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CLINICAL TRIAL PROTOCOL

A Multicenter Phase II Clinical Trial of PM01183 in BRCA 1/2-Associated or Unselected Metastatic Breast Cancer

INVESTIGATIONAL MEDICINAL PRODUCT: PM01183
Protocol No.: PM1183-B-003-11
EudraCT No.: 2011-006108-11
NCT Code: 01525589

Protocol version 4.0 (including amendments #1 dated 3 December 2013, #2 dated 28 October 2014, and #3 dated 8 March 2016)

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

PRINCIPAL INVESTIGATORS

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

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SYNOPSIS

TITLE	A Multicenter Phase II Clinical Trial of PM01183 in BRCA 1/2-Associated or Unselected Metastatic Breast Cancer
PROTOCOL CODE	PM1183-B-003-11
INVESTIGATORS / TRIAL LOCATION	A full list of investigators will be available as a separate document.
STUDY OBJECTIVES	**Primary:** • To assess the antitumor activity of PM01183 in terms of overall response rate (ORR), according to RECIST v1.1, in each cohort of metastatic breast cancer (MBC) patients. **Secondary:** • To further characterize the antitumor activity of PM01183 in terms of duration of response (DR), clinical benefit [ORR or stable disease lasting over three months (SD > 3 months)], progression free survival (PFS), and one-year overall survival (1y-OS). • To evaluate whether the presence of a known germline mutation in BRCA 1/2 predicts response to PM01183 in MBC patients. • To explore the activity of PM01183 in specific breast cancer subpopulations according to hormonal receptor status, HER-2 overexpression, number and/or type of prior therapies, or according to other available histological/molecular classifications/parameters. • To evaluate the safety profile of this PM01183 administration schedule [Day 1 every three weeks (q3wk)] in this patient population. • To analyze the pharmacokinetics (PK) of PM01183 in this patient population. • To explore PK/PD (pharmacokinetic/ pharmacodynamic) correlations, if applicable. • To evaluate the pharmacogenomic (PGx) expression profile of selected putative markers potentially predictive of response to PM01183, in tissues from tumor samples.
STUDY DESIGN	This is a multicenter, open-label, exploratory, phase II clinical trial evaluating the efficacy and safety of PM01183 administration to patients with previously treated MBC. Two cohorts of patients with advanced breast cancer will be prospectively evaluated in the trial according to germline BRCA1/2 status (mutated [cohort A] *vs*. unselected [cohort B]). A third cohort (A1) will include advanced breast cancer

	patients with deleterious BRCA1/2 mutation who received prior treatment with poly (ADP-ribose) polymerase (PARP) inhibitors: • Cohort A (BRCA+ cohort): At least 53 evaluable patients with known deleterious BRCA1/2 mutation status at study entry. • Cohort A1 (BRCA+/PARPi cohort): 20 evaluable patients with known deleterious BRCA1/2 mutation status and prior treatment with PARP inhibitors (PARPi). • Cohort B (unselected cohort): At least 64 evaluable patients without known deleterious BRCA1/2 mutation status at study entry, i.e., either: o Patients known to have no deleterious BRCA1/2 mutations (BRCA−), or o Patients whose BRCA 1/2 mutation status is unknown (BRCA-UK). BRCA1/2 germline mutation status will be assessed in all patients in this subgroup responding to PM01183 treatment. An interim analysis based on the primary endpoint (ORR) is planned after 20 and 30 evaluable patients have been treated in cohorts A and B, respectively. No interim analysis is planned for cohort A1. If less than four out of 20 patients in Cohort A, or less than three out of 30 patients in Cohort B achieve an objective confirmed response (as per RECIST v1.1), recruitment to that cohort will be terminated. Otherwise, recruitment will continue until at least 53 and 64 evaluable patients are included in cohort A and cohort B, respectively. Sample size and cohort design will be re-evaluated at this point in order to estimate the 95% confidence interval (CI) with the desired precision. Recruitment to either cohort (e.g., Cohort B) might be halted while interim analysis is being performed, if appropriate.
PATIENT ELIGIBILITY **Inclusion criteria**	**All patients** 1. Women ≥ 18 and ≤ 75 years of age. 2. Voluntary signed informed consent form (ICF), obtained before any specific study procedure. 3. Histologically proven diagnosis of metastatic breast carcinoma. 4. No more than three prior chemotherapy-containing regimens for MBC. 5. Patients with known HER-2 overexpressing tumors must have failed at least one prior trastuzumab-containing regimen for metastatic disease. 6. Measurable disease as defined by RECIST v1.1. 7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1. 8. Adequate major organ function:

	a. Hemoglobin ≥ 9 g/dl, prior red blood cell (RBC) transfusions are allowed if clinically indicated; absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l; and platelet count ≥ 100 x 10^9/l. b. Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3.0 x upper limit of normal (ULN). c. Total bilirubin ≤ 1.5 x ULN or direct bilirubin ≤ ULN. d. Albumin ≥ 3 g/dl. e. Serum creatinine ≤ 1.5 x ULN. f. Creatine phosphokinase (CPK) ≤ 2.5 x ULN. 9. Washout periods prior to Day 1 of Cycle 1: a. At least three weeks since the last chemotherapy (six weeks if therapy contained nitrosureas or systemic mitomycin C). b. At least four weeks since the last monoclonal antibody (MAb) containing therapy or radiotherapy (RT) > 30 Gy. c. At least one week since the last hormonal therapy. d. At least two weeks since the last biological/investigational therapy (excluding MAbs) or palliative RT (≤ 10 fractions or ≤ 30 Gy total dose). 10. Grade ≤ 1 toxicity due to any previous cancer therapy according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v4). Grade ≤ 2 is allowed in case of alopecia, skin toxicity, asthenia and/or peripheral sensory neuropathy. 11. Patients of child-bearing potential must agree to use a medically approved contraception method until at least six weeks after the last study drug administration**.** **Patients in Cohorts A and A1** 12. Known deleterious germline mutation of BRCA1/2. **Patients in Cohort A1** 13. Prior treatment with PARP inhibitors.
Exclusion criteria	**All patients** 1. Prior treatment with PM01183 or trabectedin. 2. Prior RT in more than 35% of the bone marrow. 3. Prior or concurrent malignant disease unless in complete remission for more than five years. Exceptions are contralateral ductal or lobular breast carcinoma, adequately treated *in situ* carcinoma of the cervix, basal or squamous skin cell carcinoma, *in situ* melanoma, and *in situ* transitional bladder cell carcinoma, which are allowed to enter the study. 4. Histology other than ductal or lobular carcinoma of the

	breast. 5. Symptomatic, steroid requiring or progressive central nervous system (CNS) involvement. In case of known brain metastasis, clinical stability and lack of radiological progression of lesions should be demonstrated for at least the immediate six weeks before study entry. 6. Exclusively bone-limited disease. 7. Relevant diseases or clinical situations which may increase patient's risk: a. History of cardiac disease: myocardial infarction or symptomatic/uncontrolled angina within the year prior to enrollment; or congestive heart failure defined as abnormal left ventricular ejection fraction (LVEF) ≤ 50% assessed by multiple-gated acquisition scan (MUGA) or equivalent by ultrasound (US); or symptomatic or treatment-requiring arrhythmia. b. Grade ≥ 3 dyspnea or daily intermittent oxygen requirement c. Active uncontrolled infection. d. Unhealed wound or presence of any external drainage. e. Chronically active hepatitis B virus (HBV) or hepatitis C virus (HCV). f. Immunocompromised patients, including those known to be infected by human immunodeficiency virus (HIV). g. Known myopathy or persistent CPK elevations > 2.5 x ULN in two different determinations performed one week apart. 8. Pregnant or breastfeeding women. 9. Impending need for RT (uncontrolled painful bone metastasis and/or risk of spinal cord compression). 10. Limitation of the patient's ability to comply with the treatment or to follow-up the protocol. **Patients in Cohort B** 11. Known deleterious germline mutation of BRCA1/2.
No. of patients	About 110 evaluable patients are expected to be finally included in the three cohorts: Cohort A (BRCA+), Cohort A1 (BRCA+/PARPi), and Cohort B (unselected).
No. of sites	This is a multicenter study. A full list of investigators will be available as a separate document.

<table>
<tr><td>STUDY DRUG
Formulation</td><td>PM01183 drug product (DP) is presented as a lyophilized powder for concentrate for solution for infusion with two strengths, 1 mg and 4 mg vials, which will be supplied by the Sponsors for the purposes of this study.
Before use, the 1-mg vial and 4-mg vial should be reconstituted with 2 ml and 8 ml of water for injection, respectively, to give a solution containing 0.5 mg/ml PM01183. For administration to patients as an i.v. infusion, reconstituted vials should be diluted either 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 is 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>1.00 mg</td><td>4.00 mg</td><td>0.50 mg/ml</td></tr>
<tr><td>Sucrose</td><td>200.00 mg</td><td>800.00 mg</td><td>100.00 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>
<tr><td>Route of administration, starting dose, and schedule</td><td>Patients included under protocol versions 1.0 and 2.0 will receive PM01183 intravenously (i.v.) as a one-hour infusion on Day 1 q3wk at a starting dose of 7.0 mg (FD) (three weeks = one treatment cycle).
Patients included from protocol version 3.0 onward (after implementation of amendment no. 2) will receive PM01183 i.v. as a one-hour infusion on Day 1 q3wk at a starting dose of 3.5 mg/m^2 (three weeks = one treatment cycle). Dose will be capped at BSA of 2.0 m^2 (i.e., dose will not exceed 7 mg). BSA will be calculated according to standard practice at each center.
PM01183 will be administered over a minimum total volume of 100 ml of solution for infusion (either on 5% glucose or 0.9% sodium chloride) through a central catheter or over a minimum total volume of 250 ml if through a peripheral line, always over one hour at a fixed infusion rate.</td></tr>
<tr><td>Antiemetic prophylactic medication</td><td>Patients must receive standard antiemetic prophylactic medication at least 30 minutes before the administration of PM01183, as follows:
Corticosteroids (dexamethasone i.v. or equivalent at institutional standard antiemetic doses)
Serotonin (5-HT3) antagonists (ondansetron 8 mg i.v. or equivalent)
If necessary and in addition to the above, any of the following could apply:
Administration of 10 mg of metoclopramide (or equivalent) every eight hours
Extended treatment with 5-HT3 antagonists and/or</td></tr>
</table>

<table>
<tr><td></td><td>dexamethasone
Aprepitant and directly related agents (e.g., fosaprepitant) are forbidden.
An optimal antiemetic prophylaxis is defined, for the purpose of safety evaluations, as any of the aforementioned medications at their respectively maximum dosages.</td></tr>
<tr><td>Treatment continuation criteria</td><td>
<table>
<tr><th rowspan="2">Variable</th><th>Re-treatment</th></tr>
<tr><th>Day 1</th></tr>
<tr><td>ECOG-PS</td><td>≤ 2</td></tr>
<tr><td>Hemoglobin*</td><td>≥ 8.0 g/dl</td></tr>
<tr><td>ANC</td><td>≥ 1.5 x 10^9/l</td></tr>
<tr><td>Platelets</td><td>≥ 75 x 10^9/l</td></tr>
<tr><td>AST/ALT</td><td>≤ 3.0 x ULN</td></tr>
<tr><td>Total bilirubin or
direct bilirubin</td><td>≤ 1.5 x ULN or
x ULN</td></tr>
<tr><td>Albumin</td><td>≥ 2.7 g/dl</td></tr>
<tr><td>Serum creatinine</td><td>≤ 2.0 x ULN</td></tr>
<tr><td>CPK</td><td>Grade ≤ 1</td></tr>
<tr><td>Other non-hematological drug-related AEs (except isolated increased GGT and/or AP¥, grade 3 asthenia lasting < 1 week, non-optimally treated nausea and/or vomiting)</td><td>Grade ≤ 2</td></tr>
</table>
* Patients may receive packed red blood cells (PRBC) transfusion and/or erythropoietin (EPO) treatment, if clinically indicated, to increase/maintain adequate hemoglobin levels.
¥ Any grade accepted for non-drug-related increase of GGT and/or AP.
AE, adverse event; ANC, absolute neutrophil count; AP, alkaline phosphatase; AST/ALT, aspartate aminotransferase/alanine aminotransferase; CPK, creatinine phosphokinase; ECOG, Eastern Cooperative Oncology Group; GGT, gamma-glutamyltransferase; PS, performance status; ULN, upper limit of normal.

If a patient does not meet the requirements for re-treatment on Day 1 of any following cycle, regardless of the reason, re-assessments will be performed every 48-72 hours. Treatment will be then withheld, up to a maximum of three weeks beyond its due date, until appropriate recovery.
Patients not meeting re-treatment criteria after a maximum three-week delay must be withdrawn from the trial, except in case of objective clinical benefit (upon Sponsors' agreement).
For any delay lasting more than one week due to treatment-related toxicity (unless exclusively due to neutropenia), a dose reduction must be implemented upon recovery following the rules explained in the next section. Conversely, if the delay was exclusively due to neutropenia related to PM01183, treatment may continue without dose reduction but with appropriate secondary prophylaxis with granulocyte colony-stimulating factor (G-CSF).</td></tr>
</table>

Dose reduction criteria

Study treatment may continue with an appropriate dose reduction (see table below) if patient's benefit is perceived by the Investigator (upon Sponsors' agreement), even after the patient experienced any of the following:

- Grade ≥ 3 treatment-related non-hematological toxicity. Exceptions are: grade ≥ 3 nausea and/or vomiting not optimally treated, grade 3 asthenia lasting < 1 week, grade 3 diarrhea lasting ≤ 2 days or not optimally treated, grade 3-4 hypersensitivity and/or extravasation reactions, grade 3 transient ALT/AST elevations which are rapidly reversible and not leading to subsequent delays, and/or not clinically relevant biochemical abnormalities [i.e., in gamma-glutamyltransferase (GGT), lactate dehydrogenase (LDH) and/or alkaline phosphatase (AP) levels], none of which require dose reduction to be implemented.
- Grade 4 thrombocytopenia or grade 3 thrombocytopenia concomitantly with grade ≥3 bleeding.
- Frequent or prolonged (>1 week) dose delays due to treatment-related toxicity.

