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CLINICAL TRIAL PROTOCOL

A Multicenter Phase II Clinical Trial of Lurbinectedin (PM01183) in Selected Advanced Solid Tumors

INVESTIGATIONAL MEDICINAL PRODUCT: Lurbinectedin
Protocol No.: PM1183- B-005-14
EudraCT No.: 2014-003773-42
NCT Code: NCT02454972

Protocol version 8.0: 5 June 2020

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CLINICAL TRIAL PROTOCOL

PM1183-B-005-14

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INVESTIGATIONAL MEDICINAL PRODUCT: Lurbinectedin (PM01183)

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Protocol version 8.0 including substantial amendments #1 dated 13 May 2015, #2 dated 04 February 2016, #3 dated 22 March 2016, #4 dated 19 July 2016, #5 dated 08 March 2017, #6 dated 18 July 2018 and #7 dated 5 June 2020.

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

Confidentiality statement

PRINCIPAL INVESTIGATORS

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

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SYNOPSIS

TITLE	A Multicenter Phase II Clinical Trial of Lurbinectedin (PM01183) in Selected Advanced Solid Tumors.
PROTOCOL CODE	PM1183-B-005-14
NUMBER OF SITES / TRIAL LOCATION	This is a multicenter study. A full list of investigators will be available as a separate document.
STUDY OBJECTIVES	**Primary:** • To assess the antitumor activity of lurbinectedin (PM01183) in terms of overall response rate (ORR), according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1, in the following advanced solid tumors: small cell lung cancer (SCLC), head and neck carcinoma (H&N), neuroendocrine tumors (NETs), biliary tract carcinoma, endometrial carcinoma, BRCA 1/2-associated metastatic breast carcinoma, carcinoma of unknown primary site, germ cell tumors (GCTs), and Ewing's family of tumors (EFTs). **Secondary:** • To further characterize the antitumor activity of PM01183 in terms of duration of response (DR), clinical benefit [ORR or stable disease (SD) lasting over four months (SD ≥ 4 months)], progression-free survival (PFS) by Investigator's assessment (IA), and overall survival (OS) in each cohort of advanced solid tumors. • To further investigate the antitumor activity of PM01183 in terms of ORR, DR, clinical benefit (ORR or SD ≥ 4 months) and PFS by an Independent Review Committee (IRC) in the cohort of SCLC patients. • To characterize the plasma pharmacokinetics (PK) of PM01183. • To conduct an exploratory pharmacogenomic (PGx) and pharmacogenetic analysis. • To evaluate the safety profile of PM01183 in this patient population.
STUDY DESIGN	Multicenter, open-label, exploratory, phase II clinical trial to evaluate the efficacy and safety of PM01183 in previously treated patients with the following advanced solid tumors: SCLC, H&N, NETs, biliary tract carcinoma, endometrial carcinoma, BRCA 1/2-associated metastatic breast carcinoma, carcinoma of unknown primary site, GCTs, and EFTs. Patients with each of the aforementioned tumors will be

	enrolled in nine cohorts. Up to 25 evaluable patients are planned to be enrolled in each cohort (50 in the endometrial carcinoma and 100 in the SCLC cohort). To consider that PM01183 has antitumor activity in any of the tumor types analyzed, at least two confirmed responses [complete (CR) or partial response (PR)] per RECIST v.1.1 out of the 25 patients of each cohort are expected. • If no confirmed responses are observed in the first 15 evaluable patients of each cohort, the recruitment of the corresponding cohort will be stopped. • If one confirmed response is observed in the first 15 evaluable patients of each cohort, the recruitment of this cohort will continue to up to 25 evaluable patients. o In the cohort of endometrial carcinoma, if ≥2 confirmed responses occur in the first 25 evaluable patients, the sample size will be doubled to 50 evaluable patients. o In the cohort of SCLC, if ≥2 confirmed responses occur in the first 25 evaluable patients, the sample size will be increased to 100 evaluable patients. • If two confirmed responses are observed in the first 15 evaluable patients of each cohort, the recruitment of the corresponding cohort can be stopped. Only in the SCLC cohort, an IRC will determine the best patient's response and assign the date of first documentation of response and progression/censoring according to RECIST v.1.1. Operational details for the IRC and the algorithm and its validation by an expert panel is described in detail in the IRC charter. In addition, for safety reasons: • If two patients have a treatment-related death in a cohort, the recruitment of the corresponding cohort will be stopped. • If six patients have treatment-related deaths in the whole population, the study will be stopped. Finally, • A determined cohort can be early closed by the Sponsor in case of a low recruitment rate. • Once the target of patients included in each cohort is reached, recruitment in this cohort will be kept "on hold" during the period of patients' data analysis to assess their evaluability and the response rate. After this period, if the number of evaluable patients does not reach the planned target, recruitment will be re-opened and non-evaluable patients will be replaced.
STUDY POPULATION	Previously treated patients with the following advanced solid tumors: SCLC, H&N, NETs, biliary tract carcinoma, endometrial carcinoma, BRCA 1/2-associated metastatic breast carcinoma, carcinoma of unknown primary site, GCTs,

	and EFTs.
STUDY POPULATION **Inclusion criteria**	1) Age ≥ 18 years. 2) Voluntary signed informed consent (IC) of the patient before any study-specific procedure. 3) Pathologically proven diagnosis of any of the following malignancies: a) Small cell lung cancer (SCLC). b) Head and neck carcinoma (H&N). Salivary glands tumors are excluded. c) Neuroendocrine tumors (NETs), grade 2 and grade 3 according to World Health Organization (WHO) classification. d) Biliary tract carcinoma. e) Endometrial carcinoma. f) BRCA 1/2- associated metastatic breast carcinoma g) Carcinoma of unknown primary site. h) Germ cell tumor (GCTs), excluding immature teratoma, or teratoma with malignant transformation. i) Ewing's family of tumors (EFTs). 4) Prior treatment. Patients must have received: a) SCLC: one prior chemotherapy-containing line. b) H&N: one or two prior chemotherapy-containing lines. c) NETs: one or two prior chemotherapy-containing lines. No more than three prior hormone or biological therapy lines. d) Biliary tract carcinoma: one or two prior chemotherapy-containing lines. e) Endometrial carcinoma: one prior chemotherapy-containing line. f) BRCA 1/2-associated metastatic breast carcinoma: at least one but no more than three prior chemotherapy-containing lines. g) Carcinoma of unknown primary site: one or two prior chemotherapy-containing lines. h) GCTs: no limit of prior therapy (patients with no other clinical therapeutic options). i) EFTs: no more than two prior chemotherapy-containing lines in the metastatic/recurrent setting. 5) Measurable disease as defined by RECIST v.1.1, and documented progression before study entry. 6) Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2. 7) Adequate major organ function: a) Hemoglobin ≥ 9 g/dl, prior red blood cell (RBC) transfusions are allowed if clinically indicated; absolute

	neutrophil count (ANC) ≥ 2.0 × 10^9/l; and platelet count ≥ 100 × 10^9/l. b) Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3.0 × upper limit of normal (ULN). c) Total bilirubin ≤ 1.5 × ULN, or direct bilirubin ≤ULN. d) Albumin ≥ 3 g/dl. e) Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 30 ml/min. f) Creatine phosphokinase (CPK) ≤ 2.5 × ULN. 8) 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 gray (Gy). c) At least two weeks since the last biological/investigational therapy (excluding MAbs) or palliative RT (≤ 10 fractions or ≤ 30 Gy total dose). 9) Grade ≤ 1 toxicity due to any previous cancer therapy according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v.4). Grade 2 is allowed in case of alopecia and/or peripheral sensory neuropathy. 10) Women of childbearing potential must have pregnancy excluded by appropriate testing before study entry. Fertile women must agree to use a medically acceptable method of contraception throughout the treatment period and for at least three months after treatment discontinuation. Fertile men must agree to refrain from fathering a child or donating sperm during the trial and for four months after the last infusion.
Exclusion criteria	1) Prior treatment with PM01183 or trabectedin. 2) Prior or concurrent malignant disease unless in complete remission for more than five years, except treated *in situ* carcinoma of the cervix, basal or squamous cell skin carcinoma, and *in situ* transitional cell bladder carcinoma. 3) Known central nervous system (CNS) involvement. In patients with SCLC, brain computed tomography (CT)-scan or magnetic resonance imaging (MRI) results must be provided at baseline. 4) Relevant diseases or clinical situations which may increase the patient's risk: a) History within the last year or presence of unstable angina, myocardial infarction, congestive heart failure, or clinically relevant valvular heart disease or

	symptomatic arrhythmia or any asymptomatic ventricular arrhythmia requiring ongoing treatment. b) Grade ≥ 3 dyspnea or daily intermittent oxygen requirement within two weeks prior to the study treatment onset. c) Active infection. d) Unhealed wounds or presence of any external drainage. e) Known chronic active hepatitis or cirrhosis. f) Immunocompromised patients, including known infection by human immunodeficiency virus (HIV). 5) Women who are pregnant or breast-feeding, and fertile patients (men and women) who are not using an effective method of contraception. * 6) Impending need for RT (e.g., painful bone metastasis and/or risk of spinal cord compression). 7) Limitation of the patient's ability to comply with the treatment or to follow-up the protocol. * Women of childbearing potential (WOCBP) must agree to use an effective contraception method to avoid pregnancy during the course of the trial (and for at least three months after the last infusion). Valid methods to determine the childbearing potential, adequate contraception and requirements for WOCBP partners are described in APPENDIX 2. Fertile men must agree to refrain from fathering a child or donating sperm during the trial and for four months after the last infusion.
INCLUSION CRITERIA FOR THE PHARMACOGENOMIC AND PHARMACOGENETIC SUB-STUDY	Only patients who voluntarily sign the written informed consent (IC) for the pharmacogenomic (PGx) and pharmacogenetic sub-study will participate. Refusal to participate in this sub-study will not affect patient participation in the clinical study PM1183-B-005-14.
EXPECTED NUMBER OF PATIENTS	A minimum of 135 evaluable patients are planned. If response rate exceeds the one defined in the stopping rule, the recruitment can proceed to up to 350 evaluable patients (see Statistical Methods).
REPLACEMENT OF PATIENTS	Patients will be replaced if they are not evaluable for the primary endpoint of the study (ORR as per RECIST v. 1.1), specifically if (any of the following): • They are not eligible. • They have not received the study treatment. • 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. o Early death due to malignant disease. All replaced patients who received study treatment will be included in the safety analysis.
STUDY DRUG FORMULATION	PM01183 drug product (DP) is presented as a lyophilized powder for concentrate for solution for infusion in 4-mg vials, which will be supplied by the Sponsor for the purposes of this study. For administration to patients as an i.v. infusion, reconstituted vials are diluted with glucose 50 mg/ml (5%) solution for infusion or sodium chloride 9 mg/ml (0.9%) solution for infusion. The full composition of the PM01183 4-mg vials and the reconstituted solution per ml is as shown in Table 1.
ROUTE OF ADMINISTRATION	PM01183 will be administered over a (either on 5% glucose or 0.9% sodium chloride), through a central catheter, or over a if administered through a peripheral line, always over one hour at a fixed infusion rate.
STARTING DOSES AND SCHEDULE	Starting dose will be 3.2 mg/m^2. Dose will be capped at BSA of 2.0 m^2 (i.e., dose will not exceed 6.4 mg). Patients will receive PM01183 i.v. as a one-hour infusion on Day 1 every three weeks (q3wk) (three weeks = one treatment cycle).
PROPHYLACTIC MEDICATION	All patients will receive standard antiemetic prophylaxis before each treatment infusion. The i.v. formulations of these agents must be used in this setting: • Corticosteroids (dexamethasone 8 mg or equivalent). • Serotonin (5-HT$_3$) antagonists (ondansetron 8 mg or equivalent). • Extended treatment with oral 5-HT$_3$ antagonists and oral dexamethasone for two consecutive days. • If necessary, and in addition to the above, administration of 10 mg of oral or i.v. metoclopramide (or equivalent)

<table>
<tr><td></td><td>every eight hours.
Aprepitant and equivalent agents (e.g., fosaprepitant) are forbidden in patients treated with PM01183.</td></tr>
<tr><td>CRITERIA FOR TREATMENT CONTINUATION</td><td>Further treatment cycles (i.e., Cycle 2 or subsequent) will be administered q3wk (± 48 hours) if the patient fulfills all the re-treatment criteria defined in Table 2.
Table 2. Criteria for treatment continuation.
<table>
<tr><th>Variable</th><th>Re-treatment (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 × 10^9/l</td></tr>
<tr><td>Platelets</td><td>≥ 100 × 10^9/l</td></tr>
<tr><td>AST/ALT</td><td>≤ 3.0 × ULN</td></tr>
<tr><td>Total bilirubin or direct bilirubin</td><td>≤ 1.5 × ULN or × ULN</td></tr>
<tr><td>Albumin</td><td>≥ 3 g/dl</td></tr>
<tr><td>Serum creatinine</td><td>≤ 1.5 × ULN or creatinine clearance ≥ 30 ml/min</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 2 asthenia, constipation, alopecia, peripheral neuropathy, or non-optimally treated nausea and/or vomiting)</td><td>Grade ≤ 1</td></tr>
<tr><td>Active infection (including sepsis) and/or bleeding (any grade)</td><td>Absence</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.
AE(s), adverse event(s); 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 at least 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 3-week delay must be withdrawn from trial. In case of objective clinical benefit, the patient could continue receiving the treatment (upon the Sponsors' agreement).
For any delay due to treatment-related adverse events lasting for more than one week, a dose reduction must be implemented upon recovery, following the rules explained in the next section.</td></tr>
<tr><td>DOSE REDUCTION</td><td>Patients may continue the study treatment at a reduced dose if they present 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 ≤ 3 days, grade 3 diarrhea lasting ≤ 2 days or not optimally treated, grade</td></tr>
</table>

<table>
<tr><td></td><td>3 transient ALT/AST elevations which are rapidly reversible and not leading to subsequent delays, and non-clinically relevant biochemical abnormalities.
• Grade 4 thrombocytopenia or grade 3 thrombocytopenia concomitantly with grade ≥3 bleeding.
• Grade 4 neutropenia, any grade febrile neutropenia or neutropenia associated with infection/sepsis.
• Frequent or prolonged (>1 week) dose delays due to treatment-related adverse events.
Patients who experience grade 3/4 hypersensitivity reactions will be discontinued from study treatment.
Dose reduction levels are shown in Table 3.
Table 3. Criteria for dose reduction.<table><tr><th>Dose reduction</th><th>PM01183 dose*
(mg/m^2)</th></tr><tr><td>1 (starting dose)</td><td>3.2**</td></tr><tr><td>−1</td><td>2.6</td></tr><tr><td>−2</td><td>2.0</td></tr></table>*Dose rounded to the first decimal.
**Dose will be capped at BSA of 2.0 m^2 (i.e., dose will not exceed 6.4 mg).
BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; PS, performance status.
Up to two dose reductions are allowed per patient.
Patients who continue to experience treatment-related toxicity and/or frequent dose delays after permitted dose reductions must be withdrawn from the study. They can continue receiving the study medication if objective clinical benefit is adequately documented by the Investigator, and upon agreement with the Sponsor. Once the dose has been reduced for an individual patient, it will not be re-escalated under any circumstances.</td></tr>
<tr><td>ALLOWED MEDICATIONS/ THERAPIES</td><td>• 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 the American Society of Clinical Oncology (ASCO) guidelines.
• Erythropoietin (EPO) treatment according to the ASCO guidelines.
• Anticoagulation therapy.</td></tr>
<tr><td>PROHIBITED MEDICATIONS/ THERAPIES</td><td>• Any other antineoplastic therapy, except somatostatin analogues for NETs.
• Any other investigational agents.
• Primary G-CSF prophylaxis.</td></tr>
</table>

	• Immunosuppressive therapies other than corticosteroids for antiemetic prophylaxis and/or pain control. • Medroxyprogesterone (patients with endometrial cancer). • Aprepitant, fosaprepitant or related compounds. • Radiotherapy.
DRUG-DRUG INTERACTIONS	*In vitro* studies have shown PM01183 may inhibit CYP3A4. The magnitude of the interaction is unknown at present. Therefore, caution should be exercised when PM01183 is administered concomitantly with 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 possible.
EFFICACY EVALUATIONS	The primary objective of this study is to assess the antitumor activity of PM01183 in terms of **overall response rate (ORR)**, primary endpoint, supported by the secondary endpoint duration of response (DR), both assessed by the IA. ORR will be assessed using the RECIST v.1.1 on a set of measurable lesions identified at baseline as target lesions or as non-target lesions (if any), and followed until disease progression (PD) by an appropriate method (e.g., helical CT-scan, MRI). Radiological tumor assessment will be performed at baseline, and every two cycles from the onset of the study treatment until Cycle 6 or evidence of PD. After Cycle 6, tumor assessment will be performed every three cycles until evidence of PD. If an objective response is observed, according to the RECIST v1.1, it must be confirmed by the same method at least four weeks after the date of the first documentation of response. ORR is defined as the percentage of evaluable patients with a confirmed response, either complete (CR) or partial response (PR), from the start of treatment to the date of progression or the start of a subsequent therapy or end of patient's follow-up, according to the RECIST (v. 1.1). DR will be calculated from the date of first documentation of response to the date of first documented PD, recurrence or death due to any cause in the responder patients. The date of response, the date of radiological or clinical PD, according to the investigator assessment and the independent assessment by IRC when applicable (i.e., SCLC cohort), and the date of death will be registered and documented, as appropriate. In case of objective tumor response, a copy of CT-scans or

	MRIs can be requested by the Sponsor. In SCLC patients, anonymized copies of all the images obtained throughout the study must be submitted to the Sponsor. These copies of CT scans, MRIs and any other documented methods to evaluate tumor response or progression in the SCLC cohort should be available for external radiological review by an IRC. The IRC will determine the patient's best response and assign the date of first documentation of response and progression/censoring according to RECIST v.1.1.
PHARMACOKINETIC EVALUATIONS	The plasma PK of PM01183 will be evaluated during Cycle 1 and 2 in all treated patients. The sampling schedule will be as shown in Table 4 and Table 5 for Cycle 1 and Cycle 2, respectively. **Table 4.** Blood **s**amples for pharmacokinetic evaluations in Cycle 1. **Sample No.** / **Day** / **Sampling time** / **Sampling window** **#1** / D1 / Before infusion start / -- **#2 *** / D1 / 5 min before EOI / +/- 4 min **#3** / D1 / 30 min after EOI / +/- 4 min **#4** / D1 / 1 hour after EOI / +/- 10 min **#5** / D1 / 3 hours after EOI / +/- 10 min **#6** / D2 / 24 hours after EOI / +/- 2 hours **#7** / D4 / 72 hours after EOI / +/- 24 hours **#8** / D8 / 168 hours after EOI / +/- 24 hours * Sample #2 must be collected before EOI. D, day; EOI, end of infusion. **Table 5.** Blood **s**amples for pharmacokinetic evaluations in Cycle 2. **Sample No.** / **Day** / **Sampling time** / **Sampling window** **#9** / D1 / Before infusion start / -- **#10 *** / D1 / 5 min before EOI / +/- 4 min **#11** / D1 / 30 min after EOI / +/- 4 min **#12** / D1 / 1 hour after EOI / +/- 10 min **#13** / D1 / 3 hours after EOI / +/- 10 min **#14** / D8 / 168 hours after EOI / +/- 24 hours * Sample #10 must be collected before EOI D, day; EOI, end of infusion. PK parameters will be calculated using non-compartmental analysis (NCA) and population methods if appropriate, after pooling data from this study with data obtained from other studies. The plasma PK of PM01183 will be evaluated during Cycle 1 and 2 in all treated patients. The sampling schedule will be as shown in Table 4 and Table 5 for Cycle 1 and Cycle 2, respectively.

