SPONSOR
Pharma Mar, S.A.
Avda de los Reyes, 1
Polígono Industrial "La Mina"
28770 Colmenar Viejo (Madrid), Spain
Phone: + 34 918 466 000
Fax: + 34 918 466 003

PharmaMar USA, Inc.
230 Park Avenue, suite 1000
New York, NY 10169
USA
Phone: +1 212 309 8737
Fax: +1 646 435 5846

CLINICAL TRIAL PROTOCOL

Phase III Randomized Clinical Trial of Lurbinectedin (PM01183)/Doxorubicin (DOX) versus Cyclophosphamide (CTX), Doxorubicin (DOX) and Vincristine (VCR) (CAV) or Topotecan as Treatment in Patients with Small-Cell Lung Cancer (SCLC) Who Failed One Prior Platinum-containing Line (ATLANTIS Trial

INVESTIGATIONAL MEDICINAL PRODUCTS: Lurbinectedin (Zepzelca®), and doxorubicin.

Protocol No.: PM1183-C-003-14

EudraCT No.: 2015-001641-89

NCT Code: NCT02566993

Protocol version 4.0: 3 May 2018

SPONSOR
Pharma Mar S.A.
Avda de los Reyes, 1
Polígono Industrial "La Mina"
28770 Colmenar Viejo (Madrid) Spain
Phone: + 34 91 846 6000
Fax:+ 34 91 846 6003

Pharma Mar USA, Inc.
205 East 42nd Street, suite 15003
New York, NY 10017, USA
Phone: + 1 646 880 4429
Fax : + 1 646 893 5856

CLINICAL TRIAL PROTOCOL

PM1183-C-003-14

Phase III Randomized Clinical Trial of Lurbinectedin (PM01183)/ Doxorubicin (DOX) *versus* Cyclophosphamide (CTX), Doxorubicin (DOX) and Vincristine (VCR) (CAV) or Topotecan as Treatment in Patients with Small-Cell Lung Cancer (SCLC) Who Failed One Prior Platinum-containing Line (ATLANTIS Trial)

INVESTIGATIONAL MEDICINAL PRODUCTS: Lurbinectedin (PM01183), doxorubicin, cyclophosphamide, vincristine and topotecan.

Protocol Code: PM1183-C-003-14

EudraCT No: 2015-001641-89

Protocol version 4.0 including amendments #1 dated 18 March 2016, #2 dated 3 October 2016 and #3 dated 3 May 2018.

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

Confidentiality statement

Information and data included in this protocol contain trade secrets and privileged or confidential information which is the property of the Sponsor. No person is authorized to make it public without written permission of the Sponsor. These restrictions on disclosure will apply equally to all future information supplied to you which is indicated as privileged or confidential. This material may be disclosed to and used by your staff and associates as it may be necessary to conduct the clinical study.

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SYNOPSIS

TITLE	**Phase III Randomized Clinical Trial of Lurbinectedin (PM01183)/Doxorubicin (DOX) *versus* Cyclophosphamide (CTX), Doxorubicin (DOX) and Vincristine (VCR) (CAV) or Topotecan as Treatment in Patients with Small-Cell Lung Cancer (SCLC) Who Failed One Prior Platinum-containing Line (ATLANTIS Trial).**
PROTOCOL CODE	PM1183-C-003-14
NUMBER OF SITES / TRIAL LOCATION	This is a multicenter study. A full list of Investigators will be available as a separate document.
STUDY OBJECTIVES	**Primary:** • To determine whether there is a difference in overall survival (OS) between lurbinectedin (PM01183)/doxorubicin (DOX) and a control arm consisting of best Investigator's choice between cyclophosphamide (CTX), doxorubicin (DOX) and vincristine (VCR) (CAV) or topotecan, as treatment in SCLC patients after failure of one prior platinum-containing line. **Secondary:** • To analyze: o Difference in OS between PM01183/DOX and CAV, in patients with CAV as best Investigator's choice. o OS/PFS in patients with and without baseline central nervous system (CNS) involvement. Subgroup analyses restricted to the sensitive and resistant populations (i.e., chemotherapy-free interval [CTFI] ≥90 days and CTFI <90 days) will also be performed. o Progression-free survival (PFS) by an Independent Review Committee (IRC). o Antitumor activity by IRC according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1. o Safety profile. **Tertiary:** • To analyze: o Mid- and long-term survival (OS at 12, 18 and 24 months, respectively). o Efficacy and safety profiles in the subgroups of the PM01183/DOX arm vs. CAV or topotecan. o PFS by Investigator's Assessment (IA). o Antitumor activity by IA according to the RECIST v.1.1. o Patient-reported outcomes (PRO).

	○ Pharmacokinetics (PK) of the combination in patients treated in the experimental arm (PM01183/DOX). ○ PK/pharmacodynamic (PDy) correlations in the experimental arm, if any. ○ Pharmacogenetics of known polymorphisms in patients treated in the experimental arm.
STUDY DESIGN	Multicenter, open-label, randomized, controlled phase III clinical trial to evaluate and compare the activity and safety of an experimental arm consisting of PM01183/DOX combination followed by PM01183 alone, if applicable *vs.* best Investigator's choice between CAV or topotecan as a control arm, in SCLC patients who failed one prior platinum-containing line but no more than one prior chemotherapy-containing line. Central randomization will be implemented; patients will be assigned to each arm at a 1:1 ratio. If the patient is randomized to the control arm, the assigned treatment will be based on the reported Investigator's preference between CAV or topotecan. Stratification will be performed according to the CTFI after first line [≥180 days (very sensitive, VS) *vs.* 90-179 days (sensitive; S) *vs.* <90 days (resistant; R)], Eastern Cooperative Oncology Group performance status (ECOG PS) (0 *vs.* 1-2), baseline CNS involvement *vs.* no involvement, prior immunotherapy against either programmed cell death protein-1 (PD-1) or programmed death ligand-1 (PD-L1) (Yes *vs.* No) and Investigator's preference (best Investigator's choice prior to randomization) between topotecan and CAV. An Independent Review Committee (IRC), blinded to the treatment assigned to the patients, will determine the best patient response and assign the date of objective response or progression/censoring according to RECIST v.1.1. An Independent Data Monitoring Committee (IDMC) will oversee the conduct of the study. The IDMC should have access to unblinded efficacy and safety data throughout the trial to enable timely and informed judgments about risks and benefits. The primary endpoint of the trial is the overall survival (OS). Secondary endpoints comprise difference in OS between PM01183/DOX and CAV, in patients with CAV as best Investigator's choice; OS/PFS per RECIST v.1.1 in patients with and without baseline central nervous system (CNS) involvement; PFS per RECIST v.1.1 by an IRC; best antitumor response as per RECIST v.1.1 and duration of response (DR) (both assessed by IRC); and safety profile. Tertiary endpoints comprise mid- and long-term survival assessed by measuring OS at 12/18/24 months, PFS per RECIST v.1.1 by IA, best antitumor response as per RECIST v.1.1 and DR (both assessed by IA), PRO, subgroup analyses, PK, PK/PDy correlations, and pharmacogenetics. In order to evaluate the overall safety in both arms, an interim

	safety analysis is planned after the recruitment of 150 patients (i.e., ~75 patients into each arm). Recruitment will not be put on hold while the interim safety analysis is being performed. Efficacy parameters will not be formally analyzed in this interim evaluation. Further safety and efficacy analyses could be performed upon request from the IDMC. If any formal interim OS/PFS analysis is performed, unblinded only to the IDMC, a type I error correction according to the Lan and DeMets error spending function that corresponds to the O'Brien-Fleming boundary will be used, calculated during the interim analyses to preserve an overall (one-sided) 0.005 false positive error rate; if early termination does not occur, the alpha level of the final analysis will be chosen to preserve an overall (one-sided) 0.025 false positive error rate. Crossover is not allowed.
STUDY POPULATION	Adult SCLC patients with ECOG PS 0-2 who have failed one prior platinum-containing line but no more than one chemotherapy-containing line (re-challenge is not allowed) without symptomatic or progressing CNS involvement at randomization.
STUDY POPULATION **Inclusion criteria**	1) Voluntary written informed consent of the patient obtained before any study-specific procedure. 2) Adult patients aged ≥ 18 years. 3) Histologically or cytologically confirmed diagnosis of limited or extensive stage SCLC which failed one prior platinum-containing regimen and with a chemotherapy-free interval (CTFI, time from the last dose of first-line chemotherapy to the occurrence of progressive disease) ≥ 30 days. Small-cell carcinoma of unknown primary site with or without neuroendocrine features confirmed in histology test(s) performed on metastatic lesion(s) are eligible, if Ki-67/MIB-1 is expressed in >50% of tumor cells. 4) ECOG PS ≤ 2. 5) Adequate hematological, renal, metabolic and hepatic function in an assessment performed within 7 days (+ 3 day window) of randomization: a) Hemoglobin ≥ 9.0 g/dl [patients may have received prior red blood cell (RBC) transfusion, if clinically indicated]; absolute neutrophil count (ANC) ≥ 2.0 x 10^9/l, and platelet count ≥ 100 x 10^9/l. b) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 x upper limit of normal (ULN). c) Total bilirubin ≤ 1.5 x ULN or direct bilirubin ≤ ULN. d) Albumin ≥ 3.0 g/dl. e) Calculated creatinine clearance (CrCL) ≥ 30 ml/minute

	(using Cockcroft and Gault's formula). f) Left ventricular ejection fraction (LVEF) by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan within normal range (according to institutional standards). g) Creatine phosphokinase (CPK) ≤ 2.5 x ULN (≤ 5.0 x ULN is acceptable if elevation is disease-related). 6) At least three weeks since last prior anticancer treatment and recovery to grade ≤ 1 from any adverse event (AE) related to previous anticancer treatment (excluding sensory neuropathy, anemia, asthenia and alopecia, all grade ≤ 2) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v.4). 7) Prior radiotherapy (RT): At least four weeks since completion of whole-brain RT (WBRT), at least two weeks since completion of prophylactic cranial irradiation (PCI), and to any other site not previously specified. 8) Evidence of non-childbearing status for women of childbearing potential (WOCBP). WOCBP must agree to use a highly effective contraceptive measure up to six weeks after treatment discontinuation. Valid methods to determine the childbearing potential, adequate contraception and requirements for WOCBP partners are described in APPENDIX 2. Fertile male patients with WOCBP partners should use condoms during treatment and for four months following the last investigational medicinal product (IMP) dose.
Exclusion criteria	1) More than one prior chemotherapy-containing regimen (including patients re-challenged with same initial regimen). 2) Patients who never received any platinum-containing regimen for SCLC treatment. 3) Prior treatment with PM01183, topotecan or anthracyclines. 4) Limited-stage patients who are candidates for local or regional therapy, including PCI, thoracic RT or both, must have been offered that option and completed treatment or refused it prior to randomization. 5) Impending need for palliative RT or surgery for pathological fractures and/or for medullary compression within four weeks prior to randomization. 6) Symptomatic, or steroid-requiring, or progressing CNS disease involvement during at least four weeks prior to randomization (asymptomatic, non-progressing patients taking steroids in the process of already being tapered within two weeks prior to randomization are allowed). 7) Concomitant diseases/conditions:

	a) History (within one year prior to randomization) or presence of unstable angina, myocardial infarction, congestive heart failure or clinically significant valvular heart disease. b) Symptomatic or uncontrolled arrhythmia despite ongoing treatment. c) Patients with any immunodeficiency, including those known to be or have been infected by human immunodeficiency virus (HIV). d) Ongoing, treatment-requiring, non-neoplastic chronic liver disease of any origin. For hepatitis B, this includes positive tests for both Hepatitis B surface antigen (HBsAg) and quantitative Hepatitis B polymerase chain reaction (PCR). For hepatitis C, this includes positive tests for both Hepatitis C antibody and quantitative Hepatitis C PCR. e) Active infection or increased risk due to external drainages. f) Intermittent or continuous oxygen requirement within two weeks prior to randomization. Patients with confirmed or suspected diagnosis of diffuse interstitial lung disease (ILD) or pulmonary fibrosis. g) Patients with a second invasive malignancy treated with chemotherapy and/or RT. Patients with a previous malignancy that was completely resected with curative intention three or more years prior to randomization, and who has been continuously in remission since then will be permitted. h) Limitation of the patient's ability to comply with the treatment or to follow the protocol. i) Documented or suspected invasive fungal infections requiring systemic treatment within 12 weeks of randomization. 8) Pregnant or breast feeding women.
EXPECTED NUMBER OF PATIENTS	Approximately 600 patients with SCLC for whom one prior platinum-containing chemotherapy line failed will be stratified and randomized at a 1:1 ratio over 24 months (~25 patients/month). In order to evaluate the overall safety in both arms, an interim safety analysis is planned after the recruitment of 150 patients (i.e., ~75 patients into each arm). Recruitment will not be put on hold while the analysis is being performed. Further safety and efficacy analyses could be performed upon request from the IDMC.
REPLACEMENT OF PATIENTS	No patients will be replaced. All efficacy analyses will be done on an intention-to-treat (ITT) basis.

<table>
<tr>
<td>STUDY DRUGS FORMULATION</td>
<td>
<u>EXPERIMENTAL ARM:</u>

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

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

The full composition of the PM01183 4-mg vials and the reconstituted solution per ml is shown in Table 1.

Table 1. Composition of lurbinectedin (PM01183) vials.
<table>
<tr><th>Component</th><th>Concentration/vial</th><th>Concentration/vial after reconstitution</th></tr>
<tr><td>PM01183</td><td>4.0 mg</td><td>0.5 mg/ml</td></tr>
<tr><td>Sucrose</td><td>800 mg</td><td>100 mg/ml</td></tr>
<tr><td>Lactic acid</td><td>22.08 mg</td><td>2.76 mg/ml</td></tr>
<tr><td>Sodium hydroxide</td><td>5.12 mg</td><td>0.64 mg/ml</td></tr>
</table>

<u>Doxorubicin (DOX):</u>
Commercially available presentations of vials containing DOX will be provided as appropriate.

<u>CONTROL ARM:</u>

<u>Topotecan:</u>
Commercially available i.v. presentations of vials containing topotecan will be provided as appropriate.
<u>CAV:</u>

Cyclophosphamide (CTX): Commercially available presentations of vials containing CTX will be provided as appropriate.
Doxorubicin (DOX): Commercially available presentations of vials containing DOX will be provided as appropriate.
Vincristine (VCR): Commercially available presentations of vials containing VCR will be provided as appropriate.

</td>
</tr>
<tr>
<td>ROUTE OF ADMINISTRATION</td>
<td>
<u>EXPERIMENTAL ARM:</u>

<u>Doxorubicin</u>: i.v. through peripheral or central lines (according to local label), followed by
<u>PM01183:</u> i.v. infusion over one hour over a minimum of 100 ml dilution on 5% glucose or 0.9% sodium chloride (at

</td>
</tr>
</table>

	a fixed rate) via a central line (or a minimum of 250 ml dilution if a peripheral line is used). **CONTROL ARM:** • **Topotecan:** i.v. infusion daily through peripheral or central lines (according to local label), or • **CAV:** CTX i.v. through peripheral or central lines (according to local label), DOX i.v. through peripheral or central lines (according to local label), and VCR i.v. through peripheral or central lines (according to local label).
STARTING DOSES AND SCHEDULE	**EXPERIMENTAL ARM:** • **DOX** at 40.0 mg/m^2 on Day 1, followed by, • **PM01183** at 2.0 mg/m^2 on Day 1 q3wk (three weeks ± 48 hours = one treatment cycle). **Note:** in cycles with PK sampling, no more than ten minutes may pass between the end of DOX infusion and the start of PM01183 infusion. Up to a maximum of 10 cycles. Then, if applicable, DOX will be discontinued definitively and remaining patients will continue on maintenance until disease progression (PD), patient refusal or unacceptable toxicity despite applicable dose reductions, at: o PM01183 at 3.2 mg/m^2 on Day 1 q3wk. (if no more than one dose reduction applied while on combination therapy), or: o PM01183 at 2.6 mg/m^2 on Day 1 q3wk. (if more than one dose reduction applied while on combination therapy). **CONTROL ARM:** • **Topotecan:** o Topotecan at 1.50 mg/m^2 daily on Days 1-5 q3wk (three weeks ± 48 hours = one treatment cycle) for patients with calculated CrCL ≥ 60 ml/min. o Topotecan at 1.25 mg/m^2 daily on Days 1-5 q3wk (three weeks ± 48 hours = one treatment cycle) for patients with calculated CrCL between 40 and 59 ml/min. o Topotecan at 0.75 mg/m^2 daily on Days 1-5 q3wk (three weeks ± 48 hours = one treatment cycle) for patients with calculated CrCL between 30 and 39 ml/min. • **CAV:** o CTX at 1000 mg/m^2 on Day 1, o DOX at 45.0 mg/m^2 on Day 1, and o VCR at 2.0 mg **total flat dose** on Day 1 q3wk (three weeks ± 48 hours = one treatment cycle).

	Up to a maximum of 10 cycles **(Note: patients older than 70 years should not receive a total cumulative DOX dose of more than 400 mg/m^2).** Then, if applicable, DOX will be discontinued definitively and the remaining patients will continue on maintenance until PD, patient refusal or unacceptable toxicity despite applicable dose reductions. Patients who are experiencing grade 2 neuropathy before receiving a new CAV cycle will not receive any further VCR infusions until neuropathy resolution to grade 1 is documented. Any recurrence of grade 2 neuropathy during treatment will result in a definitive discontinuation of VCR. Doses in both arms, experimental and control, will be capped at a body surface area (BSA) of 2.0 m^2 for individuals exceeding this BSA value. Doses, except for VCR, will have to be recalculated for patients showing a ≥ 10% variation in total body weight from baseline or from last dose adjustment. PM01183 total doses in mg will be rounded to the first decimal, if necessary. DOX, CTX or topotecan total doses will be rounded, if applicable, according to institutional guidelines/standard practice.
PROPHYLACTIC MEDICATION	All patients, irrespectively of treatment arm will receive primary prophylaxis subcutaneously, with granulocyte colony-stimulating factors (G-CSF). Type, dose, and scheme to be used may vary according to institutional/standard practices or guidelines, if available. Nevertheless, a mandatory window of at least 24 hours and up to 72 hours must be allowed from the last dose of study treatment, until G-CSF prophylaxis is started. In addition, all patients will also receive standard antiemetic prophylaxis before each treatment infusion, as follows: • Intravenous corticosteroids (dexamethasone 8 mg, or equivalent, or at institutional antiemetic doses). • Intravenous serotonin (5-HT$_3$) antagonists (ondansetron 8 mg, or equivalent). If necessary, in addition to the above, the duration of treatment with 5-HT$_3$ antagonists and/or dexamethasone could be extended orally (if needed) (i.e. 4-8 mg/day for three consecutive days) and/or 10 mg of metoclopramide orally every eight hours could be added. For the purpose of safety evaluations, an optimal prophylaxis is defined as all the aforementioned allowed medications at their respectively maximum dose. Aprepitant or any other NK-1 antagonist or related Substance P-antagonists are forbidden in all patients allocated to the experimental arm.

CRITERIA FOR TREATMENT CONTINUATION

In order to be re-treated, or to start treatment if first dosing was extended beyond the first 72 hours after randomization, patients will have to fulfill the criteria defined in Table 2.

Table 2. Criteria for treatment continuation.

Variable	Topotecan or CAV (Day 1)	PM01183/DOX (Day 1), or PM01183 alone (Day 1) whenever is applicable
ECOG PS	≤ 2	≤ 2
ANC	≥ 1.5 x 10^9/l	≥ 1.5 x 10^9/l
Platelets	≥ 100 x 10^9/l	≥ 100 x 10^9/l
Hemoglobin [a]	≥ 9.0 g/dl	≥ 9.0 g/dl
Total bilirubin	≤ 1.5 x ULN [b], or direct bilirubin ≤ ULN	≤ 1.5 x ULN, or direct bilirubin ≤ ULN
Albumin	≥ 2.7 g/dl	≥ 2.7 g/dl
AST/ALT	≤ 3.0 x ULN	≤ 3.0 x ULN
CPK	-	Grade ≤ 1 (or ≤ 2 if disease-related grade ≤ 2 at baseline)
Calculated CrCL (Cockcroft and Gault's formula)	≥ 30 ml/min [c]	≥ 30 ml/min
LVEF *	* Patients assigned to CAV treatment: within normal limits and not > 10% decrease (by MUGA) or > 20% decrease (by ECHO) from baseline before Cycle 3, Cycle 6 and Cycle 9, and if DOX cumulative dose ≤ 405 mg/m^2	Within normal limits and not > 10% decrease (by MUGA) or > 20% decrease (by ECHO) from baseline before Cycle 3, Cycle 6 and Cycle 9, and if DOX cumulative dose ≤ 360 mg/m^2
Other non-hematological drug-related AEs (except increased AP, or grade 2 alopecia, asthenia, and not optimally treated nausea and/or vomiting) [d]	Grade ≤ 1	Grade ≤ 1

[a] Patients may receive PRBC transfusion and/or EPO treatment if clinically indicated to increase/maintain adequate hemoglobin levels.

[b] Patients assigned to CAV with total bilirubin between 1.25-1.5 x ULN or direct bilirubin ≥ ULN will receive a maximum of 1.5 mg of VCR.