Patients experiencing grade 4 neutropenia or febrile neutropenia during the preceding cycle, or treatment delays exclusively due to neutropenia that lasted > 1 week, may continue treatment without any dose reduction but must receive secondary prophylaxis with G-CSF instead. The G-CSF secondary prophylaxis will be administrated subcutaneously at 300 μg/day for five consecutive days starting on Day +3 of the corresponding cycle. If despite appropriate G-CSF prophylaxis, grade 4 neutropenia or febrile neutropenia re-occurs, then dose reduction should be implemented.

The guidelines for dose reduction are shown in the table below:

Dose reduction level*	**PM01183 dose (mg, FD)** Patients included under protocol versions 1.0, 2.0	**PM01183 dose (mg/m^2)** Patients included from protocol version 3.0 onward**
1	7.0	3.5
−1	6.0	2.6
−2	5.0	2.0

* Except for grade ≥ 3 nausea and/or vomiting not optimally treated, grade 3 asthenia lasting < 1 week, grade 3 diarrhea lasting ≤ 2 days or not optimally treated, grade 3-4 hypersensitivity and/or extravasation reactions, grade 3 transient ALT/AST elevations which are rapidly reversible and not leading to subsequent delays, and/or not clinically relevant biochemical abnormalities (i.e., in GGT, LDH and/or AP levels), none of which require dose reduction to be implemented.

**Dose will be capped at BSA of 2.0 m^2 (starting dose will not exceed 7 mg). BSA will be calculated according to standard practice at each center.

ALT/AST, aspartate aminotransferase/alanine aminotransferase; AP, alkaline phosphatase; FD, flat dose GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase.

Up to two dose reductions are allowed per patient.

Once the dose has been reduced for an individual patient, it will not be re-escalated under any circumstances.

Allowed medication/therapy	• Therapies for pre-existing and treatment-emergent medical conditions, including pain management. • Blood products and transfusions, as clinically indicated. • Bisphosphonates. • In case of nausea or vomiting, secondary prophylaxis and/or symptomatic treatment for emesis according to American Society of Clinical Oncology (ASCO) guidelines. • Erythropoietin (EPO) according to ASCO guidelines. • Granulocyte colony-stimulating factor (G-CSF) for the treatment of grade 4 neutropenia, any grade febrile neutropenia or neutropenic infection. After Cycle 1, secondary prophylaxis is allowed if applicable. • Anticoagulation therapy for the treatment or secondary prophylaxis of deep vein thrombosis. • Luteinizing hormone-releasing hormone (LHRH) agonists, in women of reproductive age.
Prohibited medication/therapy	• Concomitant administration of any other antineoplastic therapy, except therapy with LHRH agonist if applicable. • Any other investigational agents. • Immunosuppressive therapies other than corticosteroids. • Primary G-CSF prophylaxis or treatment of non-febrile grade $\leq$ 3 neutropenia with G-CSF (unless previously agreed case-by-case between the Investigator and the Sponsor). • Aprepitant, fosaprepitant, and directly related compounds. • Radiotherapy (RT), except for limited-field bone radiation for pain control purposes.
PM01183 drug-drug interactions	*In vitro* studies using human liver microsomes have shown that PM01183 has the potential to inhibit cytochrome CYP2B6, CYP2C8 and CYP3A4. Moreover, the Ki values compared with the achieved maximum plasma concentration (C_{max}) values at relevant doses indicate that the likelihood of a clinically relevant inhibition of PM01183 is possible for CYP2B6 and CYP2C8 ([I]/Ki>0.1) and likely for CYP3A4 ([I]/Ki>1). Additional *in vitro* studies have demonstrated no time dependent inhibition or irreversible inhibition for cytochrome CYP3A4. The magnitude of the interaction is unknown at present. Therefore, caution should be exercised when PM01183 is administered concomitantly with CYP2B6, CYP2C8 and CYP3A4 substrates. Additionally, *in vitro* studies with human microsomes have shown that CYP3A4 is the major CYP isoform involved in the metabolism of PM01183, followed by CYP2E1, CYP2D6 and CYP2C9. The estimated contribution of the other CYP isoenzymes to the PM01183 metabolism is considered to be

	negligible. Therefore, concomitant drugs which induce or inhibit any of these cytochromes, especially CYP3A4, should be carefully monitored or avoided, whenever is possible. A potentially significant interaction with aprepitant is suggested by available phase II data from ovarian cancer patients. Four patients treated with aprepitant in Cycle 2 with available PK data had their PM01183 clearance reduced by 50%, approximately, compared to their Cycle 1 exposure. Aprepitant use was forbidden in Cycle 1 in all patients. Clinically, some of these patients had unusually long-lasting neutropenia and/or severe thrombocytopenia during Cycle 2 as well. Although all patients eventually recovered, the use of aprepitant is currently forbidden in all phase II/III PM01183 studies.
EFFICACY EVALUATIONS	The primary objective of the study is to assess the antitumor activity of PM01183 as the **overall response rate** (**ORR**), defined as the percentage of evaluable patients with a response, either complete (CR) or partial (PR). Overall response rate (ORR) will be assessed using RECIST v1.1, on a set of measurable lesions identified at baseline as target lesions, and non-target lesions (if any) identified at baseline as non-target lesions and followed until PD by an appropriate method [helical computerized tomography (CT) scan, magnetic resonance imaging (MRI) and/or clinical assessment]. Radiological and/or clinical (whenever appropriate) tumor assessment will be performed at baseline and every six weeks (two cycles) until Cycle 6 or evidence of PD. After Cycle 6, tumor assessment will be performed every nine weeks (three cycles) until evidence of PD. If an objective response is observed, according to RECIST v1.1, it must be confirmed by the same method at least four weeks after the date of the first documentation of response. The date of response, the date of clinical or radiological PD, and the date of death will be registered and documented as appropriate. A copy of the imaging tests conducted on the patients during this clinical trial may be requested by the Sponsor for evaluation. In addition, an independent radiological review committee may be set up, upon Sponsors' request, to review tumor assessment performed for all responding patients (partial or complete response) after study completion. Patients will be categorized as "treatment failure" if: • Discontinue treatment due to any treatment-related toxicity before an appropriate tumor assessment has been performed, or • Withdraw PM01183 after more than two weeks on treatment without any formal evaluation. These data will be included as non-evaluable (NE) in the

<table>
<tr><td></td><td>analysis of objective response as per RECIST v1.1, although these patients will not need to be replaced as they will be considered evaluable for efficacy.</td></tr>
<tr><td>BRCA1/2 germline mutation analysis</td><td>In patients included in Cohort B who respond to PM01183 treatment and whose BRCA 1/2 mutation status is unknown at study entry, an analysis will be performed in order to confirm or exclude deleterious germline BRCA 1/2 mutation. To this end, a blood sample will be collected at the time of response.</td></tr>
<tr><td>SAFETY EVALUATIONS</td><td>Patients will be evaluable for safety if they received at least one partial or complete infusion of PM01183.
All adverse events (AEs) will be graded according to NCI-CTCAE v4.
The safety profile of patients will be monitored throughout treatment and up to 30 days after the last PM01183 infusion (EOT) or until the date of death, whichever occurs first.
Treatment delays, dose reduction requirements, G-CSF and/or transfusions requirements, and reasons for treatment discontinuation will be monitored throughout the study.
Any treatment-related AEs will be followed until recovery to grade ≤ 1 or stabilization of symptoms, whenever possible.</td></tr>
<tr><td>PHARMACOKINETICS</td><td>PK parameters of plasma PM01183 will be evaluated immediately before and during the first two cycles with a limited sampling schedule of ten samples in at least 30 treated patients in cohorts A or B. The sampling schedule during each cycle will be as shown below.

<table>
<tr><th>Sample</th><th>Time</th></tr>
<tr><td># 1</td><td>Before infusion</td></tr>
<tr><td># 2</td><td>5 min before the end of the infusion (EOI)</td></tr>
<tr><td># 3</td><td>15 minutes after EOI</td></tr>
<tr><td># 4</td><td>1 hour after EOI</td></tr>
<tr><td># 5</td><td>2 hours after EOI</td></tr>
<tr><td># 6</td><td>4 hours after EOI</td></tr>
<tr><td># 7*</td><td>5 hours and 30 min after EOI</td></tr>
<tr><td># 8**</td><td>24 hours after EOI</td></tr>
<tr><td># 9***</td><td>72 hours after EOI</td></tr>
<tr><td># 10****</td><td>168 hours after EOI</td></tr>
</table>
* There is a 30-minute window (before and after the stated point) in the sampling time.
** There is a two-hour window (before and after the stated point) in the sampling time.
*** There is a two-hour window before the stated point, or until 24 hours after the stated point in the sampling time (this sample must be collected within Day 4 or 5).
**** Preferred time; if weekends or other reasons make the sampling on time difficult, it may be obtained with a 24-hour window before or after the stated time. In any case, the sampling time should differ by at least 24 hours from the prior sample.
EOI, End of Infusion; h, hour(s); min, minutes.</td></tr>
</table>

	PK parameters will be calculated using non-compartmental analysis (NCA) and population methods, after pooling data from this study with data obtained from other PM01183 clinical studies.
PHARMACOGENOMIC (PGx) SUBSTUDY	**<u>Objective</u>** The main objective of the PGx study (optional for cohorts A and B, required for cohort A1) is the identification of potential biomarkers of sensitivity or resistance to PM01183 and whose expression might be predictive of the clinical outcome after treatment with PM01183. **<u>Requirements</u>** • PM01183-treated patients with prior paraffin-embedded tumor samples, if available. • For cohorts A and B, patients who voluntarily sign the ICF for the PGx study will participate (refusal will not affect patient participation in the clinical study PM1183-B-003-11). • For cohort A1, availability of a baseline (taken at any time between the end of last antitumor therapy and before first study drug infusion) tumor biopsy is also required. For those patients whose disease is not amenable to tumor biopsy, approval by the Sponsors must be requested prior to inclusion. **<u>Pharmacogenomic evaluations</u>** Potential biomarkers of PM01183 activity will be analyzed on paraffin-embedded tumor samples obtained at baseline. Additionally, if archived tumor samples are available from the primary tumor and/or from metastases, analyses will be performed in both. Samples will be labeled according to its origin: diagnosis (primary tumor or metastasis) or baseline sample. The expression levels and subcellular localization of selected molecules involved in different DNA repair mechanisms, such as nucleotide excision repair (e.g., XPG), homologous recombination repair (e.g., RAD51), among others, will be analyzed. Specifically, mRNA and protein from tumor samples will be subjected to quantitative reverse transcription polymerase chain reaction (qRT-PCR) and immunohistochemistry (IHC) in tissue microarrays (TMA), and immunofluorescence in whole tumor sections. The polymorphisms and mutational status of genes involved in DNA repair mechanisms or related to the mechanism of action of PM01183 or to the disease might also be analyzed, if relevant.

STATISTICAL METHODS	**Primary Endpoint** • Overall response rate (ORR), according to RECIST v1.1. **Secondary Endpoints** • Duration of response (DR). • Clinical benefit, defined as the percentage of patients with ORR or SD > 3 months, according to RECIST v1.1. • Progression-free survival (PFS). • Overall survival rate at one year (1y-OS). • Treatment safety: AEs, serious AEs (SAEs) and laboratory abnormalities will be graded according to the NCI-CTCAE (v4). • PK analysis and PK/PD correlation, if applicable. • PGx expression profile, in tissues from tumor samples. **Sample Size Considerations** The primary endpoint for this phase II study is to evaluate ORR. • Cohort A (BRCA+): At least 53 evaluable patients will be recruited to test the null hypothesis that ORR is 20% or less ($p \leq 0.20$) *vs.* the alternative hypothesis that 40% or more patients have objective response ($p \geq 0.4$). With these assumptions, if the number of evaluable patients with objective response is ≥ 17, then this would allow the rejection of the null hypothesis. • Cohort A1 (BRCA+/PARPi): At least 20 evaluable patients will be recruited for an exploratory analysis: if the number of patients responding is ≥ 4 (20%), the lower limit of the exact binomial 95% confidence interval will be higher than 5% and lack of activity in this subpopulation will be ruled out. • Cohort B (unselected): At least 64 evaluable patients will be recruited to test the null hypothesis that ORR is 10% or less ($p \leq 0.10$) *vs.* the alternative hypothesis that 25% or more patients have objective response ($p \geq 0.25$). With these assumptions, if the number of evaluable patients with objective response is ≥ 12, then this would allow the rejection of the null hypothesis. The variance of the standardized tests is based on the null hypothesis. The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is <0.1; hence, statistical power is > 90%. Futility analyses controlled by the Gamma family boundary will be performed when 20 and 30 patients have been evaluated in cohorts A [Gm(-2)] and B [Gm(-1.5)], respectively. If less than four out of 20 patients in Cohort A,

	or less than three patients out of 30 in Cohort B achieve an objective response, recruitment to that cohort will be stopped. About 110 evaluable patients are expected to be included finally in the three cohorts: Cohort A (BRCA+), Cohort A1 (BRCA+/PARPi), and Cohort B (unselected). **Safety Stopping Rule** In addition to sample size considerations, a decision for early study termination due to safety issues will be taken within the initial 30 evaluable patients (regardless of the cohort), whenever any of the following occurs: • Two or more eligible patients die due to treatment-related AEs (>5% of related deaths), or • Ten or more patients need to discontinue treatment within the first two cycles due to any grade 4 treatment-related AEs (NCI-CTCAE v4).
DURATION OF STUDY PERIOD (per patient)	Patients will be individually evaluated at scheduled visits within three study periods: • **Screening:** from signature of the ICF to first infusion of PM01183. • **Treatment:** from the first infusion of PM01183 to **end of treatment** (EOT). **EOT** is defined as 30 days after the date of PM01183 last administration, unless the patient starts a new antitumor therapy or dies within those 30 days, in which case the date of administration of this new antitumor therapy or the date of death will be considered as EOT. • **Follow-up:** after EOT, patients will be followed for any ongoing treatment-related AEs every four weeks until recovery to grade ≤1, or until symptoms stabilization whenever possible. Patients will be followed for at least one year after their first infusion. Those who discontinued treatment without PD will be assessed every two months during the first six months after last tumor assessment and every three months thereafter, until PD, start of other antitumor therapy, death, or study completion, whichever occurs first. After documented PD or start of a new antitumor therapy, patients will be followed every six months until death or study completion, whichever occurs first (a documented phone contact will be acceptable). Patients will be considered to be **on-study** from the signature of the clinical ICF to the end of the follow-up period (or screening failure). Patients will be considered to be **on-treatment** from the date of first infusion until EOT.