Table 4. Blood **s**amples for pharmacokinetic evaluations in Cycle 1.

Sample No.	Day	Sampling time	Sampling window
#1	D1	Before infusion start	--
#2 *	D1	5 min before EOI	+/- 4 min
#3	D1	30 min after EOI	+/- 4 min
#4	D1	1 hour after EOI	+/- 10 min
#5	D1	3 hours after EOI	+/- 10 min
#6	D2	24 hours after EOI	+/- 2 hours
#7	D4	72 hours after EOI	+/- 24 hours
#8	D8	168 hours after EOI	+/- 24 hours

* Sample #2 must be collected before EOI.
D, day; EOI, end of infusion.

Table 5. Blood **s**amples for pharmacokinetic evaluations in Cycle 2.

Sample No.	Day	Sampling time	Sampling window
#9	D1	Before infusion start	--
#10 *	D1	5 min before EOI	+/- 4 min
#11	D1	30 min after EOI	+/- 4 min
#12	D1	1 hour after EOI	+/- 10 min
#13	D1	3 hours after EOI	+/- 10 min
#14	D8	168 hours after EOI	+/- 24 hours

* Sample #10 must be collected before EOI
D, day; EOI, end of infusion.

PK parameters will be calculated using non-compartmental analysis (NCA) and population methods if appropriate, after pooling data from this study with data obtained from other studies.

PHARMACOGENETIC EVALUATIONS

Pharmacogenetic sub-study:

To explore factors that may help to explain individual variability in main PK parameters, the presence or absence of germline mutations or polymorphisms that may be involved in the metabolism and/or transport of PM01183 will be analyzed in leukocyte DNA extracted from a blood sample obtained at any time during the study, but preferably just before treatment start in Cycle 1.

PHARMACOGENOMIC EVALUATIONS

Pharmacogenomic sub-study:

The analysis of potential predictive factors to PM01183 treatment will be analyzed on prior available paraffin-embedded tumor tissue samples from consenting patients. These factors will include genes involved in DNA repair mechanisms (such as nucleotide excision repair, homologous recombination repair or mismatch repair) and other factors related to the mechanism of action of PM01183 or to the pathogenesis of the disease, and their expression will be analyzed at the mRNA or protein level by quantitative polymerase chain reaction (PCR) and immunohistochemistry (IHC), respectively; their polymorphisms and mutations might be also analyzed, if relevant.

SAFETY EVALUATIONS	Patients will be evaluable for safety if they have received any partial or complete infusion of PM01183. All adverse events (AEs) will be graded according to the NCI-CTCAE, v.4. The safety profile of patients will be monitored throughout the treatment and up to 30 days after the last PM01183 infusion (end of treatment, EOT), or until the patient starts a new antitumor therapy or until the date of death, whichever occurs first. Treatment delays, dose reduction requirements, transfusions, and reason for treatment discontinuation will be monitored throughout the study. Any treatment-related AEs will be followed until recovery to at least grade 1 or stabilization of symptoms or until the start of a new antitumor therapy, whichever occurs first.
STUDY ENDPOINTS	**Primary endpoint:** • **Overall Response Rate (ORR)** in each tumor type. ORR is defined as the percentage of patients with a confirmed response, either complete (CR) or partial (PR), according to the RECIST (v. 1.1). **Secondary endpoints:** **Efficacy (all cohorts):** • **Duration of Response (DR) by IA**, defined as the time between the date when the response criteria (PR or CR, whichever one is first reached) are fulfilled to the first date when PD, recurrence or death is documented. • **Clinical Benefit by IA**, defined as ORR or stable disease lasting over four months (SD ≥ 4 months). • **Progression-free Survival (PFS) by IA**, defined as the period of time from the date of first infusion to the date of PD, death (of any cause), or last tumor evaluation. • **PFS4/PFS6 by IA**, defined as the Kaplan-Meier estimates of the probability of being free from progression and death after the first infusion at these time points (4 and 6 months). • **OS**, defined as the period of time from the date of first infusion to the date of death or last contact in case of patients lost to follow-up or alive at the clinical cut-off established for the cohort. • **OS6/OS12,** defined as the Kaplan-Meier estimates of the probability of being alive after the first infusion at these time points (6 and 12 months). **Efficacy (only in the SCLC cohort):** • **ORR, Clinical Benefit, DR, PFS and PFS4/PFS6 by IRC.** The same definitions detailed for IA will be used.

	Plasma Pharmacokinetics (PK) of PM01183 Non-compartmental (NCA) PK parameters: area under the curve (AUC), C_{max}, clearance (CL) and half-life ($t_{1/2}$). Population PK parameters of the compartment model to be developed (initially based on Volumes and Clearance), and PK/PD correlation parameters, if applicable. **Pharmacogenetics** This analysis will be performed in those patients who signed the IC for the pharmacogenetic sub-study. The presence or absence of known polymorphisms from a single sample collected at any time during the study, but preferably just before treatment start in Cycle 1, will be assessed to explain the individual variability in the main PK parameters. **Pharmacogenomics (PGx):** This exploratory analysis will be performed in those patients treated in any arm who signed the IC for the PGx sub-study. mRNA or protein expression levels of factors involved in DNA repair mechanisms, or related to the mechanism of action of lurbinectedin, will be evaluated from prior available tumor tissue samples obtained at diagnosis or relapse. Their mutational status might be also analyzed. Their correlation with the clinical response and outcome after treatment will be assessed. **Safety Profile:** • Clinical examinations. • Clinical assessment of AEs and serious adverse events (SAEs). • Changes in laboratory parameters (hematological and biochemical, including liver function tests). • Reasons for treatment discontinuations. • Reasons for dose reduction and treatment delays.
STATISTICAL METHODS	This phase II trial is designed to assess the antitumor activity of PM01183 in terms of ORR according to the RECIST v.1.1 assessed by IA in different selected advanced solid tumors: SCLC, H&N, NETs, biliary tract carcinoma, endometrial carcinoma, BRCA 1/2-associated metastatic breast carcinoma, carcinoma of unknown primary site, GCTs, and EFTs. In addition, in the SCLC cohort, tumor evaluation will be also done by IRC. **Sample Size:** Up to 25 evaluable patients in each tumor type will be recruited to test the null hypothesis that 1% or less patients get a response ($p \leq 0.01$) *versus* the alternative hypothesis that 10% or more patients get a response ($p \geq 0.10$). The variance of the standardized test 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 0.2 (normal approximation; ~0.3 if exact binomial distribution); hence, statistical power is 80% (normal approximation; ~70% if exact binomial distribution). With these assumptions, if the number of patients who achieve a confirmed response is ≥ 2, then this would allow the rejection of the null hypothesis. Endometrial carcinoma: Up to 50 evaluable patients will be recruited to test the null hypothesis that 10% or less patients get a response ($p \leq 0.10$) *versus* the alternative hypothesis that 25% or more patients get a response ($p \geq 0.25$). The variance of the standardized test 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 0.144 (normal approximation; ~0.16 if exact binomial distribution); hence, statistical power is ~86% (normal approximation; ~84% if exact binomial distribution). With these assumptions, if the number of patients who achieve a confirmed response is ≥ 10, then this would allow the rejection of the null hypothesis. SCLC: Up to 100 evaluable patients will be recruited to test the null hypothesis that 15% or less patients get a response ($p \leq 0.15$) *versus* the alternative hypothesis that 30% or more patients get a response ($p \geq 0.30$). The variance of the standardized test 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 0.051 (normal approximation; ~0.05 if exact binomial distribution); hence, statistical power is 95% (normal approximation; ~95% if exact binomial distribution). With these assumptions, if the number of patients who achieve a confirmed response is ≥ 23, then this would allow the rejection of the null hypothesis. The judgement of patient's evaluability and replacement of non-evaluable patients in each cohort for the interim analyses will be guided by the investigator assessment. **Interim Analyses:** An interim analysis to reject H0 (non-binding) or to reject H1 (futility) in each tumor type is planned after the recruitment of 15 evaluable patients in each cohort. The Gamma family boundary will be used to control the type I error, the parameter to reject H0 is fixed as -1 and the parameter to reject H1 is fixed as 0. If none of the first 15 evaluable patients in a determined cohort has a confirmed response, the alternative hypothesis will be rejected, according to boundaries and sample size assumptions, and recruitment will be stopped. If the number of responding patients is already two or more at the interim analysis, then H0 could be rejected and the study will have enough power to be stopped. On the contrary, if there is one confirmed response, the recruitment will be continued to up to 25 evaluable patients. • A phase III trial of PM01183 combined with

	doxorubicin in SCLC is ongoing. Hence, the sample size for the SCLC cohort of this study will be increased to 100 evaluable patients if the success boundary (≥2 confirmed responses) is reached in the first 25 evaluable patients. The type I/II error will be controlled with a Gamma family boundary (-1 to reject Ho, 0 to reject H1) • A phase I trial of PM01183 combined with doxorubicin has shown encouraging antitumor activity in endometrial carcinoma. Hence, the sample size for the endometrial carcinoma cohort of this study will be doubled to 50 evaluable patients if the success boundary (≥2 confirmed responses) is reached in the first 25 evaluable patients. The type I/II error will be controlled with a Gamma family boundary (-1 to reject Ho, -3 to reject H1) With the sample size of 100 and 50 evaluable patients in each indication (SCLC and endometrial), the obtained confidence interval will be narrower and its half-width will be confined to ±15%. **Statistical Analysis** Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. The study protocol contains a general description; specific details will be provided in the Statistical Analysis Plan. Frequency tables will be prepared for categorical variables, and continuous variables will be described by means of summary tables, which will include the median, mean, standard deviation, minimum, and maximum of each variable. **Efficacy Analyses:** Counts and percentages, with their corresponding exact 95% confidence intervals, will be calculated for the binomial endpoints (e.g., ORR, clinical benefit). Time-to-event variables (OS, PFS and DR) and their set time estimates (i.e., PFS 4/6 and OS 6/12) will be analyzed according to the Kaplan-Meier method. In the SCLC cohort, the evaluation of the efficacy endpoints evaluated by IA and IRC will be analyzed and compared. The rate of concordance between both evaluation methods for best response, progression status and progression-free survival will be presented with 2-way frequency tables and measures of agreement. Waterfall plots will be used to describe the best variation of the sum of target lesions during treatment. The number of patients recruited in any cohort may differ from that pre-specified according to the sample size assumptions. Therefore, the main efficacy results will be calculated according to the planned cohort sample size and, if any cohort sample size differs at least 10% from the assumptions, a sensitivity analysis using all evaluable patients recruited (adjusting the corresponding boundaries to test the null hypothesis) will be performed.

	Pharmacokinetic Analyses: PK data will be listed in the population PK-report for all patients with available PM01183 concentrations. PK analysis of plasma concentration-time data of PM01183 will be performed using non-linear mixed-effects modeling and/or non-compartmental analysis. Data may be combined with those of a selection of phase I or II studies to support a relevant structural model. Available patient characteristics (e.g., demographics, laboratory variables, genotypes) will be tested as potential covariates affecting PK parameters. **Pharmacogenetic Analyses:** The influence of known polymorphisms on main PK parameters will be assessed by Student's test or Mann-Whitney's U test as appropriate. **Pharmacogenomics Analyses:** Analysis of RNA/protein expression, polymorphisms and mutations will be performed blind and with clinical data compiled only after all analyses are completed. A Fisher´s exact test/logistic regression for categorical variables and log rank test/Cox regression for time to event variables will be used to test whether a specific profile is associated with clinical outcome. The prognosis value of markers will be explored for objective response, PFS and OS. In each case, if applicable, a multivariate model will be developed by stepwise selection. All tests of statistical significance will be two-sided, and significance will be set at 0.05. **Safety Analyses:** AEs, SAEs, deaths, laboratory evaluations, dose delays/reductions and study drug discontinuations due to AEs will be tabulated in a descriptive way. Counts and percentages will be used for categorical variables, and summary tables will be used for continuous variables.
DURATION OF STUDY PERIOD (per patient)	Patients will be evaluated at scheduled visits within three study periods: • **Pre-treatment:** from signature of IC to the first infusion of the study treatment. • **Treatment:** from the first infusion of the study treatment to the end of treatment (EOT). • **Follow-up:** after EOT, patients will be followed-up every four weeks until resolution or stabilization of all drug-related adverse events, if any, or until start a new antitumor therapy. Patients will be followed-up for at least one year after their first PM01183 infusion. Patients who finish treatment without disease progression (PD) will be followed-up every two months during the first six months and every three months thereafter until PD, start of a new antitumor therapy, death or until the end of study date (clinical cutoff). After PD is documented or a new antitumor therapy is started, each cohort (except

	SCLC) will be followed-up at least every six months and up to 12 months after the last patient enrolled received the first PM01183 infusion (a documented phone contact will be acceptable). Patients in the SCLC cohort, after PD, will be followed-up every six months for at least 18 months after the last patient enrolled received the first PM01183 infusion (a documented phone contact will be acceptable). Patients will be considered to be **on-study** from the signature of the informed consent form (ICF) until the end of the follow-up period. Patients will be considered to be **on-treatment** for the duration of their treatment and until the day of EOT, immediately before the start of the follow-up period. This EOT is defined as 30 days after the day of the last PM01183 infusion, unless the patient starts a new antitumor therapy or dies (whichever occurs first). An end-of-treatment visit (EOT visit) will be performed within 30 days (± 7 days) after the last study treatment administration, unless the patient starts any subsequent antitumor therapy, in which case the EOT visit should be performed immediately before the start of the new therapy. Patients will receive the study treatment while it is considered to be in their best interest. Specifically, treatment will continue until: • Disease progression. • Unacceptable toxicity. • Treatment delay > three weeks from the treatment due date (except in case of clear clinical benefit, upon Sponsors' approval). • Requirement of > two dose reductions. • Intercurrent illness of sufficient magnitude to preclude safe continuation of the study. • A major protocol deviation that may affect the risk/benefit ratio for the participating patient. • Investigator's decision. • Non-compliance with study requirements. • Patient's refusal.
PLANNED TRIAL PERIODS (for the whole study)	The total duration of the study will be approximately 52 months, including approximately a 40-month enrolment period. **Planned start date** (first patient on study): 3Q2015. **Planned enrolment period**: 40 months. **Planned end-of-study date** (clinical cutoff for each cohort except SCLC): when all evaluable patients within each cohort have at least 12 months of follow-up from the first PM01183 infusion. Patients in the SCLC cohort will be followed-up for at least 18 months after the last patient enrolled received the first PM01183 infusion.

SCHEDULE OF ASSESSMENTS AND PROCEDURES

Assessments and procedures	Screening* (days)	Treatment								Follow-up
		Cycle 1			Cycle 2			Further cycles	End of treatment (EOT) ‡	
		D1	D8	D15	D1	D8	D15	D1		
Written informed consents (general and PGx/pharmacogenetic sub-study)	Before any study procedure	-	-	-	-		-	-	-	-
Demographic data	-28 to 0	-	-	-	-		-	-	-	-
Primary diagnosis and prior treatment(s)	-28 to 0 (+1 week)	-	-	-	-		-	-	-	-
Medical and cancer history/baseline conditions	-14 to 0 (+1 week)	-	-	-	-		-	-	-	-
Assessment of disease signs and symptoms	-7 to 0 (+1 day)	-	-	-	-		-	-	-	-
Complete physical examination, including weight and height and calculation of BSA (1)	-7 to 0 (+1 day)	●	-	-	●	-	-	●	●	-
ECOG PS	-7 to 0 (+1 day)	●	-	-	●	-	-	●	●	-
Vital signs (heart rate, blood pressure, temperature)	-7 to 0 (+1 day)	●	-	-	●	-	-	●	●	-
Coagulation panel	-7 to 0	-	-	-	●	-	-	●	●	-
Hematology (2, 3) †	-7 to 0	● (4)	●	●	●	●	●	● (5)	●	-
Biochemistry A (2) †	-7 to 0	-	●	●	●	●	●	● (5)	●	-
Biochemistry B †	-7 to 0	-	-	-	●	-	-	●	●	-
Pharmacokinetics and AAGP	-	● (6)	-	-	● (7)	-	-	-	-	-
Pharmacogenetic sub-study (only if written informed consent given)	One blood sample collected at any time during the study, but preferably just before treatment start in Cycle 1									-
Pharmacogenomic (PGx) sub-study (only if written informed consent given)	Available stored paraffin-embedded tumor tissue samples, assessed at any time during the study.									-
Pregnancy test (8) †	-7 to 0	●	-	-	●	-	-	●	●	-
ECG (9)	-7 to 0 (+3 days)	Repeat if clinically indicated								-
LVEF by ECHO or MUGA(9)	-28 to 0 (+3 days)	Repeat if clinically indicated								-
Radiological tumor assessment (10)	-28 to 0 (+1 week)	Every two cycles from the onset of the study treatment until Cycle 6 and every three cycles thereafter (11)								● (12)
Concomitant therapies	-14 to 0 (+1 week)	Throughout the ”on-treatment period”								-
Adverse events	- §	Throughout the ”on-treatment period”								● (13)

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

† Day 0 is when eligibility is confirmed and a patient is registered: for the purposes of assessment windows, it is assumed that Day 0 is the calendar day before Day 1 of Cycle 1. If this is not the case and first infusion is administered more than one week after screening window, laboratory tests (hematology, biochemistry A, B and pregnancy test if applicable) must be repeated within the three days prior to first infusion.

‡ At 30 ±7 days after the last treatment infusion, an EOT visit should be performed. The listed assessments will have to be done if no recent data are available (i.e. within last 10 days prior to the EOT visit) or if the last data available show a grade ≥ 2 alteration.
§ Only information on SAEs that occur after signature of informed consent form is required. Grading should be as per NCI-CTCAE v. 4.

