodies or within four weeks after surgery or paracentesis should not be taken into account.

Definition of Progression free survival and duration of response by CA-125

PFS based on CA-125 will be defined as the time from first study drug infusion until the GCIC-Rustin-modified criteria of progression are met, or until the date of death (with or without disease progression).Duration of CA-125 response will be defined as the time between when the CA-125 was first documented to have decreased by 50% in a patient who meets all the GCIG-Rustin-modified criteria for a CA-125 response, and the time the CA-125 is first documented to have risen to the point where the patient meets GCIG criteria of disease progression.

GCIC-Rustin-modified definition of progressive disease according to CA-125 criteria		
	Definition of progression	Date of progression
Patients with elevated CA-125 before treatment and normalization of CA-125 during treatment	CA-125 ≥ 2 X ULN documented on 2 occasions*	Date CA-125 is first elevated to ≥ 2 X ULN
Patients with elevated CA-125 pretreatment that never normalizes	CA-125 ≥ 2 X nadir value on 2 occasions*	Date CA-125 is first elevated to ≥ 2 X nadir value
Patients with CA-125 in normal range pretreatment	CA-125 ≥ 2 X ULN documented on 2 occasions*	Date CA-125 is first elevated to ≥ 2 X ULN
*Repeat CA-125 anytime but normally not less than one week after the first elevated CA-125 level. CA-125 levels in samples obtained after administration of mouse antibodies or within four weeks after surgery or paracentesis should not be taken into account.		

In patients for whom response to treatment is evaluated by both RECIST and CA-125 criteria, the date of response and progression will be the earliest date of the two methods.

[4] Rustin GJ, Quinn M, Thigpen T, du Bois A, Pujade-Lauraine E, Jakobsen A, *et al.* Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). *J Natl Cancer Inst* 2004;96(6):487-8.

APPENDIX 4: COCKCROFT AND GAULT'S FORMULA

For calculating creatinine clearance:

$$\text{Creatinine clearance (ml/min)} = \frac{[(140\text{-age (years)}) \times \text{weight (Kg)}]}{72 \times \text{serum creatinine (mg/dl)}} \times G^{1}$$

$$\text{Creatinine clearance (ml/min)} = \frac{[(140\text{-age (years)}) \times \text{weight (Kg)}]}{72 \times \text{serum creatinine } (\mu\text{mol/l}) \times 0.0113} \times G^{1}$$

[1]G(Gender)= 0.85 if Female; 1 if Male.

Reference:

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

APPENDIX 5: L IST 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,	Alfentanil, astemizole, (7) cisapride, (7) cyclosporine, dihydroergotamine, ergotamine,

CYP enzymes	Sensitive substrates (2)	Substrates with narrow therapeutic range (3)
	lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine (7)
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 6: 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.