TREATMENT DISCONTINUATION	Patients will receive study medication as long as it is considered to be in their best interest. Specifically, treatment will continue until: • Disease progression. • Unacceptable toxicity (except in case of clear clinical benefit, with the Sponsors' approval), after appropriate dose reduction. • Intercurrent illness of sufficient magnitude to preclude safe continuation of the study. • Patient refusal and/or noncompliance with study requirements. • Investigator's decision. • Protocol deviation with an effect on the management of the patient's risk/benefit ratio. • Treatment delay > 3 weeks from the treatment due date (except in case of clear clinical benefit, upon Sponsors' approval). • Requirement of > 2 dose reductions.
REPLACEMENT OF PATIENTS	Patients will be replaced if they are not evaluable for the primary endpoint of the study (ORR as per RECIST v1.1), specifically (any of the following): • They are not eligible. • They have not been treated or have not completed at least one PM01183 infusion. • They are not evaluable for ORR as per RECIST v1.1 and they are not categorized as "treatment failures". Treatment failures will not be replaced and are defined as patients who: o Discontinue treatment due to any treatment-related toxicity before an appropriate tumor assessment has been performed, or o Withdraw PM01183 after more than two weeks on treatment without any formal evaluation All replaced patients who received treatment will be included in the general safety analysis, if appropriate.
DURATION OF STUDY (as a whole)	The total duration of the study will be approximately 72 months. **Planned start date** (first patient on study): second quarter 2012 (2Q12). **Planned enrollment period**: 60 months. **Planned study completion date** (clinical cut-off): nine months after the last patient-last treatment visit in the study, or 12 months after the last evaluable patient is enrolled (whichever occurs first).

SCHEDULE OF ASSESSMENTS AND PROCEDURES

STUDY PERIODS [1] / PROCEDURES		Screening (days)	Treatment							Follow-up [2]
			Cycle 1			Cycle 2		Further Cycles	End of treatment (EOT)	
			D1	D8	D15	D1	D10	D1		
Written informed consent		Before any study procedure	-	-	-	-	-	-	-	-
Written informed consent - PGx substudy (optional for cohorts A and B)		Before any study procedure	-	-	-	-	-	-	-	-
Demographic data		-28 to 0	-	-	-	-	-	-	-	-
Primary diagnosis & prior treatment(s)		-28 to 0	-	-	-	-	-	-	-	-
Medical history & prior conditions		-14 to 0	-	-	-	-	-	-	-	-
Assessment of signs and symptoms		-7 to 0	-	-	-	-	-	-	-	-
PM01183 administration		NA	•	-	-	•	-	•	-	-
Complete physical examination, including weight and height [3]		-7 to 0	-	-	-	•	-	•	•	-
Performance status (ECOG)		-7 to 0	-	-	-	•	-	•	•	-
Vital signs (heart rate, blood pressure, temperature)		-7 to 0	-	-	-	•	-	•	•	-
Coagulation panel		-7 to 0	-	-	-	•	-	•	•	-
Hematology [4]		-7 to 0	-	•	•	•	•	•[5]	•	-
Biochemistry A [4]		-7 to 0	-	•	•	•	•	•[5]	•	-
Biochemistry B		-7 to 0	-	-	-	•	-	•	•	-
Pregnancy test [6]		-7 to 0	Repeat if clinically indicated							-
ECG [7]		-7 to 0	Repeat if clinically indicated							-
LVEF by ECHO or MUGA		-28 to 0	Repeat if clinically indicated							-
Radiological and/or clinical tumor assessment[8]		-28 to 0	Every 6 weeks until Cycle 6 and every 9 weeks thereafter [9]							• [10]
Pharmacokinetics (PK) [11]		-	Immediately before and during Cycles 1 and 2 only.						-	-
PGx (paraffin embedded tumor tissue) [12]	From available prior tumor samples	-	-							-
	From a recent biopsy (cohort A1)	After last treatment to 0								
Intercurrent events, concomitant diseases and treatments		-14 to 0	Throughout the "on-treatment period"							-
Adverse events (AEs)		NA [13]	Throughout the "on-treatment period"							• [13]
BRCA1/2 germline mutation analysis		• [14]	BRCA unknown patients in cohort B: One blood sample at the time of the response [15]							-

→ See footnotes on next page

Footnotes refer to table on previous page

1. A 3-day window will be allowed for laboratory procedures, a 14-day window for radiological procedures (helical CT-scan or MRI) and LVEF assessments, a 24-hour window for clinical assessments (ECOG, physical examination, vital signs, ECG, weight, BSA, etc.), and a 7-day window for the assessments at end of treatment.
2. After documented progression or start of new antitumor therapy, patients will be followed every six months, until death or study completion, whichever occurs first.
3. Height is only required at baseline.
4. **Any patient presenting a grade ≥ 3 treatment-related AE should have all relevant tests re-assessed at least every 48-72 hours until recovery to grade ≤ 2.**
5. From Cycle 3 onwards Hematology and Biochemistry A tests on Day 10 are to be performed only in patients who experienced non-hematological grade ≥3 or hematological grade 4 treatment-related toxicities, or who required any dose adjustments or GSF prophylactic therapy, in the preceding cycle.
6. In patients of childbearing potential only; if serum human chorionic gonadotropin (HCG) results are abnormally high, pregnancy must be clinically discarded by an additional test (i.e. US) before any other study procedure. Pregnancy and suspected pregnancy occurring while the patient is on study drug or within six weeks from the patient's last PM01183 administration are considered immediately reportable events.
7. Cardiac rhythm will be identified in ECG intervals of at least 30 seconds of duration, PR interval, QT interval (raw), heart rate (HR) and QRS complex.
8. Contrast enhanced helical CT-scan or MRI as clinically indicated of all measurable sites of disease involvement and of all non-measurable sites of disease should be done at baseline by appropriate testing (radiological and/or clinical). While on treatment, appropriate evaluation of all original sites of disease involvement at baseline, should be done as per RECIST v.1.1. Should be repeated at end of treatment visit, if not previously done, and if the reason for treatment discontinuation was other than PD. The same initial method must be used throughout the study.
9. Patients showing a response must have a confirmatory assessment at least 4 weeks later. Patients with previously known CNS involvement at study entry must have documented non-PD by appropriate method at baseline.
10. Only patients who discontinued treatment without PD will be assessed radiologically and/or clinically as appropriate. The assessments will be performed every two months during the first six months after last tumor assessment and every three months thereafter until PD, start of other antitumor therapy, death, or study completion, whichever occurs first.
11. In at least 30 treated patients in cohorts A or B.
12. Prior available stored paraffin-embedded tumor samples from the primary tumor and/or from metastases. For Cohort A1 patients only: a baseline tumor biopsy must also be available (taken at any time between the end of last antitumor therapy until before first study drug infusion). For cohort A1patients whose disease is not amenable to tumor biopsy, approval by the Sponsors must be requested prior to inclusion. In any case, the origin of the sample must be specified: diagnosis (primary tumor or metastasis) or baseline sample.
13. From ICF signature to PM01183 treatment only SAEs must be reported. After the end of treatment, all AEs and SAEs suspected to be related to PM01183 must be followed-up until recovery to grade ≤ 1 or symptoms stabilization.
14. To be conducted on patients with unknown germline BRCA mutation status who meet criteria for consideration of BRCA 1/2 genetic testing, according to the National Comprehensive Cancer Network (NCCN) (see Appendix 3).
15. In patients included in Cohort B who respond to PM01183 treatment and whose BRCA 1/2 mutation status is unknown at study entry, an analysis will be performed in order to confirm or exclude deleterious germline BRCA 1/2 mutation. To this end, a blood sample will be collected at the time of response.

Coagulation: PT/INR and PTT.
Hematology: Hemoglobin, platelet counts, and differential WBC including neutrophils, monocytes and lymphocytes.
Biochemistry A: Serum electrolytes (Na^+, K^+, Cl^-), AST, ALT, AP, GGT, total bilirubin (direct bilirubin to be measured only if total bilirubin is abnormally high), LDH, creatinine, glucose, and CPK (CPK-MB fraction and troponin T or I should only be measured if CPK is abnormally high or if clinically indicated).
Biochemistry B: Total proteins, albumin, CRP, Ca^{++}, phosphorus, Mg^{++}. CA 15-3 or 27.29 will be measured at baseline and repeated thereafter only in those patients with abnormally elevated values at baseline. Alpha-1 acid glycoprotein, total cholesterol, triglycerides, and LDL will be evaluated at baseline and before Cycle 2 only.

AE(s), adverse event(s); ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CA-15-3 or 27.29: cancer antigens 15-3 and 27-29 respectively; CNS, central nervous system; CPK, creatinine phosphokinase; CPK-MB, creatinine phosphokinase MB isoenzyme; CRP, C-reactive protein; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG-PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; GGT, gamma glutamyltransferase; HCG, human chorionic gonadotropin; HR, heart rate; ICF, informed consent form; 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; NA, not applicable; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, progressive disease; PGx, pharmacogenomic(s); PK, pharmacokinetic(s); PT, pro-thrombin time; PTT, partial thromboplastin time; US, ultrasound; WBC, white blood cells.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

5-HT_3	Serotonin
ADR	Adverse Drug Reaction
AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AUC	Area Under the Curve
AUC_{inf}	Area Under the Curve from time zero to infinity
AP	Alkaline Phosphatase
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BRCA1/2	Breast Cancer 1 or Breast Cancer 2 Gene
BSA	Body Surface Area
CA 15-3	Cancer Antigen 15.3
CA 19-9	Cancer Antigen 19-9
CA 27.29	Cancer Antigen 27.29
CI	Confidence Interval
CL	Clearance
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CPK MB	Creatine Phosphokinase Isoenzyme-MB fraction
CR	Complete Response
CRC	Colorectal Cancer
CrCl	Creatinine Clearance
CRF	Case Report Form
CT	Computed Tomography
DLT	Dose-limiting Toxicity
DNA	Deoxyribonucleic Acid
DP	Drug Product
DR	Duration of Response
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
ECG	Electrocardiogram

ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EOI	End of Infusion
EOT	End of Treatment
EPO	Erythropoietin
ER	Estrogen Receptor
FD	Flat Dose
FFS	Fast Fact Sheet
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-stimulating Factor
GGT	Gamma-glutamyltransferase
GMT	Greenwich Meridian Time
Gy	Grays
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCG	Human Chorionic Gonadotropin
HER-2	Human Epidermal Growth Factor Receptor 2
HR	Heart Rate
HIV	Human Immunodeficiency Virus
[I]	Inhibitor Concentration
IB	Investigator's Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Investigational Ethics Committee
i.v.	Intravenous(ly)
IG_{50}	Half Maximal Growth Inhibition
IHC	Immunohistochemistry
INR	International Normalized Ratio
IRB	Institutional Review Board
k	Terminal Rate Constant
k_i	Dissociation Constant for Inhibitor Binding
LDH	Lactate Dehydrogenase
LHRH	Luteinizing hormone-releasing hormone
LVEF	Left Ventricular Ejection Fraction
MAb	Monoclonal Antibody

MBC	Metastatic Breast Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MTMD	Multiple Maximum Tolerated Multiple Dose
MUGA	Multiple-gated Acquisition Scan
NCA	Non-compartmental Analysis
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
ORR	Overall Response Rate
OS	Overall Survival
PARP	Poly (ADP-ribose) Polymerase
PARPi	Poly (ADP-ribose) Polymerase Inhibitor
PD	Progressive Disease / Pharmacodynamic(s)
PFS	Progression-free Survival
PFS6	Progression-free Survival Rate at Six Months
PGx	Pharmacogenomics
PhV	Pharmacovigilance
PK	Pharmacokinetics
PR	Partial Response
PRBC	Packed Red Blood Cells
PS	Performance Status
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
q3wk	Every Three Weeks
qRT-PCR	Reverse Transcription Polymerase Chain Reaction
RBC	Red Blood Cell
RD	Recommended Dose
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic Acid
RT	Radiotherapy
SAE(s)	Serious Adverse Event(s)
SD	Stable Disease
SUAE	Serious Unlisted Associated Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction

$t_{1/2}$	Half-life
T/C	Therapy Over Control
TMA	Tissue Microarray
TN	Triple Negative
Uk	Unknown
ULN	Upper Limit of Normal
US	Ultrasound
vs.	*Versus*
WBC	White Blood Cells
Wk	Week(s)
WMA	World Medical Association

1. INTRODUCTION

1.1. BREAST CANCER

Breast cancer is the most common cancer in women in western countries. Worldwide, it is estimated that more than one million women are diagnosed annually and that more than 410,000 will die of the disease (1), thus ranking as second and third cause of cancer-related death in women in US and Europe respectively (2, 3).

Despite the many advances that have been achieved in the treatment of breast cancer, the prognosis for patients with metastatic breast cancer (MBC) remains poor (4). Breast cancer is a heterogeneous disease in which a strong interplay between genetic and environmental factors seems crucial to define the disease phenotype and clinical behavior. Significant advances have been made in the characterization of different breast cancer types according to molecular features and gene expression profile, in addition to other existing classifications focused primarily upon cell morphology and histology. These findings support that breast cancer is in fact a group of miscellaneous diseases with possibly different pathogenesis and natural history. Perhaps most importantly, this would allow that clinically relevant subgroups to be specifically targeted or treated differently depending on the presence or absence of some of these characteristics (5, 6).