A 3-day window will be allowed for laboratory procedures and ECG, a 1-week window for radiological tumor assessments (helical CT-scan or MRI) and LVEF assessments, a 1-day window for clinical assessments (ECOG PS, physical examination, vital signs, weight, BSA), and a 7-day window for the assessments at EOT.

1. Body surface area (BSA) will be recalculated on Day 1 of each treatment cycle. Dose will be adjusted if BSA change is ≥ 10% (higher or lower) of the previous value. Height is only required at baseline.
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. Any patient having febrile neutropenia of any grade, grade 4 neutropenia, and/or grade 4 thrombocytopenia, should have relevant tests repeated daily until recovery to grade ≤ 3 and up to the next day after fever resolution, if applicable.
4. Two blood samples (24 hours and 72 hours after the end of PM01183 infusion) will be collected at the same time than PK samples #6 and #7 in Cycle 1 for monocyte count.
5. From Cycle 2 onwards, Hematology and Biochemistry A tests on Days 8 and 15 are to be performed only in patients who present biochemical grade ≥3 or hematological grade > 4 treatment-related toxicities, or who required dose adjustments due to hematological or biochemical abnormalities in the preceding cycle.
6. Eight blood samples (before PM01183 infusion start, 5 min before the end of PM01183 infusion and 30 min, 1 hour, 3 hours, 24 hours, 72 hours and 168 hours after the end of PM01183 infusion) will be collected for pharmacokinetic analyses in Cycle 1. In addition, one blood sample for the evaluation of AAGP will be collected before PM01183 infusion start.
7. Six blood samples (before PM01183 infusion start, 5 min before the end of PM01183 infusion and 30 min, 1 hour, 3 hours and 168 hours after the end of PM01183 infusion) will be collected for pharmacokinetic analyses in Cycle 2. In addition, one blood sample for the evaluation of AAGP will be collected before PM01183 infusion start.
8. Beta subunit-human chorionic gonadotropin (ß-hCG) (urine or serum). In patients of childbearing potential (except germ cell tumor patients), if ß-hCG levels are elevated, pregnancy must be clinically discarded by an additional test (i.e., ultrasound) before any other study procedure. Pregnancy during treatment or within three months from the patient's last PM01183 administration is considered an immediately reportable event.
9. ECG: 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. LVEF: impaired cardiac function is defined as LVEF < 50 % as measured by multiple-gated acquisition scan (MUGA) or echocardiography (ECHO).
10. Evaluation by 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. While on treatment, evaluation of all original sites of disease involvement at baseline should be done as per RECIST v.1.1. Evaluation should be repeated at end of treatment visit, if not previously done, and if the reason for treatment discontinuation is other than PD. The same initial method must be used throughout the study. In SCLC patients, brain CT-scan or MRI will be requested at baseline within two weeks before the planned treatment onset to rule out CNS involvement. In SCLC patients, anonymized copies of all the images obtained throughout the study must be submitted to the Sponsor.
11. Patients showing a response must have a confirmatory assessment at least four weeks later.
12. Only patients who discontinue treatment without PD will have radiological evaluations. The assessments will be performed every two months during the first six months and every three months thereafter until PD, start of a new antitumor therapy, death, or until the date of study termination (clinical cutoff for each cohort except SCLC: when all evaluable patients within each cohort have at least 12 months of follow-up from the first PM01183 infusion). Patients with SCLC will be followed-up for at least 18 months after the last patient enrolled received the first PM01183 infusion (a documented phone contact will be acceptable).
13. Patients withdrawn from the study treatment with an ongoing drug-related AE should be followed every four weeks until event recovery to at least grade 1 or stabilization or until onset of a new antitumor therapy.

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 >1.5xULN), LDH, creatinine, glucose, and CPK.
Biochemistry B: Albumin, total proteins, total calcium and Mg^{++}. Albumin assessments on Day 1 of every cycle during the study are mandatory for all patients. Total proteins, total calcium and Mg^{++} will be measured at baseline and repeated thereafter only in those patients with abnormal baseline values.
In patients with germ cell tumors, ß-hCG and AFP will be measured at baseline and repeated thereafter in those patients with elevated values at baseline.

AAGP, alpha-1 acid glycoprotein; AFP, alpha fetoprotein; AE(s), adverse event(s); ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; ß-hCG, beta subunit of human chorionic gonadotropin; CNS, central nervous system; CPK, creatinine phosphokinase; CPK-MB, creatinine phosphokinase MB isoenzyme; 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, pharmacogenomics; PK, pharmacokinetic(s); PT, pro-thrombin time; PTT, partial thromboplastin time; SCLC, small cell lung cancer; WBC, white blood cells.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

1y-OS	One-year Overall Survival
5-FU	5-Fluorouracil
5-HT_3	Serotonin
AAGP	Alpha-1 Acid Glycoprotein
AE(s)	Adverse Event(s)
AFP	Alpha-Fetoprotein
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
β-hCG	Beta Subunit of Human Chorionic Gonadotropin
BEP	Bleomycin, Etoposide and Cisplatin
BSA	Body Surface Area
C_{max}	Maximum Plasma Concentration
CAV	Cyclophosphamide, Doxorubicin (Adriamycin) and Vincristine
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CR	Complete Response
CRA	Clinical Research Assistant
CRF	Case Report Form
CSF	Colony-stimulating Factors
CT	Computed Tomography
d/D	Day(s)
DNA	Deoxyribonucleic Acid
DP	Drug Product
DR	Duration of Response
DSB	Double-strand Breaks
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
EFTs	Ewing Family of Tumors
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
EOI	End of Infusion
EOT	End of Treatment
EPO	Erythropoietin

EU	European Union
FD	Flat Dose
FDA	Food and Drug Administration
FUP	Follow-up
GCP	Good Clinical Practice
GCTs	Germ Cell Tumors
GDPR	General Data Protection Regulation
GEP-NETs	Gastroenteropancreatic Neuroendocrine Tumors
GGT	Gamma Glutamyltransferase
GMT	Greenwich Meridian Time
Gy	Gray
H&N	Head and Neck Carcinoma (Cancer)
hCG	Human Chorionic Gonadotropin
HER-2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio/Homologous Recombination
IA	Investigator's Assessment
IB	Investigator's Brochure
IC	Informed Consent
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committees
IG_{50}	Concentration that Results in 50% of Cell Growth Inhibition
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
irPFS	Immune-related PFS
i.v.	Intravenous (ly)
LC-MS/MS	Liquid Chromatography/Mass Spectrometry/Mass Spectrometry
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MAb	Monoclonal Antibody
MBC	Metastatic Breast Cancer
mg	Milligram
MRI	Magnetic Resonance Imaging
mTOR	Mammalian Target of Rapamycin

MUGA	Multiple-gated Acquisition Scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NER	Nucleotide Excision Repair
NET(s)	Neuroendocrine tumor(s)
NSCLC	Non-small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
PARP	Poly (ADP-Ribose) Polymerase
PCR	Polymerase Chain Reaction
PD	Progressive Disease/Disease Progression
PFS	Progression-free Survival
PhV	Pharmacovigilance
PGx	Pharmacogenomics
PK	Pharmacokinetics
PM01183	Lurbinectedin
PNET	Peripheral Neuroectodermic Tumor
PR	Partial Response
PRBC	Packed Red Blood Cells
PRE TT	Pre-treatment
PS	Performance Status
PT	Pro-thrombin Time
PTEN	Phosphatase and Tensin Homolog
PTT	Partial Thromboplastin Time
q3wk	Every Three Weeks
Q7dx3	Three Consecutive Weekly Doses (D-0,7,14)
Qdx5x2	Two Cycles of Five Daily Doses
RBC(s)	Red Blood Cell(s)
RD	Recommended Dose
RECIST	Response Evaluation Criteria In Solid Tumors
RR	Response Rate
RT	Radiotherapy
SAE(s)	Serious Adverse Event(s)
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SUSAR/SUA	Suspected Unexpected Serious Adverse Reaction
T/C	Treatment/Control
TAP	Cisplatin, Doxorubicin, plus Paclitaxel

TIP	Paclitaxel, Ifosfamide and Cisplatin
TT	Treatment
TTP	Time to Progression
UK	United Kingdom
ULN	Upper Limit of Normal
US/USA	United States/United States of America
VIP	Etoposide, Ifosfamide and Cisplatin (Vinblastine-based)
WBC	White Blood Cells
WHO	World Health Organization
wk/wks	Week/weeks
WOCBP	Women of Childbearing Potential
WMA	World Medical Association

1. INTRODUCTION

This will be a multicenter, phase II clinical trial to evaluate the efficacy and safety of lurbinectedin (PM01183) in patients with the following advanced solid tumors.

1.1 SMALL CELL LUNG CANCER (SCLC)

Small cell lung cancer (SCLC) is a particularly aggressive type of lung cancer, related to smoking, which comprises approximately 10-15% of all lung cancers. It is characterized by rapid growth, early dissemination and acquired resistance to drugs [1]. SCLC is classically staged into limited stage or extensive stage disease. Limited stage disease is potentially curable with aggressive therapy consisting of concurrent chemoradiotherapy, prophylactic cranial irradiation, and occasionally, surgery [2, 3]. However, despite best management, the 5-year overall survival (OS) in limited stage SCLC is still only 15% to 25%. In addition, nearly two-thirds of SCLC patients have extensive stage disease at diagnosis. Extensive stage disease is not curable and patients are treated with palliative intent, with a median survival of 7 to 11 months and less than 5% being alive at 2 years [1, 4].

Standard first-line chemotherapy consists of a platinum compound, such as cisplatin or carboplatin, in combination with etoposide [5]. Most treated patients show disease relapse and are eligible for second-line therapy. Selection of second-line chemotherapy depends on the duration of the response to the first-line one. If the duration of response is > 3 months, the disease is considered sensitive, oppositely to resistant, with a duration of response of < 3 months, and refractory, which does not respond or progresses on initial treatment [6, 7]. Patients with sensitive disease have a much greater likelihood of responding to further systemic treatment, and are often re-challenged with the first-line regimen. Patients with refractory and resistant disease are usually treated with a different chemotherapy regimen in second-line. Second-line treatment in refractory or resistant disease usually is the combination of cyclophosphamide, doxorubicin and vincristine (CAV) or topotecan. Topotecan was approved for use in the second-line setting because it demonstrated efficacy similar to CAV: response rate 24.3% *vs.* 18.3%; median time to progression 13.3 weeks *vs.* 12.3 weeks, and median survival 25 weeks *vs.* 24.7 weeks, and tolerability was better [8-10].

A phase II study evaluated ipilimumab plus paclitaxel/carboplatin in extensive stage disease SCLC. One hundred and thirty chemotherapy-naïve patients were randomized 1: 1: 1 to receive paclitaxel (175 mg/m^2)/carboplatin (area under the curve = 6) with either placebo or ipilimumab 10 mg/kg in two alternative regimens: concurrent (ipilimumab plus paclitaxel/carboplatin followed by placebo plus paclitaxel/carboplatin) or phased (placebo plus paclitaxel/carboplatin followed by ipilimumab plus paclitaxel/carboplatin). Treatment was administered every 3 weeks (q3wk) for a maximum of 18 weeks (induction), followed by maintenance ipilimumab or placebo every 12 weeks. Endpoints included progression-free survival (PFS), best overall response rate (ORR), OS and safety. Phased ipilimumab, but not concurrent ipilimumab, improved immune-related PFS (irPFS) *versus* control [hazard ratio (HR)=0.64; p=0.03]. No improvement in PFS (HR=0.93; p=0.37) or OS (HR=0.75; p=0.13) was observed. Phased ipilimumab, concurrent ipilimumab and control, respectively, were associated with median irPFS of 6.4, 5.7 and 5.3 months, and median OS of 12.9, 9.1 and 9.9 months. Overall rates of grade 3/4 adverse events (AEs) were

17%, 21% and 9% for phased ipilimumab, concurrent ipilimumab and control, respectively [11].

Results of the phase III ACT-1 trial showed that amrubicin, a topoisomerase II inhibitor, had advantages over topotecan as second-line treatment for SCLC. Both drugs achieved similar OS: 7.5 months in the amrubicin arm *versus* 7.8 months in the topotecan arm, but amrubicin improved response rates (31.1% *vs.* 16.9%) and PFS (4.1 months *vs.* 3.5 months) and also improved control of lung cancer-associated symptoms. In addition, amrubicin appeared to have some advantage in OS of patients with refractory disease (6.2 months *vs.* 5.7 months) [12]. Amrubicin is approved in Japan for SCLC.

However, patients who respond to second-line treatment will invariably progress and a decision will need to be made about further therapy. High quality evidence to guide treatment decisions for SCLC in the third-line is scarce; several agents have been tried, but no drug or combination regimen is approved in this setting [1, 13, 14].

There is a critical need for effective therapy in advanced forms of this disease and, whenever possible, patients should be given the opportunity to participate in clinical trials.

1.2 HEAD AND NECK CANCER (H&N)

Head and neck cancer (H&N) accounts for approximately 6.6% of all cancers. The vast majority of these cancers arise from the epithelium lining the oral cavity, oropharynx, hypopharynx and larynx, and are, therefore, epidermoid carcinomas [15]. Environmental contributory factors to the development of H&N include smoking, alcohol consumption and human papillomaviruses. Despite advances in the diagnosis and treatment of H&N, survival has not improved significantly. If detected early, surgery is the mainstay treatment for this cancer. However, most patients present with advanced disease. The 5-year survival for H&N is 64%. Forty-five percent of these cancers are treated with surgery alone, 26% are treated with surgery and radiation therapy, and 30% receive radiation therapy alone [16]. Several clinical trials confirmed the superiority in regard to tumor control of altered fractionation schedules as compared to standard (conventional) fractionation. However, improvement in patients' survival has not been consistent. Clinical investigations show that improvement in locoregional disease control and consistent gain in survival have been achieved with combinations of radiotherapy and concurrent chemotherapy in patients with mostly stage IV carcinomas. Cisplatin-based chemoradiotherapy is nowadays the standard of care for advanced H&N patients [17, 18]; nevertheless, disease control occurs at the expense of increased morbidity. Consequently, concurrent radiochemotherapy is now preferred for non-surgical treatment of patients with locally advanced carcinomas, while altered fractionation is generally selected for patients with intermediate-stage tumors or who are medically unfit to receive chemotherapy [19].

Targeted therapies have also played an important role in the treatment of head and neck carcinoma. The epidermal growth factor receptor (EGFR) has a strong influence in H&N development, growth, angiogenesis and metastatic spread. The addition of cetuximab to radiotherapy significantly increased the 3-year locoregional control rates (47% *vs.* 34%) and OS rates (55% *vs.* 45%) compared to radiotherapy alone in a trial on 424 patients [20]. The combined effect of cetuximab and cisplatin-based chemoradiotherapy was also studied in a phase II trial in patients with advanced H&N. Although the 3-year OS and locoregional control rates were 76% and 71%, respectively, the study was closed due to significant toxicity [21].

Combination therapies with antiangiogenic agents have also been evaluated. A phase II clinical trial in patients with advanced H&N that involved bevacizumab and cisplatin-based chemotherapy combined with intensity-modulated radiotherapy achieved a PFS at 2 years of 75.9% and an OS rate at 2 years of 88% [22].

The latest radiotherapy techniques combined with adjuvant and/or targeted therapies succeeded in increasing locoregional control in advanced H&N patients. The downside is the increased rate of side effects. Furthermore, OS in this patient group has not improved considerably over the last decades. Advanced unresectable H&N are still a clinical challenge and their optimal treatment is yet to be established [23].

1.3 NEUROENDOCRINE TUMORS (NETS)

Neuroendocrine tumors (NETs) originate from the neuroendocrine network, which comprises the gastrointestinal tract, the lungs, the paraganglia, including the adrenal medulla, and the neuroendocrine cells scattered in the skin, thymus, prostate and other tissues. NETs are characterized by their ability to secrete a large number of peptide hormones that can lead to the development of distinct clinical syndromes. Based on this, NETs are broadly subdivided into functional or non-functional tumors. However, the functional status of these tumors may change over time or with treatment.

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), also known as carcinoids and islet cell tumors (in pancreas), are derived from neuroendocrine cells that can occur anywhere along the gastrointestinal tract and comprise a heterogeneous family of neoplasms with a wide spectrum of clinical behavior. These tumors have been considered rare diseases, although the most recent data from the US Surveillance Epidemiology and End Results show an increase of more than 400% in the incidence of this disease over a period of 29 years, from 1.09 per 100000 population in 1973 to 5.25 per 100000 population in 2004 [24]. This can partially be due to improved detection methods.

Surgery is the only potentially curative therapeutic strategy in localized disease. No adjuvant therapy is recommended in completely resected, well-differentiated localized GEP-NETs. For advanced disease, somatostatin analogues have proven to be effective in ameliorating symptoms of hormone overproduction in functional tumors; however, options regarding systemic therapy continue to be limited [25].

The role of chemotherapy is controversial. 5-fluorouracil (5-FU), streptozocin, capecitabine, temozolamide, dacarbazine, doxorubicin, lomustine, platinum drugs and etoposide have been used in various combinations. Pancreatic tumors often respond better to chemotherapy than other NETs, while most types of chemotherapy are less effective for carcinoid tumors. Streptozocin was approved in 1976 by the US Food and Drug Administration (FDA) for pancreatic NETs; however, earlier trials often used criteria to measure outcomes that are not accepted today, namely, physical examinations were sometimes used to document response to therapy and cross-sectional imaging was not uniformly used to measure tumor size. Two retrospective studies of 84 and 45 patients with advanced pancreatic NETs treated with streptozocin-based chemotherapy demonstrated response rates by the Response Evaluation Criteria In Solid Tumors (RECIST) or World Health Organization (WHO) criteria of 39% and 36%, respectively, but treatment was associated with significant toxicity [26, 27]. Finally, no published data have documented improvements in PFS or OS compared with best supportive care [28, 29].

Other regimens using temozolomide-based chemotherapy have also been studied in small prospective studies that included small numbers of NETs, but need confirmation in larger studies. A phase II study investigating the combination of temozolomide and thalidomide demonstrated an objective response rate of 45% in a subset of 11 patients with NETs [30]. A retrospective study of temozolomide with capecitabine in 30 chemo-naïve patients reported an objective radiological response rate of 70% and a median PFS of 18 months [31]. A phase II trial of temozolomide and bevacizumab reported a response rate of 33% in a more heavily pretreated subpopulation with advanced NETs [32].