[c] Patients with CrCL between 40 and 59 ml/min must be re-treated with 1.25 mg/m^2 of i.v. topotecan daily, and patients with CrCL between 30 and 39 ml/min must receive no more than 0.75 mg/m^2 of topotecan daily.

[d] Any grade accepted for increased AP.

Those patients who experience grade ≥ 2 neuropathy while receiving CAV will stop VCR exclusively until resolution to at least grade 1 and, if applicable, will have their VCR dose reduced to 1.5 mg/cycle subsequently after resolution. If grade ≥ 2 neuropathy re-occurs at any time, or if there is no resolution of the first episode to at least grade 1 after a minimum of four weeks of follow-up, VCR will be discontinued definitively.

AEs, adverse events; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AP, alkaline phosphatase; AST, aspartate aminotransferase; CAV, CTX DOX and VCR; CPK, creatine phosphokinase; CrCL, creatinine clearance; CTX, cyclophosphamide; DOX, doxorubicin; ECHO, echocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; EPO, erythropoietin; LVEF, left ventricular ejection fraction; MUGA, multiple-gated acquisition scan; PRBC, packed red blood cells; ULN, upper limit of normal; VCR, vincristine.

<table>
<tr><td></td><td>If a patient does not meet the requirements for treatment continuation on Day 1 of any cycle after Cycle 1, re-assessments will be performed periodically at intervals of at least 72 hours and treatment will be withheld until appropriate recovery, for a maximum of 22 days after the treatment due date. If there is no recovery after a 22-day delay, treatment must be discontinued and the EOT visit performed, except if objective clinical benefit is observed in tumor assessments, upon the Sponsor's agreement, in which case up to 15 additional days will be allowed to recover and meet the aforementioned requirements for treatment continuation.</td></tr>
<tr><td>DOSE REDUCTION</td><td>Patients who experience any grade ≥ 3 treatment-related non-hematological toxicity (according to the NCI-CTCAE v.4) or febrile neutropenia or neutropenic infection or sepsis, and/or grade 4 thrombocytopenia or neutropenia, or treatment-related dose delays of more than five days, or frequent shorter dose delays (or skipped infusions if on topotecan) may only continue treatment, after appropriate dose reduction (see Table 3).
Patients experiencing treatment-related non-optimally treated grade 3 nausea and/or vomiting, grade 3 fatigue/asthenia lasting < 3 days, grade 3 diarrhea lasting ≤ 2 days or not optimally treated, and/or non-clinically relevant isolated biochemical abnormalities (e.g. AP), may continue treatment at the same prior dose without dose reduction being applied, provided optimal concomitant treatment is given for the applicable toxicity.
Patients assigned to CAV treatment in the control arm with total bilirubin levels 1.25-1.5 x ULN or abnormally high direct bilirubin levels before the start of a new cycle will receive a maximum of 1.5 mg of VCR. Those patients assigned to CAV who experience grade ≥ 2 neuropathy will stop receiving VCR until resolution to at least grade 1. After resolution, treatment will be resumed at 1.5 mg of VCR; however, if there is re-occurrence of grade ≥ 2 neuropathy after re-introduction of VCR, or if there is no resolution of the first episode to at least grade 1 after a minimum of four weeks of follow-up, VCR will be discontinued definitively.
Table 3. Levels of dose reduction in each treatment arm.
<table>
<tr><th>Dose reduction</th><th colspan="3">Topotecan daily dose (q3wk) (mg/m^2)</th><th>CAV (q3wk)§</th><th>DOX/ PM01183 (q3wk) (mg/m^2)</th><th>PM01183 alone (q3wk) (mg/m^2)</th></tr>
<tr><td>1 (starting dose)</td><td>1.50[a]</td><td>1.25[b]</td><td>0.75[c, d]</td><td>CTX: 1000 mg/m^2
DOX: 45 mg/m^2
VCR: 2.0 mg FD</td><td>40 / 2.0</td><td>3.2</td></tr>
<tr><td>-1</td><td>1.25</td><td>1.00</td><td>NA</td><td>CTX: 750 mg/m^2
DOX: 45 mg/m^2
+/-VCR: 1.5 mg FD</td><td>30 / 2.0</td><td>2.6[e]</td></tr>
<tr><td>-2</td><td>1.00</td><td>0.75[d]</td><td>NA</td><td>CTX: 750 mg/m^2
DOX: 35 mg/m^2
+/-VCR: 1.5 mg FD</td><td>30 / 1.5</td><td>2.0</td></tr>
</table>
</td></tr>
</table>

All doses will be capped at a BSA of 2.0 m^2.
PM01183 total doses in mg will be rounded to the first decimal, if necessary. DOX and topotecan total doses will be rounded, if applicable, according to institutional guidelines/standard practice.
[§] Patients who continue maintenance treatment after DOX discontinuation beyond Cycle 10 will, under no circumstances, have their CTX dose reduced below 750 mg/m^2 or their VCR dose reduced below 1.5 mg FD (although VCR could be discontinued, if needed).
[a] Starting dose for patients treated with topotecan with calculated CrCL $\geq$ 60 ml/min.
[b] Starting dose for patients treated with topotecan with calculated CrCL of 40-59 ml/min.
[c] Starting dose for patients treated with topotecan with calculated CrCL of 30-39 ml/min.
[d] No dose reduction below 0.75 mg/m^2/day will be implemented under any circumstances.
[e] Starting dose for patients who had two prior dose reductions while on PM01183/DOX.
BSA, body surface area; CAV, CTX DOX and VCR; CrCL, creatinine clearance; CTX, cyclophosphamide; DOX, doxorubicin; FD, flat dose; mg, milligram; NA, not available; q3wk, every three weeks; VCR, vincristine.

Regardless of treatment arm, patients who experience any treatment-related grade 4 hypersensitivity and/or extravasations will permanently discontinue treatment.

Up to two dose reductions are allowed per patient, if needed, excluding those patients starting topotecan at 0.75 mg/m^2 or those starting PM01183 alone at 2.6 mg/m^2 after DOX discontinuation. Any patient who continues to experience treatment-related toxicity despite all applicable dose reductions, or who requires one after receiving topotecan at 0.75 mg/m^2, must stop treatment. Once the dose has been reduced for an individual patient, it will not be re-escalated under any circumstances.

Note: patients enrolled in the experimental arm (PM01183/DOX), or those assigned to CAV treatment in the control arm, who had one or no dose reductions while on the combination will discontinue DOX and remain on treatment from Cycle 11 onwards (or at any other time if DOX is discontinued earlier due to cardiac issues) with PM01183 alone at 3.2 mg/m^2 and may undergo up to two additional dose reductions, whereas those who had two dose reductions while on the combination will discontinue DOX and remain on treatment from Cycle 11 onwards (or at any other time if DOX is discontinued earlier due to cardiac issues) with PM01183 alone at 2.6 mg/m^2 and may undergo one additional dose reduction. Patients assigned to CAV treatment in the control arm may continue treatment after DOX discontinuation on Cycle 11 with CTX +/- VCR, either at 1000 mg/m^2/2.0 mg FD or at 750 mg/m^2/1.5 mg, respectively, as applicable. No individual dose reductions below CTX 750 mg/m^2 or VCR 1.5 mg FD are allowed. No single-agent PM01183 dose reduction below 2.0 mg/m^2 will be implemented under any circumstances.

Dose recalculations due to changes in BSA will not be considered dose reductions, as long as the targeted BSA dose remains unchanged.

ALLOWED MEDICATIONS/ THERAPIES	• Therapies for pre-existing and treatment-emergent medical conditions, including pain management and local management of mucositis/stomatitis. • Blood products and transfusions, as clinically indicated. • Bisphosphonates. • In case of nausea or vomiting, extended symptomatic treatment for emesis will be allowed. • Erythropoietin treatment according to the American Society of Clinical Oncology (ASCO) guidelines. • Low-molecular weight heparin (LMWH) and/or any other anticoagulants, as clinically indicated. • CNS irradiation if required, and/or limited field bone RT for pain control outside the thoracic wall. • Megestrol acetate for wasting syndrome.
PROHIBITED MEDICATIONS/ THERAPIES	• Concomitant administration of any other antineoplastic therapy. • Other investigational agents. • Immunosuppressive therapies other than corticosteroids for antiemetic prophylaxis or pain control, or low-dose replacement in patients requiring this approach. • Aprepitant and other NK-1 antagonists (for patients allocated to the experimental arm). • Concomitant RT other than CNS irradiation, or limited-field RT for pain control.
DRUG-DRUG INTERACTIONS	*In vitro* studies with human microsomes have shown that CYP3A4 is the major CYP isoform involved in the metabolism of PM01183, followed by CYP2E1, CYP2D6 and CYP2C9. The estimated contribution of the other CYP isoenzymes to the PM01183 metabolism is considered to be negligible. Therefore, concomitant drugs which induce or inhibit any of these cytochromes, especially CYP3A4, should be carefully monitored or avoided, whenever is possible. A potentially significant interaction with aprepitant is suggested by available phase II data from ovarian cancer patients and phase I data from the PM1183-A-008-13 study. PM01183 clearance was reduced by 50%, approximately, in the presence of aprepitant. Although all patients eventually recovered, the use of aprepitant is currently forbidden in all phase II/III PM01183 studies. A recent analysis of PK data from the PM1183-A-003-10 trial found that PM01183 exposure (area under the curve, AUC) reduced DOX clearance slightly (from 45 l/h to 35 l/h; a 20% reduction) and more markedly doxorubicinol clearance (from 150 l/h to 75 l/h; a 50% reduction). A mechanistic explanation for this interaction is currently being studied. Taking into account these results, the DOX dose of 40.0 mg/m^2 used in the

	experimental arm in the present study is not expected to result in patient exposure to supratherapeutic levels of DOX or doxorubicinol.
EFFICACY EVALUATIONS	Antitumor activity will be assessed using the RECIST v.1.1 and followed until PD by the appropriate method [computed tomography (CT) scan or magnetic resonance imaging (MRI)]. Irrespectively of treatment arm, radiological and clinical tumor assessment will be performed at baseline and every six weeks (± one week) after randomization until evidence of PD. A special effort will be made to continue follow-up and report tumor assessments in patients discontinuing the study treatment without progression by RECIST v.1.1. Adequate CNS imaging (contrast enhanced-CT or MRI, if applicable) will be performed at baseline to document any disease involvement. In the event of CNS involvement being found, this assessment will be repeated while on treatment, regardless of treatment arm; otherwise, it will only be repeated if clinically indicated. Irrespectively of treatment arm, patients with documented clinical benefit during treatment (either response or tumor shrinkage in target lesions and without clinical deterioration) may continue treatment while CNS irradiation is given, if appropriate. After radiological PD is documented or a new systemic antitumor therapy is started, patients will be followed for survival every three months (± two weeks) during the first 18 months after randomization, and then once every six months (± four weeks) until death or date of study termination, whichever occurs first. Once the whole recruitment is completed, the survival follow-up procedure will change: patients who discontinue treatment will be followed every three months according to a fixed calendar time (e.g., July, October, January, etc.) until death or study completion. For survival follow-up purposes, after radiological PD is documented or new therapy is started, a documented telephone call from the investigational sites will be adequate. The date of clinical and/or radiological PD and the date of death will be registered and documented as appropriate. Copies of CT scans, MRIs and any other documented means to evaluate tumor response or progression should be available for external radiological review by an IRC. The IRC will determine the patient's best response and assign the date of objective response or progression/censoring according to the RECIST v.1.1. In order to evaluate the overall safety in both arms, an interim safety analysis is planned when 150 patients are recruited (i.e., ~75 patients into each arm). Recruitment will not be put on hold while the interim safety analysis is being performed. Efficacy parameters will not be formally analyzed in this

	interim evaluation. Further safety and efficacy analyses could be performed upon request from the IDMC. If any formal interim OS/PFS analysis is performed, unblinded only to the IDMC, a type I error correction according to the Lan and DeMets error spending function that corresponds to the O'Brien-Fleming boundary will be used, calculated during the interim analyses to preserve an overall (one-sided) 0.005 false positive error rate; if early termination does not occur, the alpha level of the final analysis will be chosen to preserve an overall (one-sided) 0.025 false positive error rate.
SAFETY EVALUATIONS	Patients will be evaluable for safety if they have received any partial or complete treatment infusion. All AEs will be graded according to the NCI-CTCAE, v.4. Treatment delays, dose omissions (if applicable), dose reductions, and reason for treatment discontinuation will be monitored throughout the study. The safety profile of patients will be monitored throughout the treatment and up to 30 days after the last treatment infusion (end of treatment, EOT), or until the patient starts a new antitumor therapy or until the date of death, whichever occurs first. Any treatment-related AEs will be followed until recovery to at least grade 1 or stabilization of symptoms, whenever is possible. Any patient having any treatment-related grade ≥ 3 AEs should have appropriate tests re-assessed at least every 72 hours until recovery to at least grade 2. Safety evaluations will also be performed by the IDMC during the interim analysis, to be conducted when 150 patients are recruited (i.e., ~75 patients into each arm).
PATIENT-REPORTED OUTCOMES (PRO)	PRO will be assessed at baseline and every six weeks (± one week) from randomization until EOT, to determine if efficacy and side effects are accompanied by measurable changes in the quality of life of patients. The EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires will be used.
PHARMACOKINETIC EVALUATIONS	Blood samples (detailed in Table 4) will be collected from all patients enrolled exclusively in the experimental arm to analyze PM01183, DOX and its metabolite doxorubicinol. The samples will be obtained in two cycles: Cycle 1, and a second cycle between Cycles 2 and 4. The second cycle with PK sampling will be assigned once the patient has been randomized into the experimental arm.

	Table 4. Samples for pharmacokinetic evaluations. **Sample No.** | **Time** | **Acceptable window times** | **Sampling time: For DOX** | **Sampling time: For PM01183** **#1** | 0 | 1 to 5 min before treatment start | Predose | Preinfusion **#2** | 5 min | ± 2 min | 5 min after EOA | - **#3** | 1 h | ± 4 min | - | 5 min before EOI **#4** | 2 h | ± 10 min | 2 h after EOA | 1 h after EOI **#5** | 96 h | ± 24 h | 96 h after EOA | 95 h after EOI DOX, doxorubicin; EOA, end of administration; EOI, end of infusion; h, hour; min, minute.
PHARMACOGENETIC EVALUATIONS	**Pharmacogenetic sub-study:** To explore factors that may help to explain individual variability in main pharmacokinetic parameters, the presence or absence of germline mutations or polymorphisms will be analyzed in leukocyte DNA extracted from a blood sample obtained at any time during the study in the experimental arm.
STUDY ENDPOINTS	**Primary endpoint:** • **Overall survival (OS)** will be calculated from the date of randomization to the date of death (death event) or last contact (in this case, survival will be censored on that date). **Secondary endpoints:** • **Difference in OS between PM01183/DOX and CAV, in patients with CAV as best Investigator's choice.** • **Overall survival (OS)/progression-free survival (PFS) per RECIST v.1.1 in patients with and without baseline CNS involvement.** Subgroup analyses restricted to the sensitive and resistant populations will also be performed. • **Progression-free survival (PFS) by IRC** is defined as the time from the date of randomization to the date of documented progression per RECIST v.1.1 or death (regardless of the cause of death). If the patient receives further antitumor therapy or is lost to follow-up before PD, PFS will be censored at the date of last tumor assessment before the date of subsequent antitumor therapy. • **Best antitumor response by IRC** will be the best response obtained in any evaluation according to RECIST v.1.1. • **Duration of response (DR) by IRC** will be calculated from the date of first documentation of response per RECIST v.1.1 (complete or partial response, whichever comes first) to the date of documented PD or death. The censoring rules defined above for PFS will be used for DR. • **Treatment safety profile:** AEs, serious adverse events (SAEs) and laboratory abnormalities will be coded by the Medical Dictionary for Regulatory Activities (MedDRA), graded according to the NCI-CTCAE v.4 and analyzed.

	Dose reductions or delays required due to treatment-related AEs, and reasons for treatment discontinuations will also be assessed. **Tertiary endpoints:** • **Landmark analyses:** ○ **Mid- and long-term survival (OS at 12/18/24 months)** will be the Kaplan-Meier estimates of the probability of being alive at these time points. • **Subgroup analyses:** Subgroup analyses of efficacy and safety profiles in the PM01183/DOX arm *vs.* CAV based on Investigator's preference will be performed to isolate the contribution of PM01183 in the PM01183/DOX combination arm. Patients for whom the preference of the Investigator prior to randomization is CAV will be analyzed to test the combination of PM01183/DOX *vs.* CAV. Patients for whom the Investigator's preference is topotecan will also be analyzed independently. • **Progression-free survival (PFS) per RECIST v.1.1 by IA.** • **Best antitumor response by IA**. • **Duration of response (DR) by IA**. • **Patient-reported outcomes (PRO):** To measure the quality of life of patients, the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires will be analyzed at baseline and every six weeks (± one week) until EOT. • **Plasma pharmacokinetics (PK) of PM01183 and DOX** will be evaluated using a sparse sampling scheme in patients treated in the experimental arm. Details will be given in a population PK analysis plan, and results will be presented in a separate report. • **PK/PDy correlation:** Population PK correlations of drug exposure with safety and efficacy will be explored in the experimental arm. Details will be given in specific population PK/PDy analysis plans, and results will be presented in separate reports. • **Pharmacogenetics:** This analysis will be performed in patients treated in the experimental arm who specifically consent to participate in this sub-study. The presence or absence of known polymorphisms from a single sample collected at any time during the study will be assessed to explain the individual variability in the main PK parameters.
STATISTICAL METHODS	This phase III clinical trial is designed to determine whether there is a statistically significant difference in the OS between PM01183/DOX *vs.* CAV or topotecan as second-line treatment in SCLC patients after failure of one platinum-containing chemotherapy line. The primary study analysis (OS) will be performed by means

	of the stratified log-rank test selecting the actual CNS and CTFI values of the stratification factors on the intention-to-treat (ITT) population, defined as all randomized patients analyzed in the group where they were allocated. **Sample size calculation:** As mentioned above, this study is primarily designed to determine whether there is a statistically significant difference in the OS between patients treated with PM01183/DOX (experimental arm) and those treated with either CAV or topotecan (control arm). The prospective assumptions are a one-sided 2.5% significance level with at least 90% power to detect a 25% decrease in the risk of death to be achieved with the experimental arm (hazard ratio, HR=0.75). OS with either CAV or topotecan is expected to be 7.5 months. To obtain the required 508 events, approximately 600 patients with SCLC who failed one prior platinum-containing chemotherapy line will be stratified and randomized at a 1:1 ratio. With the aforementioned prospective assumptions, recruitment is foreseen to be completed in 24 months, and a total study duration for final OS analysis of about three and a half years is planned. The IDMC will oversee the conduct of the study. In order to evaluate the overall safety in both arms, an interim safety analysis is planned after the recruitment of 150 patients (i.e., ~75 patients into each arm). Recruitment will not be put on hold while the interim safety analysis is being performed. Efficacy parameters will not be formally analyzed in this interim evaluation. If formal interim analyses are conducted by the IDMC, a Lan and DeMets error spending function that corresponds to the O'Brien-Fleming boundary will be used, calculated during the interim analyses to preserve an overall (one-sided) 0.005 false positive error rate; if early termination does not occur, the alpha level of the final analysis will be chosen to preserve an overall (one-sided) 0.025 false positive error rate. **Randomization:** Central randomization will be implemented. Patients will be assigned to each group at a 1:1 ratio. If the patient is randomized to the control arm, the assigned treatment will be based on the reported Investigator's preference between CAV or topotecan. **Stratification:** Stratification will be performed according to the CTFI after first line [≥180 days (VS) *vs.* 90-179 days (S) *vs.* <90 days (R)], ECOG PS (0 *vs.* 1-2), baseline CNS involvement *vs.* no such involvement, and prior immunotherapy against either PD-1 or PD-L1 (Yes *vs.* No) and Investigator's preference (best Investigator's choice prior to randomization) between topotecan and CAV.