It is currently estimated that 5-10% of all breast cancers are hereditary due to germline mutations in BRCA 1 and/or BRCA 2 genes. The BRCA 1 and BRCA 2 proteins participate in deoxyribonucleic acid (DNA) repair and homologous recombination as well as other cellular processes (7). There has been a long debate regarding the prognosis of hereditary breast cancers as compared to that of sporadic disease. Several retrospective trials have failed to demonstrate a worst prognosis in BRCA 1/2 mutated breast cancers. However, the fact that disease with both a lack of hormone receptors and a lack of human epidermal growth factor receptor 2 (HER-2) overexpression, known as triple negative (TN) breast cancer, is more common in BRCA-mutated patients has re-opened the debate. In particular, BRCA 1-associated hereditary breast cancer might be a more aggressive form of disease than sporadic breast cancer, with medullar or atypical features, p53 mutations and/or overexpression, high level expression of epithelial growth factor (EGF) and Ki-67, and absence of HER-2 overexpression (8). BRCA 2 mutations are heterogeneous and often present in relatively high grade tumors which display substantially less tubule formation (9). Moreover, BRCA 1/2 mutated breast cancer has recently come into focus due to the development of new molecules able to inhibit the poly (ADP-ribose) polymerase (PARP), a nuclear enzyme responsible for signaling in the presence of DNA damage facilitating recognition and repair of DNA by specific enzymes such as BRCA 1/2 proteins. Indeed, BRCAness tumors are more sensitive to PARP inhibition than wild type tumors, which may escape through alternative pathways to such inhibition. Thus, the possibility of selectively target these tumors had brought along a lot of interest. Though comparative trials are still pending to define a role for these molecules, promising response rates up to 41% were recently reported in a phase II trial in advanced breast cancer with a novel oral PARP inhibitor, olaparib (10).

Metastatic disease at diagnosis is uncommon in breast cancer, occurring in only 6% of newly diagnosed cases (11). Nevertheless, approximately 30% of women initially diagnosed with early breast cancer will eventually develop recurrent advanced or metastatic disease, despite effective adjuvant treatment. In fact, the majority of breast

cancer patients die as a result of complications from recurrent or metastatic disease. Unfortunately, metastatic disease remains incurable, with the goal of therapy being tumor control and symptoms palliation with a survival improvement. The median survival time of MBC patients is usually between 18 to 30 months.

There is no single standard of care for MBC patients, as treatment plans require an individualized approach based on multiple factors. As aforementioned, these include both disease and patient-related factors such as: specific tumor biology, disease growth rate, presence or absence of visceral metastases, history of prior therapy and tumor responsiveness, age and menopausal status, specific toxicities risk, and patient preferences (4).

A growing pool of treatments have increased the response rates, the progression-free survival (PFS), and/or the overall survival (OS) of MBC patients (12). After the introduction of taxanes, trastuzumab, vinorelbine and capecitabine in the mid-to-late 1990s, the last decade has seen the arrival of anastrozole, letrozole, exemestane, fulvestrant, gemcitabine, ixabepilone, nanoparticle albumin-bound paclitaxel (nab-paclitaxel), bevacizumab, and lapatinib to the current available therapeutic arsenal. Eribulin was approved by EMA in 2011, and the list is continuously growing. Such a wide range of available treatment options makes rather difficult to set a unique standard above the others, although it seems logical that patients with HER-2 overexpressing tumors must have trastuzumab as part of the upfront treatment (13). Apart from bevacizumab, these novel agents essentially act at the same level as other previously available molecules such as aromatase inhibitors, estrogen receptor (ER) blockers, antimicrotubule interactive agents, antimetabolites and HER-2 blockers.

Once the first-line treatment of MBC has failed, management becomes more challenging. The likelihood of response subsequently decreases by approximately one half with respect to each prior regimen the patient has received. Hence, response rates may be as high as 60-80% with first-line treatment in patients, while they may only reach between 30%, and 15% in patients who have received two or three regimens respectively (14). Hormonal therapy tends to have a lesser role in pretreated progressing metastatic patients, as endocrine resistance is common in this setting. The use of anthracyclines and taxanes in early settings makes subsequent treatment selection more challenging and drug resistance often limits therapeutic options. Drugs with novel mechanism of action, likely to lack cross-resistance with other established or commonly used agents, are thus needed for pretreated MBC patients, particularly after second-line failure (15).

1.2. INFORMATION ON STUDY DRUGS

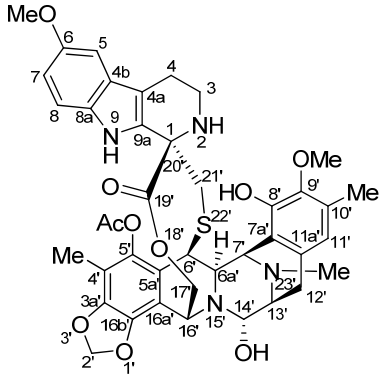
1.2.1. PM01183

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. Chemical structure of PM01183.



1.2.1.1. Non-clinical Data

1.2.1.1.1. Antineoplastic Activity In Vitro

PM01183 is a new chemical entity, structurally related to trabectedin, which also binds the deoxyribonucleic acid (DNA) minor groove, leading to the formation of DNA double-strand breaks, thus inducing apoptosis and delaying progression through the cell cycle S/G2 phase (16). PM01183 has a negative COMPARE analysis (17) when compared against other 98 standard anticancer agents in a panel of 36 cell lines. Thus, its mechanism of action is likely to differ significantly from theirs. As expected, based on preclinical data, PM01183 only showed a positive correlation (S-rank > 0.8) with trabectedin (18).

In vitro, PM01183 has shown broad cytotoxic activity against different tumor derived cell lines. In breast cancer, cytotoxic activity was observed in BT-474, MCF-7, and MDA-MB-231 cell lines (half maximal growth inhibition, IG_{50}: 1.3 10^{-9} M, 1.7 10^{-9} M and 3.5 10^{-9} M, respectively).

1.2.1.1.2. Antineoplastic Activity In Vivo

The *in vivo* "Proof of Concept" for PM01183 was accomplished by using a panel of six human 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. Tumor growths in PM01183-treated animals were monitored and compared with those of the untreated group. PM01183 demonstrated a statistically significant antitumor activity (p<0.05) against breast, colon, gastric, and kidney xenografts at different time points during the experiment.

The antitumor effectiveness of PM01183 was further analyzed in human derived xenografted tumors, namely breast (MAXF 401) and prostate (22RV1), after determination of maximum tolerated multiple dose (MTMD) levels in athymic mice. Specifically, PM01183 was administered in two different schedules: two doses on Days 0 and 14, or five consecutive doses repeated on Days 0-4 and 14-18 (qdx5x2); the MTMD values were determined as 0.3 mg/kg and 0.06 mg/kg (0.9 and 0.18 mg/m^2), respectively. Also, the effect of therapy over control (T/C) was assessed. Partial or complete remissions of tumors were seen in the MAXF 401 model, showing the strongest activity at 0.3 mg/kg (0.9 mg/m^2) on Days 0 and 14 (T/C = 0.0 % on Day 35).

PM01183 was further evaluated for *in vivo* activity in breast (MDA-MB-231 and MX-1 cell lines) as well as in other xenografted models. PM01183 demonstrated antitumor

activity in breast, kidney, ovary and lung, but had a more moderate antitumorigenic profile against bladder, pancreas and prostate.

For more information on preclinical PK and safety pharmacology data refer to PM01183 Investigator's Brochure (IB).

1.2.1.2. PM01183 Clinical Data

As of November 2011, the first-in-human clinical study with PM01183 (PM1183-A-001-08) has been completed. This study was started in March 2009 based on the promising preclinical results. 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 recommended dose (RD) of PM01183 for phase II studies, when administered as a single one-hour i.v. infusion every three weeks (q3wk). The RD was defined at 4.0 mg/m^2/q3wk; after pharmacokinetic (PK) data analysis, PM01183 clearance (CL) was found to be unrelated to body surface area (BSA) and, consequently, all remaining patients (n=9) at the RD in the expansion cohort were treated at an equivalent flat dose (FD) of 7.0 mg q3wk. Overall, 15 patients were treated at the RD level and only one had a dose-limiting toxicity (DLT), that consisted of a grade 4 thrombocytopenia. Preliminary results were presented in 2010 at the 22nd Annual Symposium on Molecular Targets and Cancer Therapeutics (19).

Toxicity was generally mild and reversible. Standard antiemetic prophylaxis was made compulsory at the RD to prevent moderate nausea and/or vomiting. Myelosuppression, particularly grade 4 non-febrile neutropenia, was the most relevant toxicity (found in 40% of patients treated at the RD). Neutropenia was short-lasting and caused no treatment delays at the RD, with nadir generally occurring during the second week (Day +13). This hematological event lasted a median of three days without requiring colony-stimulating factors treatment. The severity of neutropenia correlated more closely with the observed PM01183 area under the curve (AUC) than with the dose administrated according to body surface. Treatment was very well tolerated by the majority of patients and there were no treatment-related deaths in this highly selected patient population. Of note, despite patients were eligible with ECOG performance status (PS) between 0 and 2 and no maximum limit of age was set in this trial, none of the patients treated at the RD were PS=2 or over 75 years-old. Therefore caution should be used concerning the generalization of the data obtained in this trial. In particular, previous findings may apply to younger and less symptomatic patients but not to particularly vulnerable populations at greater risk for myelosuppression, such as elderly and highly symptomatic cancer patients.

Regarding the antitumor activity, 14 of the 15 patients treated at the RD were evaluable for efficacy, and seven among them had been diagnosed with colorectal cancer (CRC). This was also the most frequent tumor type in the study, with nearly 60% of all treated patients having CRC; it is worth mentioning that none of the 31 treated patients had breast cancer in this study. One patient with a progressive, refractory pancreatic adenocarcinoma had a confirmed partial response (PR) as per the Response Evaluation Criteria in Solid Tumors (RECIST) after three cycles of PM01183, and also had serum tumor marker [cancer antigen 19-9 (CA 19-9)] normalization after the fourth cycle. Three other patients with previously progressing tumors at study entry (one melanoma and two soft tissue sarcomas) had clinically meaningful disease stabilizations lasting around six months. This finding further supported that clinically active PM01183

concentrations are achieved at the RD (7.0 mg FD) as one-hour i.v. infusion q3wk, and that this dose is safe and tolerable in solid tumor relapsed/refractory patients.

Phase II studies, using this RD, in metastatic pancreatic cancer as second-line treatment after gemcitabine-based therapy failure and in platinum-resistant or refractory advanced ovarian cancer are currently ongoing.

1.3. STUDY RATIONALE

Metastatic breast cancer (MBC) is a clinically heterogeneous and an aggressive disease from which most patients will ultimately die. Unfortunately a cure by the means of currently available treatment options still seems an elusive goal. Cytotoxic chemotherapy remains a crucial component of the therapeutic armamentarium and there is a need to develop more selective approaches to identify subgroups of patients with higher tumor sensitivity that may benefit the most.

PM01183 is a new chemical entity that induces double-strand DNA breaks through binding to the DNA minor groove. Results of the COMPARE analysis (20) revealed that is unlikely that this drug shares a similar mechanism of action with any of the other 98 standard cytotoxic agents compared.

PM01183 has significant *in vitro* and *in vivo* wide antitumor activity, particularly in several breast cancer models.

PM01183 exposure primarily induces DNA damage, particularly to homologous recombinant deficient cells *in vitro* (see IB); thus, patients with BRCA deleterious mutation might be more sensitive to its antitumor effects than other patients. In order to test this hypothesis, two cohorts of patients with advanced breast cancer will be prospectively evaluated in the trial according to their germline BRCA1/2 mutation status: known mutation (BRCA+, Cohort A) *vs*. unselected (BRCA– or -UK, Cohort B). The goal of the trial is, on one hand, to find out whether the presence of a BRCA 1/2 mutation in Cohort A is associated with a higher response rate in MBC patients; and, on the other hand, to explore and benchmark the activity of PM01183 in MBC unselected patients. The study design has taken into account the higher sample heterogeneity of Cohort B by planning the recruitment of more patients in this group. Also, according to the BRCA status in the trial setting, a response rate of 40% or more in Cohort A (sample of patients with known deleterious BRCA 1/2 mutations) will be considered clinically worthy of further research, as well as a response rate of 25% or more in Cohort B.

The first-in-human phase I clinical trial found a RD of 7.0 mg FD of PM01183 when given as a one-hour i.v. infusion q3wk. This dose was safe, tolerable and manageable for a highly selected patient population. In particular, PM01183 induced predictable and short-lasting non febrile neutropenia as the most relevant toxicity (up to 40% of patients treated at the RD). None of the patients treated at the RD were older than 75 years and/or had PS >1. Therefore, it is uncertain at this time if PM01183 RD is as tolerable and safe for a particularly vulnerable and frail population given the degree of myelosuppression observed so far. Because toxicity, especially in aging patients, is usually an important consideration in order to select the more suitable treatment, it seems safer to exclude patients over 75 years old and/or with PS≥2 until more information regarding safety and pharmacokinetics of the drug becomes available.

2. OVERALL STUDY DESIGN

This is a multicenter, open-label, exploratory, phase II clinical trial evaluating the efficacy and safety of PM01183 administration to patients with previously treated MBC, as follows.

Two cohorts of MBC patients will be prospectively evaluated in the trial according to germline BRCA1/2 status (mutated [cohort A] *vs*. unselected [cohort B]). A third cohort (A1) will include advanced breast cancer patients with deleterious BRAC1/2 mutation who received prior treatment with poly (ADP-ribose) polymerase (PARP) inhibitors:

- Cohort A (BRCA+ cohort): At least 53 evaluable patients with previously known deleterious BRCA1/2 mutation status at study entry.
- Cohort A1 (BRCA+/PARPi cohort): 20 evaluable patients with known deleterious BRCA1/2 mutation status and prior treatment with PARP inhibitors (PARPi).
- Cohort B (unselected cohort): At least 64 evaluable patients without known deleterious BRCA1/2 mutation status at study entry, i.e., either:
    - Patients known to have no deleterious BRCA1/2 mutations (BRCA−), or
    - Patients whose BRCA 1/2 mutation status is unknown (BRCA-UK); BRCA1/2 germline mutation status will be assessed in PM01183 responding patients in this subgroup.

The primary efficacy endpoint of the study is the **overall response rate** (**ORR**), defined as the percentage of patients with a response, either complete (CR) or partial (PR), according to RECIST v1.1 (Section 8.1).

An interim analysis based on the primary endpoint (ORR) is planned after 20 and 30 evaluable patients have been treated in cohorts A and B, respectively (see Section 8.2 for details). No interim analysis is planned for cohort A1. If less than four out of 20 patients in Cohort A, or less than three out of 30 patients in Cohort B achieve an objective confirmed response, recruitment to that cohort will be terminated. Otherwise, recruitment will continue until at least 53 and 64 evaluable patients are included in cohort A and cohort B, respectively. Sample size and cohort design will be re-evaluated at this point in order to estimate the 95% confidence interval (CI) with the desired precision. Recruitment to either cohort (e.g., Cohort B) might be halted while interim analysis is being performed, if appropriate.