The mammalian target of rapamycin (mTOR) has a role to play in islet cell tumors in patients with tuberous sclerosis as well as in sporadic NETs [33]. Thirty-six patients with advanced NETs and evidence of progressive disease were treated with the mTOR inhibitor, temsirolimus, as a single agent in a phase II study. Disease stabilization occurred in 58 cases and partial radiological response in two cases (6%) with median time to progression of 6 months. Adverse events such as fatigue, rash and hyperglycemia occurred in a number of patients [34]. A phase II study evaluating everolimus monotherapy *versus* everolimus plus octreotide in patients with advanced pancreatic NET who had progressed on first-line yielded 80% of stable disease and 4.4% partial response with a median PFS of 16.7 months in the combined treatment arm. In the everolimus monotherapy arm, partial responses were observed in 9.6% and stable disease in 67.8%; median PFS was 9.7 months [35]. These promising results led to the conduction of two everolimus trials, RADIANT-2 and RADIANT-3. The first one was a randomized, double-blind, placebo-controlled, multicenter, phase III study of octreotide combined with everolimus or placebo in patients with advanced NETs. It showed an improvement in PFS from 11 months in the placebo arm to 16 months in the active treatment arm. On central radiologic review, the statistical significance of this trial was borderline (P = 0.026) [36]. RADIANT-3 was a randomized, double-blind, placebo-controlled, multicenter phase III study of everolimus plus best supportive care *vs.* placebo and best supportive care in patients with progressive advanced pancreatic NETs. Results from this study demonstrated a statistically and clinically significant PFS improvement , with medians of 11.0 months with everolimus compared with 4.6 months with placebo [37]. In addition, a phase III study compared sunitinib *vs.* placebo in advanced, progressive well-differentiated pancreatic NETs. The study was stopped at interim analysis, after enrollment of 171 patients, due to a significant improvement in median PFS from 5.5 months in the placebo arm to 11.4 months in the treatment arm (HR 0.418; p=0.0001). Unblinding at the interim analysis allowed the majority of placebo patients to cross over to the treatment arm. A trend toward improved OS was observed, which did not meet statistical significance. Side effects included hypertension, palmar-plantar erythrodysesthesia, fatigue, diarrhea, and cytopenias [38].

Although randomized, placebo-controlled studies have demonstrated statistically significant improvements in PFS for everolimus and sunitinib, response rates associated with these agents are quite low (5% to 9.3%) and there are no supporting randomized trials with active controls. Temozolomide- and streptozocin-based regimens appear to yield substantially higher response rates, but these regimens have not been studied in randomized clinical trials. At present, no proven predictive factors can help guide treatment selection for patients with advanced NET, and the guidelines of the National Comprehensive Cancer Network (NCCN) include somatostatin analogs, everolimus, sunitinib, cytotoxic chemotherapy, as treatment options, but do not recommend a

particular sequence of treatments. Further clinical studies with new therapeutic agents in advanced NET are warranted.

1.4 BILIARY TRACT CARCINOMA

Biliary tract carcinoma (mostly adenocarcinoma) is the primary cancer of the epithelial cells of the bile ducts arising along the intrahepatic or extra-hepatic biliary tree. It is the second-most common primary liver cancer and accounts for an estimated 15% of primary liver cancer worldwide. Its incidence varies highly in different areas of the world, with 1-2 cases per 100000 population per year in the United Kingdom (UK) and the USA, and 5.5 and 7.3 cases per 100000 people per year in Japan and Israel, respectively. There is a high incidence of cholangiocarcinoma in Southeast Asian countries, due to chronic endemic infestation with different species of trematoda [39].

Most cases occur over 60 years. Risk factors include primary sclerosing cholangitis, Crohn's disease, parasitic infestation, industrial chemical and thorium exposure and congenital abnormalities of the bile ducts. Hepatitis C, human immunodeficiency virus (HIV) infection and diabetes have been recently associated with intrahepatic cholangiocarcinoma [40, 41].

Owing to the lack of randomized controlled trials, no standard chemotherapy exists in the treatment of advanced biliary tract carcinoma. 5-FU or gemcitabine are recommended based on small phase II trials. An analysis of all chemotherapy trials published from 1985 to July 2006 as well as of the American Society of Clinical Oncology (ASCO) abstracts from 1999 to 2006 was done. Response rate (RR), tumor control rate, time to progression (TTP), OS and toxicity were studied in 104 trials comprising 112 trial arms and 2810 patients (with 634 responders and 1368 patients with tumor control). Pooled RR and tumor control rate were 22.6 and 57.3%, respectively. Significant correlations of RR and tumor control rate with survival times were observed. Subgroup analysis showed superior RRs for gallbladder carcinoma compared with cholangiocarcinoma, but shorter OS for the former. Furthermore, superior RRs and tumor control rate of gemcitabine and platinum-containing regimens were found with higher RR and tumor control rate in the combination subgroup. Based on the published results of these phase II trials, gemcitabine combined with platinum compounds represents the provisional standard of chemotherapy in advanced biliary tract cancer [42].

1.5 ENDOMETRIAL CARCINOMA

Endometrial carcinoma is the most common gynecological malignancy in Europe and North America. It is the seventh most common cause of death from cancer in women in Western Europe, accounting for 1-2% of all deaths from cancer. In the United States, endometrial cancer accounts for 6% of all cancers in women. Median age of occurrence is 63 years and more than 90% of women are older than 50-years-old [43, 44]. Risk factors for developing endometrial cancer are: obesity, nulliparity, late menopause, diabetes mellitus and prolonged exposure to estrogen, tamoxifen and oral contraceptives.

The most common type is endometrioid adenocarcinoma. Clear cell and papillary serous endometrial carcinoma are histologically similar to those arising in the ovary and the fallopian tube, and their prognosis is worse relative to adenocarcinomas.

Based on histopathology, molecular profile and clinical course, endometrial cancers are divided into two categories. Type I include low-grade (I–II) adenocarcinomas that are

usually estrogen-related and have a favorable prognosis. Type II endometrial cancer is not hormone dependent and comprise grade III endometrioid adenocarcinomas, papillary serous, clear cell carcinomas and other non-carcinomatous tumor types. They are associated with early spread and worse prognosis. Type II endometrial cancers have p53 mutations and loss of heterozygosity at several chromosomal *loci*. Some type II tumors may have molecular alterations found in type I such as K-ras, phosphatase and tensin homolog (PTEN), β-catenin and microsatellite instability, which indicates that type II tumors can arise from dedifferentiation of a pre-existing type I cancer [45, 46].

Endometrial carcinoma is generally associated with a good prognosis, largely because approximately 75% of patients are diagnosed with stage I disease and 13% of patients with stage II disease [47]. For early-stage disease, surgery alone or in combination with local therapy is generally curative. For patients with stage III or stage IV disease and for those with recurrent endometrial cancer, the prognosis remains poor and the optimal adjuvant therapy is yet to be established. Women with advanced stage disease at presentation may also be appropriate candidates for systemic and local therapies. Treatment choice depends largely on the localization of disease, the patient's performance status and previous treatment history, as well as on the tumor's hormonal receptor status. Radiotherapy is appropriate for isolated vaginal recurrences in patients with no previous history of radiation therapy. Patients with recurrent low-grade tumors overexpressing estrogen and progesterone receptors may be treated with progestin therapy. Systemic therapy with platinum-based chemotherapy is appropriate for patients with disseminate recurrences or advanced stage disease at presentation, or for those with receptor-negative tumors. The two most commonly used regimens to treat metastatic endometrial cancer are carboplatin plus paclitaxel, or the triple drug combination of cisplatin, doxorubicin plus paclitaxel (TAP) [48]. Of these, carboplatin and paclitaxel is the most used regimen because it has similar activity to TAP in terms of PFS and OS, but is associated with less toxicity [49].

Women who have disease progression despite first-line chemotherapy have a poor prognosis. They are usually treated with supportive care and referred to palliative care regardless of whether second-line treatment is administered. For women who desire subsequent treatment, the choice of second-line therapy depends on the type of treatment administered in the first-line setting. Single agent therapy in second line with anthracyclines, taxanes, alkylators or topoisomerase inhibitors has shown responses in 4 to 27% of the patients [50]. These responses are often short-lived and median OS across studies is typically less than one year. New active therapies are urgently needed for this group of patients.

1.6 BRCA 1/2-ASSOCIATED METASTATIC BREAST CANCER

Despite of the advances achieved in the treatment of breast cancer, the prognosis for patients with metastatic breast cancer (MBC) remains poor [51]. Metastatic disease at diagnosis occurs in only 6% of newly diagnosed cases [52], but approximately 30% of women with early breast cancer will eventually develop recurrent advanced or metastatic disease. MBC remains incurable, with a median survival time between 18 and 30 months, and there is no single standard of care for these patients, as treatment requires an individualized approach based on multiple factors.

It is currently estimated that 5-10% of all breast cancers are hereditary due to germline mutations in BRCA 1 and 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 [53]. The fact that hormone unresponsive MBC lacking human epidermal growth factor receptor 2 (HER-2) overexpression, known as triple negative (TN) breast cancer, is more common in BRCA-mutated patients suggest a worse prognosis for these hereditary breast cancers. In particular, BRCA 1-associated hereditary breast cancer may be more aggressive than sporadic breast cancer, with medullar or atypical features, p53 mutations and/or high level expression of epidermal growth factor (EGF) and Ki-67 [54]. BRCA 2 mutations are heterogeneous and often present in relatively high grade tumors [55]. BRCA 1/2-associated breast cancer has 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 its repair 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; thus, the possibility of selectively target these tumors had brought along a lot of interest. Promising response rates up to 41% were reported in a phase II trial in advanced breast cancer with a novel oral PARP inhibitor, olaparib [56] and several large phase III trials of PARP inhibitors have been conducted in relapsed and MBC. Drugs with novel mechanism of action, lacking cross-resistance with other commonly used agents, are needed for MBC in patients with deleterious BRCA 1/2 mutations [57].

1.7 CARCINOMA OF UNKNOWN PRIMARY SITE

The site of origin of a histologically documented carcinoma is not identified clinically in approximately 3% of patients; this situation is often referred to as carcinoma of unknown primary origin or occult primary malignancy. The definition of carcinoma of unknown primary site includes patients who present with histologically confirmed metastatic cancer in whom a detailed medical history, complete physical examination including pelvic and rectal examination, full blood count and biochemistry, urinalysis and stool occult blood testing, histopathological review of biopsy material with the use of immunohistochemistry, chest radiography, abdominal and pelvis computed tomography and, in certain cases, mammography, fail to identify the primary site. The majority of them are adenocarcinomas or undifferentiated tumors, or, less commonly, squamous cell carcinoma, melanoma, sarcoma, and neuroendocrine tumors [58].

Carcinomas of unknown primary are by definition metastatic; therefore, the prognosis is poor. As a group, the median survival is approximately 3 to 4 months, with less than 25% and 10% of patients alive at 1 and 5 years, respectively. Chemotherapy regimens have been explored in over 35 prospective clinical trials, most of them phase II. Combination doublets, (usually platinum and taxane-containing) appear to be superior to single-agent regimens while triplet combinations do not appear to be better than doublets. High-dose regimens do not appear to be superior to regular regimens. One of the best outcomes from a phase II trial is from a combination of a platinum/taxane doublet with bevacizumab and erlotinib; median OS for this regimen was 12.6 months (n=60). A randomized phase II trial in 80 patients showed better efficacy/toxicity ratio with the cisplatin/gemcitabine than with the cisplatin/irinotecan regimen [59]. The only phase III trial performed in carcinomas of unknown primary site, comparing paclitaxel, carboplatin, and etoposide with gemcitabine and irinotecan (n=198), showed no statistically significant difference between either arm (median OS 7.4 *vs.* 8.5 months). Overall median OS from chemotherapy combinations yields survival rates of 9 to 13 months, which parallels the median survival rates of thoracic, gastrointestinal, and urothelial malignancies that comprise most of these cancers. It is likely that advances in

oncology regimens for difficult-to-treat cancers may improve outcomes in carcinoma of unknown primary site [60].

1.8 GERM CELL TUMORS (GCTS)

Testicular germ cell tumors (GCTs) account for between 1% and 1.5% of male neoplasms. Germ cell tumors (seminomatous and non-seminomatous) are the most common cancers of young adult men, and their incidence is increasing rapidly. Over 90% of these tumors arise in the testes. Ovarian germ cell malignant tumors are very infrequent; they represent less than 2% of all ovarian cancers. Extragonadal primary sites also occur, usually in the retroperitoneum, mediastinum, and pineal/suprasellar region. Extragonadal tumors commonly metastasize to the regional lymph nodes, lungs, and other sites. Undescended testis, contralateral testicular tumor and familial testis cancer are risk factors for testicular GCTs. Prognosis is related not only to anatomic extent of spread, but also to the primary site (extragonadal or gonadal) and to the extent of production of the tumor markers alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and lactate dehydrogenase (LDH), which may reflect the underlying biologic aggressiveness [61]. Serum AFP increase is observed in 40% to 60% of men with non-seminomas. Seminomas do not produce AFP. Patients with elevated serum AFP should be considered to have a mixed GCT. Increase of the beta subunit of hCG is found in approximately 14% of the patients with stage I pure seminoma and in about half of patients with metastatic seminoma. Approximately 40% to 60% of men with non-seminomas have an elevated serum beta-hCG. Serum tumor markers are also very useful for monitoring all stages of non-seminomas and for monitoring metastatic seminomas because elevated marker levels are often the earliest sign of relapse [62].

Patients with localized seminoma can be cured with radical orchiectomy and adjuvant radiotherapy. In low risk localized non-seminomatous GCTs, surveillance computed tomography scanning at three and 12 months post-surgery is recommended. Serum markers should be checked before and after surgery and weekly thereafter until normal. Measurement of serum AFP and HCG is essential in the follow up of patients with non-seminomatous GCTs.

For patients with metastatic disease, the combination of bleomycin, etoposide and cisplatin (BEP) is the standard therapy. At first relapse most patients retain platinum sensitivity and standard-dose salvage regimens are based on cisplatin and ifosfamide. Response rates are generally around 50% with long term disease-free survival rates of 20-30%. The largest body of evidence for standard-dose salvage therapy is for the paclitaxel-based, TIP (paclitaxel, ifosfamide and cisplatin) or vinblastine-based, VIP (etoposide, ifosfamide and cisplatin) ones. TIP is being increasingly used although there is no randomized comparison between these two regimens.

In patients who relapse after standard-dose salvage therapy, only high-dose chemotherapy offers a chance of cure. For others, further lines of treatment are generally considered to be palliative. The choice of third-line therapy will be heavily dependent on the patient's bone marrow reserve, performance status and resolution of toxicity from prior regimens. There are a number of single agents and combination regimens, containing gemcitabine, oxaliplatin, paclitaxel and epirubicin, none of which have been tested in comparative studies. These regimens lead to a low overall response rate of 18-24% with short duration of response [63].

1.9 EWING FAMILY OF TUMORS (EFTS)

Ewing family of tumors (EFTs) comprises several tumors derived from the same primordial bone marrow-derived mesenchymal stem cell, including bone and extraskeletal Ewing's sarcoma, peripheral neuroectodermic tumor (PNET) and Askin tumor (thoracic wall). They have in almost all instances a clonal translocation in the long arms of chromosomes 11 and 22, which fuses the EWS gene of chromosome 22 to the FLI1 gene of chromosome 11 [64].

The incidence of EFTs is approximately three cases per 1 million per year and has remained unchanged for 30 years [65].The median age of patients with EFTs is 15 years, and more than 50% are adolescents. Based on data from 1,426 patients entered into the European Intergroup Cooperative Ewing Sarcoma Studies, 59% of patients were male and 41% female. For extraosseous sarcoma, the most common sites are trunk (32%), limbs (26%), head and neck (18%), retroperitoneum (16%) and other sites (9%) [66].

The prognosis of EFTs varies depending on primary tumor site, presence of metastases and tumor size. The overall 5-year disease-free survival rate for localized sarcoma treated with surgery, radiation and multi-agent chemotherapy is 65-76% [67]. However, the 5-year disease-free survival rate drops to 30% if metastases are present at diagnosis. Limited improvement of survival rates has been achieved for metastatic Ewing's sarcoma. Similarly, relapsed patients have a poor outcome, with very common failure to second-line therapy and low 5-year survival rates (13%) [68].

A multidisciplinary approach, including surgery, chemotherapy, and radiotherapy (RT) is mandatory. Multi-agent chemotherapy is essential for Ewing's sarcoma due to the high risk of micrometastatic disease. It includes vincristine, doxorubicin, ifosfamide, and etoposide. Most protocols use cyclophosphamide as well and some incorporate dactinomycin. Duration of primary chemotherapy ranges from six months to one year [69].

In high-risk cases of Ewing's sarcoma, myeloablative chemotherapy followed by autologous stem cell transplantation has been used as consolidation therapy. Although better survival than expected was reported with this approach, large prospective trials are needed to properly evaluate the potential utility of this therapy in Ewing's sarcoma patients [70].

The management of relapsed or recurrent disease is not standardized and, in most cases, consists of different combinations of the same agents used as adjuvant therapy. Patients are often treated with more than one regimen to reduce disease burden to the minimum. Ifosfamide and etoposide are active in treating Ewing's tumor of bone and should be considered for patients who have not previously received these agents. Combinations such as cyclophosphamide plus topotecan and irinotecan plus temozolomide have also been active in patients with recurrent or refractory disease [71, 72]. Radiotherapy of lung and bone, and surgical removal of metastases are also included in the management of these patients. However, patients with relapsed disease have a poor outcome; failure to second-line therapy is very common, with 5-year survival rates around 13% [44]. In addition, the toxicity, morbi-mortality, and long-term complications of these agents (cardiac, renal, pulmonary, gonadal and secondary neoplasias) are considerable. Therefore, there is an urgent need for new therapeutic agents with different mechanisms of action to manage this patient population.

1.10 INFORMATION ON THE STUDY DRUG

1.10.1 Lurbinectedin (PM01183)

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

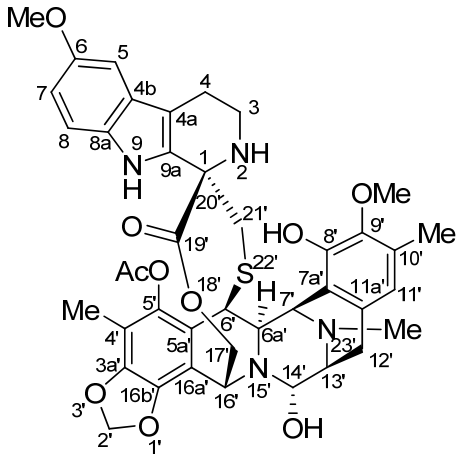
1.10.1.1 *Name and Chemical Information*

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

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

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

Figure 1. Molecular formula of lurbinectedin (PM01183).