	Statistical analysis: Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. The study protocol contains a general description; specific details will be provided in the Statistical Analysis Plan. Frequency tables will be prepared for categorical variables, and continuous variables will be described by means of summary tables, which will include the median, mean, standard deviation, minimum, and maximum of each variable. **Efficacy analyses:** Time-to-event variables (OS, PFS and DR) and their set time estimates (e.g., OS 12/18/24) will be analyzed according to the Kaplan-Meier method. The stratified log-rank test (primary analysis) and the unstratified log-rank test on the ITT population will be used to compare the time-to-event variables. Cox regression will be used to calculate the risk reduction (OS, PFS and DR) and to evaluate the influence of the stratification variables and other potential prognostic factors on the time-to-event efficacy endpoints. Continuous variables that would have been categorized as discrete variables will also be investigated in the continuum range, and if the adjustment is better, then the continuous variable will be kept in the regression model.Counts and percentages, with their corresponding exact 95% confidence intervals, will be calculated for the binomial endpoints (e.g., response rate). The Fisher's exact test (univariate analyses) and logistic regressions will be used to compare the rates of the experimental arm and the control arm. Waterfall plots will be used to describe the best variation of the sum of target lesions during the treatment. **Safety analyses:** AEs, SAEs, deaths, laboratory evaluations, dose delays/omissions/reductions and study drug discontinuations due to AEs will be tabulated in a descriptive way. Counts and percentages will be used for categorical variables, and summary tables will be used for continuous variables. Exploratory Fisher's exact tests will be performed to compare grade 4 or grade 3/4 between treatment arms. Patients having any grade ≥3 laboratory abnormalities and/or treatment-related AEs must have the relevant tests re-assessed at least every 48-72 hours until recovery to at least grade 2 has been documented. **Patient-reported outcome (PRO) analyses:** PRO will be analyzed to determine if efficacy and side effects are accompanied by measurable changes. The analysis will be performed on summary scores of the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires, as well as on subscales, and individual symptoms. **Pharmacokinetic (PK) analyses:** Pharmacokinetic data will be listed in the population PK report for all patients treated with PM01183 and DOX in the

	experimental arm who had available concentrations of PM01183, DOX or doxorubicinol. Patients will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (e.g., improper handling of PK samples; incomplete administration of the study agent; missing time or dosing information). All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. All patients and samples excluded from the analysis will be retained in the dataset, but they will be flagged out and the criteria for exclusion documented. Population PK analysis of plasma concentration-time data of PM01183, DOX and doxorubicinol will be performed using non-linear mixed-effects modeling. Data may be combined with additional trials to support a relevant structural model. Available patient characteristics (demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan, and results will be presented in a separate report. **Pharmacokinetic/pharmacodynamic correlation:** Population PK data correlations of drug exposure with safety and efficacy parameters will be explored. Details will be given in specific population PK/PDy analysis plans, and results will be presented in separate reports. **Pharmacogenetic analyses:** The influence of genetic polymorphisms on main PK parameters will not be assessed or reported for individual clinical trials. Pharmacogenetic analysis will instead be performed using data aggregated from across the PM01183 clinical development program and presented in a separate report.
DURATION OF STUDY PERIOD (per patient)	Patients will be evaluated at scheduled visits in three study periods: • **Pre-treatment:** from signature of ICF to first infusion of the study treatment. • **Treatment:** from first infusion of the study treatment to the end of treatment (EOT). • **Follow-up:** after EOT, patients will be followed every four weeks until resolution or stabilization of all toxicities, if any. Patients who discontinue treatment regardless of the reason but without documented disease progression at the time of discontinuation will be followed every six weeks (± one week) until disease progression or start of a new antitumor therapy, death or until the date of study termination (clinical cutoff), whichever occurs first. After disease progression is documented or a new antitumor therapy is started, patients will be followed every three months (± two weeks) during the first 18 months after randomization, and then once every six months (± four weeks) until death of any cause or date of

	study termination, whichever occurs first. Once the whole recruitment is completed, the survival follow-up procedure will change: patients who discontinue treatment will be followed every three months according to a fixed calendar time (e.g., July, October, January, etc.) until death or study completion. Patients will be considered to be **on-study** from the signature of the ICF to the end of the follow-up period. Patients will be considered to be **on-treatment** for the duration of their treatment and until the day of EOT, immediately before the start of the follow-up period. This EOT is defined as 30 days after the day of the last study treatment infusion, unless the patient starts a new antitumor therapy or dies (whichever occurs first). An end-of-treatment visit (EOT visit) will be performed at 30 days (± 10 days) after the last study treatment administration, unless the patient starts any subsequent antitumor therapy, in which case the end-of-treatment visit should be performed immediately before the start of the new therapy, whenever possible. Patients will receive the study treatment(s) while it is considered to be in their best interest. Specifically, individual treatment of a given patient will continue until: • Documented disease progression (unless exclusively asymptomatic CNS involvement, in an otherwise responding patient). • Unacceptable toxicity after allowed/applicable dose reductions. • Intercurrent illness of sufficient magnitude to preclude safe continuation of the study. • Patient's refusal and/or non-compliance with study requirements. • A major protocol deviation that may affect the risk/benefit ratio for the participating patient.
PLANNED TRIAL PERIODS (for the whole study)	The total duration of the study will be approximately 42 months. **Planned start date** (first patient on study): 2Q2016. **Planned enrollment period**: approximately ~24 months. **Planned end-of-study date** (clinical cutoff): approximately 18 months after the last patient is randomized.

SCHEDULE OF ASSESSMENTS AND PROCEDURES

Assessments and procedures	Screening (days) *	Treatment (q3wk)						End of treatment (EOT) ‡	Follow-up
		Cycle 1		Cycle 2**		Further cycles**			
		D1	D10 †	D1	D10 †	D1	D10 †		
Written informed consent	Before any study procedure	-	-	-	-	-	-	-	-
Demographic data	-14 to 0	-	-	-	-	-	-	-	-
Medical and cancer history/baseline conditions	-14 to 0	-	-	-	-	-	-	-	-
Assessment of signs and symptoms	-7 to 0	-	-	-	-	-	-	-	-
Treatment (1)	NA	•	-	•	-	•	-	NA	-
Complete physical examination, including weight, height and BSA (2)	-7 to 0	-	-	•	-	•	-	•	-
ECOG PS	-7 to 0	-	-	•	-	•	-	•	-
Vital signs (heart rate, blood pressure, temperature)	-7 to 0	-	-	•	-	•	-	•	-
Hematology (3)	-7 to 0	-	• **(3)**	• **(3)**	• **(3)**	• **(3)**	Always if grade ≥ 3 hematological abnormalities or a dose modification occurred in the preceding cycle, and before the first cycle after DOX discontinuation (C11) in patients treated in the experimental arm, and in patients assigned to CAV in the control arm	• **(3)**	-
Biochemistry (3)	-7 to 0	-	• **(3)**	• **(3)**	• **(3)**	• **(3)**	Always if grade ≥ 3 non-hematological abnormalities or a dose modification occurred in the preceding cycle	• **(3)**	-
LVEF assessment (by MUGA or ECHO)	-14 to 0	• Experimental arm: repeat before Cycles 3, 6, 9 and 11 (first cycle after DOX discontinuation), and whenever clinically indicated due to suspicion of CHF • Control arm (topotecan): repeat whenever clinically indicated due to suspicion of CHF • Control arm (CAV): repeat before Cycles 3, 6, 9 and 11 (first cycle after DOX discontinuation), and whenever clinically indicated due to suspicion of CHF							-
Pregnancy test (if applicable) (4)	-7 to 0	-	-	•	-	•	-	•	-
ECG (5) (+ cardiac assessment, if required)	-7 to 0	• Experimental arm: repeat before Cycles 6 and 11 (first cycle after DOX discontinuation), and whenever clinically indicated • Control arm (topotecan): repeat whenever clinically indicated • Control arm (CAV): repeat before Cycles 6 and 11 (first cycle after DOX discontinuation), and whenever clinically indicated							-

Assessments and procedures	Screening (days) *	Treatment (q3wk)						End of treatment (EOT) ‡	Follow -up
		Cycle 1		Cycle 2**		Further cycles**			
		D1	D10 †	D1	D10 †	D1	D10 †		
Pharmacokinetics (experimental arm only, in Cycle 1 and in another cycle randomly between Cycle 2 and Cycle 4)	-	• (6)	-	• (6)	-	• (6)	-	-	-
Pharmacogenetics (polymorphisms), only if specific written informed consent is given (7)	One blood sample collected at any time during the study from patients treated in the experimental arm								-
Clinical and radiological tumor assessment (contrast enhanced helical CT-scan or MRI)	-14 to 0	Every 6 weeks (± one week) (from randomization)							• **(8)**
CNS radiological assessment (contrast enhanced CT-scan or MRI)	-14 to 0	Repeat in the event of baseline CNS involvement, and also if clinically indicated							-
Patient-reported outcomes questionnaires	-7 to 0	Every 6 weeks (± one week) (from randomization)							-
Survival information	NA	Throughout the "on-treatment period"							•
Concomitant therapies	-7 to 0	Throughout the "on-treatment period"							-
Adverse events	- §	Throughout the "on-treatment period"							• **(9)**

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

Day 0 = day of randomization. Treatment (Day 1 of Cycle 1) must start within 72 hours after randomization. Otherwise, all applicable assessments outside accepted windows must be repeated and eligibility criteria must be reassessed. Concomitant medications or signs and symptoms with onset or any change occurring between Day 0 and Day 1 of Cycle 1 must also be reported

* During screening, an additional 3-day window will be allowed for assessment of signs and symptoms, complete physical examination, ECOG PS, vital signs, laboratory procedures, pregnancy tests, ECG, patient-reported outcomes and concomitant therapies; and a 14-day window for the assessment of demographic data, medical and cancer history, LVEF, radiological procedures and tumor assessments. Standard of care procedures prior to consent may be used for this study.

** Cycle 2 and further cycles will be administered every three weeks (± 48 hours) if the patient fulfills all re-treatment criteria.

† A ±3-day window will be allowed for Day 10 assessments, if applicable.

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

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

During treatment, a 3-day window will be allowed for clinical assessments (disease-related signs and symptoms, ECOG PS, vital signs, weight, BSA, etc.), laboratory procedures, and pregnancy tests; a 7-day window for ECG assessments, radiological procedures, tumor assessments and patient-reported outcomes; a 14-day window for LVEF assessments; and a 10-day window for the assessments at EOT.

1. Treatment will consist of the following:
   - In the experimental arm: DOX as an i.v. infusion + PM01183 as a 1-hour i.v. infusion, both on Day 1 q3wk. Upon reaching 10 cycles of PM01183/DOX combination, non-progressing patients may continue treatment with PM01183 alone, at single-agent doses, on Day 1 q3wk.
   - In the control arm: topotecan as an i.v. infusion daily on Days 1-5 q3wk, or CAV on Day 1 q3wk. Upon reaching 10 cycles of the CAV combination, non-progressing patients may continue treatment with CTX +/- VCR, as applicable, on Day 1 q3wk.
2. Height and BSA, calculated using the DuBois formula, need to be measured at baseline only; then, BSA must be recalculated whenever a ≥10% variation in total body weight from baseline or from last dose adjustment occurs, before treatment administration in subsequent cycles.
3. **Any patient having any grade ≥ 3 laboratory abnormalities and/or treatment-related AEs must have the relevant tests re-assessed at least every 48-72 hours until recovery to at least grade 2 has been documented.**
4. Assessment of β-hCG only if the patient is a WOCBP. If abnormally elevated, an US should be performed in order to rule out a pregnancy. During the on-treatment period, testing should be repeated before every cycle (or, at least, monthly).
5. 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, with specialist assessment/judgment of further evaluation if appropriate.
6. A total of five blood samples will be collected for pharmacokinetic analyses of PM01183, DOX and its metabolite doxorubicinol: four on Day 1 (before treatment start, 5 min after DOX administration, 5 min before the end of PM01183 infusion, and 1 hour after the end of PM01183 infusion) and one on Day 5 (at 95 hours after the end of PM01183 infusion).
7. One blood sample will be collected at any time during the study from patients treated in the experimental arm.
8. Patients who have withdrawn from the study without PD documentation should undergo tumor assessment every six weeks (±

Assessments and procedures	Screening (days) *	Treatment (q3wk)						End of treatment (EOT) ‡	Follow -up
		Cycle 1		Cycle 2**		Further cycles**			
		D1	D10 †	D1	D10 †	D1	D10 †		

one week) until PD, start of a new antitumor therapy, death or date of study termination (clinical cutoff), whichever occurs first. After PD is documented or a new antitumor therapy is started, patients will be followed for survival every three months (± two weeks) during the first 18 months after randomization, and then once every six months (± four weeks) until death of any cause or date of study termination, whichever occurs first. Once the whole recruitment is completed, the survival follow-up procedure will change: patients who discontinue treatment will be followed every three months according to a fixed calendar time (e.g., July, October, January, etc.) until death or study completion.

9. Patients who have withdrawn from the study with a drug-related AE should be followed every four weeks until recovery or stabilization.

Hematology: Differential WBC counts, including absolute neutrophil and lymphocyte counts, platelet count and hemoglobin.
Biochemistry: Liver function test: ALT, AST, AP, total bilirubin (direct bilirubin if total is abnormally elevated); albumin, creatinine, CPK, glucose, calculated CrCL, serum electrolytes (Na^+, K^+, Ca^{++}), LDH, and CRP (mandatory at baseline; then to be repeated only if clinically indicated). In addition, AAGP will be evaluated exclusively in patients enrolled into the experimental arm, at baseline and on Day 1 of cycles with PK sampling.

AAGP, alpha-1 acid glycoprotein; AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BSA, body surface area; C, treatment cycle; CAV, CTX DOX and VCR; CHF, congestive heart failure; CPK, creatine phosphokinase; CrCL, creatinine clearance; CRP, C-reactive protein; CT, computed tomography; CTX, cyclophosphamide; D, day; DOX, doxorubicin; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group Performance Status; EOT, end of treatment; hCG, human chorionic gonadotropin; i.v., intravenous; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NA, not applicable; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, progressive disease; PS, performance status; q3wk, every three weeks; RECIST, Response Evaluation Criteria In Solid Tumors; SAE, serious adverse event; ULN, upper limit of normal; US, ultrasound; VCR, vincristine; WBC, white blood cells; WOCBP, woman of childbearing potential.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

5-HT$_3$	Serotonin
95% CI	95% Confidence Interval
ACE	Doxorubicin, Cyclophosphamide and Etoposide
AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUCR	Area Under the Curve Ratio
β-hCGs	Beta Subunit of Human Chorionic Gonadotropins
BSA	Body Surface Area
BSC	Best Supportive Care
C	Treatment Cycle
CAV	Cyclophosphamide, Doxorubicin and Vincristine
CDDP	Cisplatin
CE	Carboplatin and Etoposide
CEV	Cyclophosphamide, Epirubicin and Vincristine
CHF	Congestive Heart Failure
CHOP	Cyclophosphamide, Doxorubicin, Vincristine and Prednisone
C_{max}	Maximum Plasma Concentration
CI	Combination Index
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine Phosphokinase
CR	Complete Response
CrCL	Creatinine Clearance
CRF	Case Report Form
CRP	C-reactive Protein
CT	Computed Tomography scan
CTFI	Chemotherapy-free Interval
CTX	Cyclophosphamide
d/D	Day(s)
DLT	Dose-limiting Toxicity
DNA	Deoxyribonucleic Acid

DOX	Doxorubicin
DP	Drug Product
DR	Duration of Response
DSB	Double-strand Breaks
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EOA	End of Administration
EOI	End of Infusion
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
EP	Etoposide and Cisplatin
EPO	Erythropoietin
ES	Extensive-stage disease
FD	Flat Dose
FDA	U.S. Food and Drug Administration
FiM	First-in-man (study)
FN	Febrile Neutropenia
FUP	Follow-up
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-stimulating Factor
GMT	Greenwich Meridian Time
h	Hours
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio; Homologous Recombination
IA	Investigator's Assessment
IB	Investigator's Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICL	Interstrand Crosslink
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committees
IG_{50}	Concentration that Results in 50% of Cell Growth Inhibition
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product

INR	International Normalized Ratio
IP	Irinotecan and Cisplatin
IRB	Institutional Review Board
IRC	Independent Review Committee
IST	Investigator-sponsored Trial
ITT	Intention-to-treat
i.v.	Intravenous
LC-MS/MS	Liquid Chromatography/Mass Spectrometry/Mass Spectrometry
LDH	Lactate Dehydrogenase
LMWH	Low Molecular Weight Heparin
LS	Limited-stage disease
LVEF	Left Ventricular Ejection Fraction
MCD	Maximum Cumulative Dose
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mo	Months
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple-gated Acquisition Scan
NA	Not Applicable; Not Available
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NET	Neuroendocrine Tumor
NHL	Non-Hodgkin's Lymphoma
NIHS	National Institute of Health Sciences
NR	Not Reported
NSCLC	Non-small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
PBPK	Physiologically-based Pharmacokinetic
PCI	Prophylactic Cranial Irradiation
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PD-1	Programmed Cell Death Protein-1
PD-L1	Programmed Death Ligand-1
PDy	Pharmacodynamic(s)
PFS	Progression-free Survival
PhV	Pharmacovigilance
PK	Pharmacokinetic(s)

PR	Partial Response
PRBC	Packed Red Blood Cells
PRE TT	Pre-treatment
PRO	Patient-reported Outcomes
q3wk	Every Three Weeks
Qdx5x2	Two cycles of Five Daily Doses
Q7dx3	Three Consecutive Weekly Doses (D-0, 7, 14)
R	Resistant
RBC(s)	Red Blood Cell(s)
RD	Recommended Dose
RECIST	Response Evaluation Criteria In Solid Tumors
RT	Radiotherapy
S	Sensitive
SAE(s)	Serious Adverse Event(s)
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion
STS	Soft Tissue Sarcoma
T/C	Treatment/Control
TCD	Total Cumulative Dose
TC-NER	Transcription-Coupled Nucleotide Excision Repair
TGD	Tumor Growth Delay
TOPO II	Topoisomerase II
TT	Treatment
TTP	Time to Progression
Uk	Unknown
ULN	Upper Limit of Normal
U.S.	United States of America
US	Ultrasound
VCR	Vincristine
VS	Very Sensitive
WBC	White Blood Cells
WBRT	Whole Brain Radiotherapy
wk	Week(s)
WMA	World Medical Association
WOCBP	Women Of Childbearing Potential

1. INTRODUCTION

1.1 SMALL CELL LUNG CANCER

Lung cancer is the most deadly cancer in Western countries, and despite recent advances in diagnosis, staging and evolving treatments, it remains the top-listed cause of cancer-related mortality [1]. In 2013, it caused approximately 160,000 deaths in the United States (U.S.) alone [2]. Small cell lung cancer (SCLC) constitutes approximately 13% of all cases. SCLC is a unique disease that is distinct from non-small cell lung cancer (NSCLC), with histological features of neuroendocrine differentiation [3]. Its natural history of aggressive clinical behavior with early metastatic potential and wide dissemination at diagnosis carries the worst prognosis among all lung cancer subtypes. SCLC is intimately related to tobacco use; restrictive policies implemented during the last decades regarding tobacco consumption in the US had led to a sharp decline in incidence, from above 20% of lung cases in the 1970s [4].

Traditionally, the staging of SCLC separated those patients with limited-stage (LS) disease (with disease confined to thorax) from patients with extensive-stage (ES) disease (with disease showing involvement beyond the thorax). Approximately, 20% of all SCLC patients may present with central nervous system (CNS) metastases, and up to 30% with bony and/or bone marrow involvement [5]. Therefore, the surgical management option is only restricted to diagnostic purposes or individual patients, not even those with limited-stage only because of potential occult metastases.

SCLC typically shows high chemosensitivity, closer to what is commonly observed in non-Hodgkin lymphoma (NHL) patients, compared with other solid tumors. Unfortunately, this chemosensitivity is also typically short-lasting, as eventually resistance emerges. These features led to multiple-agent combination chemotherapy being used upfront as a strategy to improve outcome. Since the late 1980s, platinum-based chemotherapy remains the mainstay of therapy in both stages. Roth et al. [6] compared EP [etoposide + cisplatin (CDDP)] to an anthracycline-containing regimen closely related to the cyclophosphamide (CTX), doxorubicin (DOX), vincristine (VCR) and prednisone (CHOP) combination used in aggressive lymphomas but without prednisone, CAV (CTX + DOX + VCR). No superiority was found in patients with ES disease. However, in another trial [7] in patients with LS disease, EP showed a higher median overall survival (OS) (14.5 *vs.* 9.7 months; p=0.0001) compared to CEV (epirubicin instead of DOX). In ES disease, the results did not reach statistical significance although a trend was noted (8.4 *vs.* 6.5 months; p=0.21). Investigators from the European Organization for Research and Treatment of Cancer (EORTC) [8] also compared EP to another DOX-containing regimen also used in lymphomas: the ACE (DOX, CTX and etoposide). Results regarding overall response rate (ORR) and 1-year survival rates were as follows: 77% *vs.* 72%, and 38% *vs.* 34%, respectively. However, the significant higher proportion of grade 3/4 neutropenia and infections with ACE (90% *vs.* 73% and 57 *vs.* 29%; p=0.005) supported the choice of EP as a standard first-line therapy. More recently, a metaanalysis of several first-line trials [9] showed equivalence between carboplatin and CDDP, when combined with etoposide; therefore, the EP and CP regimens might be interchangeable, and the different safety profile of each of these regimens can be adapted to a patient's particular situation. In addition to chemotherapy, patients with LS disease may benefit from regional radiotherapy (RT) as well as those without CNS involvement at diagnosis benefit from prophylactic cranial irradiation (PCI) [10]. Stage at diagnosis remains an important prognostic factor

regarding likelihood of complete responses and OS [11]. Patients with LS have a median OS of approximately 16 months compared to only 7-8 months in patients with ES at diagnosis.

Despite initial responses in up to 80% of patients, almost all patients will ultimately relapse/progress and die due to SCLC. Median- or long-term survivorship is extremely rare in this disease, with 5-year survival rates usually below 2-5% [12]. Investigational approaches, including alternating regimens without cross-resistance, maintenance therapy or chemotherapy intensification with colony-stimulating factor support did not show any improvement compared with standard EP or carboplatin and etoposide (CE) treatment for 4-6 cycles initially, and have not been widely used in SCLC patients [13, 14]. In Western countries, randomized trials aiming to improve results over EP (or CE) have repeatedly failed to show any improvement [15]. In Japan, however, results with irinotecan replacing the etoposide (i.e. IP *vs*. EP) showed an improved progression-free survival (PFS) and OS (6.9 *vs*.4.8 months; p=0.003 and 12.8 *vs*. 9.4 months; p=0.002, respectively) as well as a 2-year survival rate of 19.5% for IP compared to only 5.2% when given as first-line treatment [16]. Unfortunately, these results were not reproducible in two large US randomized studies in non-Japanese patients [17].