Patients will receive treatment in the absence of progressive disease (PD) or unacceptable toxicity for as long as it is considered to be in their own benefit (see Section 6.2.1.2 for details).

Patients will be evaluated using clinical and laboratory assessments before each treatment cycle (Sections 6.3 and 6.6). Appropriate radiological and/or clinical tumor assessments will be done every six weeks until evidence of PD (Section 7.1). Patients no longer receiving study treatment will be followed up for survival (Section 6.8).

Any treatment-related AE will be followed until recovery to grade ≤ 1 or stabilization of symptoms, whenever possible (Section 7.2). Reasons for dose reduction, treatment delays and/or treatment discontinuation will be documented as appropriate.

3. STUDY OBJECTIVES

3.1. PRIMARY

- To assess the antitumor activity of PM01183 in terms of ORR, according to RECIST v1.1, in each cohort of MBC patients.

3.2. SECONDARY

- To further characterize the antitumor activity of PM01183 in terms of duration of response (DR), clinical benefit [ORR or stable disease lasting over three months (SD > 3 months)], PFS, and one-year overall survival (1y-OS).
- To evaluate whether the presence of a known germline mutation in BRCA 1/2 predicts response to PM01183 in MBC patients.
- To explore the activity of PM01183 in specific breast cancer subpopulations according to hormonal receptor status, HER-2 overexpression, number and/or type of prior therapies, or according to other available histological/molecular classifications/parameters.
- To evaluate the safety profile of this PM01183 administration schedule (Day 1, q3wk) in this patient population.
- To analyze the pharmacokinetics (PK) of PM01183 in this patient population.
- To explore PK/PD (pharmacokinetic / pharmacodynamic) correlations, if applicable.
- To evaluate the pharmacogenomic (PGx) expression profile of selected putative markers potentially predictive of response to PM01183, in tissues from tumor samples.

4. SELECTION OF PATIENTS

4.1. INCLUSION CRITERIA

In order to be included into the trial, patients have to fulfill **all** of the following criteria:

<u>All patients</u>

1. Women ≥ 18 and ≤ 75 years of age.
2. Voluntary signed informed consent form (ICF), obtained from the patient before the beginning of any specific study procedure.
3. Histologically proven diagnosis of metastatic breast carcinoma.
4. No more than three prior chemotherapy-containing regimens for MBC.
5. Patients with known HER-2 overexpressing tumors must have failed at least one prior trastuzumab-containing regimen for metastatic disease.
6. Measurable disease as defined by RECIST v1.1.
7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1.
8. Adequate major organ function:
   a. Hemoglobin ≥ 9 g/dl, prior red blood cell (RBC) transfusions are allowed if clinically indicated; absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l; and platelet count ≥ 100 x 10^9/l.
   b. Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3.0 x upper limit of normal (ULN).

c. Total bilirubin ≤ 1.5 x ULN or direct bilirubin ≤ ULN.
d. Albumin ≥ 3 g/dl.
e. Serum creatinine ≤ 1.5 x ULN.
f. Creatine phosphokinase (CPK) ≤ 2.5 x ULN.

9. Washout periods prior to Day 1 of Cycle 1:
   a. At least three weeks since the last chemotherapy (six weeks if therapy contained nitrosureas or systemic mitomycin C).
   b. At least four weeks since the last monoclonal antibody (MAb) containing therapy or radiotherapy (RT) > 30 Gy.
   c. At least one week since the last hormonal therapy.
   d. At least two weeks since the last biological/investigational therapy (excluding MAbs) or palliative RT (≤ 10 fractions or ≤ 30 Gy total dose).
10. Grade ≤ 1 toxicity due to any previous cancer therapy according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v4). Grade ≤ 2 is allowed in case of alopecia, skin toxicity, asthenia and/or peripheral sensory neuropathy.
11. Patients of child-bearing potential must agree to use a medically approved method of contraception method until at least six weeks after the last study drug administration**.**

Patients in Cohorts A and A1

12. Known deleterious germline mutation of BRCA1/2.

Patients in Cohort A

13. Prior treatment with PARP inhibitors.

4.2. EXCLUSION CRITERIA

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

All patients

1. Prior treatment with PM01183 or trabectedin.
2. Prior RT in more than 35% of the bone marrow.
3. Prior or concurrent malignant disease unless in complete remission for more than five years. Exceptions are contralateral ductal or lobular breast carcinoma, adequately treated *in situ* carcinoma of the cervix, basal or squamous skin cell carcinoma, *in situ* melanoma, and *in situ* transitional bladder cell carcinoma, which are allowed to enter the study.
4. Histology other than ductal or lobular carcinoma of the breast.
5. Symptomatic, steroid requiring or progressive central nervous system (CNS) involvement. In case of known brain metastasis, clinical stability and lack of radiological progression of lesions should be demonstrated for at least the immediate six weeks before study entry.
6. Exclusively bone-limited disease.
7. Relevant diseases or clinical situations which may increase patient's risk of serious adverse events (AEs) (any of the following):

a. History of cardiac disease: myocardial infarction or symptomatic/uncontrolled angina within the year prior to enrollment; or congestive heart failure defined as abnormal left ventricular ejection fraction (LVEF) ≤ 50% assessed by multiple-gated acquisition scan (MUGA) or equivalent by ultrasound (US); or symptomatic or treatment-requiring arrhythmia.
b. Grade ≥ 3 dyspnea or daily intermittent oxygen requirement.
c. Active uncontrolled infection.
d. Unhealed wound or presence of any external drainage.
e. Chronically active hepatitis B virus (HBV) or hepatitis C virus (HCV).
f. Immunocompromised patients, including those known to be infected by human immunodeficiency virus (HIV).
g. Known myopathy or persistent CPK elevations > 2.5 x ULN in two different determinations performed one week apart.

8. Pregnant or breastfeeding women.
9. Impending need for RT (uncontrolled painful bone metastasis and/or risk of spinal cord compression).
10. Limitation of the patient's ability to comply with the treatment or to follow-up the protocol.

Patients in Cohort B

11. Known deleterious germline mutation of BRCA1/2.

5. TREATMENT

5.1. STUDY MEDICATIONS

5.1.1. Study Drug Formulation and Supply

PM01183 drug product (DP) is presented as a lyophilized powder for concentrate for solution for infusion with two strengths: 1 mg/vial and 4 mg/vial, which will be supplied by the Sponsors for the purposes of this study.

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

Table 1. Composition of vials.

Component	PM01183 1 mg	PM01183 4 mg	Concentration per vial after reconstitution
PM01183	1.00 mg	4.00 mg	0.50 mg/ml
Sucrose	200.00 mg	800.00 mg	100.00 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 and disposal, please refer to the Preparation Guide for PM01183 and the PM01183 IB, both provided as separate documents.

5.2. ADMINISTRATION OF STUDY MEDICATIONS

5.2.1. Route of administration, starting dose, and schedule

Patients included under protocol versions 1.0 and 2.0 will receive PM01183 i.v. as a one-hour infusion on Day 1 q3wk at a starting dose of 7.0 mg FD (three weeks = one treatment cycle).

Patients included from protocol version 3.0 onward (after implementation of amendment no. 2) will receive PM01183 i.v. as a one-hour infusion on Day 1 q3wk at a starting dose of 3.5 mg/m^2 (three weeks = one treatment cycle). Dose will be capped at BSA of 2.0 m^2 (i.e., dose will not exceed 7 mg). BSA will be calculated according to standard practice at each center.

PM01183 will be administered over a minimum total volume of 100 ml of solution for infusion (either on 5% glucose or 0.9% sodium chloride) through a central catheter or over a minimum total volume of 250 ml if through a peripheral line, always over one hour at a fixed infusion rate.

5.2.2. Criteria for Treatment Continuation

Before the administration of each dose (re-treatment) on Day 1 of each cycle, patients must fulfill all of the criteria defined in Table 2.

Table 2. Criteria for continuation of treatment.

Variable	Re-treatment
	Day 1
ECOG-PS	≤ 2
Hemoglobin*	≥ 8 g/dl
ANC	≥ 1.5 x 10^9/l
Platelets	≥ 75 x 10^9/l
AST/ALT	≤ 3.0 x ULN
Total bilirubin or direct bilirubin	≤ 1.5 x ULN or x ULN
Albumin	≥ 2.7 g/dl
Serum creatinine	≤ 2.0 x ULN
CPK	Grade ≤ 1
Other non-hematological drug-related AEs (except isolated increased GGT and/or AP¥, grade 3 asthenia lasting < 1 week, non-optimally treated nausea and/or vomiting)	Grade ≤ 2

* Patients may receive packed red blood cells (PRBC) transfusion and/or erythropoietin (EPO) treatment, if clinically indicated, to increase/maintain adequate hemoglobin levels.

¥ Any grade accepted for non-drug-related increase of GGT and/or AP.

AE(s), adverse event(s); ANC, absolute neutrophil count; AP, alkaline phosphatase; AST/ALT, aspartate aminotransferase/alanine aminotransferase; CrCl, creatinine clearance; CPK, creatinine phosphokinase; ECOG, Eastern Cooperative Oncology Group; GGT, gamma-glutamyltransferase; PS, performance status; ULN, upper limit of normal.

If a patient does not meet the requirements for re-treatment on Day 1 of any following cycle, regardless of the reason, re-assessments will be performed every 48-72 hours. Treatment will be then withheld, up to a maximum of three weeks beyond its due date, until appropriate recovery.

Patients not meeting re-treatment criteria after a maximum three-week delay the patient must be withdrawn from the trial, except in case of objective clinical benefit (upon Sponsors' agreement).

For any delay lasting more than one week due to treatment-related toxicity (unless exclusively due to neutropenia), a dose reduction must be implemented upon recovery following the rules explained in the next section. Conversely, if the delay was exclusively due to neutropenia related to PM01183, treatment may continue without dose reduction but with appropriate secondary prophylaxis with granulocyte colony-stimulating factor (G-CSF).

5.2.3. Dose Reduction

Study treatment may continue with an appropriate dose reduction (Table 3) if patient benefit is perceived by the Investigator (upon Sponsors' agreement), even after the patient experienced any of the following:

- Grade ≥ 3 treatment-related non-hematological toxicity. Exceptions are: grade 3 nausea and/or vomiting not optimally treated, grade 3 asthenia lasting < 1 week, grade 3 diarrhea lasting ≤ 2 days or not optimally treated, grade 3-4 hypersensitivity and/or extravasation reactions, grade 3 transient ALT/AST elevations which are rapidly reversible and not leading to subsequent delays, and/or not clinically relevant biochemical abnormalities [i.e., in gamma-glutamyltransferase (GGT), lactate dehydrogenase (LDH) and/or alkaline phosphatase (AP) levels], none of which require dose reduction to be implemented.
- Grade 4 thrombocytopenia or grade 3 thrombocytopenia concomitantly with grade ≥3 bleeding.
- Frequent or prolonged (>1 week) dose delays due to treatment-related toxicity.

Patients experiencing grade 4 neutropenia or febrile neutropenia during the preceding cycle, or treatment delays exclusively due to neutropenia that lasted >1 week, may continue treatment without any dose reduction but must receive secondary prophylaxis with G-CSF instead. The G-CSF secondary prophylaxis will be administrated subcutaneously at 300 µg/day for five consecutive days starting on Day +3 of the corresponding cycle. If despite appropriate G-CSF prophylaxis, grade 4 neutropenia or febrile neutropenia re-occurs, then dose reduction should be implemented.

Table 3. Guidelines for dose reduction.

Dose reduction level*	**PM01183 dose (mg, FD)** Patients included under protocol versions 1.0, 2.0	**PM01183 dose (mg/m^2)** Patients included from protocol version 3.0 onward**
1	7.0	3.5
−1	6.0	2.6
−2	5.0	2.0

* Except for grade ≥ 3 nausea and/or vomiting not optimally treated, grade 3 asthenia lasting < 1 week, grade 3 diarrhea lasting ≤ 2 days or not optimally treated, grade 3-4 hypersensitivity and/or extravasation reactions, grade 3 transient ALT/AST elevations which are rapidly reversible and not leading to subsequent delays, and/or isolated not

clinically relevant biochemical abnormalities (i.e., GGT, LDH and/or AP), none of which require dose reduction to be implemented.
**Dose will be capped at BSA of 2.0 m^2 (starting dose will not exceed 7 mg). BSA will be calculated according to standard practice at each center.
ALT/AST, aspartate aminotransferase/alanine aminotransferase; AP, alkaline phosphatase; FD, flat dose; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase.

Up to two dose reductions are allowed per patient.

Once the dose has been reduced for an individual patient, it will not be re-escalated under any circumstances.

5.2.4. Dose Escalation

No dose escalation will be allowed in this clinical trial.

5.3. CONCOMITANT MEDICATION

5.3.1. Prophylactic Medications

Patients must receive standard antiemetic prophylactic medication at least 30 minutes before the administration of PM01183, as follows:

- Corticosteroids (dexamethasone i.v. or equivalent at institutional standard antiemetic doses)
- Serotonin (5-HT3) antagonists (ondansetron 8 mg i.v. or equivalent)

If necessary and in addition to the above, any of the following could apply:

- Administration of 10 mg of metoclopramide (or equivalent) every eight hours
- Extended treatment with 5-HT3 antagonists and/or dexamethasone

Aprepitant and directly related agents (e.g., fosaprepitant) are forbidden.

An optimal antiemetic prophylaxis is defined, for the purpose of safety evaluations, as any of the aforementioned medications at their respectively maximum dosages.

5.3.2. Allowed Medications/Therapies

The following medications or therapies are allowed to be administered during the study:

- 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 ASCO guidelines.
- Erythropoietin (EPO) treatment according to ASCO guidelines.
- Granulocyte colony-stimulating factor (G-CSF) for the treatment of grade 4 neutropenia, any grade febrile neutropenia, or neutropenic infection. After Cycle 1, secondary prophylaxis is allowed if applicable.
- Anticoagulation therapy for the treatment or secondary prophylaxis of deep vein thrombosis.
- Luteinizing hormone-releasing hormone (LHRH) agonists, in women of reproductive age.