1.10.1.2 *Non-clinical Data*

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

PM01183 has a negative COMPARE analysis when compared against other 98 standard anticancer agents in the standard National Cancer Institute (NCI) panel of 36 cell lines. Thus, its mechanism of action is likely to differ significantly from all the other drugs. It only showed a positive correlation (S-rank > 0.8) with trabectedin [73].

In vitro, PM01183 demonstrated cytotoxic effects against a broad selection of tumor-derived cell lines with half maximal inhibitory concentration (IC_{50}) values in the low to very low nanomolar range (approximately median IC_{50} of 1^{-10} M). PM01183 also has *in vivo* antitumor activity against different murine models of xenografted human-derived tumor types.

The antineoplastic *in vitro* activity of PM01183 was evaluated in a panel of solid tumor cell lines (some of which are shown in Table 1), which were exposed to a range of

PM01183 concentrations for 72 hours and then assayed for viability by a MTT short-term assay [74].

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

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

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

The antineoplastic *in vivo* activity of PM01183 was demonstrated in a panel of several different human-derived tumor types, i.e., breast, colon, lung, ovarian and prostate (Table 2). The resulting tumor susceptibility was analyzed in xenografts grown in athymic mice, when unformulated PM01183 was administered at the rodent maximum tolerated dose [0.3 mg/kg (0.9 mg/m^2)] as single bolus intravenous (i.v.) injection. PM01183 demonstrated statistically significant antitumor activity ($p<0.05$) against breast, lung and ovarian xenografts at different time points during the experiment, but had a more moderate antitumor profile against bladder, pancreas and prostate [75].

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

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

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

Toxicology studies in rats and dogs showed that the main target organs were the bone marrow and the liver. The effect of a single bolus injection of PM01183 on cardiovascular parameters [arterial blood pressure, heart rate and lead II electrocardiogram (ECG)] was evaluated in dogs for six hours [76]. This study showed no effects on heart, blood pressure, lead II ECG variables (PR, QT, QTcF and QTcV intervals, and QRS duration), ECG gross morphology or rhythm in dogs treated with PM01183 at doses up to 0.01 mg/kg (0.2 mg/m^2). Additionally, two different studies found no electrophysiological alterations in the heart rate and ECGs of dogs following single or repeated PM01183 administration at doses up to 0.05 mg/kg (1 mg/m^2) [77, 78].

The antineoplastic *in vitro* activity of PM01183 was also evaluated in combination with other antineoplastic agents in solid and non-solid tumor cell lines [79, 80]. In solid tumor models, two combinations were strongly synergistic: PM01183 combined with topotecan (colon HT29, pancreas PANC-1 and glioblastoma U87MG cell lines) and PM01183 combined with erlotinib (lung A-549, gastric HGC-27 and prostate PC-3 cell lines). Some other standard agents, including platinum agents like oxaliplatin and cisplatin, showed synergistic activity in combination with PM01183 in different cell lines.

Part of the *in vivo* antitumor activity of lurbinectedin (PM01183) could be related to host-mediated effects that occur *in vivo* but not *in vitro*. Recent studies have highlighted the ability of trabectedin to modify the tumor microenvironment; particularly the drug seems to induce a decrease in the tumor-associated macrophages with significant down-regulation of cytokines, chemokines and angiogenic factors [81-85]. Although these effects have been demonstrated for trabectedin, initial data suggest that some of these effects are shared by lurbinectedin (PM01183) (P.Allavena, unpublished data) [86].

1.10.1.3 *Clinical Data*

Based on the positive preclinical results described above, the clinical development program of PM01183 was started in March 2009. Currently, this program comprises five phase I single-agent studies (four in solid tumors and one in acute adult leukemia patients); six phase Ib combination studies with gemcitabine, capecitabine, doxorubicin, cisplatin, irinotecan, or paclitaxel with or without bevacizumab, in patients with selected advanced solid tumors; five phase II studies: three studies as single agent in second-line pancreatic cancer, in BRCA-mutated or in BRCA-unselected metastatic breast cancer patients, and the current basket trial, and two randomized studies in patients with platinum-resistant/refractory ovarian cancer (PM01183 single agent *vs.* topotecan), and in combination with gemcitabine as second-line therapy in advanced non-small cell lung cancer (NSCLC) (PM01183 plus gemcitabine *vs.* PM0183 *vs.* docetaxel); and two phase III randomized controlled trials in platinum resistant ovarian carcinoma (PM01183 *vs.* PLD or topotecan) and NSCLC (PM01183 plus doxorubicin vs. CAV or topotecan). One QT evaluation study in patients already participating in the phase II trial PM1183-B-005-14; and three investigator-sponsored studies (ISTs: one with single-agent PM01183 in mesothelioma; one with PM01183 in combination with olaparib in advanced solid tumors; and one with PM01183 alone or in combination with doxorubicin or gemcitabine in soft tissue sarcoma).As of 15 January 2018, 2060 patients have been enrolled in PM01183 clinical studies, and of these 1584 have been treated with PM01183 alone or combined therapy: 501 in phase I trials, 543 in phase II trials, 404 in phase III trials and 136 in investigator sponsored trials.

The two phase I trials which explore single-agent PM01183 schedules in solid tumor patients (PM1183-A-001-08 and PM1183-A-005-11) have finished recruitment and a recommended dose (RD) was selected for further study in phase II trials. The first-in-human study (PM1183-A-001-08) explored PM01183 administered as a 1-hour i.v. infusion on Day 1 q3wk in patients with solid tumors. The RD was established at 4.0 mg/m^2/q3wk [87]; since PM01183 clearance was found to be unrelated to body surface area (BSA), all patients in the RD expansion cohort were treated at an equivalent flat dose (FD) of 7.0 mg q3wk. In this and subsequent studies, the median terminal plasma half-life was around 60 hours, though inter-individual variability was high. No evidence of drug accumulation was found. Non-hematological toxicity was generally mild and reversible. Standard antiemetic prophylaxis was used at the RD to control grade 2

nausea and/or vomiting. Hematological toxicity, particularly grade 4 non-febrile neutropenia, was the most relevant toxicity and occurred in 40% of patients at the RD in the single-agent phase I studies. Neutropenia was generally predictable and short-lasting, and rarely caused treatment delays. In the first-in-human study (Day 1, q3wk) nadir usually occurred during the second week. One of 15 patients treated at the RD had a dose-limiting toxicity (grade 4 thrombocytopenia). No cases of febrile neutropenia occurred in this study, although patient selection may have played a role.

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

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

Antitumor activity has been observed with PM01183 either as single agent or in combination with other cytotoxics. Objective responses have been observed in patients with ovarian, pancreatic cancer, breast cancer, NSCLC, SCLC, and other tumor types (neuroendocrine tumors, endometrial carcinoma, bladder carcinoma, and soft tissue sarcoma).

1.11 STUDY RATIONALE

- The management of advanced SLCL, H&N, NETs, biliary tract carcinoma, endometrial carcinoma, BRCA 1/2-associated metastatic breast carcinoma, carcinoma of unknown primary site, GCTs and EFTs represent an unmet medical need. Cytotoxic chemotherapy remains a crucial component of their therapeutic armamentarium but there is a need to develop new anticancer agents that broaden the clinical benefit.
- PM01183 is a new chemical entity that induces double-strand DNA breaks through binding to the DNA minor groove. Results of the COMPARE analysis [88] 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 shown antitumor activity in most of the tumor types selected in this clinical study. In the combination trial of PM01183 at 4.0 mg FD with 50 mg/m^2 of doxorubicin q3wk (PM1183-A-003-10), five of 12 evaluable patients with SCLC achieved partial response (42.0%), with a median TTP of 2.0 months. In endometrial carcinoma, two of three patients treated with the combination PM01183 plus doxorubicin at the aforementioned dose and schedule had a complete response and a partial response, respectively. The third patient had disease stabilization longer than 4 months. The median TTP was 10.1 months. Also with this combination, a patient with NET had a partial response with a TTP of 4.5 months. In a phase II clinical trial of PM01183 as single agent in MBC, one of 54 patients with germline BRCA 1/2 mutation had a complete response (2%) and 21

patients had partial response (39%). Twenty-three additional patients had disease stabilization (43%). One patient with H&N carcinoma treated with PM01183 as single agent at 2.6 mg/m^2 q3wk achieved a disease stabilization of 4 months duration. Finally, one patient with a carcinoma of unknown primary site treated with PM01183 as single agent at 7 mg FD q3wk had disease stabilization for 2.6 months.

- The inclusion of patients with EFTs is based mainly on the similar mechanism of action of PM01183 and its related compound trabectedin. In sarcomas associated to translocations, such as myxoid liposarcoma, in which the translocation produces a fusion protein (FUS-CHOP) that acts as a deregulated transcription factor, trabectedin has been shown to interfere with the binding of this protein to specific DNA promoters, hence with the synthesis of downstream proteins. Based on the structural and functional similarities of these fusion proteins, trabectedin could induce on other translocation-related sarcomas similar effects to those described in myxoid liposarcoma. In fact, trabectedin has shown efficacy in advanced pretreated patients with Ewing's sarcoma: three partial responses and seven disease stabilizations in 20 patients, with a 25% 6-month PFS rate [89]. Since PM01183 has a favorable pharmacokinetic (PK) profile in comparison to trabectedin, manifested by a tolerated dose four times higher and an exposure 15.3 times that of trabectedin at the RD, it has been postulated that its effect on rapidly growing tumors such as EFTs would be superior. In addition, an improved therapeutic index of PM01183 relative to trabectedin, as well as suppression of the EFTs fusion protein EWS/FLI1 activity by PM01183 at clinically achievable concentrations has been shown [90].
- PM01183 activity in aggressive tumors with high proliferation index, such as neuroendocrine tumors and SCLC led to the inclusion of GCTs and biliary tract carcinoma in this study.
- In conclusion, this clinical trial has been designed to establish or confirm the proof of concept of PM01183 anticancer activity in several difficult-to-treat tumors for their potential further development.

1.12 RATIONALE FOR THE DOSE

Initially, the starting dose for the current phase II trial was 4.0 mg/m^2 administered intravenously (i.v.) (1-hour infusion) on Day 1 every three weeks (q3wk). This was the dose recommended from the first-in-human trial. Use of colony-stimulating factors (CSFs) was considered due to the high risk of febrile neutropenia. Furthermore, a dose reduction of 25% was established for fragile patients [i.e., those with an ECOG performance status (PS) of 2 or aged > 70 years old].

A safety analysis of data from 216 patients treated with PM01183 in phase II trials or at the RD in phase I trials comparing different intended dose levels showed that a PM01183 dose reduction of 20% (i.e., from 4.0 to 3.2 mg/m^2) decreased the incidence of life-threatening neutropenia, thrombocytopenia and febrile neutropenia. Thus, grade 3/4 neutropenia decreased from 70% to 38% (46% reduction), grade 3/4 thrombocytopenia from 24% to 16% (33% reduction), and febrile neutropenia from 14% to 6% (57% reduction). Therefore, the dose of 3.2 mg/m^2 was considered safe.

Furthermore, in 22 patients with ECOG PS=2 and/or aged > 70 years treated with PM01183 at doses equivalent to 4.0 mg/m^2, the incidence was 73% (n=16) for grade 3/4 neutropenia, 18% (n=4) for grade 3/4 thrombocytopenia, and 9% (n=2) for febrile

neutropenia. These percentages were similar to those found in the overall population. Hence, a PM01183 dose reduction of 20% from the initial recommended dose might decrease toxicity in a similar magnitude in this subset of patients, who therefore might not require further dose adjustment.

Based on these findings, the mandatory CSF prophylaxis was removed (see details in Amendment No.1, dated 13 May 2015) and the new starting dose of PM01183 for the current phase II study was set at 3.2 mg/m^2 for all patients included in the trial, without differentiation according to PS score or age.

1.13 PHARMACOGENETIC SUB-STUDY RATIONALE

Germline mutations or polymorphisms may be involved in the metabolism and/or transport of PM01183. Then, to explore factors that may help to explain individual variability in the main pharmacokinetic parameters, the presence or absence of germline mutations or polymorphisms will be analyzed in leukocyte DNA extracted from one blood sample obtained at any time during the study, but preferably just before treatment start in Cycle 1.

1.14 PHARMACOGENOMICS SUB-STUDY RATIONALE

The antitumor activity of PM01183 is associated with the following cell events, as described in Leal *et al*. [91]:

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

Objective of the Pharmacogenomic Sub-study

- The experimental data indicate that PM01183 binds to DNA and interferes with NER pathway, inducing DSBs and cell death by apoptosis. Thus, it seems of interest to conduct studies correlating the tumor/patient and genes/proteins determinant in the efficiency/deficiency of the DNA repair pathways and the outcome of patients exposed to PM01183. The ultimate goal is the characterization of such patients who shall be prone to respond or show resistance to PM01183, in order to implement a customized therapy in the future.

- Initially, the mRNA and/or protein expression levels of genes involved in DNA repair mechanisms (such as nucleotide excision repair, homologous recombination repair or mismatch repair) and other factors related to the mechanism of action of PM01183 or to the pathogenesis of the disease will be determined in paraffin-embedded tumor tissue blocks from consenting patients. Their polymorphisms and mutations might be also analyzed, if relevant.

2. STUDY OBJECTIVES

2.1 PRIMARY

- To assess the antitumor activity of lurbinectedin (PM01183) in terms of ORR, according to the RECIST v.1.1, in the following advanced solid tumors: small cell lung cancer (SCLC), head and neck carcinoma (H&N), neuroendocrine tumors (NETs), biliary tract carcinoma, endometrial carcinoma, BRCA 1/2-associated metastatic breast carcinoma, carcinoma of unknown primary site, germ cell tumors (GCTs), and Ewing's family of tumors (EFTs).

2.2 SECONDARY

- To further characterize the antitumor activity of PM01183 in terms of duration of response (DR), clinical benefit [ORR or stable disease (SD) lasting over four months (SD $\geq$ 4 months)], progression-free survival (PFS) by Investigator's assessment (IA), and overall survival (OS) in each cohort of advanced solid tumors.
- To further investigate the antitumor activity of PM01183 in terms of ORR, DR, clinical benefit (ORR or SD $\geq$ 4 months) and PFS by an Independent Review Committee (IRC) in the cohort of SCLC patients.
- To characterize the plasma pharmacokinetics (PK) of PM01183.
- To conduct an exploratory pharmacogenomic (PGx) and pharmacogenetic analysis.
- To evaluate the safety profile of PM01183 in this patient population.

3. OVERALL STUDY DESIGN

Multicenter, open-label, exploratory, phase II clinical trial to evaluate the efficacy and safety of PM01183 in previously treated patients with the following advanced solid tumors: SCLC, H&N, NETs, biliary tract carcinoma, endometrial carcinoma, BRCA 1/2-associated metastatic breast carcinoma, carcinoma of unknown primary site, GCTs, and EFTs.

Patients with each of the aforementioned tumors will be enrolled in nine cohorts. Up to 25 evaluable patients are planned to be enrolled in each cohort (50 in the endometrial carcinoma and 100 in the SCLC cohort). To consider that PM01183 has antitumor activity in any of the tumor types analyzed, at least two confirmed responses [complete (CR) or partial response (PR)] per RECIST v.1.1 out of the 25 patients of each cohort are expected.

- If no confirmed responses are observed in the first 15 evaluable patients of each cohort, the recruitment of the corresponding cohort will be stopped.
- If one confirmed response is observed in the first 15 evaluable patients of each cohort, the recruitment of this cohort will continue to up to 25 evaluable patients.

- In the cohort of endometrial carcinoma, if ≥2 confirmed responses occur in the first 25 evaluable patients, the sample size will be doubled to 50 evaluable patients.
- In the cohort of SCLC, if ≥2 confirmed responses occur in the first 25 evaluable patients, the sample size will be increased to 100 evaluable patients.

- If two confirmed responses are observed in the first 15 evaluable patients of each cohort, the recruitment of the corresponding cohort can be stopped.

Only in the SCLC cohort, an IRC will determine the best patient's response and assign the date of first documentation of response and progression/censoring according to RECIST v.1.1. Operational details for the IRC and the algorithm and its validation by an expert panel is described in detail in the IRC charter.

In addition, for safety reasons:

- If two patients have a treatment-related death in a cohort, the recruitment of the corresponding cohort will be stopped.
- If six patients have treatment-related deaths in the whole population, the study will be stopped.

Finally,

- A determined cohort can be early closed by the Sponsor in case of a low recruitment rate.
- Once the target of patients included in each cohort is reached, recruitment in this cohort will be kept "on hold" during the period of patients' data analysis to assess their evaluability and the response rate. After this period, if the number of evaluable patients does not reach the planned target, recruitment will be re-opened and non-evaluable patients will be replaced.

Patients will receive the study treatment as long as it is considered to be in their best interest. Specifically, treatment will continue until disease progression, unacceptable toxicity, treatment delay > three weeks from the treatment due date (except in case of clear clinical benefit, upon Sponsors' approval), requirement of > two dose reductions, intercurrent illness of sufficient magnitude to preclude safe continuation of the study, a major protocol deviation that may affect the risk/benefit ratio for the participating patient, investigator's decision, non-compliance with study requirements and/or patient's refusal.

All adverse events (AEs) will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4. Treatment delays, dose reduction requirements and reason for treatment discontinuation will be monitored throughout the study. The safety profile of patients will be monitored throughout the treatment and up to 30 days (±7 days) after the last treatment infusion (end of treatment, EOT), until the patient starts a new antitumor therapy or until the date of death, whichever occurs first. Any treatment-related AEs will be followed until recovery to at least grade 1 or stabilization of symptoms or until the start of a new antitumor therapy, whichever occurs first.

Patients will be evaluated at scheduled visits on three study periods: Pre-treatment, Treatment and Follow-up (see Section 5.2). This clinical trial will finish (clinical cutoff for each cohort except SCLC) when all evaluable patients within each cohort have at least 12 months of follow-up from the first PM01183 infusion. Patients with SCLC will be followed-up for at least 18 months after the last patient enrolled received the first PM01183 infusion.

3.1 PRIMARY ENDPOINT

- **Overall Response Rate (ORR)** in each tumor type. ORR is defined as the percentage of patients with a confirmed response, either CR or PR, according to the RECIST (v. 1.1).

3.2 SECONDARY ENDPOINTS

Efficacy (all cohorts):

- **Duration of Response (DR) by IA**, defined as the time between the date when the response criteria (PR or CR, whichever one is first reached) are fulfilled to the first date when disease progression (PD), recurrence or death is documented.
- **Clinical Benefit by IA**, defined as ORR or SD lasting over four months (SD $\geq$ 4 months).
- **Progression-free Survival (PFS) by IA**, defined as the period of time from the date of first infusion to the date of PD, death (of any cause), or last tumor evaluation.
- **PFS4/PFS6 by IA**, defined as the Kaplan-Meier estimates of the probability of being free from progression and death after the first infusion at these time points (4 and 6 months).
- **OS**, defined as the period of time from the date of first infusion to the date of death or last contact in case of patients lost to follow-up or alive at the clinical cut-off established for the cohort.
- **OS6/OS12,** defined as the Kaplan-Meier estimates of the probability of being alive after the first infusion at these time points (6 and 12 months).