Patient outcome after failure of first-line treatment usually depends on chemotherapy-free interval (CTFI) until progressive disease (PD) occurs. Exploratory small phase II studies showed that the ORR to subsequent therapies like paclitaxel, ifosfamide, gemcitabine [18], carboplatin or others is markedly dependent on this CTFI [19, 20]. Patients somewhat arbitrarily are usually categorized as resistant (R) if relapse occurs within less than 90 days from the last chemotherapy (usually also including refractory patients with a CTFI of 0 days), or as sensitive (S) if relapse occurs with a CTFI of 90 days or more. Usually ORRs in the range of 0-5% are reported for R patients, while ORRs of 18-40% are commonly observed in S patients [21]. Of note, patients relapsing at six months or more after the end of the initial platinum-based treatment might especially benefit from re-challenging with the same treatment, with ORRs of as much as 65% being reported in some series/studies [22]. Hence, this is an option for this very selected population, although not universally accepted.

Available options after failure of first-line EP/CE in Western countries for both S and R patients are very limited. In fact, in Western countries regulatory approval is available only for topotecan, either as a standard intravenous (i.v.) formulation, or more recently for an oral formulation that has shown similar results in patients with decreased Eastern Cooperative Oncology Group performance status (ECOG PS) scores [23]. Standard topotecan was originally approved based on results from Von Pawel et al. [24] where 211 patients were randomized and similar results compared to CAV were observed regarding antitumor activity (ORR: 24.3% *vs.* 18.3%, p=0.285; time-to-progression (TTP): 13.3 *vs.* 12.3 weeks, p=0.552; OS: 25.0 *vs.* 24.7 weeks, p=0.795) in a selected second-line patient population that excluded refractory patients and those progressing or relapsing within 60 days of initial therapy. In this study, topotecan was associated with significantly less grade 4 neutropenia and better patient symptom improvement, but with worst grade 4 thrombocytopenia and grade 3/4 anemia than CAV. It should be noted that, even though the study was not originally designed as a non-inferiority trial (to demonstrate that topotecan was not inferior to CAV in terms of response rate and duration), the lack of any statistically significant difference between topotecan and CAV for any of the major efficacy parameters evaluated as primary endpoints led to the initial regulatory approval of topotecan in the U.S. and most European countries. This study was published in 1999; unfortunately, since then no other treatments have shown any

improvement over topotecan or CAV in this setting despite some recent spectacular advances in the treatment of most other solid tumors. It seems that relapsed SCLC reflects the last frontier, representing a truly unmet medical need in which no significant improvement over a dismal median OS of around six months has been achieved for the last 30 years. Almost every single randomized trial done in this setting has failed. More recently [25], amrubicin, which has been approved in Japan as second-line treatment in SCLC, failed to improve results over standard topotecan in 637 patients randomized 2:1 (median OS: 7.5 *vs.* 7.8 months, respectively; p=0.170). Nevertheless, it showed an improved ORR of 31.1% over 16.9% (p<0.001) and a marginal improvement in PFS of 4.1 *vs.* 3.5 months, respectively (p<0.018). Active or rapidly progressing patients with CNS involvement, and very symptomatic patients with poor ECOG PS scores or especially frail with extensive bone involvement are usually excluded from clinical trials and are only offered best supportive care (BSC) or sometimes oral topotecan, because treatment-associated toxicity is not negligible in this situation and, as already mentioned, clinical benefit is often not a realistic goal. Comorbidities usually include those related to baseline conditions such as long exposure to tobacco [chronic obstructive pulmonary disease (COPD) and/or vascular disease], age, and some related to prior treatments such as prior mediastinal and/or extensive irradiation, cisplatin-induced neuropathy or nephropathy. Finally, tumor-related paraneoplastic syndromes are very often associated with SCLC due to its neuroendocrine features, such as syndrome of inappropriate antidiuretic hormone secretion (SIADH), Cushing's disease, malignant hypercalcemia, hyperviscosity syndrome related to polycythemia, Raynaud's phenomena or thrombophlebitis, etc. These comorbidities sometimes conspire to make SCLC patients poor candidates for clinical trials.

Table 1. Efficacy results of selected salvage chemotherapy in relapsed SCLC patients.

Study (reference)	N	Treatment arms	ORR (%)	TTP (mo)	OS (mo)
Von Pawel *et al.* 2014 [25]	637	Amrubicin (n=424)	31.1	4.1	7.5
		Topotecan (n=213)	16.9	3.5	7.8
O'Brien *et al.* 2006 [23]	141	Topotecan (n=71)	7	3.8	6.0
		BSC (n=70)	NR	NR	3.2
Joos *et al*. 2004 [26]	93	Paclitaxel	20	3.0	4.0
Ando *et al.* 2004 [27]	25	IP	80	3.6	7.9
Masters *et al.* 2003 [18]	42	Gemcitabine	12	NR	7.1
Von Pawel *et al.* 1999 [24]	211	Topotecan (n=104)	24.3	3.1	5.8
		CAV (n=107)	18.3	2.8	5.7
Lopez *et al.* 1985 [28]	30	EP	27	NR	3.7

BSC, best supportive care; CAV, CTX DOX and VCR; CTX, cyclophosphamide; DOX, doxorubicin; EP, etoposide and cisplatin; IP, irinotecan and cisplatin; mo, months; NR, not reported; ORR, overall response rate; OS, overall survival; TTP, time to progression; VCR, vincristine.

As shown in Table 1, most single agents and combinations tested in this setting have shown ORRs within the 20-30% range: Median TTP is typically around 3.5 months, which unfortunately leads to death occurring within one to three months after disease progression. Available therapies beyond second line are exploratory, and usually applicable only under exceptional circumstances, because most patients do not reach the option for additional treatment(s).

1.2 INFORMATION ON THE STUDY DRUGS

1.2.1 Lurbinectedin (PM01183)

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

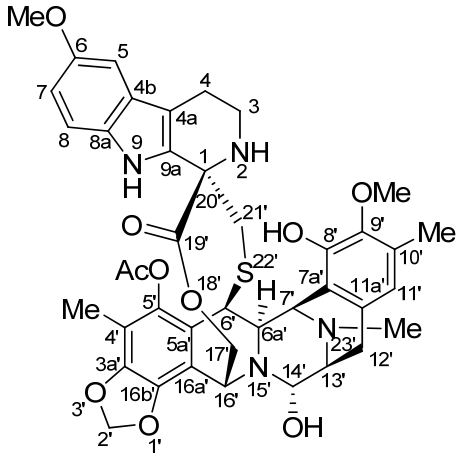
1.2.1.1 *Name and Chemical Information*

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

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

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

Figure 1. Molecular formula of lurbinectedin (PM01183).



1.2.1.2 *Non-clinical Data*

PM01183 contains a pentacyclic skeleton composed of two fused tetrahydroisoquinoline rings with an additional tetrahydro β-carboline moiety. The pentacyclic skeleton is mostly responsible for DNA minor groove recognition and binding. PM01183 reacts with the exocyclic amino group of guanines in the minor groove of DNA forming a covalent bond. PM01183 preferentially binds the following triplet of bases: AGC > CGG > TGG > AGG (the middle guanine being the site for covalent adducts formation) [29]. The resulting adduct is additionally stabilized through the establishment of van der Waals interactions and one or more hydrogen bonds with neighboring nucleotides in the opposite strand of the DNA double helix, thus creating the equivalent to a functional interstrand crosslink (ICL). The additional tetrahydro β-carboline moiety protrudes from the DNA minor groove and could be interacting directly with specific factors involved in DNA repair and transcription pathways.

PM01183 induces a rapid and massive degradation of transcribing RNA Pol II in several human tumor cell lines [30]. Lurbinectedin-mediated RNA Pol II degradation was abrogated in the presence of the transcriptional inhibitor DRB or the proteasome

inhibitor MG132, indicating that it is dependent on active transcription and the presence of functional proteasome machinery. In addition, the effect of lurbinectedin on RNA Pol II was dependent on the presence of a functional Transcription-Coupled Nucleotide Excision Repair (TC NER) repair system. These results suggest that RNA Pol II degradation mediated by lurbinectedin is dependent on transcription, proteasome and TC NER.

The resolution of functional ICLs is known to occur through the coordinated action of multiple DNA repair pathways, including homologous recombination (HR), a process that gives rise to double-strand breaks (DSBs). PM01183 treatment at nanomolar concentrations does indeed give rise to a high proportion of DSB-positive tumor cells with abundant γ-H2AX foci per cell [31]. Moreover, PM01183 induces a delayed progression of the S-phase and a G2/M arrest at both low and high nanomolar concentrations. Altogether these findings indicate that some of the PM01183-DNA adducts are eventually transformed into DSB inducing apoptosis. Of note, PM01183 is more active against HR-deficient cell lines [32].

On the other hand, PM01183 is able to interfere with the TC-NER machinery thereby attenuating the repair of specific NER substrates [33]. It is possible that the additional tetrahydro β-carboline moiety present in PM01183 interacts with TC-NER factors and could interfere with the repair mechanism. In fact, it was recently found that PM01183 was less potent in NER deficient cells compared with NER-proficient cells indicating that this compound could be also targeting TC-NER-dependent DNA repair. Resistance to DNA alkylators and platinum regimens is often accompanied by increased NER activity indicating that these tumor cells could be particularly sensitive to PM01183.In this sense, PM01183 show unchanged or even enhanced activity towards two cisplatin resistant ovarian carcinoma cell lines and oxaliplatin-resistant colon carcinoma cell lines.

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

The antineoplastic *in vitro* activity of PM01183 was evaluated in a panel of solid tumor cell lines (some of which are shown in Table 2), which were exposed to a range of PM01183 concentrations for 72 hours and then assayed for viability by a MTT short-term assay [34].

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

Tumor	**Cell line**	**IG_{50} (M)**
Breast	BT-474	$1.3 \cdot 10^{-9}$
	MDA-MB-231	$3.5 \cdot 10^{-9}$
	MCF-7	$1.7 \cdot 10^{-9}$
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	$9.8 \cdot 10^{-9}$

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, lung, bladder and ovarian (Table 3). The resulting tumor susceptibility was analyzed in xenografts grown in athymic mice, when unformulated PM01183 was administered at the rodent maximum tolerated dose [0.3 mg/kg (0.9 mg/m^2)] as single bolus 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 xenografts [35].

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

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

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

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 [36-40]. 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) [41].

Combination of PM01183 and Doxorubicin

The *in vivo* antitumor activity of PM01183 administered alone and in combination with DOX was investigated in mice bearing A2780 xenografted tumors [42]. Treatments administered were: i) placebo; ii) PM01183 at four different dose levels, i.e. the maximum tolerated dose (MTD) (0.180 mg/kg), 0.75·MTD, 0.5·MTD and 0.25·MTD; iii) DOX at four different dose levels, MTD (8 mg/kg), 0.75·MTD, 0.5·MTD and 0.25·MTD; and, iv) PM01183/DOX, administered with the combination at (1+1), (0.75+0.75), (0.50+0.50) and (0.25+0.25) of their respective MTDs. DOX was found to induce modest and dose-dependent antitumor activity in A2780-bearing animals; tumors were significantly ($p<0.05$) smaller with DOX than with placebo in all groups, except at the lowest dose level. The highest-dosed cohort also showed modest tumor growth delay (TGD), which was calculated as 90.0%. Single therapy of PM01183 in mice bearing A2780 xenografts also resulted in very modest though dose-dependent antitumor activity. Nevertheless, the combination of PM01183 and DOX showed a strong and dose-dependent antitumor activity: all groups of animals treated with the combination (except the lower) showed a highly significant ($p < 0.01$) reduction of tumor volume compared to placebo-treated animals. Of note, the group treated at (1+1)·MTD experienced a TGD of 184.0%. The antitumor effect induced by any treatment (single-agent or combination) was analyzed using the median-effect principle [43]. The results suggested a synergistic combination index (CI), with values ≤ 1, in mice bearing ovarian (A2780) xenografted tumors.

1.2.1.3 *Clinical Data*

The clinical development program of PM01183 was started in March 2009. Until 2016, this program comprises three single-agent phase I studies (two in solid tumors and one in acute adult leukemia/myelodysplastic syndrome patients); five combination phase Ib studies with gemcitabine, capecitabine, DOX, cisplatin, or paclitaxel with or without bevacizumab in patients with selected advanced solid tumors; five phase II studies (one as single agent or in combination with gemcitabine as second-line therapy in advanced NSCLC, and four as single agent in second-line pancreatic cancer, in BRCA-mutated or BRCA-unselected metastatic breast cancer, in platinum-resistant/refractory ovarian cancer, and in selected advanced solid tumors); one single-agent phase III study in platinum-resistant ovarian cancer trial; and two investigator-sponsored trials (ISTs) with PM01183 alone or in combination with DOX or gemcitabine in soft tissue sarcoma, and in combination with olaparib in advanced solid tumors. Until 15 January 2016, 932 patients have been included in PM01183 clinical studies and 802 have been treated with PM01183-containing therapy: 440 in phase I trials, 267 in phase II trials, 63 in one phase III trial, and 32 in ISTs.

PM1183-A-001-08 Phase I Study

The first-in-man study (FiM) (PM1183-A-001-08) explored PM01183 administered as a 1-hour i.v. infusion every three weeks (q3wk) in patients with solid tumors. The recommended dose (RD) was established at 4.0 mg/m^2 q3wk or as an equivalent flat dose (FD) of 7.0 mg q3wk [44]. PM01183 clearance was not found to be related to body surface area (BSA) at the time, and thus the patients treated at the RD expansion cohort were treated with the FD. 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 required at the RD to prevent or ameliorate nausea and 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 FiM study. Neutropenia was predictable and short-lasting, and rarely caused treatment delays. With the schedule used in the FiM study (Day 1, q3wk) nadir occurred during the second week (median was Day 13, range: Day 10-Day 15). One of 15 patients treated at the RD had grade 4 thrombocytopenia [the only dose-limiting toxicity (DLT) at the RD]; no grade 3 cases were reported. No cases of febrile neutropenia occurred in this phase I study. Evidence of antitumor activity was observed at the RD as a proof-of-concept, including one confirmed partial response (PR) according to the Response Evaluation Criteria In Solid Tumors (RECIST) in a pretreated pancreatic cancer patient.

Selected Single-agent Phase II Studies

PM01183 has *in vitro* and *in vivo* anticancer activity in several platinum-sensitive but also in resistant ovarian cancer-derived cell lines (IGROV-1, OVA9, A2780 and IGROV-1/CDDP, OVA9-RT, A2780/CDDP) and in mice-bearing tumor xenografts (both platinum-sensitive and resistant). Thus, a controlled, phase II exploratory clinical trial (PM1183-B-002-11) was conducted to evaluate the activity and safety of PM01183 as a single agent in platinum-resistant/refractory advanced ovarian cancer. In the second stage of this study, 59 patients were stratified according to platinum resistance or refractoriness and randomized 1:1 to receive PM01183 at its single-agent RD of 7.0 mg FD q3wk or the control treatment, which was standard or weekly i.v. topotecan according to the Investigators' preference.

The primary efficacy endpoint of the study was the overall response rate (ORR), defined as the percentage of patients with a response, CR or PR, according to the RECIST v.1.1 or by Gynecologic Cancer Intergroup (GCIG) criteria (in patients with disease not measurable as per RECIST). Secondary endpoints included time-to-event variables (PFS and OS) and safety profile of PM01183. ORR was significantly better for PM01183: 23% *vs.* no responses in the topotecan arm. Ten of the 12 confirmed responses were obtained in patients with platinum-resistant disease (response rate=30% in this subpopulation). In addition, median PFS was significantly longer with PM01183 (3.9 months) than with topotecan (2.0 months). The difference in median PFS between the two treatment arms was higher in patients with platinum-resistant disease: 5.0 months (95% CI, 2.7-6.9 months) in the PM01183 arm *vs.*1.7 months (95% CI, 1.3-3.2 months) in the topotecan arm (HR: 0.34; log-rank test p=0.0018), thus confirming single-agent PM01183 activity in this specific subset of patients after platinum-containing therapy failure/resistance.

Additionally, there are three ongoing phase II trials: one with PM01183 as single agent in metastatic breast cancer patients with known BRCA1-2 germline mutations; one designed to establish or confirm the proof of concept of single-agent PM01183 anticancer activity in several difficult-to-treat tumors; and one randomized trial in NSCLC patients that is comparing docetaxel with PM01183 alone or in combination with gemcitabine as second-line therapy. One SCLC patient (regardless of treatment line) had been treated with single-agent PM01183 in these ongoing studies; this patient showed SD for less than four months and was still on treatment at cutoff (15 January 2016).

Pooled Phase II Safety Analysis

The dose and schedule initially evaluated in phase II studies with single-agent PM01183 were those determined in the FiM study (PM1183-A-001-08), i.e. 7.0 mg FD (4.0 mg/m^2) as a 1-hour infusion q3wk. This was changed to a BSA-based dose and was reduced by 20% to 3.2 mg/m^2 in order to limit severe myelosuppression, following the finding that occurrence of grade 3/4 neutropenia and thrombocytopenia could be related to BSA.

Available preliminary information on the adverse events (AEs) related to PM01183 and the laboratory abnormalities observed in phase II studies with single-agent PM01183 is shown below. This information is given separately for PM01183 administered at 7.0 mg FD and 3.2 mg/m^2.

Adverse Events Related to PM01183 Given as a Flat Dose of 7.0 mg

The following tables show the AEs related to PM01183 given at 7.0 mg FD to 183 patients in phase II studies PM1183-B-001-10, PM1183-B-002-10, PM1183-B-003-11 and PM1183-B-004-13.

Table 4. Adverse events related (or with unknown relationship) to single-agent PM01183 at 7.0 mg FD with a frequency of ≥ 2% from ongoing phase II trials (worst grade per patient).

AE SOC/MedDRA PT	NCI-CTCAE grade v 4.0				Total (n=183)
	1	2	3	4	
	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system disorders					
Febrile neutropenia	.	.	23 (12.6%)	9 (4.9%)	32 (17.5%)
Gastrointestinal disorders					
Abdominal pain	13 (7.1%)	3 (1.6%)	1 (0.5%)	.	17 (9.3%)
Constipation	22 (12.0%)	10 (5.5%)	.	.	32 (17.5%)
Diarrhea	18 (9.8%)	10 (5.5%)	.	.	28 (15.3%)
Nausea	60 (32.8%)	43 (23.5%)	9 (4.9%)	.	112 (61.2%)
Stomatitis	9 (4.9%)	5 (2.7%)	.	.	14 (7.7%)
Vomiting	42 (23.0%)	27 (14.8%)	8 (4.4%)	.	77 (42.1%)
General disorders and administration site conditions					
Edema peripheral	4 (2.2%)	1 (0.5%)	.	.	5 (2.7%)
Fatigue	40 (21.9%)	56 (30.6%)	30 (16.4%)	.	126 (68.9%)
Pyrexia	10 (5.5%)	1 (0.5%)	.	.	11 (6.0%)
Metabolism and nutrition disorders					
Decreased appetite	18 (9.8%)	12 (6.6%)	3 (1.6%)	.	33 (18.0%)
Hypomagnesemia	5 (2.7%)	.	.	.	5 (2.7%)
Nervous system disorders					
Dysgeusia	7 (3.8%)	.	.	.	7 (3.8%)
Headache	6 (3.3%)	1 (0.5%)	.	.	7 (3.8%)
Peripheral neuropathy	6 (3.3%)	3 (1.6%)	.	.	9 (4.9%)
Respiratory, thoracic and mediastinal disorders					
Dyspnea	5 (2.7%)	1 (0.5%)	2 (1.1%)	.	8 (4.4%)
Skin and subcutaneous tissue disorders					
Alopecia	7 (3.8%)	.	.	.	7 (3.8%)
Rash	3 (1.6%)	2 (1.1%)	.	.	5 (2.7%)
Vascular disorders					
Phlebitis	2 (1.1%)	5 (2.7%)	.	.	7 (3.8%)

AE, adverse event; FD, flat dose; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PT, preferred term; SOC, System Organ Class.

Table 5. Hematological and biochemical abnormalities with single-agent PM01183 at 7.0 mg FD in phase II trials, regardless of relationship (worst grade per patient).

	NCI-CTCAE grade v 4.0				Total (n=183)
	1	2	3	4	
	n (%)	n (%)	n (%)	n (%)	n (%)
Hematological abnormalities					
Anemia	54 (29.5%)	79 (43.2%)	40 (21.9%)	.	173 (94.5%)
Leukopenia (n=182)	14 (7.7%)	37 (20.3%)	60 (33.0%)	48 (26.4%)	159 (87.4%)
Lymphopenia (n=182)	30 (16.5%)	65 (35.7%)	44 (24.2%)	22 (12.1%)	161 (88.5%)
Neutropenia	4 (2.2%)	20 (10.9%)	39 (21.3%)	91 (49.7%)	154 (84.2%)
Thrombocytopenia	61 (33.3%)	22 (12.0%)	21 (11.5%)	32 (17.5%)	136 (74.3%)
Biochemical abnormalities					
ALT increased	76 (41.5%)	37 (20.2%)	37 (20.2%)	4 (2.2%)	154 (84.2%)
AP increased (n=180)	81 (45.0%)	23 (12.8%)	11 (6.1%)	.	115 (63.9%)
AST increased	96 (52.5%)	18 (9.8%)	16 (8.7%)	2 (1.1%)	132 (72.1%)
Bilirubin increased	25 (13.7%)	6 (3.3%)	2 (1.1%)	3 (1.6%)	36 (19.7%)
CPK increased (n=176)	12 (6.8%)	2 (1.1%)	.	1 (0.6%)	15 (8.5%)
Creatinine increased	124 (67.8%)	20 (10.9%)	8 (4.4%)	1 (0.5%)	153 (83.6%)

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; FD, flat dose; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 6. All grade 3/4 adverse events related (or with unknown relationship) to single-agent PM01183 at 7.0 mg FD in phase II trials (worst grade per patient).