5.3.3. Prohibited Medications/Therapies

The following medications or therapies are not allowed to be administered during the study:

- Concomitant administration of any other antineoplastic therapy, except therapy with LHRH agonist if applicable.
- Any other investigational agents.
- Immunosuppressive therapies other than corticosteroids.
- Primary G-CSF prophylaxis or treatment of non-febrile grade ≤ 3 neutropenia with G-CSF (unless previously agreed case-by-case between the Investigator and the Sponsor).
- Aprepitant, fosaprepitant and directly related compounds.
- Radiotherapy (RT), except for bone limited-field bone radiation for pain control purposes.

5.3.4. 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 (21) (see also Appendix 4).

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.

5.3.5. Protein Binding

The plasma protein binding of PM01183 ranged from 88 to 98% in all species tested. In human, about 97% of PM01183 was bound to plasma proteins, and this was independent of the drug concentration. Caution is therefore recommended when concomitant medication known to be highly protein-bound (e.g., warfarin) is administered together with PM01183.

5.3.6. Urinary Excretion

Less than 1% (mean 0.53%, n=13) of the unchanged parent compound was recovered from the urine of the patients treated in the PM1183-A-001-08 clinical study; thus, urinary excretion is not likely to be a major elimination route for PM01183.

5.4. 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 Sponsors will be properly destroyed at the study site. Documentation of this procedure must be provided to the clinical trial monitor. If Sponsors agree, unused drug supplies may be returned to the drug repository.

5.5. TREATMENT COMPLIANCE

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

6. PLAN OF THE STUDY

6.1. DURATION OF STUDY (WHOLE POPULATION)

The total duration of the study (including both stages) will be approximately 72 months.

- **Planned start date (first patient on study):** second quarter 2012 (2Q12).
- **Planned enrollment period:** 60 months.
- **Planned end-of-study date (clinical cut-off**): nine months after the last patient-last treatment visit in the study, or 12 months after the last evaluable patient is enrolled (whichever occurs first).

6.2. DURATION OF STUDY (PER PATIENT)

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

- **Screening:** from signature of the ICF to first infusion of PM01183.
- **Treatment:** from first infusion of PM01183 to **end of treatment** (EOT). **EOT** is defined as 30 days after the date of PM01183 last administration, unless the patient starts a new antitumor therapy or dies within those 30 days, in which case the date of administration of this new antitumor therapy or the date of death will be considered as EOT.
- **Follow-up:** after EOT, patients will be followed for any ongoing treatment-related AEs every four weeks until recovery to grade ≤1, or until symptoms stabilization, whenever possible.
  Patients will be followed for at least one year after their first infusion. Those who discontinued treatment without PD will be assessed every two months during the first six months after last tumor assessment and every three months thereafter, until

PD, start of other antitumor therapy, death, or study completion, whichever occurs first.

After documented PD or start of a new antitumor therapy, patients will be followed every six months until death or study completion, whichever occurs first. For the purpose of collecting information on the patient's survival exclusively, a documented telephone call would be acceptable.

Patients will be considered to be **on-study** from the signature of the clinical ICF to the end of the follow-up period (or screening failure).

Patients will be considered to be **on-treatment** from the date of first infusion of PM01183 until EOT.

6.2.1. End of Treatment and Off-study

6.2.1.1. End of Treatment

Treatment discontinuation occurs when an enrolled patient ceases to receive the study medication, regardless of the circumstances. By convention, the date of end of treatment will be 30 days after the date of last administration of study drug, unless the patient starts a new antitumor therapy or dies within those 30 days, 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 primary reason for any discontinuation will be recorded on the patient's Case Report Form (CRF).

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

6.2.1.2. Reasons for End of Treatment

Patients will receive study drug as long as it is considered to be in their best interest. Specifically, the assigned treatment will continue until:

- Disease progression.
- Unacceptable toxicity (except in case of clear clinical benefit, with the Sponsors' approval), after appropriate dose reduction.
- Intercurrent illness of sufficient magnitude to preclude safe continuation of the study.
- Patient refusal and/or noncompliance with study requirements.
- Investigator's decision.
- Protocol deviation with an effect on the management of the patient's risk/benefit ratio.
- Treatment delay > 3 weeks from the treatment due date (except in case of clear clinical benefit, upon Sponsors' approval).
- Requirement of > 2 dose reductions.

Regardless of the reason, patients who discontinue the treatment must not be re-treated at any time.

6.2.1.3. Off-study

Off-study occurs when an enrolled patient ceases to participate in the study, regardless of the reason. Patients have the right to withdraw consent at any time; if this is the case, no further follow-up should be performed.

The date and reason for study discontinuation will be clearly documented on the patient's CRF. If a patient is lost to follow-up an attempt will be made to collect the information on the patient's survival and date of death (when applicable).

6.2.2. 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/Institutional Review Board (IEC/IRB) and Competent Authorities. Therefore, this applies to deviations related to patient inclusion and clinical procedures (e.g., assessments to be conducted or parameters to be determined), and also to other procedures described in the protocol that concern the Good Clinical Practice (GCP) guidelines or ethical issues (e.g., issues related to obtaining the patients' Informed Consent, data reporting, the responsibilities of the investigator, etc.).

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

- Deviations that might affect the clinical trial objectives, such as those involving the inclusion/exclusion criteria (which could mean that the patient is not eligible for the trial) and those having an effect on patient evaluability.
- Deviations that might affect the patient's well-being and/or safety, such as an incorrect dosing of the study drug (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.

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 considered particularly relevant, which are related to ethical issues, fulfillment of GCP guidelines and trial procedures, will be notified to the pertinent IEC/IRB and, if pertinent, to the relevant authorities as established by local regulations.

For those patients in Cohort A1 whose disease is not amenable to biopsy, non-availability of the biopsy specimen will not be considered a deviation but the patient can only be included after Sponsor approval.

6.3. SCREENING EVALUATIONS

During the screening period, and once the patient has signed the ICF, the Investigator will confirm the patient's eligibility for the study by conducting the assessments described in Table 4.

Note that a 3-day window will be allowed for laboratory procedures, a 14-day window for radiological procedures [helical computed tomography (CT)-scan or magnetic resonance imaging (MRI)] and LVEF assessments, and a 24-hour window for clinical assessments [ECOG, physical examination, vital signs, electrocardiogram (ECG), weight, BSA, etc.].

Additional information on the collection and processing of pharmacogenomic (PGx) samples will be provided as a separate document. For details on PGx procedures please refer to Section 10.

Table 4. Screening assessments.

	SCREENING ASSESSMENT	TIME [1]
1. Medical history and clinical examination	◆ Written informed consent. ◆ Written PGx substudy informed consent (optional for cohorts A and B).	Prior to any specific study procedures.
	◆ Demographic data. ◆ Primary diagnosis and prior treatment(s). ◆ LVEF by ECHO or MUGA.	Within 28 days prior to Day 1 of Cycle 1.
	◆ Medical history and prior conditions ◆ Intercurrent events, concomitant diseases and treatments.	Within 14 days prior to Day 1 of Cycle 1.
	◆ Assessments of signs and symptoms. ◆ Complete physical examination, including weight and height. ◆ Performance status (ECOG PS; see Appendix 1). ◆ Vital signs: heart rate, blood pressure and body temperature. ◆ ECG [2].	Within 7 days prior to Day 1 of Cycle 1.
2. Laboratory tests	◆ **Coagulation panel:** PT/INR and PTT. ◆ **Hematology:** hemoglobin, platelet counts, and differential WBC including neutrophils, monocytes, and lymphocytes. ◆ **Biochemistry A:** serum electrolytes (Na^+, K^+, Cl^-), AST, ALT, AP, GGT, total bilirubin (direct bilirubin to be measured only if total bilirubin is abnormally high), LDH, creatinine, glucose, and CPK (CPK-MB fraction and troponin T or I should only be measured if CPK is abnormally high or if clinically indicated). ◆ **Biochemistry B:** total proteins, albumin, CRP, Ca^{++}, phosphorus, Mg^{++}. CA 15-3 or 27.29. Alpha-1 acid glycoprotein, total cholesterol, triglycerides, and LDL.	Within 7 days prior to Day 1 of Cycle 1.
3. Pregnancy test [3]	◆ In patients of childbearing potential only.	Within 7 days prior to Day 1 of Cycle 1.
4. Radiological and/or clinical tumor assessment	◆ Contrast enhanced helical CT-scan or MRI (if indicated) of all measurable sites of disease involvement, as per RECIST v.1.1 (see Appendix 2). ◆ Appropriate test (radiological or clinical) of all non-measurable sites of disease.	Within 28 days prior to Day 1 of Cycle 1 [4].
5. PGx paraffin-embedded tumor tissue [5]	◆ From available prior tumor samples (primary tumor and/or metastasis). ◆ For Cohort A1 patients only: a baseline tumor biopsy.	- Archived biopsy sample from diagnosis. - Recent biopsy sample taken at any time between the end of last antitumor therapy until before first study drug infusion.
6. AEs	◆ All events should be graded as per NCI-CTCAE v4.	SAEs will be collected from the signing of the ICF.
7. BRCA1/2 germline mutation analysis	To be conducted on patients with unknown germline BRCA mutation status, who meet criteria for consideration of BRCA 1/2 genetic testing. [6]	-

1. A 3-day window will be allowed for laboratory procedures, a 14-day window for radiological procedures (contrast enhanced helical CT-scan or MRI) and LVEF assessments, a 24-hour window for clinical assessments (ECOG, vital signs, ECG, weight, BSA, etc.).
2. Cardiac rhythm will be identified in ECG intervals of at least 30 seconds of duration, PR interval, QT interval (raw), heart rate (HR) and QRS complex.
3. If serum human chorionic gonadotropin (HCG) results are abnormally high, pregnancy must be clinically discarded by an additional test (i.e., US) before any other study procedure.

4. Patients with previously known CNS involvement at study entry must have documented non-PD by appropriate method.
5. Prior available stored paraffin-embedded tumor samples from the primary tumor and/or from metastases. For cohort A1 patients whose disease is not amenable to tumor biopsy, approval by the sponsor must be requested prior to inclusion. In any case, the origin of the sample must be specified: diagnosis (primary tumor or metastasis) or baseline sample.
6. National Comprehensive Cancer Network (NCCN) criteria for consideration of BRCA1/2 genetic testing (see Appendix 3).

AE(s), adverse event(s); ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CA 15-3 or 27.29, cancer antigen 15-3 or 27.29; CNS, central nervous system; CPK, creatinine phosphokinase; CPK-MB, creatinine phosphokinase muscle band; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; GGT, gamma-glutamyltransferase; ICF, informed consent form; INR, international normalized ratio; LDH, lactic dehydrogenase; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition scan; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, progressive disease; PS, performance status; PT, prothrombin time; PTT, partial thromboplastin time; RECIST, Response Evaluation Criteria In Solid Tumors; RT, radiotherapy; SAE, serious adverse event; WBC, white blood cells.

6.4. PATIENT REGISTRATION

After the patient has signed the ICF and upon ensuring that she meets all eligibility criteria, the patient will be entered into the trial by contacting the clinical trial monitor designated by the Sponsors and faxing the completed Patient Registration Form (Fast Fact Sheet, FFS). The FFS will be checked and eligibility confirmed by the Sponsors. A patient number will be provided to the site of enrollment within one working day. This patient number should be used on all future documentation and correspondence referring to this patient. Investigators are under no circumstances allowed to treat any patient before appropriate reception of the patient registration number, which confirms the Sponsors' agreement. Any patient treated prior to registration without the Sponsors' agreement and/or before receipt of the appropriate documentation may not be considered evaluable for the study and may need to be replaced.

6.5. PATIENT RANDOMIZATION

Not applicable.

6.6. EVALUATIONS DURING TREATMENT

The assessments to be done while the patient is on treatment are shown in Table 5.Note that a window of duration similar to that for each of the procedures during the screening will be allowed.

Table 5. Evaluations during treatment.

	TREATMENT ASSESSMENT	TIME [1]
1. Clinical examination	◆Complete physical examination, including weight (height is only required at baseline). ◆ Performance status (ECOG PS; see Appendix 1). ◆ Vital signs: heart rate, blood pressure and body temperature.	Repeat on Day 1 from Cycle 2 onwards, always prior to PM01183 administration.
	◆ Intercurrent events, concomitant therapies and treatments.	Throughout the "on treatment" period (i.e., during treatment plus 30 ± 7 days after the last PM01183 administration).
2. Laboratory tests	◆ **Hematology**[2]**:** hemoglobin, platelet counts, and differential WBC including neutrophils, monocytes, and lymphocytes. ◆ **Biochemistry A**[2]**:** serum electrolytes (Na^+, K^+, Cl^-), liver function test (AST, ALT, AP, GGT, and total bilirubin; direct bilirubin to be measured only if total bilirubin is abnormally high;), LDH, creatinine, glucose, CPK (CPK-MB fraction and troponin T or I should only be measured if CPK is abnormally high or if clinically indicated).	Repeat in Cycle 1 (Days 8 and 15) and on Day 1 (prior to PM01183 administration) and Day 10 of further cycles.[3]
	◆ **Coagulation panel:** PT/INR and PTT. ◆ **Biochemistry B:** total proteins, albumin, CRP, and serum electrolytes (Ca^{++}, phosphorus, Mg^{++}). CA 15-3 or 27.29 only in those patients with abnormally elevated values at baseline. Alpha-1 acid glycoprotein, total cholesterol, triglycerides, and LDL, before Cycle 2 only.	Repeat on Day 1 (prior to PM01183 administration).
3. Pregnancy test [4]	◆ In patients of childbearing potential.	Repeat if clinically indicated.
4. ECG [5]		Repeat if clinically indicated.
5. LVEF	◆ By ECHO or MUGA. The same initial method must be used throughout the study.	Repeat if clinically indicated.
6. Radiological and/or clinical tumor assessment	◆ Contrast enhanced helical CT-scan or MRI and/or clinical evaluation if indicated, of all original sites of disease involvement evaluated at baseline, as per RECIST v.1.1 (see Appendix 2). Always the same method must be used throughout the study.	Every six weeks (starting from first treatment administration) up to Cycle 6 and every 9 weeks thereafter [6].
8. PK	◆ At least 30 treated patients in cohorts A and B.	Immediately before and during Cycles 1 and 2 only.
9. AEs	◆ All events should be graded as per NCI-CTCAE v4.	Throughout the "on treatment" period (i.e., during treatment plus 30 ± 7 days after the last PM01183 administration).
10. BRCA1/2 germline mutation analysis		BRCA unknown patients in cohort B: One blood sample at the time of the response.