Efficacy (only in the SCLC cohort):

- **ORR, Clinical Benefit, DR, PFS and PFS4/PFS6 by IRC.** The same definitions detailed for IA will be used.

Plasma Pharmacokinetics (PK) of PM01183

- Non-compartmental (NCA) PK parameters: area under the curve (AUC), maximum plasma concentration (C_{max}), clearance (CL) and half-life ($t_{1/2}$). Population PK parameters of the compartment model to be developed (initially based on Volumes and Clearance), and PK/PD correlation parameters, if applicable.

Pharmacogenetics:

- This analysis will be performed in those patients who signed the written informed consent (IC) for the pharmacogenetic sub-study. The presence or absence of known polymorphisms from a single sample collected at any time during the study, but preferably just before treatment start in Cycle 1, will be assessed to explain the individual variability in the main PK parameters.

Pharmacogenomics (PGx):

- This exploratory analysis will be performed on prior available paraffin-embedded tumor tissue samples from consenting patients of any arm. This sub-study will include factors involved in DNA repair mechanisms (such as nucleotide excision repair, homologous recombination repair and mismatch repair) and other factors related to the mechanism of action of PM01183 or to the pathogenesis of the disease, and their expression will be analyzed at the mRNA or protein level by

quantitative polymerase chain reaction (PCR) and immunohistochemistry (IHC), respectively; their polymorphisms and mutations might be also analyzed, if relevant. Their correlation with clinical response and outcome after treatment will be assessed (see Section 7.4 for evaluation of PGx).

Safety Profile:

- Clinical examinations.
- Clinical assessment of AEs and serious adverse events (SAEs).
- Changes in laboratory parameters (hematological and biochemical, including liver function tests).
- Reasons for treatment discontinuations.
- Reasons for dose reduction and treatment delays.

4. SELECTION OF PATIENTS

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

4.1 INCLUSION CRITERIA

1) Age ≥ 18 years.
2) Voluntary signed informed consent (IC) of the patient before any study-specific procedure.
3) Pathologically proven diagnosis of any of the following malignancies:
   a) Small cell lung cancer (SCLC).
   b) Head and neck carcinoma (H&N). Salivary glands tumors are excluded.
   c) Neuroendocrine tumors (NETs), grade 2 and grade 3 according to WHO classification [92].
   d) Biliary tract carcinoma.
   e) Endometrial carcinoma.
   f) BRCA 1/2-associated metastatic breast carcinoma
   g) Carcinoma of unknown primary site.
   h) Germ cell tumor (GCTs), excluding immature teratoma, or teratoma with malignant transformation.
   i) Ewing's family of tumors (EFTs).
4) Prior treatment. Patients must have received:
   a) SCLC: one prior chemotherapy-containing line.
   b) H&N: one or two prior chemotherapy-containing lines.
   c) NETs: one or two prior chemotherapy-containing lines. No more than three prior hormone or biological therapy lines.
   d) Biliary tract carcinoma: one or two prior chemotherapy-containing lines.
   e) Endometrial carcinoma: one prior chemotherapy-containing line.
   f) BRCA 1/2-associated metastatic breast carcinoma: at least one but no more than three prior chemotherapy-containing lines.

g) Carcinoma of unknown primary site: one or two prior chemotherapy-containing lines.

h) GCTs: no limit of prior therapy (patients with no other clinical therapeutic options).

i) EFTs: no more than two prior chemotherapy-containing lines in the metastatic/recurrent setting.

5) Measurable disease as defined by the RECIST v.1.1, and documented progression before study entry.

6) Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 (see APPENDIX 1).

7) Adequate major organ function:

a) Hemoglobin ≥ 9 g/dl, prior red blood cell (RBC) transfusions are allowed if clinically indicated; absolute neutrophil count (ANC) ≥ 2.0×10^9/l; and platelet count ≥ 100×10^9/l.

b) Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3.0 × upper limit of normal (ULN).

c) Total bilirubin ≤ 1.5 × ULN, or direct bilirubin ≤ ULN.

d) Albumin ≥ 3 g/dl.

e) Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 30 ml/min.

f) Creatine phosphokinase (CPK) ≤ 2.5 × ULN.

8) 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 gray (Gy).

c) At least two weeks since the last biological/investigational therapy (excluding MAbs) or palliative RT (≤ 10 fractions or ≤ 30 Gy total dose).

9) Grade ≤ 1 toxicity due to any previous cancer therapy according to the NCI-CTCAE, v.4. Grade 2 is allowed in case of alopecia and/or peripheral sensory neuropathy.

10) Women of childbearing potential must have pregnancy excluded by appropriate testing before study entry. Fertile women must agree to use a medically acceptable method of contraception throughout the treatment period and for at least three months after treatment discontinuation. Fertile men must agree to refrain from fathering a child or donating sperm during the trial and for four months after the last infusion.

4.2 EXCLUSION CRITERIA

1) Prior treatment with PM01183 or trabectedin.

2) Prior or concurrent malignant disease unless in complete remission for more than five years, except treated *in situ* carcinoma of the cervix, basal or squamous cell skin carcinoma, and *in situ* transitional cell bladder carcinoma.

3) Known central nervous system (CNS) involvement. In patients with SCLC, brain computed tomography (CT)-scan or MRI results must be provided at baseline.

4) Relevant diseases or clinical situations which may increase the patient's risk:

a) History within the last year or presence of unstable angina, myocardial infarction, congestive heart failure, or clinically relevant valvular heart disease or symptomatic arrhythmia or any asymptomatic ventricular arrhythmia requiring ongoing treatment.
b) Grade ≥ 3 dyspnea or daily intermittent oxygen requirement within two weeks prior to the study treatment onset.
c) Active infection.
d) Unhealed wounds or presence of any external drainage.
e) Known chronic active hepatitis or cirrhosis.
f) Immunocompromised patients, including known infection by human immunodeficiency virus (HIV).

5) Women who are pregnant or breast feeding and fertile patients (men and women) who are not using an effective method of contraception. *
6) Impending need for RT (e.g., painful bone metastasis and/or risk of spinal cord compression).
7) Limitation of the patient's ability to comply with the treatment or to follow-up the protocol.

* Women of childbearing potential (WOCBP) must agree to use an effective contraception method to avoid pregnancy during the course of the trial (and for at least three months after the last infusion). Valid methods to determine the childbearing potential, adequate contraception and requirements for WOCBP partners are described in APPENDIX 2. Fertile men must agree to refrain from fathering a child or donating sperm during the trial and for four months after the last infusion.

4.3 PATIENTS FOR THE PHARMACOGENOMIC (PGX) AND PHARMACOGENETIC EVALUATIONS

Only patients who voluntarily sign the IC for the PGx and pharmacogenetic sub-study will participate. Refusal to participate in this sub-study will not affect patient participation in the clinical study PM1183-B-005-14.

5. PLAN OF THE STUDY

5.1 PLANNED TRIAL PERIODS (FOR THE WHOLE STUDY)

The total duration of the study will be approximately 52 months, including approximately a 40-month enrolment period.

Planned start date (first patient on study): 3Q2015.

Planned enrolment period: 40 months.

Planned end-of-study date (clinical cutoff for each cohort except SCLC): when all evaluable patients within each cohort have at least 12 months of follow-up from the first PM01183 infusion. Patients with SCLC will be followed-up for at least 18 months after the last patient enrolled received the first PM01183 infusion.

5.2 PLANNED TRIAL PERIODS (INDIVIDUALLY PER PATIENT)

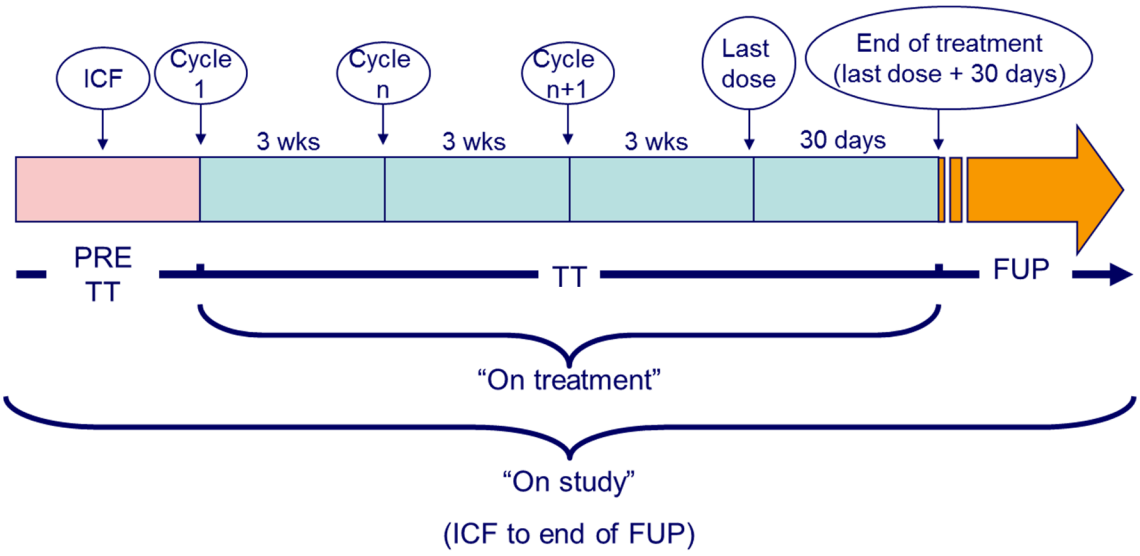
Patients will be evaluated at scheduled visits within three study periods:

- **Pre-treatment:** from signature of IC to the first infusion of study treatment.

- **Treatment:** from the first infusion of the study treatment to *end of treatment* (EOT) (see Section 5.2.1.1).
- **Follow-up:** after EOT, patients will be followed-up every four weeks until resolution or stabilization of all drug-related toxicities, if any, or until start of a new antitumor therapy. Patients will be followed-up for at least one year after their first PM01183 infusion. Patients who finish treatment without PD will be followed-up every two months during the first six months and every three months thereafter until PD, start of a new antitumor therapy, death or until the end of study date (clinical cutoff). After PD is documented or a new antitumor therapy is started, each cohort (except SCLC) will be followed-up at least every six months and up to 12 months after the last patient enrolled received the first PM01183 infusion (a documented phone contact will be acceptable). Patients in the SCLC cohort, after PD, will be followed-up every six months for at least 18 months after the last patient enrolled received the first PM01183 infusion (a documented phone contact will be acceptable).

Patients will be considered to be **on-study** from the signature of the informed consent form (ICF) until the end of the follow-up period. Patients will be considered to be **on-treatment** for the duration of their treatment and until the day of EOT, immediately before the start of the follow-up period. This EOT is defined as 30 days after the day of the last PM01183 infusion (see Figure 2), unless the patient starts a new antitumor therapy or dies (whichever occurs first). An end-of-treatment visit (EOT visit) will be performed within 30 days (± 7 days) after the last study treatment administration, unless the patient starts any subsequent antitumor therapy, in which case the EOT visit should be performed immediately before the start of the new therapy.

Figure 2. Study periods.



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

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

5.2.1 Discontinuations

5.2.1.1 *Treatment Discontinuation*

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

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

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

5.2.1.2 *Reasons for Treatment Discontinuation*

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

- Disease progression.
- Unacceptable toxicity.
- Treatment delay > three weeks from the treatment due date (except in case of clear clinical benefit, upon Sponsors' approval).
- Requirement of > two dose reductions.
- Intercurrent illness of sufficient magnitude to preclude safe continuation of the study.
- A major protocol deviation that may affect the risk/benefit ratio for the participating patient.
- Investigator's decision.
- Non-compliance with study requirements.
- Patient's refusal.

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

5.2.1.3 *Study Discontinuation*

Study discontinuation occurs when an enrolled patient ceases to participate in the study, regardless of the reason (as detailed under "Follow-up" in Section 5.2). Patients have the right to withdraw consent at any time; if this is the case, no further study procedures should be performed.

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

5.2.2 Protocol Deviations

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

related to obtaining the patients' Informed Consent, data reporting or the responsibilities of the Investigator).

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

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

No deviations that may have an effect on the risk/benefit ratio of the clinical trial will be authorized. All protocol deviations detected during the study will be appropriately documented, and those considered particularly relevant (i.e., those related to ethical issues, to fulfillment of GCP guidelines and with an effect on the risk/benefit ratio) will be notified to the pertinent IEC/IRB and, if applicable, to the Competent Authorities as established by local regulations.

5.3 REPLACEMENT OF PATIENTS

Patients will be replaced if they are not evaluable for the primary endpoint of the study (ORR as per RECIST v. 1.1), specifically if (any of the following):

- They are not eligible.
- They have not received the study treatment.
- 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.
  - Early death due to malignant disease.

All replaced patients who received study treatment will be included in the safety analysis.

5.4 PRE-TREATMENT ASSESSMENTS

During the pre-treatment period, following signature of the ICF, the Investigator will confirm the patient's eligibility for the study by conducting the assessments summarized in Table 3.

Table 3. Screening period: pre-treatment assessments.

	ASSESSMENT	TIME
1. Written informed consents (general and PGx/pharmacogenetic sub-study)		Before any study procedures.

	ASSESSMENT	TIME
2. Medical and cancer history/ clinical examination	◆ Demographic data (race/ethnicity, age, gender).	Within 28 days prior to registration.
	◆ Primary diagnosis and prior treatment(s) (with best response and TTP, when available).	Within 28 days prior to registration.*
	◆ Medical and cancer history/baseline condition. ◆ Concomitant therapies.	Within 14 days prior to registration.*
	◆ Disease-related signs and symptoms. ◆ Complete physical examination, including weight, height and calculation of BSA. ◆ Performance status (ECOG PS). ◆ Vital signs: heart rate, blood pressure and body temperature.	Within 7 days prior to registration.**
3. Laboratory tests	◆ **Coagulation panel**: PT/INR and PTT. ◆ **Hematology:** Hemoglobin, platelet counts, and differential WBC counts (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 >1.5xULN), LDH, creatinine, glucose, and CPK. ◆ **Biochemistry B:** Total proteins, albumin, total calcium and Mg^{++}. In patients with germ cell tumors, ß-hCG and AFP will be also measured.	Within 7 days prior to registration.
4. Pharmacogenetics (only if written informed consent given)	One blood sample. ***	At any time during the study, but preferably just before treatment start in Cycle 1.
5. PGx	Available stored paraffin-embedded tumor tissue samples (only if written informed consent given)	At any time during the study.
6. Pregnancy test (if women of childbearing potential)	ß-hCG (urine or serum). In patients of childbearing potential (except germ cell tumor patients), if ß-hCG levels are elevated, pregnancy must be clinically discarded by an additional test (i.e., ultrasound) before any other study procedure. Pregnancy during treatment or within three months from the patient's last PM01183 administration is considered an immediately reportable event.	Within 7 days prior to registration, if applicable.****
7. ECG	Cardiac rhythm will be identified in ECG intervals of at least 30 seconds of duration, PR interval, QT interval (raw), heart rate and QRS complex.	Within 7 days prior to registration.****
8. LVEF	LVEF measured by MUGA or ECHO.	Within 28 days prior to registration.****
9. Radiological tumor assessment	In all patients, contrast enhanced helical CT-scan or MRI, as clinically indicated.	Within 28 days prior to registration.*
	In SCLC patients, brain CT-scan or MRI to rule out CNS involvement.	Within 14 days prior to registration.*
10. Adverse events	Only information on SAEs that occurred after signature of the informed consent is required before treatment start. Grading should be as per the NCI-CTCAE v.4.	-

Day 0 is when eligibility is confirmed and a patient is registered: for the purposes of assessment windows, it is assumed that Day 0 is the calendar day before Day 1 of Cycle 1. If this is not the case and first infusion is administered more than one week after screening window, laboratory tests (hematology, biochemistry A, B and pregnancy test if applicable) must be repeated within the three days prior to first infusion.

*A 1-week window is allowed for primary diagnosis and prior treatment(s), medical and cancer history/baseline conditions, concomitant therapies and radiological tumor assessment at screening.

**A 1-day window is allowed for assessment of disease signs and symptoms, complete physical examination, ECOG PS, and vital signs at screening.

***One blood sample will be collected to evaluate the presence or absence of known polymorphisms.

****A 3-day window is allowed for ECG and LVEF assessment at screening.

AFP, alpha fetoprotein; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; β-hCG, beta subunit of human chorionic gonadotropin; BSA, body surface area; CNS, central nervous system; CPK, creatine phosphokinase; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; GGT, gamma-glutamyltransferase; INR, international normalized ratio; LDH,

	ASSESSMENT	TIME

lactate 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; PGx, pharmacogenomics; PS, performance status; PT, pro-thrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; SAE, serious adverse event; SCLC, small cell lung cancer; TTP, time to progression; WBC, white blood cells.

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

5.5 PATIENT REGISTRATION

After the patient has signed the ICF and all eligibility criteria have been met, the patient will be included into the trial. A patient number will be provided at the time of registration. This number should be used in 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.

5.6 PATIENT RANDOMIZATION

Not applicable.

5.7 EVALUATIONS DURING TREATMENT

The following assessments will be done while the patient is on treatment (Table 4).

Table 4. Evaluations during treatment.