AE SOC / MedDRA PT	Clinical trial and indication								Total (n=183)	
	PM1183-B-001-10 Pancreas (n=44)		PM1183-B-002-11 PRROC (n=52)		PM1183-B-003-11 MBC (n=70)		PM1183-B-004-13 NSCLC (n=17)			
	NCI-CTCAE grade v 4.0									
	3 n (%)	4 n (%)	3 n (%)	4 n (%)	3 n (%)	4 n (%)	3 n (%)	4 n (%)	3 n (%)	4 n (%)
Blood and lymphatic system disorders										
Febrile neutropenia	7 (15.9%)	2 (4.5%)	9 (17.3%)	2 (3.8%)	7 (10.0%)	3 (4.3%)	.	2 (11.8%)	23 (12.6%)	9 (4.9%)
Gastrointestinal disorders										
Abdominal pain	.	.	.	.	.	.	1 (5.9%)	.	1 (0.5%)	.
Gastrointestinal toxicity	.	.	1 (1.9%)	.	.	.	.	.	1 (0.5%)	.
Nausea	.	.	6 (11.5%)	.	3 (4.3%)	.	.	.	9 (4.9%)	.
Vomiting	1 (2.3%)	.	5 (9.6%)	.	2 (2.9%)	.	.	.	8 (4.4%)	.
General disorders and administration site conditions										
Fatigue	3 (6.8%)	.	18 (34.6%)	.	7 (10.0%)	.	2 (11.8%)	.	30 (16.4%)	.
Multi-organ failure	.	.	.	.	.	1 (1.4%)	.	.	.	1 (0.5%)
Pain	.	.	.	.	.	.	1 (5.9%)	.	1 (0.5%)	.
Hepatobiliary disorders										
Hepatotoxicity	.	.	.	.	.	1 (1.4%)	.	.	.	1 (0.5%)
Infections and infestations										
Fungal infection	.	.	.	.	.	.	.	1 (5.9%)	.	1 (0.5%)
Neutropenic sepsis	.	1 (2.3%)	.	.	.	.	.	.	.	1 (0.5%)
Pneumonia	1 (2.3%)	.	.	.	.	.	.	.	1 (0.5%)	.
Sepsis	.	2 (4.5%)	.	.	.	.	.	.	.	2 (1.1%)
Streptococcal infection	1 (2.3%)	.	.	.	.	.	.	.	1 (0.5%)	.
Toxic shock syndrome	.	.	.	.	.	.	.	1 (5.9%)	.	1 (0.5%)
Injury, poisoning and procedural complications										
Medication error	.	.	.	.	1 (1.4%)	.	.	.	1 (0.5%)	.
Investigations										
GGT increase	.	.	.	.	2 (2.9%)	.	.	.	2 (1.1%)	.
Urine output decrease	.	.	.	.	.	.	.	1 (5.9%)	.	1 (0.5%)
Metabolism and nutrition disorders										
Acidosis	.	.	.	.	.	.	1 (5.9%)	.	1 (0.5%)	.
Decreased appetite	.	.	2 (3.8%)	.	1 (1.4%)	.	.	.	3 (1.6%)	.
Dehydration	.	.	.	.	1 (1.4%)	.	.	.	1 (0.5%)	.
Failure to thrive	.	.	.	.	1 (1.4%)	.	.	.	1 (0.5%)	.
Hyperglycemia	.	.	.	.	1 (1.4%)	.	.	.	1 (0.5%)	.

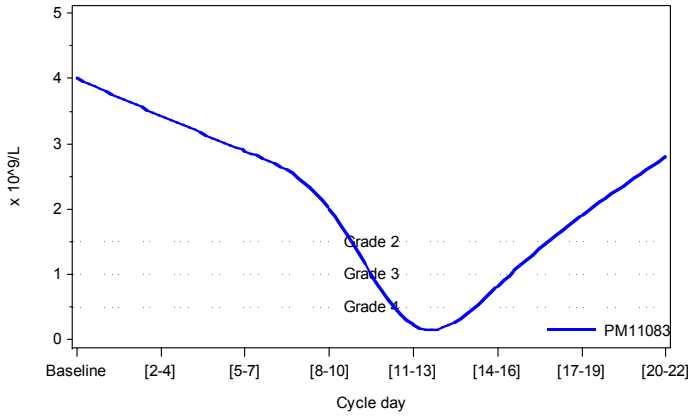
AE SOC / MedDRA PT	Clinical trial and indication								Total (n=183)	
	PM1183-B-001-10 Pancreas (n=44)		PM1183-B-002-11 PRROC (n=52)		PM1183-B-003-11 MBC (n=70)		PM1183-B-004-13 NSCLC (n=17)			
	NCI-CTCAE grade v 4.0									
	3 n (%)	4 n (%)	3 n (%)	4 n (%)	3 n (%)	4 n (%)	3 n (%)	4 n (%)	3 n (%)	4 n (%)
Hyperkalemia	1 (2.3%)	.	.	.	.	.	1 (5.9%)	.	2 (1.1%)	.
Hypoalbuminemia	.	.	.	.	.	.	1 (5.9%)	.	1 (0.5%)	.
Hypocalcemia	.	.	.	.	.	1 (1.4%)	.	.	.	1 (0.5%)
Hypokalemia	.	.	.	.	1 (1.4%)	.	.	.	1 (0.5%)	.
Hyponatremia	.	.	.	.	1 (1.4%)	.	.	.	1 (0.5%)	.
Musculoskeletal and connective tissue disorders										
Rhabdomyolysis	.	.	1 (1.9%)	.	.	.	.	.	1 (0.5%)	.
Nervous system disorders										
Depressed levels of consciousness	.	.	.	.	.	.	1 (5.9%)	.	1 (0.5%)	.
Renal and urinary disorders										
Renal failure	1 (2.3%)	.	.	.	.	.	1 (5.9%)	.	2 (1.1%)	.
Respiratory, thoracic and mediastinal disorders										
Dyspnea	.	.	.	.	2 (2.9%)	.	.	.	2 (1.1%)	.
Hemoptysis	.	1 (2.3%)	.	.	.	.	.	.	.	1 (0.5%)
Hypoxia	.	.	.	.	.	.	1 (5.9%)	.	1 (0.5%)	.
Pleuritic pain	.	.	.	.	1 (1.4%)	.	.	.	1 (0.5%)	.
Pneumonitis	.	.	.	.	1 (1.4%)	.	.	.	1 (0.5%)	.
Respiratory failure	.	.	.	.	.	.	.	1 (5.9%)	.	1 (0.5%)
Vascular disorders										
Hypertension	1 (2.3%)	.	.	.	.	.	.	.	1 (0.5%)	.
Hypotension	.	.	.	.	.	.	1 (5.9%)	.	1 (0.5%)	.

AE, adverse event; FD, flat dose; GGT, Gamma-glutamyltransferase; MedDRA, Medical Dictionary for Regulatory Activities; MBC. Metastatic breast cancer; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, Non-small cell lung cancer; PRROC, platinum-resistant/refractory ovarian cancer; PT, preferred term; SOC, System Organ Class.

In summary, myelosuppression is by far the most frequent toxicity observed at 7.0 mg FD in phase II trials with single-agent PM01183. Anemia was the hematological abnormality most frequently reported but was less likely to be severe: neutropenia and leukopenia had greater incidence in grade 3/4 events. Grade 3/4 neutropenia was characterized using Cycle 1 data from all PM01183-alone treated patients in ongoing phase II studies, to allow for uniform dose administration and no G-CSF prophylaxis that might alter results. The median duration of grade 3/4 neutropenia was 7 days (range: 2-14 days), with nadir occurring mostly by the end of the second week (median D15, range D4-D17). The time-course evolution of median neutrophils during Cycle 1 for 183 patients (grade 4 in 69 of them) treated in phase II studies at 7.0 mg FD q3wk

showed that most patients recovered to re-treatment criteria (grade 1) before the scheduled start of Cycle 2 (D22) (Figure 2). Overall, the incidence of grade 4 neutropenia increased from 44.8% of patients in phase I studies to 49.7% in all phase II studies at 7.0 mg FD, yet the overall incidence of FN remained below the 20% threshold (n=32, 17.5%) in phase II studies as a whole at cutoff (while in some specific settings, such as pancreatic cancer, ovarian cancer and BRCA+ breast cancer it is just above this threshold). Therefore, the use of primary G-CSF prophylaxis needs to be individualized carefully and cannot be recommended as a unique straightforward strategy at this point with PM01183 treatment alone.

Figure 2. Median neutrophil counts of patients in Cycle 1 treated with single-agent PM01183 at 7.0 mg FD in phase II trials (n=183).



FD, flat dose.

Grade 3/4 lymphopenia and thrombocytopenia also seem to have increased in frequency to approximately one third of patients treated at 7.0 mg FD, as compared to the highly selected phase I patient population.

Adverse Events Related to PM01183 Given as a BSA-based Dose of 3.2 mg/m^2

All AEs related to PM01183 given at 3.2 mg/m^2 to 29 patients in phase II studies PM1183-B-004-13 (n=3) and PM1183-B-005-14 (n=26) are shown in the following tables.

Table 7. Adverse events related (or with unknown relationship) to single-agent PM01183 at 3.2 mg/m^2 with a frequency of ≥ 2% from ongoing phase II trials (worst grade per patient).

AE SOC/MedDRA PT	NCI-CTCAE grade v 4.0				Total
	1	2	3	4	(n=29)
	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system disorders					
Febrile neutropenia	.	.	2 (6.9%)	.	2 (6.9%)
Gastrointestinal disorders					
Abdominal pain upper	1 (3.4%)	.	.	.	1 (3.4%)
Constipation	2 (6.9%)	2 (6.9%)	.	.	4 (13.8%)
Glossitis	1 (3.4%)	.	.	.	1 (3.4%)
Nausea	2 (6.9%)	1 (3.4%)	.	.	3 (10.3%)
Vomiting	2 (6.9%)	1 (3.4%)	1 (3.4%)	.	4 (13.8%)
General disorders and administration site conditions					
Fatigue	4 (13.8%)	6 (20.7%)	1 (3.4%)	.	11 (37.9%)
Metabolism and nutrition disorders					
Decreased appetite	3 (10.3%)	.	.	.	3 (10.3%)
Dehydration	1 (3.4%)	.	.	.	1 (3.4%)

AE SOC/MedDRA PT	NCI-CTCAE grade v 4.0				Total (n=29)
	1	2	3	4	
Electrolyte imbalance	.	.	.	1 (3.4%)	1 (3.4%)
Musculoskeletal and connective tissue disorders					
Arthralgia	1 (3.4%)	.	.	.	1 (3.4%)
Musculoskeletal pain	1 (3.4%)	.	.	.	1 (3.4%)
Nervous system disorders					
Cognitive disorder	1 (3.4%)	.	.	.	1 (3.4%)
Dysgeusia	1 (3.4%)	.	.	.	1 (3.4%)
Headache	1 (3.4%)	.	.	.	1 (3.4%)
Paresthesia	1 (3.4%)	.	.	.	1 (3.4%)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PT, preferred term; SOC, System Organ Class.

Table 8. Hematological and biochemical abnormalities with single-agent PM01183 at 3.2 mg/m^2 in phase II trials, regardless of relationship (worst grade per patient).

	NCI-CTCAE grade v 4.0				Total (n=24)
	1	2	3	4	
	n (%)	n (%)	n (%)	n (%)	n (%)
Hematological abnormalities					
Anemia	9 (37.5%)	8 (33.3%)	3 (12.5%)	.	20 (83.3%)
Leukopenia	7 (29.2%)	8 (33.3%)	2 (8.3%)	2 (8.3%)	19 (79.2%)
Lymphopenia (n=23)	4 (17.4%)	7 (30.4%)	4 (17.4%)	1 (4.3%)	16 (69.6%)
Neutropenia	3 (12.5%)	3 (12.5%)	6 (25.0%)	2 (8.3%)	14 (58.3%)
Thrombocytopenia	9 (37.5%)	1 (4.2%)	.	.	10 (41.7%)
Biochemical abnormalities					
ALT increase	12 (50.0%)	3 (12.5%)	.	.	15 (62.5%)
AP increase	11 (45.8%)	2 (8.3%)	1 (4.2%)	.	14 (58.3%)
AST increase	10 (41.7%)	1 (4.2%)	.	.	11 (45.8%)
Bilirubin increase	2 (8.3%)	1 (4.2%)	1 (4.2%)	.	4 (16.7%)
CPK increase	1 (4.2%)	.	.	.	1 (4.2%)
Creatinine increase	17 (70.8%)	3 (12.5%)	.	.	20 (83.3%)

Data not available for five patients treated in study PM1183-B-005-14.
ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Grade 3/4 hematological abnormalities found among patients treated with single-agent PM01183 at 3.2 mg/m^2 comprised neutropenia (33.3% of patients), lymphopenia (20.8%) and leukopenia (16.7%). Severe anemia was found in 12.5% of patients but did not reach grade 4. Of note, no episodes of severe thrombocytopenia or grade 4 FN were reported.

PM1183-A-003-10 Phase Ib Study (PM01183/Doxorubicin Combination)

The primary objective of this phase Ib study was to find a safe RD for further studies with this combination. Secondary objectives included assessing the safety, analyzing possible pharmacokinetic (PK) drug-drug interactions, and preliminarily assessing the antitumor activity of this combination in patients with several different solid tumors. Owing to patients with breast cancer or soft tissue sarcoma (STS) being eligible for inclusion, the chosen dose of DOX remained fixed at 50.0 mg/m^2 q3wk, up to a maximum cumulative dose (MCD) of 450 mg/m^2 throughout the study. After the MCD had been reached, patients continued treatment with PM01183 alone at its single-agent RD, for as long as treatment benefit was observed. The DOX dose was capped at 2.0 m^2 of BSA. An amendment allowed the addition of a prospective cohort of patients with primary G-CSF prophylaxis during dose escalation, in order to explore the potential of this approach to reach a higher RD.

Primary G-CSF prophylaxis did not allow further dose escalation in this study. DLTs occurring at the MTD regardless of primary G-CSF prophylaxis were not exclusively related to neutropenia and also included non-hematological toxicities (grade 3 diarrhea) and grade 4 thrombocytopenia. Accordingly, primary G-CSF prophylaxis was not implemented during RD expansion. DLTs [febrile neutropenia (FN)] were initially found in one of ten (10%) solid tumor patients without primary prophylaxis; as a result, PM01183 4.0 mg FD and DOX 50.0 mg/m^2 was defined as the RD for this combination.

Objective antitumor activity was early noted during dose escalation in patients with most tumor types included. In particular, five responses were observed in 12 SCLC patients. Remarkably, all five responses occurred exclusively in seven evaluable patients treated after first-line chemotherapy failure (ORR: 71%; 95%CI: 29-96%); in contrast, no responses were observed among the five patients treated as third-line.

Two SCLC patients out of 15 evaluable patients at the RD cohort expansion had DLTs in Cycle 1: FN (n=1) and grade 3 neutropenic infection (grade 3 lower respiratory tract infection) (n=1). Significant grade 3/4 myelosuppression occurred at all dose levels, and particularly at the RD, where grade 4 neutropenia/thrombocytopenia occurred in 86%/19% of patients, respectively, and additionally 29% had FN and 10% had associated neutropenic infections within the expansion cohort of SCLC pts. Therefore the use of primary prophylaxis upfront seems justified in this specific population. Non-hematological toxicities were mild and rarely reached grade 3/4. Nevertheless, the combination-associated myelosuppression raised the question of whether the RD defined in this cohort would be safe and tolerable in a less selected/restricted phase III population. In addition, the DOX dose used in SCLC patients is usually less than 50 mg/m^2 per cycle (either 45 mg/m^2 with G-CSF support or 40 mg/m^2 without it), as several tobacco-related comorbidities and prior mediastinal irradiation are highly prevalent in this context. As a result the phase Ib study was amended to reduce the DOX dose in the previous RD by 20% (i.e., to 40 mg/m^2) to try to limit the potentially severe myelosuppression and explore the feasibility of this dose in less selected patients (ECOG PS score=2 and without any age restriction). This amendment also adjusted the DOX dose to one that is more commonly used in these patients. The PM01183 dose was also adapted to a BSA-based dose of 2.0 mg/m^2. The rationale for this change came from the results of a logistic regression analysis of pooled data from phase II clinical trials with single-agent PM01183 in several solid tumors, which suggested that patients with the lowest BSA values could have a greater possibility of developing grade 3/4 thrombocytopenia and/or neutropenia. Hence, the PM01183 4.0 mg FD was transformed to 2.0 mg/m^2 q3wk, with the dose being capped at a BSA of 2.0 m^2 to prevent patients from receiving more PM01183 than 4.0 mg FD q3wk, previously defined as the RD. Up to January 2016, a total of 45 SCLC patients were treated with PM01183 and DOX in this study. Response was observed in 20 of 40 SCLC patients treated as second-line therapy (ORR: 50%; 95%CI, 34-66%, with one CR and 19 PR). In addition, one of five SCLC patients treated as third-line therapy also responded. Patient accrual is currently ongoing.

Up to January 2016, in addition to patients treated in the DOX combination study, data are available from seven evaluable SCLC patients treated with the PM01183 and paclitaxel combination (in the third-line setting) in another phase Ib study (the PM1183-A-007-13 trial). To that date, five of these seven patients had responded to treatment.

1.2.2 Topotecan

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

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

Topotecan has a large distribution volume in humans; only 20-40% of plasma concentration is bound to albumin. Hence, extensive peripheral tissue binding is most likely responsible for this large steady-state distribution volume. Mild to moderate hepatic dysfunction seems not to alter topotecan PK [45], but patients with moderate to severe renal dysfunction (creatinine clearance < 40 ml/min) need to have a dose adjustment [46].

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

The conventional dose and schedule of topotecan (standard regimen) is 1.5 mg/m^2/daily times x 5 q3wk [47]. A weekly regimen (Days 1, 8 and 15 every four weeks) has also been used in order to minimize the hematological toxicity. Both regimens were prospectively compared in a randomized phase II study in patients with platinum-resistant ovarian cancer [48]. Although the trial design had several limitations to draw conclusions regarding efficacy, both schedules reached similar OS rates. The weekly schedule showed a lower incidence of hematological toxicity, but objective responses were doubled (19% *vs.* 9%) and PFS values were better with the conventional schedule than with the weekly schedule. Therefore, it appears that the conventional schedule must be preferred as a standard of care. Moreover, the only regulatory approved regimen in SCLC patients is the standard as previously described or alternatively in patients with poorer ECOG PS the oral topotecan formulation was tested at 2.3 mg/m^2/daily times x 5 q3wk without G-CSF support was approved after showing improvement against BSC. Eckardt et al. published in 2007 similar results in 309 sensitive relapsed patients with the oral regimen as compared to the i.v. standard, although this trial was not adequately powered to demonstrate non-inferiority trial and conclusions must be interpreted cautiously [49]. However, the conventional dose and schedule as originally approved in by the FDA in the mid 90's is, since long, rarely used in the clinical daily practice outside clinical trials, due to the associated increased risk of infection, sepsis and myelosuppression. Alternatives are either dose reduction to 1.25 mg/m^2/daily times x 5, or even lower doses in less selected candidates or G-CSF primary prophylaxis upfront with or without prophylactic antibiotics in the more frail or risky patients. The lack of data available from adequate randomized prospective studies, to compare the efficacy or non-inferiority of initial lower doses of topotecan, makes this option inadequate in a pivotal study as a control arm. Therefore, in this study the use of primary prophylaxis with G-CSF will be universally implemented in all patients.

1.2.3 CAV

Developed in the 1970s, the CAV regimen consists of CTX, DOX and VCR. This multidrug combination was the chemotherapy backbone of the CHOP regimen (with prednisone added), used as a standard treatment to treat non-Hodgkin lymphomas

(NHL). Before cisplatin availability, CAV was widely used to treat both SCLC and NSCLC. During the 1980s, CAV was gradually replaced by the EP regimen (in the first-line setting) due to better results in some subsets (limited-stage disease), as well as a more manageable toxicity profile. As a result, CAV was relegated to the second-line setting, particularly in SCLC patients due to the lack of cross-resistance between EP and CAV [50].

Due to the rapidly evolving secondary resistance of the single agents observed in small uncontrolled clinical trials, and also to their limited efficacy, none of the drugs in the CAV combination were used to a significant extent as single agents in the clinical setting.

CTX is an alkylant agent, a pro-drug that needs hepatic activation through microsomal oxidation (CYP3A4) to 4-hydroxy-CTX, which is then converted to aldophosphamide and finally to phosphoramide mustard and/or nornitrogen mustard [51]. Despite 99% bioavailability for the parent compound at doses below 300 mg, bioavailability becomes more variable at doses around 1000-2000 mg [52], hence its more frequent use as part of multidrug regimens in breast and ovarian cancer, STS, NHL, as well as in CAV regimens.