1. A 3-day window will be allowed for laboratory procedures, a 14-day window for radiological procedures (contrast enhanced helical CT-scan or MRI) and LVEF assessments, a 24-hour window for clinical assessments (ECOG, physical examination, vital signs, ECG, weight, BSA, etc.).
2. Any patient presenting a grade ≥ 3 treatment-related AE should have all relevant tests re-assessed at least every 48-72 hours until recovery to grade ≤ 2.
3. From Cycle 3 onwards Hematology and Biochemistry A tests on Day 10 are to be performed only in patients who experienced non-hematological grade ≥3 or hematological grade 4 treatment-related toxicities, or who required any dose

adjustments or GSF prophylactic therapy, in the preceding cycle.

4. If serum human chorionic gonadotropin (HCG) results are abnormally high, pregnancy must be clinically discarded by an additional test (i.e., US) before any other study procedure. Pregnancy and suspected pregnancy occurring while the patient is on study drug are considered immediately reportable events.
5. Cardiac rhythm will be identified in ECG intervals of at least 30 seconds of duration, PR interval, QT interval (raw), heart rate (HR) and QRS complex.
6. Patients showing a response must have a confirmatory assessment at least 4 weeks later.

AE(s), adverse event(s); ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BSA, body surface area; CA 15-3 or 27.29, cancer antigen 15-3 or 27.29; CNS, central nervous system; CPK, creatinine phosphokinase; CPK MB, creatinine phosphokinase muscle band; CRP, C-reactive protein; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; GGT, gamma-glutamyltransferase; HR, heart rate; ICF, informed consent form; INR, international normalized ratio; LDH, lactic 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; PD, progressive disease; PK, pharmacokinetics, PR, partial response; PS, performance status; PT, prothrombin time; PTT, partial thromboplastin time; RECIST, Response Evaluation Criteria In Solid Tumors; SAE, serious adverse event; US, ultrasound; WBC, white blood cells.

6.7. EVALUATIONS AT END OF TREATMENT

The EOT visit will be scheduled at 30 days after the last dose of study treatment (a window of ± 7 days is allowed), unless the patient starts a new antitumor therapy or dies within those 30 days from the last dose, in which case the date of administration of this new antitumor therapy or the date of death will be considered as EOT.

For treated patients, regardless of the reason for discontinuation, if no recent data are available (i.e., within last 10 days prior to the EOT visit) or if the last data available show a grade ≥ 2 alteration, the following work-up will have to be done at this EOT visit:

- Complete physical examination, including weight (height only at baseline).
- ECOG performance status.
- Vital signs (heart rate, blood pressure, body temperature).
- Coagulation panel.
- Hematology.
- Biochemistry A.
- Biochemistry B.
- Pregnancy test, if clinically indicated.
- Electrocardiogram (ECG), if clinically indicated.
- LVEF by echocardiography (ECHO) or MUGA, if clinically indicated.
- Radiological and/or clinical tumor assessment (if not previously done and if the reason for treatment discontinuation was other than PD).
- Intercurrent events, concomitant diseases and treatments.
- Safety assessment (AEs).

Adverse events (AEs) and serious adverse events (SAEs) must be reported until 30 days after the last PM01183 administration (for safety reporting see Section 11.2).

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

Patients of childbearing potential who use adequate contraception methods while on study should be reminded to continue adequate contraception for a period of six weeks after last study drug administration.

6.8. FOLLOW-UP AFTER END-OF-TREATMENT VISIT

The date and reason of the end of study will be recorded on the patient's CRF.

After the end of treatment, all AEs and SAEs suspected to be related to PM01183 must be followed-up until recovery to grade ≤ 1 or symptoms stabilization whenever possible (for safety reporting see Section 11.2). Pregnancy and suspected pregnancy occurring within six weeks from the patient's last PM01183 administration are considered immediately reportable events.

Additionally, radiological and/or clinical tumor assessments will be done during the follow-up only to those patients who discontinue treatment without documented disease progression. Patients will be followed every two months during the first six months after last tumor assessment and every three months thereafter until PD, start of other antitumor therapy, death, or study completion (clinical cut-off), whichever occurs first.

After documented progression or start of a new antitumor therapy, patients will be followed every six months, until death or study completion (clinical cut-off), whichever occurs first**.** For this purpose of collecting information on the patient's survival exclusively, a documented telephone call would be acceptable and no visits to the hospital will be required.

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

6.9. STUDY COMPLETION (AS A WHOLE - CLINICAL CUT-OFF)

The planned study completion date (clinical cut-off) will be nine months after the last patient-last treatment visit in the study, or 12 months after the last evaluable patient is enrolled (whichever occurs first).

All patients on active treatment at the date of study completion will be offered to continue to receive treatment off-study according to the Investigator criteria and upon Sponsors' agreement.

6.10. REPLACEMENT OF PATIENTS

Patients will be replaced if they are not evaluable for the primary endpoint of the study (ORR as per RECIST v1.1), specifically (any of the following):

- They are not eligible.
- They have not been treated or have not completed at least one PM01183 infusion.
- They are not evaluable for ORR as per RECIST v1.1 and they are not categorized as "treatment failures". Treatment failures will not be replaced and are defined as patients who:
    - Discontinue treatment due to any treatment-related toxicity before an appropriate tumor assessment has been performed, or
    - Withdraw PM01183 after more than two weeks on treatment without any formal evaluation

All replaced patients will be included in the general safety analysis, if appropriate.

7. STUDY EVALUATIONS

7.1. EFFICACY

For patients to be evaluable for efficacy they must be eligible, have at least one complete infusion of PM01183, and either have at least one assessment (as per RECIST v1.1) or be categorized as "treatment failure".

Antitumor activity will be assessed using RECIST v1.1, on a set of measurable lesions identified at baseline as target lesions and non-target lesions (if any) identified at baseline as non-target lesions and followed until PD by an appropriate method (contrast enhanced helical CT-scan, MRI, and/or clinical assessment).

Radiological and/or clinical (whenever appropriate) tumor assessment will be performed at baseline and every six weeks (two cycles) until Cycle 6 or evidence of PD. After Cycle 6, tumor assessment will be performed every nine weeks (three cycles) until evidence of PD. If an objective response is observed, according to RECIST v1.1, it must be confirmed by the same method at least four weeks after the date of the first documentation of response.

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

A copy of the imaging tests conducted on the patients during this clinical trial may be requested by the Sponsor for evaluation. In addition, an independent radiological review committee may be set up, upon Sponsors' request, to review tumor assessment performed for all responding patients (partial or complete response) after study completion.

Patients will be categorized as "treatment failures" if they:

- Discontinue treatment due to any treatment-related toxicity before an appropriate tumor assessment has been performed, or
- Withdraw PM01183 after more than two weeks on treatment without any formal evaluation.

These data will be included as non-evaluable (NE) in the analysis of objective response as per RECIST v1.1, although these patients will not need to be replaced as they will be considered evaluable for efficacy.

BRCA1/2 germline mutation analysis

In patients included in Cohort B who respond to PM01183 treatment and whose BRCA 1/2 mutation status is unknown at study entry, an analysis will be performed in order to confirm or exclude deleterious germline BRCA 1/2 mutation. To this end, a blood sample will be collected at the time of response. If a BRCA 1/2 mutation is found in her sample then the patient will be analyzed along with patients included in Cohort A.

7.2. SAFETY

Patients will be evaluable for safety if they received at least one partial or complete infusion of PM01183.

All adverse events (AEs) will be graded according to NCI-CTCAE v4.

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

Treatment delays, dose reduction requirements, G-CSF and/or transfusions requirements, and reason for treatment discontinuation will be monitored throughout the study.

Any treatment-related AEs will be followed until recovery to grade ≤ 1 or stabilization of symptoms, whenever possible.

8. STATISTICAL METHODS

The statistical analysis will be done by the Sponsors or under the Sponsors' authority.

8.1. ENDPOINTS

8.1.1. Primary Endpoint

The primary evaluation endpoint for this phase II study is the ORR in the population evaluable for efficacy.

The ORR is defined as the percentage of patients with a confirmed response, either CR or PR, according to RECIST v1.1.

8.1.2. Secondary Endpoints

- Duration of response (DR), defined as the time between the date when the response criteria (PR or CR, whichever is first reached) are fulfilled to the first date when PD, recurrence or death is documented.
- Clinical benefit, defined as the percentage of patients with ORR or SD > 3 months, according to RECIST v1.1.
- Progression-free survival (PFS), defined as the period of time from the date of first infusion to the date of PD, death (due to any cause), or last tumor evaluation.
- Overall survival rate at one year (1y-OS), defined as the Kaplan-Meier estimate of the probability of patients to remain alive at one year. Overall survival (OS) will be defined as time from the date of first infusion to the date of death or last contact
- Treatment safety: AEs, SAEs, and laboratory abnormalities will be graded according to the NCI-CTCAE (v4), reasons for treatment discontinuation, dose reduction and/or treatment delays.
- PK descriptive analysis and PK/PD correlation, if applicable.
- PGx expression profile of selected putative markers potentially predictive of response to PM01183, in tissues from tumor samples.

8.2. SAMPLE SIZE

The primary endpoint for this phase II study is to evaluate ORR.

- Cohort A (BRCA+):

  At least 53 evaluable patients will be recruited to test the null hypothesis that ORR is 20% or less ($p \leq 0.20$) *vs.* the alternative hypothesis that 40% or more patients have objective response ($p \geq 0.4$). With these assumptions, if the number of evaluable patients with objective response is ≥ 17, then this would allow the rejection of the

null hypothesis.

- Cohort A1 (BRAC+/PARPi):

  At least 20 evaluable patients will be for an exploratory analysis: if the number of patients responding is ≥ 4 (20%), the lower limit of the exact binomial 95% confidence interval will be higher than 5% and lack of activity in this subpopulation will be ruled out.

- Cohort B (unselected):

  At least 64 evaluable patients will be recruited to test the null hypothesis that ORR is 10% or less ($p \leq 0.10$) *vs.* the alternative hypothesis that 25% or more patients have objective response ($p \geq 0.25$). With these assumptions, if the number of evaluable patients with objective response is ≥ 12, then this would allow the rejection of the null hypothesis.

The variance of the standardized tests is based on the null hypothesis. The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is <0.1; hence, statistical power is > 90%.

Futility analyses controlled by the Gamma family boundary will be performed when 20 and 30 patients have been evaluated in cohorts A [Gm(-2)] and B [Gm(-1.5)], respectively. If less than four out of 20 patients in Cohort A, or less than three patients out of 30 in Cohort B achieve an objective response, recruitment to that cohort will be stopped. About 110 evaluable patients are expected to be included finally in the three cohorts: Cohort A (BRCA+), Cohort A1 (BRCA+/PARPi), and Cohort B (unselected).

8.2.1. Randomization

Not applicable.

8.3. STATISTICAL ANALYSIS

Frequency tables will be prepared by cohort for categorical variables, whereas continuous variables will be described by means of summary tables that will include the median, minimum, and maximum of each variable.

8.3.1. Efficacy Analyses

For the primary endpoint (ORR) the exact binomial estimator and its 95% CI will be used.

The time-to-event variables (DR, PFS and OS) and their set time estimates (e.g., PFS3, PFS6 and 1y-OS) will be analyzed according to the Kaplan-Meier method.

Exploratory comparison of the efficacy results between the two study cohorts will be performed by means of Fisher analysis and logistic regression (ORR), and of log-rank test/Cox regression (time-to-event variables). Additionally, if clinically appropriate, the two cohorts might be pooled into one, whenever differences between cohorts are considered not relevant. In such case, the point estimates and their 95% CIs will be also reassessed in order to obtain more accurate calculations.

Exploratory subgroup analyses (e.g., triple negative, hormonal receptor status, HER-2 overexpression, etc.) will be also performed depending on the sample sizes of each subgroup, if appropriate.

8.3.2. Safety Analyses

The safety analyses will consider AEs and SAEs according to their relationship with study treatment, as well as analytical results, deaths and the reasons for treatment discontinuations, delays and/or dose reductions.

All AEs and SAEs will be graded according to the NCI-CTCAE, v4.

8.3.3. Safety Stopping Rule

In addition to sample size considerations, a decision for early study termination due to safety issues will be taken within the initial 30 evaluable patients (regardless of the cohort), whenever any of the following occurs:

- Two or more eligible patients die due to treatment-related AEs (>5% of related deaths), or
- Ten or more patients need to discontinue PM01183 treatment within the first two cycles due to any grade 4 treatment-related AEs (NCI-CTCAE v4).

9. PHARMACOKINETICS

PK parameters of plasma PM01183 will be evaluated immediately before and during the first two cycles with a limited sampling schedule of ten samples in at least 30 treated patients in cohorts A and B. The sampling schedule during each cycle will be as shown Table 6. All sample collection dates and times will be recorded on the CRF.

The infusion rate will be predetermined to ensure that the total drug dose is infused in 60 minutes at a constant rate. In order to obtain reliable PK information, the infusion rate should not be modified once the infusion begins. If a variation in the infusion time eventually occurs, it is very important to reflect it on the CRF and PK sheet, writing clearly the time of the beginning and the end of the infusion.

Table 6. Sampling schedule for the determination of PM01183 PKs

Sample	Day	Time
# 1	1	Before infusion
# 2	1	5 min before the end of the infusion (EOI)
# 3	1	15 minutes after EOI
# 4	1	1 hour after EOI
# 5	1	2 hours after EOI
# 6	1	4 hours after EOI
# 7*	1	5 hours and 30 min after EOI
# 8**	2	24 hours after EOI
# 9***	4	72 hours after EOI
# 10****	8	168 hours after EOI

* There is a 30-minute window (before and after the stated point) in the sampling time.
** There is a two-hour window (before and after the stated point) in the sampling time.
*** There is a two-hour window before the stated point, or until 24 hours after the stated point in the sampling time (this sample must be collected within Day 4 or 5).
**** Preferred time; if weekends or other reasons make the sampling on time difficult, it may be obtained with a 24-hour window before or after the stated time. In any case, the sampling time should differ by at least 24 hours from the prior sample.