	ASSESSMENT	TIME
1. Clinical examination	◆ Complete physical examination, including weight and calculation of BSA. Dose will be adjusted if BSA change is ≥ 10% (higher or lower) of the previous value.	Day 1 of each cycle (always prior to PM01183 infusion).*
	◆ Performance status (ECOG PS). ◆ Vital signs: heart rate, blood pressure and body temperature.	Day 1 of each cycle (always prior to PM01183 infusion).*
	◆ Concomitant therapies.	Throughout the "on treatment" period.**
2. Laboratory tests	◆ **Coagulation panel**: PT/INR and PTT.	Day 1 of each cycle (always prior to PM01183 infusion).*
	◆ **Hematology:** Hemoglobin, platelet counts, and differential WBC counts (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 >1.5xULN), LDH, creatinine, glucose, and CPK.	Cycle 1 and 2: Day 1, 8 and 15 (always prior to PM01183 infusion).* Two blood samples (24 hours and 72 hours after the end of PM01183 infusion) will be collected at the same time than PK samples #6 and #7 in Cycle 1 for monocyte count. Further cycles: Day 1 of each cycle (always prior to PM01183 infusion). * From Cycle 2 onwards, Hematology and Biochemistry A tests on Days 8 and 15 are to be performed only in patients who present biochemical grade ≥3 or hematological grade > 4 treatment-related toxicities, or who required dose adjustments due to hematological or biochemical abnormalities in the preceding cycle. 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. Any patient having febrile neutropenia of

	ASSESSMENT	TIME
		any grade, grade 4 neutropenia, and/or grade 4 thrombocytopenia, should have relevant tests repeated daily until recovery to grade ≤ 3 and up to the next day after fever resolution, if applicable.
	◆ **Biochemistry B:** Albumin, total proteins, total calcium and Mg^{++}. In patients with germ cell tumors, ß-hCG and AFP only in those patients with elevated values at baseline.	Albumin: Day 1 of each cycle (always prior to PM01183 infusion). * Total proteins, total calcium and Mg^{++} will be measured only in those patients with abnormal baseline values. 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.Pharmacokinetics	◆ **Cycle 1**: Eight blood samples (before PM01183 infusion start, 5 min before end of PM01183 infusion and 30 min, 1 hour, 3 hours, 24 hours, 72 hours and 168 hours after the end of PM01183 infusion) will be collected for pharmacokinetic analyses (see details in Section 7.2.1). ◆ **Cycle 2**: Six blood samples (before PM01183 infusion start, 5 min before end of PM01183 infusion and 30 min, 1 hour, 3 hours and 168 hours after the end of PM01183 infusion) will be collected for pharmacokinetic analyses (see details in Section 7.2.1).	Cycle 1 and Cycle 2.
4. AAGP	One blood sample per cycle.	On Day 1 of Cycle 1 and Cycle 2 (always prior to PM01183 infusion).
5. Pharmacogenetics (only if written informed consent given)	One blood sample.	At any time during the study, but preferably just before treatment start in Cycle 1.
6. Pregnancy test (if women of childbearing potential)	ß-hCG (urine or serum). In patients of childbearing potential (except germ cell tumor patients), if ß-hCG levels are elevated, pregnancy must be clinically discarded by an additional test (i.e., ultrasound) before any other study procedure. Pregnancy during treatment or within three months from the patient's last PM01183 administration is considered an immediately reportable event.	Day 1 of each cycle (always prior to PM01183 infusion).*
7. ECG	Cardiac rhythm will be identified in ECG intervals of at least 30 seconds of duration, PR interval, QT interval (raw), heart rate and QRS complex.	Repeat if clinically indicated.
8. LVEF	LVEF measured by MUGA or ECHO.	Repeat if clinically indicated.
9. Radiological tumor assessment	Contrast enhanced helical CT-scan or MRI, as clinically indicated.	Every two cycles from the onset of the study treatment until Cycle 6 and every three cycles thereafter.* Patients showing a response must have a confirmatory assessment at least four weeks later.
10. Adverse events	As per NCI-CTCAE v.4.	Throughout the "on treatment" period.**

*A 3-day window will be allowed for laboratory procedures and ECG, a 1-week window for radiological tumor assessments (helical CT-scan or MRI) and LVEF assessments and a 1-day window for clinical assessments (ECOG PS, physical examination, vital signs, weight, BSA).

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

AAGP, alpha-1 acid glycoprotein; AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase;

	ASSESSMENT	TIME

AST, aspartate aminotransferase; β-hCG, beta subunit of human chorionic gonadotropin; BSA, body surface area; CPK, creatine phosphokinase; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; GGT, gamma-glutamyltransferase; INR, international normalized ratio; LDH, lactate 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; PK, pharmacokinetic; PS, performance status; PT, pro-thrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cells.

5.8 EVALUATIONS AT END OF TREATMENT

The *end-of-treatment visit* will be scheduled within 30 days (± 7 days) after the last PM01183 infusion, unless the patient starts a subsequent antitumor therapy, in which case the end-of-treatment visit should be performed immediately before the start of the new therapy (ideally the day before or the same day).

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

- Complete physical examination.
- ECOG PS.
- Vital signs.
- Concomitant therapies.
- Laboratory tests (coagulation panel, hematology and biochemistry A and B).
- Pregnancy test, ECG or LVEF assessment (if clinically indicated).
- Radiological tumor assessment (the evaluation should be repeated at EOT visit, if not previously done, and if the reason for treatment discontinuation is other than PD).
- Adverse events.

These evaluations will only have to be repeated for those parameters for which no measurement is available within 10 days before the EOT visit, or for those parameters with values that were out of range in the last assessment (grade ≥ 2 according to the NCI-CTCAE v.4).

Adverse events must be reported for 30 days after the last study treatment administration. All serious adverse events (SAEs) occurring within 30 days of the last study treatment administration or until the start of a new antitumor therapy, whichever occurs first, will be reported. Beyond this period of time, only those suspected to be treatment-related SAEs will be reported (Section 7.7.2).

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

5.9 FOLLOW-UP AFTER END-OF-TREATMENT VISIT

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

Only patients who discontinue treatment without PD will have radiological evaluations during follow-up period. The assessments will be performed every two months during the first six months and every three months thereafter until PD, start of a new antitumor therapy, death, or until the end of study date (clinical cutoff). After PD is documented or

a new antitumor therapy is started, each cohort (except SCLC) will be followed-up at least every six months and up to 12 months after the last patient enrolled received the first PM01183 infusion (a documented phone contact will be acceptable). Patients in the SCLC cohort, after PD, will be followed-up every six months for at least 18 months after the last patient enrolled received the first PM01183 infusion (a documented phone contact will be acceptable).

The end-of-study date (clinical cutoff for each cohort except SCLC) is defined as the time point when all evaluable patients within each cohort have at least 12 months of follow-up from the first PM01183 infusion. Patients with SCLC will be followed-up for at least 18 months after the last patient enrolled received the first PM01183 infusion.

Patients who have withdrawn from the study treatment with an ongoing drug-related AE should be followed every four weeks until event recovery to at least grade 1 or stabilization or until onset of a new antitumor therapy.

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

6. TREATMENT

6.1 DESCRIPTION OF TREATMENT

6.1.1 Drug Formulation and Supply

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

Before use,

For administration to patients as an i.v. infusion, reconstituted vials are diluted with glucose 50 mg/ml (5%) solution for infusion or sodium chloride 9 mg/ml (0.9%) solution for infusion.

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

The full composition of the PM01183 4-mg vials and the reconstituted solution per ml is as shown in Table 5.

6.2 ADMINISTRATION OF THE STUDY MEDICATION

PM01183 will be administered over a

(either on 5% glucose or 0.9% sodium chloride), through a central catheter, or over if administered through a peripheral line, always over one hour at a fixed infusion rate

6.3 STARTING DOSES AND SCHEDULE

Starting dose will be 3.2 mg/m^2. Dose will be capped at BSA of 2.0 m^2 (i.e., dose will not exceed 6.4 mg).

Patients will receive PM01183 i.v. as a one-hour infusion on Day 1 every three weeks (q3wk) (three weeks = one treatment cycle).

6.4 PROPHYLACTIC MEDICATION

All patients will receive standard antiemetic prophylaxis before each treatment infusion. The i.v. formulations of these agents must be used in this setting:

- Corticosteroids (dexamethasone 8 mg or equivalent).
- Serotonin (5-HT$_3$) antagonists (ondansetron 8 mg or equivalent).
- Extended treatment with oral 5-HT$_3$ antagonists and oral dexamethasone for two consecutive days.
- If necessary, and in addition to the above, administration of 10 mg of oral or i.v. metoclopramide (or equivalent) every eight hours.

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

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

6.5 CRITERIA FOR TREATMENT CONTINUATION

Further treatment cycles (i.e., Cycle 2 or subsequent) will be administered every q3wk (± 48 hours) if the patient fulfills all the re-treatment criteria defined in Table 6.

Table 6. Criteria for treatment continuation.

Variable	Re-treatment (Day 1)
ECOG PS	≤ 2
Hemoglobin*	≥ 8.0 g/dl
ANC	≥ 1.5 × 10^9/l
Platelets	≥ 100 × 10^9/l
AST/ALT	≤ 3.0 × ULN
Total bilirubin or direct bilirubin	≤ 1.5 × ULN or × ULN
Albumin	≥ 3 g/dl
Serum creatinine	≤ 1.5 × ULN or creatinine clearance ≥ 30 ml/min
CPK	Grade ≤ 1
Other non-hematological drug-related AEs (except isolated increased GGT and/or AP; grade 2 asthenia, constipation, alopecia, peripheral neuropathy, or non-optimally treated nausea and/or vomiting)	Grade ≤ 1
Active infection (including sepsis) and/or bleeding (any grade)	Absence

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

AE(s), adverse event(s); 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

Variable	Re-treatment (Day 1)

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 at least 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 3-week delay must be withdrawn from trial. In case of objective clinical benefit, the patient could continue receiving the treatment (upon the Sponsors' agreement).

For any delay due to treatment-related adverse events lasting for more than one week, a dose reduction must be implemented upon recovery, following the rules explained in the next section (Section 6.6).

6.6 DOSE REDUCTION

Patients may continue the study treatment at a reduced dose if they present 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 ≤ 3 days, grade 3 diarrhea lasting ≤ 2 days or not optimally treated, grade 3 transient ALT/AST elevations which are rapidly reversible and not leading to subsequent delays, and non-clinically relevant biochemical abnormalities.
- Grade 4 thrombocytopenia or grade 3 thrombocytopenia concomitantly with grade ≥3 bleeding.
- Grade 4 neutropenia, any grade febrile neutropenia or neutropenia associated with infection/sepsis.
- Frequent or prolonged (>1 week) dose delays due to treatment-related adverse events.

Patients who experience grade 3/4 hypersensitivity reactions will be discontinued from study treatment.

Dose reduction levels are shown in Table 7.

Table 7. Criteria for dose reduction.

Dose reduction	PM01183 dose (mg/m^2) *
1 (starting dose)	3.2 **
−1	2.6
−2	2.0

*Dose rounded to the first decimal.
**Dose will be capped at BSA of 2.0 m^2 (i.e., dose will not exceed 6.4 mg).
BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Up to two dose reductions are allowed per patient.

Patients who continue to experience treatment-related toxicity and/or frequent dose delays after permitted dose reductions must be withdrawn from the study. They can continue receiving the study medication if objective clinical benefit is adequately documented by the Investigator, and upon agreement with the Sponsor. Once the dose has been reduced for an individual patient, it will not be re-escalated under any circumstances.

6.7 CONCOMITANT MEDICATION

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

6.7.1 Allowed Medications/Therapies

- Therapies for pre-existing and treatment-emergent medical conditions, including pain management.
- Blood products and transfusions, as clinically indicated.
- Bisphosphonates.
- In case of nausea or vomiting, secondary prophylaxis and/or symptomatic treatment for emesis according to the ASCO guidelines.
- Erythropoietin (EPO) treatment according to the ASCO guidelines.
- Anticoagulation therapy.

6.7.2 Prohibited Medications/Therapies

- Any other antineoplastic therapy, except somatostatin analogues for NETs.
- Any other investigational agents.
- Primary G-CSF prophylaxis.
- Immunosuppressive therapies other than corticosteroids for antiemetic prophylaxis and/or pain control.
- Medroxyprogesterone (patients with endometrial cancer).
- Aprepitant, fosaprepitant or related compounds.
- Radiotherapy.

6.7.3 Drug-drug Interactions

In vitro studies using human liver microsomes have shown that PM01183 has the potential to inhibit cytochrome CYP2C8, CYP3A4 and, to a minor extent, CYP2B6. Moreover, the calculated Ki values were 0.2, 1.4, 8.9 and 1.9 µM for CYP3A4m, CYP3A4t, CYP2B6 and CYP2C8, respectively. Additional *in vitro* studies demonstrated that time dependent inhibition or irreversible inhibition for cytochrome CYP3A4 was not present. The total mean maximum plasma concentration at the RD (or [I]) (182.2 µg/L in study PM1183-A-001-08) was *ca.* 0.23 µM (or *ca.* 0.005 µM when expressed as unbound fraction; 2.2%).

According to the recommendations in the Guideline CPMP/EWP/560/95, the risk of inhibition *in vivo* is evaluated by comparing observed K_i values. If $[I]/K_i \geq 0.02$, inhibition *in vivo* cannot be excluded. The estimated $[I]/K_i$ values were 0.023, 0.004, 0.001 and 0.003 for CYP3A4m, CYP3A4t, CYP2B6 and CYP2C8, respectively. Therefore, an inhibitory effect of PM01183 on CYP3A4 cannot be excluded.

The basic model proposed at the FDA guidance for DDI (Draft February 2012) and the NISH Drug Interaction Guideline for Drug Development and Provision of Appropriate Information (Draft 2014), results in a R_1 value for CYP3A4m of 2.15, which still suggests a potential inhibition for CYP3A4. On the other hand, when applying the mechanistic static model, AUCR=1.01 (A_h in FDA guidance or C_h in NIHS guideline was 0.98 and f_m=0.4), the inhibitory effect of PM01183 on CYP3A4 can be discarded.

As a conclusion, while and inhibitory effect of PM01183 on CYP2C8 and CYP2B6 can be ruled out, the effect on CYP3A4 deserves further exploration. Ongoing PBPK

models will explore deeply any potential effect of PM01183 as CYP3A4 inhibitor. In the meantime, caution should be exercised when PM01183 is administered concomitantly with 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 possible (see APPENDIX 3).

6.8 DRUG ACCOUNTABILITY

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

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

6.9 TREATMENT COMPLIANCE

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

7. STUDY EVALUATIONS

7.1 EFFICACY

The primary objective of this study is to assess the antitumor activity of PM01183 in terms of **overall response rate (ORR)**, primary endpoint, supported by the secondary endpoint duration of response (DR), both assessed by the IA.

ORR will be assessed using the RECIST v.1.1 (see APPENDIX 4) on a set of measurable lesions identified at baseline as target lesions or as non-target lesions (if any), and followed until disease progression (PD) by an appropriate method (e.g., helical CT-scan, MRI).

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

ORR is defined as the percentage of evaluable patients with a confirmed response, either complete (CR) or partial response (PR), from the start of treatment to the date of progression or the start of a subsequent therapy or end of patient's follow-up, according to the RECIST (v. 1.1).

DR will be calculated from the date of first documentation of response to the date of first documented PD, recurrence or death due to any cause in the responder patients.

The date of response, the date of radiological or clinical PD, according to the investigator assessment and the independent assessment by IRC when applicable (i.e., SCLC cohort), and the date of death will be registered and documented, as appropriate.

A copy of CT-scans or MRIs can be requested by the Sponsor in selected cases.

In SCLC patients, anonymized copies of all the images obtained throughout the study must be submitted to the Sponsor. These copies of CT scans, MRIs and any other documented methods to evaluate tumor response or progression in the SCLC cohort should be available for external radiological review by an IRC. The IRC will determine the patient's best response and assign the date of first documentation of response and progression/censoring according to RECIST v.1.1.

7.2 PHARMACOKINETICS

7.2.1 Blood Sampling

The plasma PK of PM01183 will be evaluated during Cycle 1 and Cycle 2 in all treated patients. The sampling schedule for Cycle 1 and Cycle 2 will be as shown in Table 8 and Table 9, respectively.

Table 8. Blood samples for pharmacokinetic evaluations in Cycle 1.

Sample No.	Day	Sampling time	Sampling window
#1	D1	Before treatment start	--
#2 *	D1	5 min before EOI	+/- 4 min
#3	D1	30 min after EOI	+/- 4 min
#4	D1	1 hour after EOI	+/- 10 min
#5	D1	3 hours after EOI	+/- 10 min
#6	D2	24 hours after EOI	+/- 2 hours
#7	D4	72 hours after EOI	+/- 24 hours
#8	D8	168 hours after EOI	+/- 24 hours

* Sample #2 must be collected before EOI.
D, day; EOI, end of infusion.

Table 9. Blood samples for pharmacokinetic evaluations in Cycle 2.

Sample No.	Day	Sampling time	Sampling window
#9	D1	Before infusion start	--
#10 *	D1	5 min before EOI	+/- 4 min
#11	D1	30 min after EOI	+/- 4 min
#12	D1	1 hour after EOI	+/- 10 min
#13	D1	3 hours after EOI	+/- 10 min
#14	D8	168 hours after EOI	+/- 24 hours

* Sample #10 must be collected before EOI.
D, day; EOI, end of infusion.

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

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

A total of 14 samples of about 4 ml each will be collected for the determination of plasma concentrations of PM01183 in Cycle 1 and Cycle 2 (about 56 ml of whole blood) at the predefined times depicted in the above tables. The Laboratory Manual describes in more 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 plasma-containing tubes will be stored frozen until their shipment with dry ice according to the Laboratory Manual instructions. AAGP samples will be shipped together with PK samples. All the material for PK procedures will be provided by the Sponsor(s).

7.2.2 Analytical Procedures

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

7.2.3 Pharmacokinetic Parameters

PK parameters will be calculated using non-compartmental analysis (NCA) and population methods if appropriate, after pooling data from this study with data obtained from other studies.

7.3 PHARMACOGENETIC EVALUATIONS

To explore factors that may help to explain individual variability in the main PK parameters, the presence or absence of germline mutations or polymorphisms that may be involved in the metabolism and/or transport of PM01183 will be analyzed in leukocyte DNA extracted from one blood sample (8 ml) obtained at any time during the study. The collection and management of the polymorphisms samples are quite different than those for PK assessment. Please, follow carefully the instructions detailed in the Laboratory Manual that will be provided. The assessment of polymorphisms is not affected by treatment, but this sample should be collected preferably just before treatment start in Cycle 1. Therefore, the Sponsor may require the collection of additional polymorphisms samples later on, if the first assessment has not been performed accurately.

7.4 PHARMACOGENOMIC (PGX) EVALUATIONS

Provision of samples for PGx analyses will be optional and performed upon patient consent by signing the PGx IC. For those patients who consent to participate in the PGx study, available tumor tissue blocks obtained at diagnosis of the disease will be collected during his/her participation in the associated clinical trial.

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

- Quantitation of mRNA expression of selected genes involved in DNA repair mechanisms and/or related to the mechanism of action of PM01183 or to the pathogenesis of the disease by real-time qRT-PCR.

- Quantitation of protein expression of selected genes involved in DNA repair mechanisms and/or related to the mechanism of action of PM01183 or to the pathogenesis of the disease by IHC in tumor tissue microarrays constructed.
- Analysis of polymorphisms and mutations of the above mentioned selected genes will be analyzed, if relevant, by qRT-PCR and/or DNA sequencing.
- Expression levels of the different markers will be correlated with the patient's clinical outcome.

7.5 SAFETY

Patients will be evaluable for safety if they have received any partial or complete infusion of PM01183. All AEs will be graded according to the NCI-CTCAE, v.4.