DOX is the most commonly used anthracycline in solid tumors and lymphomas, together with the closely related epirubicin, which has an almost identical profile at equitoxic doses. Anthracyclines are associated with an increased risk of congestive heart failure (CHF), a risk that grows exponentially after reaching a maximal cumulative dose of 450 mg/m^2 in a lifetime (900 mg/m^2 for epirubicin). Anthracyclines are known to inhibit the DNA repair enzyme topoisomerase II (TOPO II), among other postulated actions. DOX is a well-known substrate for MDR1, gp170, and MRP1, the overexpression of which is the main primary or secondary resistance mechanism to anthracyclines [53].

Finally, VCR is a vinca alkaloid, which primarily inhibits tubulin polymerization, preventing cellular mitosis. Its contribution to the clinical activity of the CAV combination might well be anecdotal, as it has been difficult to assess directly. VCR is widely used in combinations like CHOP, or in multidrug series in rhabdomyosarcoma, and in pediatric multimodality treatment for Wilms' tumor (mostly because of the high response rates observed in these patients). The dosing of vinca alkaloids should be carefully monitored and modified in patients with moderate to severe liver failure, usually according to bilirubin levels. Common toxicity includes constipation and cumulative (mostly sensory) neuropathy, which if undetected in time might become irreversible.

In order to avoid drug extravasation while being infused, the administration of both DOX and VCR requires careful monitoring, as extensive local tissue damage may occur. Local heat may help inactivate VCR locally and contribute to limit the damage. MDR1 and MRP1, gp170 are both also involved in primary resistance to VCR.

The conventional dose and schedule of CAV in SCLC is CTX 1000 mg/m^2 followed by DOX 45.0 mg/m^2 and VCR 2.0 mg total flat dose, all on Day 1 q3wk [24]. This regimen is associated with grade 3 or 4 neutropenia in approximately two-thirds of the exposed patients. Moreover, up to 25% of the neutropenic patients may experience fever or infection within 48 hours of developing grade 4 neutropenia and nearly 5% develop sepsis; therefore, and according to current available guidelines, it seems prudent to administer G-CSF primary prophylaxis to patients assigned to receive CAV treatment.

1.3 STUDY RATIONALE

Patients with relapsed SCLC have the worst prognosis among lung cancer patients, with usually a life expectancy of less than six months and few therapeutic options. New treatment options are eagerly needed, particularly agents with novel mechanisms of action and no cross-resistance with prior platinum-regimens.

No new treatment has been approved in Western countries over the last 15 years. In particular, almost none of the randomized clinical trials done over the last 30 years have shown a positive outcome improvement in this setting.

PM01183 is a new chemical entity that induces double-strand DNA breaks through binding to the DNA minor groove. According to a COMPARE analysis, it does not have an overlapping mechanism of action with other 98 standard cytotoxic agents.

Data from 40 second-line SCLC patients treated in the Phase Ib study with the PM01183 and DOX combination (PM1183-A-003-10) showed a confirmed and remarkably high activity consistent with the synergistic effects found *in vitro/in vivo*, which resulted in an ORR of 50%, including one CR. This activity is unprecedented, whereas historical data on an anthracycline-containing combination used in a similar setting show ORRs usually in the 20-30% range. Eleven of these patients were still ongoing treatment at the cutoff of January 2016; the median PFS observed was 3.6 months (95%CI: 2.6-4.8 months). Analysis of updated data from 48 second-line SCLC patients treated in both cohorts with the PM01183 and DOX combination up to June 2016 resulted in a median PFS of 4.1 months (95%CI: 2.6-5.3 months); this is higher than the median PFS of 3.5 months that is usually obtained with standard topotecan treatment. Overall, the aforementioned promising results warrant further study in a well-designed, prospective, larger, randomized study to better define the role of this combination in the treatment of relapsed SCLC patients.

The analysis of updated data from the two cohorts of SCLC patients in study PM1183-A-003-10 also found differences in the patients' response to PM01183 and DOX depending on their CTFI after first-line therapy. When both cohorts were combined, patients with CTFI <30 days (n=11) had a median PFS of 1.3 months (95%CI: 1.2-3.4 months), while those with CTFI ≥30 days (n=35) had a median PFS of 4.8 months (95%CI: 3.3-6.4 months). These findings suggested that SCLC patients with CTFI <30 days responded significantly worse to the PM01183 and DOX combination compared to patients with CTFI ≥30 days. As a result, it was decided to exclude from this study all SCLC patients with CTFI <30 days after first-line therapy.

1.3.1 Dose Rationale

The dose of the PM01183 and DOX combination that will be evaluated in the Experimental Arm in the present study will be PM01183 2.0 mg/m^2 and DOX 40.0 mg/m^2, both on Day 1 q3wk. This dose is based on the RD determined for this same schedule in trial PM1183-A-003-10 (i.e., PM01183 4.0 mg FD and DOX 50.0 mg/m^2), with the PM01183 dose adapted to a BSA-based dose (4.0 mg FD = 2.0 mg/m^2) and the DOX dose reduced by 20% to limit the incidence of myelosuppression. In addition, primary prophylaxis with subcutaneous G-CSF will be mandatory for all patients. Furthermore, a recent analysis of PK data from the PM1183-A-003-10 trial found that PM01183 reduced DOX clearance from 45 l/h to 35 l/h (a 20% reduction), and doxorubicinol clearance from 150 l/h to 75 l/h (a 50% reduction). Taking into account these results, the DOX dose of 40.0 mg/m^2 used in the experimental arm in the present

study is not expected to result in patient exposure to toxic levels of DOX or doxorubicinol.

Patients enrolled in the Experimental Arm will receive up to a maximum of 10 cycles of the PM01183 and DOX combination. Then, DOX will be discontinued and patients will receive PM01183 at a dose of 3.2 mg/m^2 on Day 1 q3wk. This dose is based on the RD determined for this schedule in trial PM1183-A-001-08 (i.e., 4.0 mg/m^2 q3wk), reduced to 3.2 mg/m^2 to limit severe myelosuppression.

The present study will also include a Control Arm where patients will receive either topotecan daily on Days 1-5 q3wk or a combination of CTX, DOX and VCR (CAV) on Day 1 q3wk. The doses chosen for these regimens are commonly used in the treatment of patients with solid tumors. Rationale for the Pharmacogenetic Sub-Study

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

2. STUDY OBJECTIVES

2.1 PRIMARY

- To determine whether there is a difference in overall survival (OS) between lurbinectedin (PM01183)/DOX and a control arm consisting of best Investigator's choice between CTX, DOX and VCR (CAV) or topotecan, as treatment in SCLC patients after failure of one prior platinum-containing line.

2.2 SECONDARY

- To analyze:
  - Difference in OS between PM01183/DOX and CAV, in patients with CAV as best Investigator's choice.
  - OS/PFS in patients with and without baseline central nervous system (CNS) involvement. Subgroup analyses restricted to the sensitive and resistant populations (i.e., chemotherapy-free interval [CTFI] ≥90 days and CTFI <90 days) will also be performed.
  - Progression-free survival (PFS) by an Independent Review Committee (IRC).
  - Antitumor activity by IRC according to the RECIST v.1.1.
  - Safety profile.

2.3 TERTIARY

- To analyze:
  - Mid- and long-term survival (OS at 12, 18 and 24 months, respectively).
  - Efficacy and safety profiles in the subgroups of the PM01183/DOX arm *vs.* CAV or topotecan.
  - PFS by Investigator's Assessment (IA).
  - Antitumor activity by IA according to the RECIST v.1.1.

- Patient-reported outcomes (PRO).
- Pharmacokinetics (PK) of the combination in patients treated in the experimental arm (PM01183/DOX).
- PK/pharmacodynamic (PDy) correlations in the experimental arm, if any.
- Pharmacogenetics of known polymorphisms in patients treated in the experimental arm.

3. OVERALL STUDY DESIGN

Multicenter, open-label, randomized, controlled phase III clinical trial to evaluate and compare the activity and safety of an experimental arm consisting of PM01183/DOX combination followed by PM01183 alone if applicable *vs.* best Investigator's choice between CAV or topotecan as a control arm, in SCLC patients who failed one prior platinum-containing line but no more than one prior chemotherapy-containing line.

Central randomization will be implemented; patients will be assigned to each arm at a 1:1 ratio. If the patient is randomized to the control arm, the assigned treatment will be based on the reported Investigator's preference between CAV or topotecan.

Stratification will be performed according to the chemotherapy-free interval (CTFI) after first line [≥180 days (very sensitive, VS) *vs.* 90-179 days (sensitive; S) *vs.* <90 days (resistant; R)], ECOG PS (0 *vs.* 1-2), baseline CNS involvement *vs.* no involvement, prior immunotherapy against either programmed cell death protein-1 (PD-1) or programmed death ligand-1 (PD-L1) (Yes *vs.* No) and Investigator's preference (best Investigator's choice prior to randomization) between topotecan and CAV.

Up to 600 patients will be included in the trial.

An Independent Review Committee (IRC), blinded to the treatment assigned to the patients, will determine the best patient response and assign the date of objective response or progression/censoring according to RECIST v.1.1. Operational details for the IRC and the algorithm and its validation by an expert panel is described in detail in the IRC charter.

An Independent Data Monitoring Committee (IDMC) will oversee the conduct of the study. The IDMC should have access to unblinded efficacy and safety data throughout the trial to enable timely and informed judgments about risks and benefits. Operational details for the IDMC will be detailed in the corresponding charter.

The primary endpoint of the trial is the overall survival (OS). Secondary endpoints comprise difference in OS between PM01183/DOX and CAV, in patients with CAV as best Investigator's choice; OS/PFS per RECIST v.1.1 in patients with and without baseline central nervous system (CNS) involvement; PFS per RECIST v.1.1 by an IRC; best antitumor response as per RECIST v.1.1 and duration of response (DR) (both assessed by IRC); and safety profile. Tertiary endpoints comprise mid- and long-term survival assessed by measuring OS at 12/18/24 months, PFS per RECIST v.1.1 by IA, best antitumor response as per RECIST v.1.1 and DR (both assessed by IA), PRO, subgroup analyses, PK, PK/PDy correlations, and pharmacogenetics.

In order to evaluate the overall safety in both arms, an interim safety analysis is planned after the recruitment of 150 patients (i.e., ~75 patients into each arm). Recruitment will not be put on hold while the interim safety analysis is being performed. Efficacy parameters will not be formally analyzed in this interim evaluation. Further safety and efficacy analyses could be performed upon request from the IDMC.

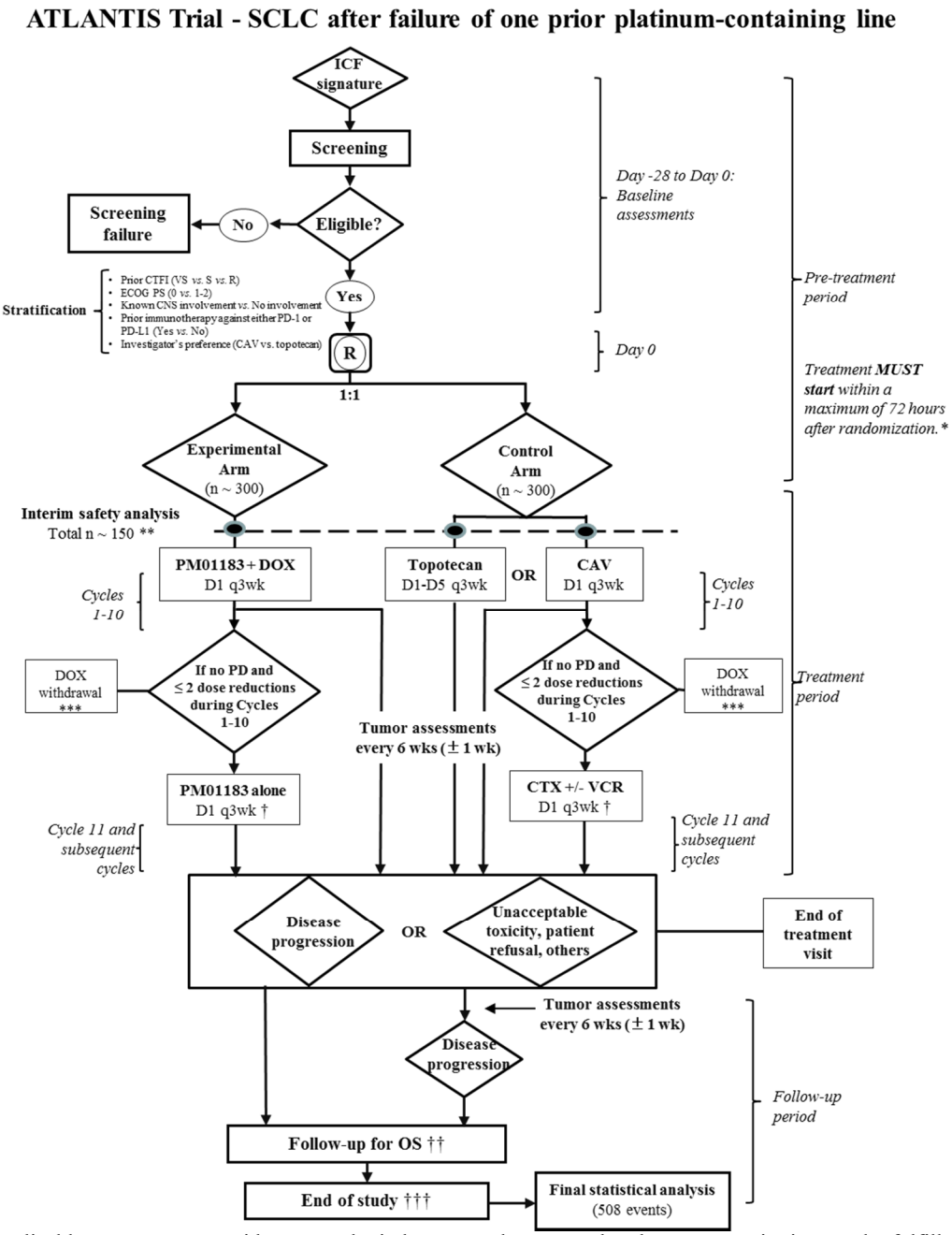
If any formal interim OS/PFS analysis is performed, unblinded only to the IDMC, a type I error correction according to the Lan and DeMets error spending function that corresponds to the O'Brien-Fleming boundary will be used, calculated during the interim analyses to preserve an overall (one-sided) 0.005 false positive error rate; if early termination does not occur, the alpha level of the final analysis will be chosen to preserve an overall (one-sided) 0.025 false positive error rate.

Crossover is not allowed.

A summary of the study design is shown in Figure 3.

Patients assigned to the experimental arm (PM01183/DOX combination), as well as those assigned to the CAV regimen in the control arm, will continue treatment until 10 cycles have been administered. After Cycle 10, non-progressing patients may continue PM01183 alone on Day 1 q3wk (experimental arm), or CTX +/- VCR (control arm), as applicable, until PD or unacceptable toxicity.

Figure 3. Study design.



* Applicable assessments outside accepted windows must be repeated and treatment criteria must be fulfilled before treatment start.
** Recruitment will not be put on hold while the interim analysis is ongoing.
*** Assessment of LVEF and ECG must be conducted at the time of DOX discontinuation.
† See Table 13 in Section 6.6 for applicable starting doses and dose reduction scheme.
†† Patients will be followed every three months (± two weeks) during the first 18 months after randomization, and then once every six months (± four weeks) until death of any cause or date of study termination, whichever occurs first. Once the whole recruitment is completed, the survival follow-up procedure will change: patients who discontinue treatment will be followed every three months according to a fixed calendar time (e.g., July, October, January, etc.) until death or study completion.
††† Until 18 months after the last patient is randomized.
CAV, CTX DOX and VCR; CNS, central nervous system; CTFI, chemotherapy-free interval; CTX, cyclophosphamide; D, day; DOX, doxorubicin; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; ICF, informed consent form; LVEF, left ventricular ejection fraction; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; R, resistant; q3wk, every three weeks; S, sensitive; VCR, vincristine; VS, very sensitive; wk, week.

Regardless of arm, patients will receive study treatment while it is considered to be in their best interest. Specifically, treatment will continue until disease progression (unless exclusively asymptomatic CNS involvement, in an otherwise responding patient), unacceptable toxicity after allowed/applicable dose reductions, intercurrent illness of sufficient magnitude to preclude safe continuation of the study, patient refusal, non-compliance with the study requirements, or a major protocol deviation that may affect the risk/benefit ratio for the participating patient.

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 omissions (if applicable), dose reductions, and reason for treatment discontinuation will be monitored throughout the study. The safety profile of patients will be monitored throughout the treatment and up to 30 days after the last treatment infusion (end of treatment, EOT), until the patient starts a new antitumor therapy or until the date of death, whichever occurs first. Any treatment-related AEs will be followed until recovery to at least grade 1 or stabilization of symptoms, whenever is possible.

Patients will be evaluated at scheduled visits during three predefined study periods: Pre-treatment, Treatment and Follow-up (see Section 5.2). This clinical trial is expected to finish (clinical cutoff) at approximately 18 months after the last patient is randomized.

3.1 PRIMARY ENDPOINT

- **Overall survival (OS)** will be calculated from the date of randomization to the date of death (death event) or last contact (in this case, survival will be censored on that date).

3.2 SECONDARY ENDPOINTS

- **Difference in OS between PM01183/DOX and CAV, in patients with CAV as best Investigator's choice.**
- **Overall survival (OS)/progression-free survival (PFS) per RECIST v.1.1 in patients with and without baseline CNS involvement.** Subgroup analyses restricted to the sensitive and resistant populations will also be performed.
- **Progression-free survival (PFS) by IRC** is defined as the time from the date of randomization to the date of documented progression per RECIST v.1.1 or death (regardless of the cause of death). If the patient receives further antitumor therapy or is lost to follow-up before PD, PFS will be censored at the date of last tumor assessment before the date of subsequent antitumor therapy.
- **Best antitumor response by IRC** will be the best response obtained in any evaluation according to RECIST v.1.1.
- **Duration of response (DR) by IRC** will be calculated from the date of first documentation of response per RECIST v.1.1 (complete or partial response, whichever comes first) to the date of documented PD or death. The censoring rules defined above for PFS will be used for DR.
- **Treatment safety profile:** AEs, serious adverse events (SAEs) and laboratory abnormalities will be coded by the Medical Dictionary for Regulatory Activities (MedDRA), graded according to the NCI-CTCAE v.4 and analyzed. Dose reductions or delays required due to treatment-related AEs, and reasons for treatment discontinuations will also be assessed.

3.3 TERTIARY ENDPOINTS

- **Landmark analyses:**
  - **Mid- and long-term survival (OS at 12/18/24 months)** will be the Kaplan-Meier estimates of the probability of being alive at these time points.
- **Subgroup analyses:** Subgroup analyses of efficacy and safety profiles in the PM01183/DOX arm *vs.* CAV based on Investigator's preference will be performed to isolate the contribution of PM01183 in the PM01183/DOX combination arm. Patients for whom the preference of the Investigator prior to randomization is CAV will be analyzed to test the combination of PM01183/DOX *vs.* CAV. Patients for whom the Investigator's preference is topotecan will also be analyzed independently.
- **Progression-free survival (PFS) per RECIST v.1.1 by IA.**
- **Best antitumor response by IA**.
- **Duration of response (DR) by IA**.
- **Patient-reported outcomes (PRO):** To measure the quality of life of patients, the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires will be analyzed at baseline and every six weeks (± one week) until EOT.
- **Plasma pharmacokinetics (PK) of PM01183 and DOX** will be evaluated using a sparse sampling scheme in patients treated in the experimental arm. Details will be given in a population PK analysis plan, and results will be presented in a separate report.
- **PK/Pharmacodynamic (PDy) correlation:** Population PK correlations of drug exposure with safety and efficacy will be explored in the experimental arm. Details will be given in specific population PK/PDy analysis plans, and results will be presented in separate reports.
- **Pharmacogenetics:** This analysis will be performed in patients treated in the experimental arm who specifically consent to participate in this sub-study. The presence or absence of known polymorphisms from a single sample collected at any time during the study will be assessed to explain the individual variability in the main PK parameters.

4. SELECTION OF PATIENTS

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

4.1 INCLUSION CRITERIA

1) Voluntary written informed consent of the patient obtained before any study-specific procedure.
2) Adult patients aged ≥ 18 years.
3) Histologically or cytologically confirmed diagnosis of limited or extensive stage SCLC which failed one prior platinum-containing regimen and with a chemotherapy-free interval (CTFI, time from the last dose of first-line chemotherapy to the occurrence of progressive disease) ≥ 30 days. Small-cell carcinoma of unknown primary site with or without neuroendocrine features confirmed in histology test(s) performed on metastatic lesion(s) are eligible, if Ki-67/MIB-1 is expressed in >50% of tumor cells.