EOI, End of Infusion; h, hour(s); min, minute(s).

The accurate recording of actual dosing and sampling times is much more important than the strict adherence to the scheduled times. Therefore, as a result of information obtained

during sample evaluation, sampling times may be changed (as long as the total number and volume of samples is maintained or decreased) in order to improve the schedule.

Blood samples for PK analysis will be obtained through a peripheral vein located in the contralateral side to that of the infusion, whenever possible. 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 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.

A total of 20 samples of about 4 ml of whole blood will be collected along the first two cycles (about 80 ml of whole blood) at the predefined times depicted Table 6. The Instruction Manual for Collection, Labeling, Storage and Shipment of Pharmacokinetic Samples describes in detail the required procedures. Please read it carefully before PK sampling. In short, after collection each sample will be centrifuged and the resulting plasma layer transferred into a new tube for the determination of PM01183 concentration. The tubes containing plasma will be stored frozen until their shipment to the Central Laboratory for Pharmacokinetic Samples (see Study Contacts). All the material for PK procedures will be provided by the Sponsors.

Once all samples from a patient's cycle have been collected, they should be shipped for analysis to the Central Laboratory for Pharmacokinetic Samples 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 obtainment of the last PK sample from a patient and the shipment of all the samples from this patient to the Central Laboratory should not exceed one month**.

Sampling PK sheets should be sent together with the samples, but never in contact with dry ice. Samples will be identified with the following data: protocol code, drug, patient number, sample number, and 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 Sponsors.

9.1. EVALUATION OF PHARMACOKINETICS

Pharmacokinetic parameters will be elucidated using standard non-compartmental analysis (NCA). The following parameters will be calculated: AUC, C_{max}, CL, and half-life ($t_{1/2}$).

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 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 *vs.* time curve. The $t_{1/2}$ will be calculated from the equation 0.693/k; total plasma 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 also be performed, and population PK analysis will be made in pooled results of the different studies. If applicable, PK/PD parameters will be correlated.

9.2. PHARMACOKINETIC STATISTICAL METHODS

PK parameters will be tabulated and selected parameters will be graphically displayed. The dose-exposure relationships for C_{max} and 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 cut-off 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, etc.), relationship with selected PK 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. PHARMACOGENOMIC SUBSTUDY

The main objective of the PGx study (optional for cohorts A and B, required for cohort A1) is the identification of potential biomarkers of sensitivity or resistance to PM01183 and whose expression might be predictive of the clinical outcome after treatment with PM01183.

Requirements

- PM01183-treated patients with prior paraffin-embedded tumor samples, if available.
- For cohorts A and B, patients who voluntarily sign the ICF for the PGx study will participate (refusal will not affect patient participation in the clinical study PM1183-B-003-11).
- For cohort A1, availability of a baseline (taken at any time between the end of last antitumor therapy and before first study drug infusion) tumor biopsy is also required. For those patients whose disease is not amenable to tumor biopsy, approval by the Sponsors must be requested prior to inclusion.

Potential biomarkers of PM01183 activity will be evaluated on paraffin-embedded tumor samples obtained at baseline. Additionally, if archived tumor samples are available from the primary tumor and/or from metastases, analyses will be also performed in both. Samples will be labeled according to its origin: diagnosis (primary tumor or metastasis) or baseline sample.

The expression levels and subcellular localization of selected molecules involved in different DNA repair mechanisms, such as nucleotide excision repair (e.g., XPG), homologous recombination repair (e.g., RAD51), among others, will be analyzed. Specifically, mRNA and protein from tumor samples will be subjected to quantitative reverse transcription polymerase chain reaction (qRT-PCR) and immunohistochemistry (IHC) in tissue microarrays (TMA), and immunofluorescence in whole tumor sections. The polymorphisms and mutational status of genes involved in DNA repair mechanisms or related to the mechanism of action of PM01183 or to the disease might also be analyzed, if relevant.

All PGx analyses will be performed in central reference laboratories selected by the Sponsors (see Study Contacts). Tissue blocks or sections will be shipped at room temperature to Pharma Mar S.A. who will coordinate the shipments and will cover all the costs. A manual describing the procedures for collection, shipping and handling of the samples will be provided as a separate document.

11. ADVERSE EVENTS

11.1. DEFINITIONS

11.1.1. 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 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, and/or
- The test result is considered to be an AE by the Investigator.

Tumor progression or appearance of new tumor lesions, or any sign or symptom clearly related with this circumstance is NOT required to be reported as AEs.

11.1.2. 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.

Tumor progression or appearance of new tumor lesions is NOT required to be reported as a SAE.

11.1.2.1. 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 to the Sponsors.

11.1.2.2. 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.

11.1.2.3. 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 11.2.2). Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the initial admission, as determined by the Investigator or treating physician.

Hospitalizations that do not meet criteria for SAE reporting are:

a. Reasons described in protocol (e.g., study drug, 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).

11.1.3. Unlisted/Unexpected Adverse Event

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

The Sponsors will use as the reference safety information for the evaluation of listedness/expectedness the most updated IB for PM01183.

11.1.4. Adverse Events Related to Study Drugs

An AE is considered an adverse drug reaction (ADR) if it is related to a study drug, i.e., if the Investigator's assessment of causal relationship to the study drug is "Y (yes)" (see Section 11.1.6).

The Investigator will assess the causal relationship of the study drug to the SAE.

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

11.1.5. Expedited Reporting

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

11.1.6. Assessment of Causal Relationship to the Study Drug

The Investigator must provide an assessment of the causal relationship of the study drug to each SAE according to the following scale:

Y There is a reasonable possibility that the study drug caused the SAE.

N There is no reasonable possibility that the study drug 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.

11.2. PROCEDURES

11.2.1. Reporting Adverse Events

The Sponsors will collect AEs until 30 days after administration of the last dose of study drug, until the start of new antitumor therapy, or until the date of death, whichever occurs first. All AEs suspected to be related to the study drug must be followed-up after the time of therapy discontinuation until the event or its sequelae resolve to grade ≤1 or stabilize at an acceptable level to the Investigator and the Sponsors.

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; 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 Sponsors 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
- Represents a reason for change in study dosing or for discontinuation from the study treatment, 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).

11.2.2. Reporting Serious Adverse Events

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

Exemptions from SAE REPORTING: Events of "disease progression", even if they fulfill any seriousness criterion (i.e., fatal, requiring hospitalization, etc), are exempted from SAE reporting and will only be reported in the applicable CRF page.

All SAEs (as defined above) regardless of relationship to the study drug must be reported immediately and always within 24 hours to the Pharma Mar S.A. Pharmacovigilance Department: using the paper SAE form by fax (+34 91 846 6004); e-mail (phv@pharmamar.com) or telephone (+34 91 823 4556) are available if a fax cannot be sent. Out of office hours [Greenwich Meridian Time (GMT)], assistance on SAE reporting can be obtained by calling the Pharmacovigilance Department at +34 91 823 4742.

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" by fax or e-mail from the investigational staff within one working day.

All SAEs suspected to be related to the study drug 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.

11.2.3. Reporting Pregnancy Cases Occurred within the Clinical Trial

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

Therefore, pregnancy and suspected pregnancy occurring while the patient is on study drug or within six weeks from the patient's last PM01183 administration 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 study drug is suspected.
- Possible exposure of a pregnant woman.
- All reports of elevated/ questionable or indeterminate beta human chorionic gonadotropins (β-HCGs).

Immediately after detecting a case of suspected pregnancy in a 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 Sponsors 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.

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 should also be reported to Pharma Mar S.A. Pharmacovigilance by facsimile within 24 hours of the Investigators' knowledge of the event.

11.3. ADVERSE EVENTS MONITORING

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

Periodic safety review of clinical data will be performed; however, no formal Data Safety Monitoring Board (DSMB) 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 the 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/IRBs, 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 study drug within the Development Safety Update Report (DSUR).

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.

12. ADMINISTRATIVE SECTION

12.1. 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 5) and will be consistent with GCP guidelines and pertinent regulatory requirements.

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

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

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

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

All protocol amendments will be agreed upon by the Sponsors 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.

12.2. 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 the Sponsors.

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 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 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 the Sponsors or external auditors contracted by the Sponsors may conduct an onsite audit visit (ICH Topic E6 Guideline for Good Clinical Practice, Section 1.6).

Participation in this trial implies acceptance of potential inspection by national or foreign health authorities.

12.3. PATIENT INFORMED CONSENT FORM

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 cohorts A or B, the Investigator or a person designated by the Investigator, must provide the patient with one copy of the ICF and one copy of the ICF for the PGx substudy. Both copies must provide written full information about the clinical trial and the PGx substudy, 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 substudy. Then, the ICFs must be freely signed and personally dated by the patient and by the person who conducted the Informed Consent discussion before the beginning of the study. In addition, the specific consent for hereditary cancer testing (BRCA 1/2 germline mutation), annexed to the ICF must be signed by those patients whose mutation status is unknown at study entry (BRCA-UK).

Cohort A and B patients willing to participate in the PGx study will voluntarily sign the PGx ICF (refusal will not affect patient participation in the clinical study PM1183-B-003-11).

A single ICF will be used for patients to be included in cohort A1 as consent to participate in the PGx substudy is obligatory for this cohort.

The patient should receive a copy of the signed ICFs and any other written information provided to study patients prior to participation in the trial.

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

12.4. CONFIDENTIALITY / IDENTIFICATION OF PATIENTS

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

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

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

The Sponsors 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.

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

12.6. INSURANCE

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

12.7. RETENTION OF RECORDS

The Investigator/Institution should maintain trial documents according to Section 8 of the ICH Topic E6 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.

12.8. USE OF INFORMATION AND PUBLICATIONS

Before the investigators of this study submit a paper or abstract for publication or otherwise publicly disclose information concerning the study drug or products, the Sponsors 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 the Sponsors determine 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 personnel from the Sponsors who have fully participated in the study must be considered for co-authorship of the publication.

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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

Reference: 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.*

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

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

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

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

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

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 computerized 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.

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.

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.

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).

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.

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

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

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

2.3 Response Criteria

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

2.3.1 Evaluation of Target Lesions

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

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

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

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

2.3.2 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).

2.4 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'.**

2.4.1 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 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 2 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 Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic

deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

2.5 Reporting Best Response Results

2.5.1 Phase II Trials

When response is the primary endpoint, and thus all patients must have measurable disease to enter the trial, all patients included in the study must be accounted for in the report of the results, even if there are major protocol treatment deviations or if they are not evaluable. Each patient will be assigned one of the following categories:

1. Complete response.
2. Partial response.
3. Stable disease.
4. Progression.
5. Inevaluable for response: specify reasons [for example: early death, malignant disease; early death, toxicity; tumor assessments not repeated/incomplete; other (specify)].

2.6 Confirmatory Measurement/Duration of Response

2.6.1 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials (see Bogaerts *et al*. Eur J Cancer 2009; 45(2): 248-260). However, in all other circumstances, i.e., in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

2.6.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the

smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of patients achieving SD for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and SD as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

2.7 Independent Review of Response and Progression

For trials where objective response (CR + PR) is the primary endpoint, and in particular where key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment. Simultaneous review of the patients' files and radiological images is the best approach.

Independent review of progression presents some more complex issues: for example, there are statistical problems with the use of central-review-based progression time in place of investigator-based progression time due to the potential introduction of informative censoring when the former precedes the latter. An overview of these factors and other lessons learned from independent review is provided in an article by Ford *et al.* Eur J Cancer 2009; 45:268–274.

2.8 Reporting Best Response Results

2.8.1 Phase II Trials

When response is the primary endpoint, and thus all patients must have measurable disease to enter the trial, all patients included in the study must be accounted for in the report of the results, even if there are major protocol treatment deviations or if they are not evaluable. Each patient will be assigned one of the following categories:

1. Complete response.
2. Partial response.
3. Stable disease.
4. Progression.
5. Inevaluable for response: specify reasons [for example: early death, malignant disease; early death, toxicity; tumor assessments not repeated/incomplete; other (specify)].

Normally, all eligible patients should be included in the denominator for the calculation of the response rate for phase II trials (in some protocols it will be appropriate to include all treated patients). It is generally preferred that 95% two-sided confidence limits are given for the calculated response rate. Trial conclusions should be based on the response rate for all eligible (or all treated) patients and should not be based on a selected 'evaluable' subset.

Appendix 3. National Comprehensive Cancer Network (NCCN) criteria for consideration of BRCA1/2 genetic testing

A. Individual from a family with a known deleterious BRCA1/BRCA2 mutation
B. Personal history of breast cancer plus one or more of the following:
▪ Diagnosed age ≤45 years
▪ Diagnosed age ≤50 years with ≥1 first-, second-, or third-degree blood relative (on the same side of the family) with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer at any age, or with a limited family history$^{\Delta}$
▪ Two breast primaries§ when first breast cancer diagnosis occurred ≤50 years
▪ Diagnosed ≤60 years with a triple negative breast cancer
▪ Diagnosed ≤50 years with a limited family history$^{\Delta}$
▪ Diagnosed at any age with ≥1 first-, second-, or third-degree blood relative (on the same side of the family) diagnosed with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer ≤50 years
▪ Diagnosed at any age with ≥2 first-, second-, or third-degree blood relatives (on the same side of the family) with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer at any age
▪ Diagnosed at any age with ≥2 first-, second-, or third-degree blood relatives (on the same side of the family) with pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age
▪ First-, second-, or third-degree male blood relative (on the same side of the family) with breast cancer
▪ For an individual of ethnicity associated with higher mutation frequency (e.g, Ashkenazi Jewish), no additional family history may be required
C. Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer

Δ Individuals with a limited family history, such as fewer than two first- or second-degree female relatives or female relatives surviving beyond 45 years in either lineage, may have an underestimated probability of a familial mutation.

§ Two breast primaries include bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.

http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf

Appendix 4. List of CYP1/CYP2/CYP3 Inhibitors, Inducers and Substrates

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

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

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

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

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

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

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

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

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

53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

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.