The safety profile of patients will be monitored throughout the treatment and up to 30 days after the last PM01183 infusion (end of treatment, EOT), or until the patient starts a new antitumor therapy or until the date of death, whichever occurs first.

Treatment delays, dose reduction requirements and reason for treatment discontinuation will be monitored throughout the study. Any treatment-related AEs will be followed until recovery to at least grade 1 or stabilization of symptoms or until the start of a new antitumor therapy, whichever occurs first.

7.6 ADVERSE EVENTS DEFINITIONS

7.6.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient who has received a pharmaceutical product which does not necessarily have a causal relationship with this treatment.

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

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

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

7.6.2 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.

7.6.3 Death

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

7.6.4 Life-threatening Event

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

7.6.5 Hospitalization or Prolongation of Hospitalization

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

Hospitalizations that do not meet criteria for SAE reporting are:

a. Reasons described in protocol [e.g., investigational medicinal product (IMP) administration, protocol-required intervention/investigations, etc.]. However, events requiring hospitalizations or prolongation of hospitalization as a result of a complication of therapy administration or clinical trial procedures will be reported as SAEs.
b. Hospitalization or prolonged hospitalization for technical, practical or social reasons, in absence of an AE.
c. Pre-planned hospitalizations: any pre-planned surgery or procedure must be documented in the source documentation. Only if the pre-planned surgery needs to be performed earlier due to a worsening of the condition, should this event (worsened condition) be reported as a SAE.

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

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

7.6.6 Unlisted/Unexpected Adverse Event

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

The Sponsor will use as the reference safety information for the evaluation of listedness/expectedness the most updated IB for lurbinectedin (PM01183).

7.6.7 Adverse Reactions

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

7.6.8 Adverse Events Related to the Study Drug

An AE is considered related to a study drug/IMP if the Investigator's assessment of causal relationship to the IMP(s) is "Y (yes)" (see Section 7.6.10).

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

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

7.6.9 Expedited Reporting

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

7.6.10 Assessment of Causal Relationship to the Study Drug

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

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

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

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

7.7 ADVERSE EVENTS REPORTING PROCEDURES

7.7.1 Reporting Adverse Events

The Sponsor will collect AEs until 30 days after administration of the last dose of the study drug(s)/IMP(s) or until the start of a new antitumor therapy, whichever occurs first. All AEs suspected to be related to the study drug/IMP must be followed-up after the time of therapy discontinuation until the event or its sequelae resolve or stabilize at an acceptable level to the Investigator and the Sponsor.

All AEs, including misuse, overdose and abuse, must be recorded in English using medical terminology in the source document and the CRF. Whenever possible, the Investigator will record the main diagnosis instead of the signs and symptoms normally included in the diagnoses.

Investigators must assess severity (grade) of the event following the NCI-CTCAE v.4 and assign a relationship to each study drug(s)/IMP(s); and pursue and obtain information adequate both to determine the outcome and to assess whether it meets the

criteria for classification as a SAE requiring immediate notification to Pharma Mar or its designated representative. The Investigator must provide any relevant information as requested by the Sponsor in addition to that on the CRF.

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

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

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

7.7.2 Reporting Serious Adverse Events

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

All SAEs (as defined above) regardless of relationship to the study drug(s)/IMP(s) must be reported immediately and always within 24 hours to the Pharma Mar S.A. Pharmacovigilance Department as appropriate: electronically (e-CRF), fax (+34 91 846 6004), e-mail (phv@pharmamar.com) or telephone (+34 91 823 4562). Out of office hours [Greenwich Meridian Time (GMT)], assistance on SAE reporting can be obtained by calling the Pharmacovigilance Department at +34 681 263 592. SAEs initially reported by phone must be followed by a completed electronic SAE reporting on e-CRF from the investigational staff within one working day.

If the SAE occurs after the patient's registration has been confirmed, this information will preferably be reported electronically by completing the applicable eCRF sections.

Those SAEs occurring during the screening phase (from ICF signature to registration) and after off-study will be reported using a paper "SAE form" that must be forwarded as mentioned above and always within 24 hours to the Pharmacovigilance Department.

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

7.7.3 Reporting Pregnancy Cases Occurred within the Clinical Trial

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

Therefore, pregnancy (including a positive pregnancy test regardless of age or disease state) of a female patient within three months from the patient's last PM01183 last administration, or the female partner of a male patient occurring while the patient is on study drugs, or within four months after the 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 IMP(s) is suspected.
- Possible exposure of a pregnant woman.
- All reports of elevated/questionable or indeterminate beta human chorionic gonadotropins (β-hCGs) and additional tests (ultrasounds).

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

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

The Investigator will follow the pregnancy until its outcome, and must notify Pharma Mar S.A. Pharmacovigilance Department 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 Department within 24 hours of the Investigator's knowledge of the event).

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

7.8 ADVERSE EVENTS MONITORING

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

At every monitoring visit performed by the designated clinical trial monitor, the consistency between the CRF/SAE data reported to the Pharmacovigilance Department and the patient's source data will be reviewed. In every case a discrepancy is found during the review, data will be amended/updated in the CRF and the SAE form/information reported to the Pharmacovigilance Department (when applicable), according to source data. An update (follow-up) with changes arisen will be signed by the Principal Investigator (or his/her designee) and then reported/provided to the Pharmacovigilance Department within 24 hours, with the CRF updated on the same dates.

Periodic safety review of clinical data will be performed. AEs will be monitored by the Investigators and by the study team at Pharma Mar S.A. The personnel in charge of this process are defined in the section "*Study Contacts*" of this protocol. Pharma Mar S.A. Pharmacovigilance Department will review the safety data of this trial on an ongoing basis.

SAEs will be continuously collected, assessed and reported throughout all the study as per the applicable Regulations by the Pharma Mar S.A. Pharmacovigilance Department. Periodic safety reviews of SAE reports are to be conducted and documented by the Pharmacovigilance Department.

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

- expedited: all serious, related, unlisted/unexpected AEs or critical safety findings (including those of special interest) from this and any other clinical trial with PM01183 and,
- periodic: all relevant safety information generated in all clinical trials with the IMP(s) within the Development Safety Update Report.

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

8. STATISTICAL METHODS

This phase II trial is designed to assess the antitumor activity of PM01183 in terms of ORR according to the RECIST v.1.1 assessed by IA in different selected advanced solid tumors: SCLC, H&N, NETs, biliary tract carcinoma, endometrial carcinoma, BRCA 1/2-associated metastatic breast carcinoma, carcinoma of unknown primary site, GCTs, and EFTs. In addition, in the SCLC cohort, tumor evaluation will be also done by IRC.

8.1 SAMPLE SIZE

Up to 25 evaluable patients in each tumor type will be recruited to test the null hypothesis that 1% or less patients get a response ($p \leq 0.01$) *versus* the alternative hypothesis that 10% or more patients get a response ($p \geq 0.10$). The variance of the standardized test 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 0.2 (normal approximation; ~0.3 if exact binomial distribution); hence, statistical power is 80% (normal approximation; ~70% if exact binomial distribution). With these assumptions, if the number of patients who achieve a confirmed response is ≥ 2, then this would allow the rejection of the null hypothesis.

An interim analysis to reject H0 (non-binding) or to reject H1 (futility) in each tumor type is planned after the recruitment of 15 evaluable patients in each cohort. The Gamma family boundary will be used to control the type I error, the parameter to reject H0 is fixed as -1 and the parameter to reject H1 is fixed as 0. If none of the first 15 evaluable patients in a determined cohort has a confirmed response, the alternative hypothesis will be rejected, according to boundaries and sample size assumptions, and recruitment will be stopped. If the number of responding patients is already two or more at the interim analysis, then H0 could be rejected and the study will have enough power to be stopped. On the contrary, if there is one confirmed response, the recruitment will be continued to up to 25 evaluable patients.

- A phase III trial of PM01183 combined with doxorubicin in SCLC is ongoing. Hence, the sample size for the SCLC cohort of this study will be expanded to 100 evaluable patients if the success boundary (≥2 confirmed responses) is reached in the first 25 evaluable patients.
- Based on the newly available information, additional patients will be recruited to test the null hypothesis that 15% or less patients get a response ($p \leq 0.15$) *versus* the alternative hypothesis that 30% or more patients get a response ($p \geq 0.30$). The variance of the standardized test 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 0.051 (normal approximation; ~0.05 if exact binomial distribution); hence, statistical power is 95% (normal approximation; ~95% if exact binomial distribution). With these assumptions, if the number of patients who achieve a confirmed response is ≥ 23, then this would allow the rejection of the null hypothesis. The judgement of patient's evaluability and replacement of non-evaluable patients in each cohort for the interim analyses will be guided by the investigator assessment.

- A phase I trial of PM01183 combined with doxorubicin has shown encouraging antitumor activity in endometrial carcinoma. Hence, the sample size for the endometrial carcinoma cohort of this study will be doubled to 50 evaluable patients if the success boundary (≥2 confirmed responses) is reached in the first 25 evaluable patients.

  Based on the newly available information, additional patients will be recruited to test the null hypothesis that 10% or less patients get a response ($p \leq 0.10$) *versus* the alternative hypothesis that 25% or more patients get a response ($p \geq 0.25$). The variance of the standardized test 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 0.144 (normal approximation; ~0.16 if exact binomial distribution); hence, statistical power is ~86% (normal approximation; ~84% if exact binomial distribution). With these assumptions, if the number of patients who achieve a confirmed response is ≥ 10, then this would allow the rejection of the null hypothesis.

With the sample size of 100 and 50 evaluable patients in each indication (SCLC and endometrial), the obtained confidence interval will be narrower and its half-width will be confined to ±15%.

8.2 STATISTICAL ANALYSIS

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

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

8.2.1 Efficacy Analyses

Counts and percentages, with their corresponding exact 95% confidence intervals, will be calculated for the binomial endpoints (e.g., ORR, clinical benefit). The confidence intervals based on the group sequential tests performed for each cohort will also be calculated.

Time-to-event variables (OS, PFS and DR) and their set time estimates (i.e., PFS 4/6 and OS 6/12) will be analyzed according to the Kaplan-Meier method.

In the SCLC cohort, the evaluation of the efficacy endpoints evaluated by IA and IRC will be analyzed and compared. The rate of concordance between both evaluation methods for best response, progression status and progression-free survival will be presented with 2-way frequency tables and measures of agreement.

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

The number of patients recruited in any cohort may differ from that pre-specified according to the sample size assumptions. Therefore, the main efficacy results will be calculated according to the planned cohort sample size and, if any cohort sample size differs at least 10% from the assumptions, a sensitivity analysis using all evaluable patients recruited (adjusting the corresponding boundaries to test the null hypothesis) will be performed.

8.2.2 Pharmacokinetic Analyses

PK data will be listed in the population PK-report for all patients with available PM01183 concentrations. PK analysis of plasma concentration-time data of PM01183 will be performed using non-linear mixed-effects modeling and/or non-compartmental analysis. Data may be combined with those of a selection of phase I or II studies to support a relevant structural model. Available patient characteristics (e.g., demographics, laboratory variables, genotypes) will be tested as potential covariates affecting PK parameters.

8.2.3 Pharmacogenetic Analyses

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

8.2.4 Pharmacogenomic Analyses

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

8.2.5 Safety Analyses

AEs, SAEs, deaths, laboratory evaluations, dose delays/reductions and study drug discontinuations due to AEs will be tabulated in a descriptive way. Counts and percentages will be used for categorical variables, and summary tables will be used for continuous variables.

8.3 INTERIM ANALYSES

An interim analysis to reject H0 (non-binding) or to reject H1 (futility) in each tumor type is planned after the recruitment of 15 evaluable patients in each cohort. The Gamma family boundary will be used to control the type I error, the parameter to reject H0 is fixed as -1 and the parameter to reject H1 is fixed as 0. If none of the first 15 evaluable patients in a determined cohort has a confirmed response, the alternative hypothesis will be rejected, according to boundaries and sample size assumptions, and recruitment will be stopped. If the number of responding patients is already two or more at the interim analysis, then H0 could be rejected and the study will have enough power to be stopped. On the contrary, if there is one confirmed response, the recruitment will be continued to up to 25 evaluable patients.

In particular, in the SCLC and endometrial carcinoma cohorts, the analysis at 25 evaluable patients will serve as second interim analysis to decide the continuation of recruitment. Two objective responses will be required to expand the accrual up to 100 and 50 evaluable patients respectively.

- For the SCLC cohort, the type I/II error will be controlled with a Gamma family boundary (-1 to reject Ho, 0 to reject H1)
- For the endometrial carcinoma cohort, the type I/II error will be controlled with a Gamma family boundary (-1 to reject Ho, -3 to reject H1)

9. ADMINISTRATIVE SECTION

9.1 ETHICS

This clinical trial will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki (see APPENDIX 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 Competent Authorities and IEC/IRB approval/favorable opinion prior to initiation, according to pertinent regulations.

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

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

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

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

9.2 MONITORING, AUDITING AND INSPECTING

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

During site visits, the trial monitor should revise original patient records, drug 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 Pharma Mar S.A. or external auditors contracted by the Sponsor may conduct an onsite audit visit (ICH Topic E6 Guideline for GCP, Section 1.6).

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

9.3 PATIENT INFORMED CONSENT

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

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

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

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

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

9.4 CONFIDENTIALITY/PATIENTS IDENTIFICATION

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

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

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

The data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Patients' personal data will be collected, processed and transmitted in a pseudonymised form.

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 Sponsor shall comply with General Data Protection Regulation (GDPR) (EU) 2016/679 effective from 25 May 2018 (repealing Directive 95/46/EC GDPR of 24 October 1995), and applicable regulations on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

9.5 CASE REPORT FORMS

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

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

The data collected in the CRF will be entered into the Sponsor' databases, which comply with General Data Protection Regulation (GDPR) (EU) 2016/679 effective from 25 May 2018 (repealing Directive 95/46/EC GDPR of 24 October 1995) on the protection of individuals with regard to the processing of personal data.

9.6 INSURANCE

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

9.7 RETENTION OF RECORDS

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

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

9.8 USE OF INFORMATION AND PUBLICATION

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

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

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

10. REFERENCES

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11. APPENDICES

APPENDIX 1: ECOG PERFORMANCE STATUS ASSESSMENT SCALE

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

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

APPENDIX 2: CONTRACEPTION AND PREGNANCY TESTING.

This document is based on the Heads of Medicines Agencies' Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials, published by the Clinical Trial Facilitation Group (CTFG) on 15 September 2014 and available at http://www.hma.eu/ctfg.html (accessed 30 July 2015).

A woman is considered of childbearing potential (WOCBP) following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Immediately after detecting a case of pregnancy in a patient, the decision on her continued participation in the clinical trial will be jointly taken by the patient, the Investigator and the Sponsor, with the patient's best interest in mind. A decision to continue the pregnancy will require immediate discontinuation any investigational medicinal product (IMP).

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy. Fertile male patients included in this study should refrain from fathering a child or donating sperm during the study and for four months following the last IMP dose. If they have WOCBP partners the male subject should use condom during treatment and for four months following the last IMP dose.

Highly effective birth control methods are:

1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1]:
    a. oral
    b. intravaginal
    c. transdermal
2. Progestogen-only hormonal contraception associated with inhibition of ovulation [1]:
    a. oral
    b. injectable
    c. implantable [2]
3. Intrauterine device (IUD) [2]
4. Intrauterine hormone-releasing system (IUS) [2]
5. Bilateral tubal occlusion [2]
6. Vasectomized partner [2,3]
7. Sexual abstinence [4]
8. Combinations of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method (see below).
[2] Contraception methods that are considered to have low user dependency.

[3] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
[4] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

Contraception methods with low user dependency should preferably be used, in particular when contraception is introduced as a result of participation in this trial. It cannot be excluded that the IMP may reduce exposure to substrates of CYP3A through enzyme induction; the efficacy of hormonal contraceptives may be reduced if co-administered with this drug.

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX 4: 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. MEASURABILITY OF TUMOR LESIONS AT BASELINE

1.1 Definitions

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

1.1.1 Measurable

Tumor Lesions:

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

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

Malignant Lymph Nodes:

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

1.1.2 Non-measurable

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

1.1.3 Special Considerations Regarding Lesion Measurability

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

Bone Lesions:

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

Cystic Lesions:

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

Lesions with Prior Local Treatment:

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

1.2. Specifications by Methods of Measurement

1.2.1 Measurement of Lesions

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

1.2.2 Method of Assessment

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

Clinical Lesions:

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

Chest X-Ray:

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

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

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in original article (Appendix II), when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans). More details concerning the use of both CT and MRI for assessment of objective tumor response evaluation are provided in the original article, Appendix II.

Ultrasound:

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

Endoscopy, Laparoscopy:

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

2. TUMOR RESPONSE EVALUATION

2.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall *tumor burden at baseline* and use this as a comparator for subsequent measurements.

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

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

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

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

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

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

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

record form (e.g., ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

2.3 Response Criteria

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

2.3.1 Evaluation of Target Lesions

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

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

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

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

2.3.2 Special Notes on the Assessment of Target Lesions

Lymph Nodes:

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

Target Lesions that Become ‘Too Small to Measure’:

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

default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that Split or Coalesce on Treatment:

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

2.3.3 Evaluation of Non-target Lesions

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

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions (Note: the appearance of one or more new lesions is also considered progression).

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

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

When the Patient Also Has Measurable Disease:

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

When the Patient Has only Non-measurable Disease:

This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal

progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. Some illustrative examples are shown in the original article, Figures 5 and 6 of Appendix II. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

2.3.5 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

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

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

2.4 Evaluation of Best Overall Response

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

2.4.1 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. **Table 1** provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 1. 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 2. Time point response: patients with non-target disease only.

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

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

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

2.4.2 Missing Assessments and Inevaluable Designation

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

2.4.3 Best Overall Response: All Time Points

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

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

Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best

response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

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

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally four weeks later). In this circumstance, the best overall response can be interpreted as in **Table 3**.

Table 3. Best overall response when confirmation of complete response (CR) and partial response (PR) is required.

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

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

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

APPENDIX 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

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

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

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

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

Preamble

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

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

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

General Principles

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

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

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

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

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

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

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

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

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

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

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

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

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

Risks, Burdens and Benefits

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

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

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

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

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

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

Vulnerable Groups and Individuals

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

    All vulnerable groups and individuals should receive specifically considered protection.

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

Scientific Requirements and Research Protocols

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

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

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

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

Research Ethics Committees

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

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

Privacy and Confidentiality

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

Informed Consent

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

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

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

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

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

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

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

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

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

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

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

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

Use of Placebo

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

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

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

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

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

Post-Trial Provisions

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

Research Registration and Publication and Dissemination of Results

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

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

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement

it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.