4) ECOG PS ≤ 2 (see APPENDIX 1).
5) Adequate hematological, renal, metabolic and hepatic function in an assessment performed within 7 days (+ 3 day window) of randomization:
   a) Hemoglobin ≥ 9.0 g/dl [patients may have received prior red blood cell (RBC) transfusion, if clinically indicated]; absolute neutrophil count (ANC) ≥ 2.0 x 10^9/l, and platelet count ≥ 100 x 10^9/l.
   b) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 x upper limit of normal (ULN).
   c) Total bilirubin ≤ 1.5 x ULN or direct bilirubin ≤ ULN.
   d) Albumin ≥ 3.0 g/dl.
   e) Calculated creatinine clearance (CrCL) ≥ 30 ml/minute (using Cockcroft and Gault's formula).
   f) Left ventricular ejection fraction (LVEF) by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan within normal range (according to institutional standards).
   g) Creatine phosphokinase (CPK) ≤ 2.5 x ULN (≤ 5.0 x ULN is acceptable if elevation is disease-related).
6) At least three weeks since last prior anticancer treatment and recovery to grade ≤ 1 from any AE related to previous anticancer treatment (excluding sensory neuropathy, anemia, asthenia and alopecia, all grade ≤ 2) according to the NCI-CTCAE v.4.
7) Prior RT: At least four weeks since completion of whole-brain RT (WBRT), at least two weeks since completion of PCI, and to any other site not previously specified.
8) Evidence of non-childbearing status for women of childbearing potential (WOCBP). WOCBP must agree to use a highly effective contraceptive measure up to six weeks after treatment discontinuation. Valid methods to determine the childbearing potential, adequate contraception and requirements for WOCBP partners are described in APPENDIX 2. Fertile male patients with WOCBP partners should use condoms during treatment and for four months following the last investigational medicinal product (IMP) dose.

4.2 EXCLUSION CRITERIA

1) More than one prior chemotherapy-containing regimen (including patients re-challenged with same initial regimen).
2) Patients who never received any platinum-containing regimen for SCLC treatment.
3) Prior treatment with PM01183, topotecan or anthracyclines.
4) Limited-stage patients who are candidates for local or regional therapy, including PCI, thoracic RT or both, must have been offered that option and completed treatment or refused it prior to randomization.
5) Impending need for palliative RT or surgery for pathological fractures and/or for medullary compression within four weeks prior to randomization.
6) Symptomatic, or steroid-requiring, or progressing CNS disease involvement during at least four weeks prior to randomization (asymptomatic, non-progressing patients taking steroids in the process of already being tapered within two weeks prior to randomization are allowed).

7) Concomitant diseases/conditions:
   a) History (within one year prior to randomization) or presence of unstable angina, myocardial infarction, congestive heart failure or clinically significant valvular heart disease.
   b) Symptomatic or uncontrolled arrhythmia despite ongoing treatment.
   c) Patients with any immunodeficiency, including those known to be or have been infected by human immunodeficiency virus (HIV).
   d) Ongoing, treatment-requiring, non-neoplastic chronic liver disease of any origin. For hepatitis B, this includes positive tests for both Hepatitis B surface antigen (HBsAg) and quantitative Hepatitis B polymerase chain reaction (PCR). For hepatitis C, this includes positive tests for both Hepatitis C antibody and quantitative Hepatitis C PCR.
   e) Active infection or increased risk due to external drainages.
   f) Intermittent or continuous oxygen requirement within two weeks prior to randomization. Patients with confirmed or suspected diagnosis of diffuse interstitial lung disease (ILD) or pulmonary fibrosis.
   g) Patients with a second invasive malignancy treated with chemotherapy and/or RT. Patients with a previous malignancy that was completely resected with curative intention three or more years prior to randomization, and who has been continuously in remission since then will be permitted.
   h) Limitation of the patient's ability to comply with the treatment or to follow the protocol.
   i) Documented or suspected invasive fungal infections requiring systemic treatment within 12 weeks of randomization.
8) Pregnant or breast feeding women.

4.3 PATIENTS FOR THE PHARMACOGENETIC EVALUATIONS

Only patients who voluntarily sign the ICF for the pharmacogenetic sub-study will participate. Refusal to participate in the pharmacogenetic sub-study will not affect patient participation in the clinical study PM1183-C-003-14.

5. PLAN OF THE STUDY

5.1 PLANNED TRIAL PERIODS (FOR THE WHOLE STUDY)

The total duration of the study will be approximately 42 months.

Planned start date (first patient on study): second quarter 2016.

Planned enrollment period: approximately 24 months.

Planned end-of-study date (clinical cutoff): approximately 18 months after the last patient is randomized.

5.2 PLANNED TRIAL PERIODS (INDIVIDUALLY PER PATIENT)

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

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

- **Treatment:** from first infusion of the study treatment to the *end of treatment* (EOT) (see Section 5.2.1.1).
- **Follow-up**: after EOT, patients will be followed every four weeks until resolution or stabilization of all toxicities, if any. Patients who discontinue treatment regardless of the reason but without documented disease progression at the time of discontinuation will be followed every six weeks (± one week) until disease progression or start of a new antitumor therapy, death or until the date of study termination (clinical cutoff), whichever occurs first. After disease progression is documented or a new antitumor therapy is started, patients will be followed every three months (± two weeks) during the first 18 months after randomization, and then once every six months (± four weeks) until death of any cause or date of study termination, whichever occurs first. Once the whole recruitment is completed, the survival follow-up procedure will change: patients who discontinue treatment will be followed every three months according to a fixed calendar time (e.g., July, October, January, etc.) until death or study completion.

Patients will be considered to be **on-study** from the signature of the ICF to the end of the follow-up period. Patients will be considered to be **on-treatment** for the duration of their treatment and until the day of EOT, immediately before the start of the follow-up period. This EOT is defined as 30 days after the day of the last study treatment infusion, unless the patient starts a new antitumor therapy or dies (whichever occurs first). An end-of-treatment visit (EOT visit) will be performed at 30 days (± 10 days) after the last study treatment administration, unless the patient starts any subsequent antitumor therapy, in which case the end-of-treatment visit should be performed immediately before the start of the new therapy, whenever possible.

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 study treatment infusion (treatment discontinuation), start of a new antitumor therapy or death, whichever occurs first, in which case the date of administration of this new therapy or the date of death will be considered the date of EOT.

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

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

5.2.1.2 *Reasons for Treatment Discontinuation*

Patients will receive the study treatment(s) while it is considered to be in their best interest. Specifically, individual treatment of a given patient will continue until:

- Documented disease progression (unless exclusively asymptomatic CNS involvement, in an otherwise responding patient).

- Unacceptable toxicity (including treatment-related grade 4 hypersensitivity and/or extravasations, and treatment-related toxicity occurring despite allowed/applicable dose reductions).
- Treatment delay >22 days from the due date (except if objective clinical benefit is observed, with the Sponsor's agreement).
- Intercurrent illness of sufficient magnitude to preclude safe continuation of the study.
- Patient's refusal and/or non-compliance with study requirements.
- A major protocol deviation that may affect the risk/benefit ratio for the participating patient.
- Any other reason that, in the Investigator's judgment, precludes treatment continuation.

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 will remain on study until patient consent withdrawal, death, or the date of study termination (clinical cutoff) established by the Sponsor. The date and reason for study discontinuation will be clearly documented in the medical records of the patient.

5.2.2 Protocol Deviations

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

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

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

No deviations that may have an effect on the risk/benefit ratio of the clinical trial will be authorized. All protocol deviations detected during the study will be appropriately documented, and those considered particularly relevant (i.e., those related to ethical issues, to fulfillment of GCP guidelines and with an effect on the risk/benefit ratio) will

be notified, if applicable, to the pertinent IEC/IRB and to the Competent Authorities as established by local regulations.

5.3 REPLACEMENT OF PATIENTS

No patients will be replaced.

5.4 PRE-TREATMENT ASSESSMENTS

During the pre-treatment period, following signature of the ICF, the Investigator will confirm the patient's eligibility for the study by conducting the assessments summarized in Table 9.

Table 9. Screening period: pre-treatment assessments.

	ASSESSMENT	TIME
1. Written informed consent (general and pharmacogenetic sub-study)		Before any study procedures.
2. Medical and cancer history/ clinical examination	◆ Demographic data.	Within 14 days prior to randomization (Day 0).**
	◆ Medical and cancer history/baseline condition: o Primary diagnosis. o Prior treatments (with best response and TTP, when available). o Documented date of relapse.	Within 14 days prior to randomization (Day 0).*/**
	◆ Disease-related signs and symptoms. ◆ Concomitant therapies. ◆ Complete physical examination, including weight, height and calculation of BSA (see APPENDIX 3). ◆ Performance status (ECOG PS). ◆ Vital signs: heart rate, blood pressure and body temperature.	Within 7 days prior to randomization (Day 0).* Concomitant medications or signs and symptoms with onset or any change occurring between Day 0 and Day 1 of Cycle 1 must also be reported.
3. Laboratory tests	◆ **Hematology:** differential WBC counts (including neutrophil and lymphocyte counts), platelet count and hemoglobin. ◆ **Biochemistry:** Liver function test (ALT, AP, AST, total bilirubin), albumin, creatinine, CPK, glucose, calculated CrCL (as per Cockcroft and Gault's formula), serum electrolytes (Na^+, K^+, Ca^{++}), LDH, CRP and AAGP.	Within 7 days prior to randomization (Day 0).* AAGP will be evaluated exclusively in patients enrolled into the experimental arm, just before treatment start.
4. LVEF	MUGA or ECHO.	Within 14 days prior to randomization (Day 0).**
5. Pregnancy test (if patient is a WOCBP)	Assessment of β-hCG (urine or serum). If abnormally elevated, an US should be performed in order to rule out a pregnancy.	Within 7 days prior to randomization (Day 0), if applicable.*
6. 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, with specialist assessment/judgment of further evaluation if required.	Within 7 days prior to randomization (Day 0).*
7. Clinical and radiological tumor assessment	Contrast enhanced helical CT-scan or MRI.	Within 14 days prior to randomization (Day 0).**
8. CNS radiological assessment	Contrast enhanced CT-scan or MRI.	Within 14 days prior to randomization (Day 0).**
9. Patient-reported outcomes	EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires.	Within 7 days prior to randomization (Day 0).*

	ASSESSMENT	TIME
10. Adverse events	Only information on SAEs that occurred after signature of the informed consent form is required before treatment start. Grading should be as per the NCI-CTCAE v.4.	-

Regardless of the treatment administered, the same schedule of assessments will apply.
* A +3-day window is allowed for assessment of signs and symptoms, complete physical examination (including weight, height and calculation of BSA), ECOG PS, vital signs, laboratory tests, pregnancy tests, ECG, and patient-reported outcomes at screening.
** A +14-day window is allowed for medical and cancer history/baseline conditions, clinical and radiological tumor assessment (as per RECIST v.1.1), CNS radiological assessment, and LVEF assessment at screening.
AAGP, alpha-1 acid glycoprotein; 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; CrCL, creatinine clearance; CRP, C-reactive protein; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; 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; RECIST, Response Evaluation Criteria In Solid Tumors, SAE, serious adverse event; TTP, time to progression; US, ultrasound; WBC, white blood cells; WOCBP, woman of childbearing potential.

5.5 PATIENT REGISTRATION

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

5.6 PATIENT RANDOMIZATION

Central randomization will be implemented; patients will be assigned to each group at a 1:1 ratio. If the patient is randomized to the control arm, the assigned treatment will be based on the reported Investigator's preference between CAV or topotecan.

Stratification will be performed according to the CTFI after first-line treatment [≥180 days (VS) *vs*. 90-179 days (S) *vs*. <90 days (R)], ECOG PS (0 *vs*. 1-2), baseline CNS involvement *vs*. no involvement, prior immunotherapy against either PD-1 or PD-L1 (Yes *vs*. No) and Investigator's preference (best Investigator's choice prior to randomization) between topotecan and CAV.

Day 0 is defined as the day of randomization. Treatment (Day 1 of Cycle 1) must start within 72 hours after randomization. Otherwise, all applicable assessments outside the accepted windows must be repeated and eligibility criteria must be reassessed if applicable.

5.7 EVALUATIONS DURING TREATMENT

The following assessments will be done while the patient is on treatment (Table 10).

Table 10. Evaluations during treatment.

	ASSESSMENT	TIME
1. Clinical examination	◆ Complete physical examination, including weight and calculation of BSA (see APPENDIX 3).	Day 1 of Cycle 2 and subsequent cycles (always prior to treatment infusion).* BSA will be recalculated whenever a ≥10% variation in total body weight from baseline or from last dose adjustment occurs.
	◆ Performance status (ECOG PS). ◆ Vital signs: heart rate, blood pressure and body temperature.	Day 1 of Cycle 2 and subsequent cycles (always prior to treatment infusion).*
	◆ Concomitant therapies.	Throughout the "on treatment" period.**

	ASSESSMENT	TIME
2. Laboratory tests	◆ **Hematology:** differential WBC counts (including neutrophil and lymphocyte counts), platelet count and hemoglobin.	Cycle 1: Day 10. * Cycle 2: Day 1 and Day 10.* Cycle 3 and beyond: Day 1 (always prior to treatment infusion). Always repeat on Day 10 if grade ≥ 3 hematological abnormalities or a dose modification occurred in the preceding cycle, and before the first cycle after DOX discontinuation (Cycle 11) in patients treated in the experimental arm, and in patients assigned to CAV in the control arm. * Any patient presenting grade ≥ 3 treatment-related AEs should have any relevant tests re-assessed at least every 48-72 hours until recovery to at least grade 2.
	◆ **Biochemistry:** Liver function test (ALT, AST, AP, total bilirubin), total proteins, albumin, creatinine, CPK, glucose, calculated CrCL (as per Cockcroft and Gault's formula), serum electrolytes (Na^+, K^+, Ca^{++}), LDH, CRP, and AAGP.	Cycle 1: Day 10.* Cycle 2: Day 1 and Day 10.* Cycle 3 and beyond: Day 1 of each cycle (always prior to treatment infusion). Always repeat on Day 10 if grade ≥ 3 non-hematological abnormalities or a dose modification occurred in the preceding cycle.* Any patient presenting grade ≥3 treatment-related AEs should have any relevant tests re-assessed at least every 48-72 hours until recovery to at least grade 2. CRP will be evaluated only if clinically indicated. AAGP will be evaluated exclusively in patients enrolled into the experimental arm on Day 1 of cycles with PK sampling (see Section 7.7.1).
3. LVEF	MUGA or ECHO.	• Experimental arm: perform before Cycles 3, 6, 9 and 11 (first cycle after DOX discontinuation), and whenever clinically indicated due to suspicion of CHF. * • Control arm (topotecan): perform whenever clinically indicated due to suspicion of CHF. * • Control arm (CAV): perform before Cycles 3, 6, 9 and 11 (first cycle after DOX discontinuation), and whenever clinically indicated due to suspicion of CHF. *
4. Pregnancy test (if patient is a WOCBP)	Assessment of β-hCG (urine or serum). If abnormally elevated, an US should be performed in order to rule out a pregnancy.	Cycle 2 and further: Day +1 (always prior to treatment administration), or at least every month **
5. ECG	Cardiac rhythm will be identified in ECG intervals of at least 30 seconds of duration, PR interval, QT interval (raw), heart rate and QRS complex, with specialist assessment/judgment of further evaluation if appropriate.	• Experimental arm: perform before Cycles 6 and 11 (first cycle after DOX discontinuation), and whenever clinically indicated. * • Control arm (topotecan): perform whenever clinically indicated.* • Control arm (CAV): perform before Cycles 6 and 11 (first cycle after DOX discontinuation), and whenever clinically indicated. *
6. Pharmacokinetics (in the experimental arm only)	-	A total of five blood samples will be collected from patients treated in the experimental arm for PK analyses of PM01183, DOX and its metabolite doxorubicinol [four on Day 1 (before treatment start, 5 min after DOX

	ASSESSMENT	TIME
		administration, 5 min before the end of PM01183 infusion, and 1 hour after the end of PM01183 infusion) and one on Day 5 (95 hours after the end of PM01183 infusion)] in **Cycle 1** and **in another cycle** (**randomly between Cycle 2 and 4**). The second cycle with blood sample collection for PK will be assigned once the patient is randomized into the experimental arm (see details in Section 7.7.1).
7. Pharmacogenetics	Only in those patients who give their written informed consent for the pharmacogenetic sub-study	One blood sample will be collected at any time during the study from patients treated in the experimental arm.
8. Clinical and radiological tumor assessment	Contrast enhanced helical CT-scan or MRI, as clinically relevant.	Every six weeks from randomization until evidence of PD.*
9. CNS radiological assessment	Contrast enhanced CT-scan or MRI.	Repeat in the event of baseline CNS involvement, and also if clinically indicated.
10. Patient-reported outcomes	EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires.	Every six weeks from randomization.*
11. Survival information	-	Throughout the "on treatment" period.**
12. Adverse events	As per NCI-CTCAE v.4.	Throughout the "on treatment" period.**

Regardless of the treatment administered, the same schedule of assessments will apply.
* A 3-day window will be allowed for clinical assessments (ECOG PS, vital signs, weight, BSA, etc.), and laboratory tests; a 7-day window for ECG assessments, radiological procedures, tumor assessments and patient-reported outcomes; a 14-day window for LVEF assessments; and a 10-day window for the assessments at EOT.
** "On treatment period" = from first infusion of the study treatment (PM01183/DOX, CAV or topotecan) to EOT [30 days after the day of the last dose administration, unless the patient starts a new antitumor therapy or dies (whichever occurs first), in which case the date of administration of this new therapy or the date of death will be considered the date of end of treatment].
AAGP, alpha-1 acid glycoprotein; AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; β-hCG, beta subunit of human chorionic gonadotropin; BSA, body surface area; CAV, CTX DOX and VCR; CHF, congestive heart failure; CNS, central nervous system; CPK, creatine phosphokinase; CrCL, creatinine clearance; CRP, C-reactive protein; CT, computed tomography; CTX, cyclophosphamide; DOX, doxorubicin; ECG, electrocardiogram; ECHO, echocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; 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; PD, progressive disease; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors; VCR, vincristine; WBC, white blood cells; WOCBP, woman of childbearing potential.

5.8 EVALUATIONS AT END OF TREATMENT

The *end-of-treatment visit* will be scheduled at 30 days (± 10 days) after the last treatment infusion, unless the patient starts any subsequent antitumor therapy, in which case the end-of-treatment visit should be performed immediately before the start of the new therapy (ideally the day before or the same day).

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

- Complete physical examination (including weight, if clinically relevant) and assessment of all ongoing AEs.
- ECOG PS.
- Vital signs.

- Laboratory tests (hematology and biochemistry), if applicable and not previously done within the accepted window.
- Pregnancy test (if patient is a WOCBP).
- Clinical and radiological tumor assessment, if PD has not been documented previously or is the primary reason for treatment discontinuation (using contrast-enhanced helical CT-scan or MRI as appropriate, according to the procedures done at baseline).
- Patient-reported outcomes, if appropriate, not previously done, or if end of treatment occurred within the timing of the schedule (EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires).
- Concomitant therapies.

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

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

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

5.9 FOLLOW-UP AFTER END-OF-TREATMENT VISIT

Patients who have withdrawn from the study without progressive disease should undergo tumor assessment every six weeks (± one week) until PD, start of a new antitumor therapy, death or date of study termination (clinical cutoff), whichever occurs first. After PD is documented or a new antitumor therapy is started, patients will be followed for survival every three months (± two weeks) during the first 18 months after randomization, and then once every six months (± four weeks) until death of any cause or date of study termination, whichever occurs first. Once the whole recruitment is completed, the survival follow-up procedure will change: patients who discontinue treatment will be followed every three months according to a fixed calendar time (e.g., July, October, January, etc.) until death or study completion.

The end-of-study date (clinical cutoff) is defined as 18 months after randomization of the last patient. The date and reason of the study discontinuation will be recorded on the patient's CRF (see Section 5.2.1.1).

All AEs suspected to be related to the study treatment must be followed after the end of treatment every four weeks until recovery or stabilization.

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 a possibly treatment-related death, autopsy data should be provided when available.

6. TREATMENT

6.1 DESCRIPTION OF TREATMENT

6.1.1 Drug Formulation and Supply

6.1.1.1 *Experimental Arm*

- **Doxorubicin:**

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

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

- **PM01183:**

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

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

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

  The full composition of the PM01183 4-mg vials and the reconstituted solution per ml is as shown in Table 11.

Table 11. Composition of lurbinectedin (PM01183) vials.

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

6.1.1.2 *Control Arm*

Topotecan: commercially available i.v. presentations of vials containing topotecan will be provided as appropriate.

CAV: commercially available presentations of vials containing CTX, DOX and VCR will be provided as appropriate.

Topotecan or CAV (CTX, DOX and VCR) will be prepared in accordance with the applicable Summary of Product Characteristics. Medication preparation records will be kept by the site.

6.2 ADMINISTRATION OF STUDY MEDICATION

6.2.1.1 *Experimental Arm*

- **Doxorubicin:**

  Intravenously through peripheral or central lines (according to local label), followed by,

- **PM01183:**

  Intravenous infusion over one hour over a minimum of 100 ml dilution on 5% glucose or 0.9% sodium chloride (at a fixed rate) via a central line (or a minimum of 250 ml dilution if a peripheral line is used).

  Microscopically, dose-dependent diffuse edema associated with acute inflammatory reaction and necrosis were reported in the treatment sites of rabbits receiving PM01183 by paravenous administration at concentration relevant to current human use (0.003 and 0.03 mg/ml). Careful handling of PM01183 is advised. Short infusion times (one hour) make extravasation unlikely. Nevertheless, should extravasation occur, standard management is advised as soon as possible in order to limit tissue damage; no specific measures or antidotes are currently advised.

6.2.1.2 *Control Arm*

- **Topotecan:**

  Intravenously daily through peripheral or central lines (according to local label).

- **CAV:**

  CTX i.v. through peripheral or central lines (according to local label),

  DOX i.v. through peripheral or central lines (according to local label), and

  VCR i.v. through peripheral or central lines (according to local label).

6.3 STARTING DOSES AND SCHEDULE

6.3.1.1 *Experimental Arm*

- **Doxorubicin** at 40.0 mg/m^2 on Day 1, followed by,
- **PM01183** at 2.0 mg/m^2 on Day 1 q3wk (three weeks ± 48 hours = one treatment cycle).

  Note: in cycles with PK sampling, no more than ten minutes may pass between the end of DOX infusion and the start of PM01183 infusion.

  Up to a maximum of 10 cycles. Then, if applicable, DOX will be discontinued definitively and remaining patients will continue on maintenance until disease progression (PD), patient refusal or unacceptable toxicity despite applicable dose reductions, at:

  - **PM01183** at 3.2 mg/m^2 on Day 1 q3wk. (if no more than one dose reduction applied while on combination therapy), or:
  - **PM01183** at 2.6 mg/m^2 on Day 1 q3wk. (if more than one dose reduction applied while on combination therapy).

Doses will be capped at a BSA of 2.0 m^2 for individuals exceeding this BSA value. Doses will have to be recalculated for patients showing a ≥ 10% variation in total body weight from baseline or from last dose adjustment. PM01183 total doses in mg will be rounded to the first decimal, if necessary. DOX doses will be rounded, if applicable, according to institutional guidelines/standard practice.

6.3.1.2 *Control Arm*

- **Topotecan:**
  - Topotecan at 1.50 mg/m^2 daily on Days 1-5 q3wk (three weeks ± 48 hours = one treatment cycle) for patients with calculated CrCL ≥ 60 ml/min.
  - Topotecan at 1.25 mg/m^2 daily on Days 1-5 q3wk (three weeks ± 48 hours = one treatment cycle) for patients with calculated CrCL between 40 and 59 ml/min.
  - Topotecan at 0.75 mg/m^2 daily on Days 1-5 q3wk (three weeks ± 48 hours = one treatment cycle) for patients with calculated CrCL between 30 and 39 ml/min.
- **CAV:**
  - CTX at 1000 mg/m^2 on Day 1,
  - DOX at 45.0 mg/m^2 on Day 1, and
  - VCR at 2.0 mg total flat dose on Day 1 q3wk (three weeks ± 48 hours = one treatment cycle).

  Up to a maximum of 10 cycles (**Note: patients older than 70 years should not receive a total cumulative DOX dose of more than 400 mg/m^2)**. Then, if applicable, DOX will be discontinued definitively and the remaining patients will continue on maintenance until PD, patient refusal or unacceptable toxicity despite applicable dose reductions. Patients who are experiencing grade 2 neuropathy before receiving a new CAV cycle will not receive any further VCR infusions until neuropathy resolution to grade 1 is documented. Any recurrence of grade 2 neuropathy during treatment will result in a definitive discontinuation of VCR.

All doses will be capped at a BSA of 2.0 m^2 for individuals exceeding this BSA value. Doses, except for VCR, will have to be recalculated for patients showing a ≥ 10% variation in total body weight from baseline or from last dose adjustment. DOX, CTX or topotecan doses will be rounded, if applicable, according to institutional guidelines/standard practice.

Skipped doses of topotecan will not be replaced.

6.4 PROPHYLACTIC MEDICATION

All patients, irrespectively of treatment arm will receive primary prophylaxis subcutaneously, with G-CSF. Type, dose, and scheme to be used may vary according to institutional/standard practices or guidelines, if available. Nevertheless, a mandatory window of at least 24 hours and up to 72 hours must be allowed from the last dose of study treatment, until G-CSF prophylaxis is started.

In addition, all patients will also receive standard antiemetic prophylaxis before each treatment infusion, as follows:

- Intravenous corticosteroids (dexamethasone 8 mg, or equivalent, or at institutional antiemetic doses).
- Intravenous serotonin (5-HT$_3$) antagonists (ondansetron 8 mg, or equivalent).

If necessary, in addition to the above, the duration of treatment with 5-HT$_3$ antagonists and/or dexamethasone could be extended orally (if needed) (i.e. 4-8 mg/day for three consecutive days) and/or 10 mg of metoclopramide orally every eight hours could be added.

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

Aprepitant or any other NK-1 antagonist or related Substance P-antagonists are forbidden in all patients allocated to the experimental arm.

6.5 CRITERIA FOR TREATMENT CONTINUATION

In order to be re-treated, or to start treatment if first dosing was extended beyond the first 72 hours after randomization, patients will have to fulfill all the re-treatment criteria defined in Table 12.

Table 12. Criteria for treatment continuation.

Variable	Topotecan or CAV (Day 1)	PM01183/DOX (Day 1), or PM01183 alone (Day 1) whenever is applicable
ECOG PS	≤ 2	≤ 2
ANC	≥ 1.5 x 10^9/l	≥ 1.5 x 10^9/l
Platelets	≥ 100 x 10^9/l	≥ 100 x 10^9/l
Hemoglobin [a]	≥ 9.0 g/dl	≥ 9.0 g/dl
Total bilirubin	≤ 1.5 x ULN [b], or direct bilirubin ≤ ULN	≤ 1.5 x ULN. or direct bilirubin ≤ ULN
Albumin	≥ 2.7 g/dl	≥ 2.7 g/dl
AST/ALT	≤ 3.0 x ULN	≤ 3.0 x ULN
CPK	-	Grade ≤ 1 (or ≤ 2 if disease-related grade ≤ 2 at baseline)
Calculated CrCL (Cockcroft and Gault's formula)	≥ 30 ml/min [c]	≥ 30 ml/min
LVEF *	* Patients assigned to CAV treatment: within normal limits and not > 10% decrease (by MUGA) or > 20% decrease (by ECHO) from baseline before Cycle 3, Cycle 6 and Cycle 9, and if DOX cumulative dose ≤ 405 mg/m^2	Within normal limits and not > 10% decrease (by MUGA) or > 20% decrease (by ECHO) from baseline before Cycle 3, Cycle 6 and Cycle 9, and if DOX cumulative dose ≤ 360 mg/m^2
Other non-hematological drug-related AEs (except increased AP, or grade 2 alopecia, asthenia, and not optimally treated nausea and/or vomiting) [d]	Grade ≤ 1	Grade ≤ 1

[a] Patients may receive PRBC transfusion and/or EPO treatment if clinically indicated to increase/maintain adequate hemoglobin levels.
[b] Patients assigned to CAV with total bilirubin between 1.25-1.5 x ULN or direct bilirubin ≥ ULN will receive a maximum of 1.5 mg of VCR.
[c] Patients with CrCL between 40 and 59 ml/min must be re-treated with 1.25 mg/m^2 of i.v. topotecan daily, and patients with CrCL between 30 and 39 ml/min must receive no more than 0.75 mg/m^2 of topotecan daily.
[d] Any grade accepted for increased AP.
Those patients who experience grade ≥ 2 neuropathy while receiving CAV will stop VCR exclusively until resolution to at least grade 1 and, if applicable, will have their VCR dose reduced to 1.5 mg/cycle subsequently after resolution. If grade ≥ 2 neuropathy re-occurs at any time, or if there is no resolution of the first episode to at least grade 1 after a minimum of four weeks of follow-up, VCR will be discontinued definitively.
AEs, adverse events; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AP, alkaline phosphatase; AST, aspartate aminotransferase; CAV, CTX DOX and VCR; CPK, creatine phosphokinase; CrCL, creatinine clearance; CTX, cyclophosphamide; DOX, doxorubicin; ECHO, echocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; EPO, erythropoietin; LVEF, left ventricular ejection fraction; MUGA, multiple-gated acquisition scan; PRBC, packed red blood cells; ULN, upper limit of normal; VCR, vincristine.

If a patient does not meet the requirements for treatment continuation on Day 1 of any cycle after Cycle 1, re-assessments will be performed periodically at intervals of at least 72 hours and treatment will be withheld until appropriate recovery, for a maximum of 22 days after the treatment due date. If there is no recovery after a 22-day delay,

treatment must be discontinued and the EOT visit performed, except if objective clinical benefit is observed in tumor assessments, upon the Sponsor's agreement, in which case up to 15 additional days will be allowed to recover and meet the aforementioned requirements for treatment continuation

6.6 DOSE REDUCTION

Patients who experience any grade ≥ 3 treatment-related non-hematological toxicity (according to the NCI-CTCAE v.4) or febrile neutropenia or neutropenic infection or sepsis, and/or grade 4 thrombocytopenia or neutropenia, or treatment-related dose delays of more than five days, or frequent shorter dose delays (or skipped infusions if on topotecan) may only continue treatment, after appropriate dose reduction (see Table 13).

Patients experiencing treatment-related non-optimally treated grade 3 nausea and/or vomiting, grade 3 fatigue/asthenia lasting < 3 days, grade 3 diarrhea lasting ≤ 2 days or not optimally treated, and/or non-clinically relevant isolated biochemical abnormalities [e.g. alkaline phosphatase (AP)], may continue treatment at the same prior dose without any dose reduction being applied, provided optimal concomitant treatment is given for the applicable toxicity.

Patients assigned to CAV treatment in the control arm with total bilirubin levels 1.25-1.5 x ULN or abnormally high direct bilirubin levels before the start of a new cycle will receive a maximum of 1.5 mg of VCR. Those patients assigned to CAV who experience grade ≥ 2 neuropathy will stop receiving VCR until resolution to at least grade 1. After resolution, treatment will be resumed at 1.5 mg of VCR; however, if there is re-occurrence of grade ≥ 2 neuropathy after re-introduction of VCR, or if there is no resolution of the first episode to at least grade 1 after a minimum of four weeks of follow-up, VCR will be discontinued definitively.

Table 13. Levels of dose reduction in each treatment arm.

Dose reduction	Topotecan daily dose (q3wk) (mg/m^2)			CAV (q3wk)§	DOX/PM01183 (q3wk) (mg/m^2)	PM01183 alone (q3wk) (mg/m^2)
1 (starting dose)	1.50[a]	1.25[b]	0.75[c, d]	CTX: 1000 mg/m^2 DOX: 45 mg/m^2 VCR: 2.0 mg FD	40 / 2.0	3.2
-1	1.25	1.00	NA	CTX: 750 mg/m^2 DOX: 45 mg/m^2 +/- VCR: 1.5 mg FD	30 / 2.0	2.6[e]
-2	1.00	0.75[d]	NA	CTX: 750 mg/m^2 DOX: 35 mg/m^2 +/- VCR: 1.5 mg FD	30 / 1.5	2.0

All doses will be capped at a BSA of 2.0 m^2.
PM01183 total doses in mg will be rounded to the first decimal, if necessary. DOX and topotecan total doses will be rounded, if applicable, according to institutional guidelines/standard practice.
§ Patients who continue maintenance treatment after DOX discontinuation beyond Cycle 10 will, under no circumstances, have their Cy dose reduced below 750 mg/m^2 or their VCR dose reduced below 1.5 mg FD (although VCR could be discontinued, if needed).
[a] Starting dose for patients treated with topotecan with calculated CrCL ≥ 60 ml/min.
[b] Starting dose for patients treated with topotecan with calculated CrCL of 40-59 ml/min.
[c] Starting dose for patients treated with topotecan with calculated CrCL of 30-39 ml/min.
[d] No dose reduction below 0.75 mg/m^2/day will be implemented under any circumstances.
[e] Starting dose for patients who had two prior dose reductions while on PM01183/DOX.
BSA, body surface area; CAV, CTX DOX and VCR; CrCL, creatinine clearance; CTX, cyclophosphamide; DOX, doxorubicin; FD, flat dose; mg, milligram; NA, not available; q3wk, every three weeks; VCR, vincristine.

Regardless of treatment arm, patients who experience any treatment-related grade 4 hypersensitivity and/or extravasations will permanently discontinue treatment.

Up to two dose reductions are allowed per patient, if needed, excluding those patients starting topotecan at 0.75 mg/m^2 or those starting PM01183 alone at 2.6 mg/m^2 after DOX discontinuation. Any patient who continues to experience treatment-related toxicity despite all applicable dose reductions, or who requires one after receiving topotecan at 0.75 mg/m^2, must stop treatment. Once the dose has been reduced for an individual patient, it will not be re-escalated under any circumstances.

Note: patients enrolled in the experimental arm (PM01183/DOX), or those assigned to CAV treatment in the control arm, who had one or no dose reductions while on the combination will discontinue DOX and remain on treatment from Cycle 11 onwards (or at any other time if DOX is discontinued earlier due to cardiac issues) with PM01183 alone at 3.2 mg/m^2 and may undergo up to two additional dose reductions, whereas those who had two dose reductions while on the combination will discontinue DOX and remain on treatment from Cycle 11 onwards (or at any other time if DOX is withdrawn earlier due to cardiac issues) with PM01183 alone at 2.6 mg/m^2 and may undergo one additional dose reduction. Patients assigned to CAV treatment in the control arm may continue treatment after DOX discontinuation on Cycle 11 with CTX +/- VCR, either at 1000 mg/m^2/2.0 mg FD or at 750 mg/m^2/1.5 mg FD, respectively, as applicable. No individual dose reductions below CTX 750 mg/m^2 or VCR 1.5 mg FD are allowed. No single-agent PM01183 dose reduction below 2.0 mg/m^2 will be implemented under any circumstances.

Dose recalculations due to changes in BSA will not be considered dose reductions, as long as the targeted BSA dose remains unchanged.

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 and local management of mucositis/stomatitis.
- Blood products and transfusions, as clinically indicated.
- Bisphosphonates.
- In case of nausea or vomiting, extended symptomatic treatment for emesis will be allowed.
- Erythropoietin treatment according to the American Society of Clinical Oncology (ASCO) guidelines.
- Low-molecular weight heparin (LMWH) and/or any other anticoagulants, as clinically indicated.
- CNS irradiation if required, and/or limited field bone RT for pain control outside the thoracic wall.
- Megestrol acetate for wasting syndrome.

6.7.2 Prohibited Medications/Therapies

- Concomitant administration of any other antineoplastic therapy.
- Other investigational agents.

- Immunosuppressive therapies other than corticosteroids for antiemetic prophylaxis or pain control, or low-dose replacement in patients requiring this approach.
- Aprepitant and other NK-1 antagonists (for patients allocated to the experimental arm).
- Concomitant RT other than CNS irradiation, or limited-field RT for pain control.

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 have demonstrated that time dependent or irreversible inhibition for 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.* 0.002 µM when expressed as unbound fraction; 1%).

According to the recommendations in the European Medicines Agency Guideline CPMP/EWP/560/95, the risk of inhibition *in vivo* was evaluated by comparing observed Ki values against unbound [I] (0.002 µM). If [I]/Ki ≥ 0.02, inhibition *in vivo* could not be excluded. The estimated [I]/Ki values were 0.011, 0.0016, 0.0003 and 0.0012 for CYP3A4m, CYP3A4t, CYP2B6 and CYP2C8, respectively. Therefore, an inhibitory effect of PM01183 on these CYPs can be ruled out.

The basic model proposed at the Food and Drug Administration (FDA) Guidance for Drug Interaction Studies (Draft February 2012) and the National Institute of Health Sciences (NIHS) Drug Interaction Guideline for Drug Development and Provision of Appropriate Information (Draft 2014) resulted in a R_1 value of 2.15 for CYP3A4m, which suggests a potential inhibition for CYP3A4. However, when applying the mechanistic static model, the area under the curve ratio (AUCR) shows a value of 1.00 (A_h in the FDA Guidance or C_h in the NIHS Guideline was 0.99 and f_m=0.4) and therefore the inhibitory effect of PM01183 on CYP3A4 can be discarded.

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 4).

A potentially significant interaction with aprepitant is suggested by available phase II data from ovarian cancer patients and phase I data from the PM1183-A-008-13 study. PM01183 clearance was reduced by 50%, approximately, in the presence of aprepitant. Although all patients eventually recovered, the use of aprepitant is currently forbidden in all phase II/III PM01183 studies.

A recent analysis of PK data from the PM1183-A-003-10 trial found that PM01183 exposure (area under the curve, AUC) reduced DOX clearance slightly (from 45 l/h to 35 l/h; a 20% reduction) and more markedly doxorubicinol clearance (from 150 l/h to 75 l/h; a 50% reduction). A mechanistic explanation for this interaction is currently being studied. Taking into account these results, the DOX dose of 40.0 mg/m^2 used in the experimental arm in the present study is not expected to result in patient exposure to supratherapeutic levels of DOX or doxorubicinol.

6.8 DRUG ACCOUNTABILITY

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

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

6.9 TREATMENT COMPLIANCE

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

7. STUDY EVALUATIONS

7.1 EFFICACY

The primary aim of this clinical trial is to determine whether there is a statistically significant difference in the OS between PM01183/DOX and either CAV or topotecan as second-line treatment in SCLC patients after failure of one chemotherapy line. Secondary endpoints of efficacy include difference in OS between PM01183/DOX and CAV, in patients with CAV as best Investigator's choice; OS/PFS per RECIST v.1.1 in patients with and without baseline central nervous system (CNS) involvement; PFS per RECIST v.1.1 by an IRC; and best antitumor response as per RECIST v.1.1 and duration of response (DR) (both assessed by IRC). Tertiary endpoints of efficacy comprise PFS per RECIST v.1.1 by IA, and best antitumor response as per RECIST v.1.1 and DR (both assessed by IA).

Antitumor activity will be assessed using the RECIST v. 1.1 (see APPENDIX 5) and followed until PD by the appropriate method [computed tomography (CT) scan or magnetic resonance imaging (MRI) of the pelvis, abdomen and chest].

Irrespectively of treatment arm, radiological and clinical tumor assessment will be performed at baseline and every six weeks (± one week) after randomization until evidence of PD.

A special effort will be made to continue follow-up and report tumor assessments in patients discontinuing the study treatment without progression by RECIST.

Adequate CNS imaging (contrast enhanced-CT or MRI, if applicable) will be performed at baseline to document any disease involvement. In the event of CNS involvement being found, this assessment will be repeated while on treatment, regardless of treatment arm; otherwise, it will only be repeated if clinically indicated.

Irrespectively of treatment arm, patients with documented clinical benefit during treatment (either response or tumor shrinkage in target lesions and without clinical deterioration) may continue treatment while CNS irradiation is given, if appropriate.

After radiological PD is documented or a new systemic antitumor therapy is started, patients will be followed for survival every three months (± two weeks) during the first 18 months after randomization, and then once every six months (± four weeks) until death or date of study termination, whichever occurs first. Once the whole recruitment

is completed, the survival follow-up procedure will change: patients who discontinue treatment will be followed every three months according to a fixed calendar time (e.g., July, October, January, etc.) until death or study completion. For survival follow-up purposes, after radiological PD is documented or new therapy is started, a documented telephone call from the investigational sites will be adequate.

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

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

In order to evaluate the overall safety in both arms, an interim safety analysis is planned when 150 patients are recruited (i.e., ~75 patients into each arm). Recruitment will not be put on hold while the interim safety analysis is being performed. Efficacy parameters will not be formally analyzed in this interim evaluation. Further safety and efficacy analyses could be performed upon request from the IDMC.

If any formal interim OS/PFS analysis is performed, unblinded only to the IDMC, a type I error correction according to the Lan and DeMets error spending function that corresponds to the O'Brien-Fleming boundary will be used, calculated during the interim analyses to preserve an overall (one-sided) 0.005 false positive error rate; if early termination does not occur, the alpha level of the final analysis will be chosen to preserve an overall (one-sided) 0.025 false positive error rate.

7.2 SAFETY

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

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

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

Any patient having any treatment-related grade ≥ 3 AEs should have appropriate tests re-assessed at least every 48-72 hours until recovery to at least grade 2.

Hematological assessments must be repeated on Day 10 of Cycles 3 and following if grade ≥ 3 hematological abnormalities or a dose modification occurred in the preceding cycle, and in the first cycle of maintenance with PM01183 alone after DOX discontinuation.

Biochemical assessments must be repeated on Day 10 of Cycles 3 and following if grade ≥ 3 non-hematological abnormalities or a dose modification occurred in the preceding cycle.

Safety evaluations will also be performed by the IDMC during the interim analysis, to be conducted when 150 patients are recruited (i.e., ~75 patients into each arm).

7.3 ADVERSE EVENTS DEFINITIONS

7.3.1 Adverse Event (AE)

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

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

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

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

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

7.3.2 Serious Adverse Event (SAE)

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

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

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

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

7.3.3 Death

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

7.3.4 Life-threatening Event

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

7.3.5 Hospitalization or Prolongation of Hospitalization

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

Hospitalizations that do not meet criteria for SAE reporting are:

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

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

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

7.3.6 Unlisted/Unexpected Adverse Event

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

The Sponsor will use as the reference safety information for the evaluation of listedness/expectedness the IB for lurbinectedin (PM01183) and the SmPC for DOX, cyclophosphamide, vincristine and topotecan.

7.3.7 Adverse Reactions

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

7.3.8 Adverse Events Related to the Study Drug

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

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

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

7.3.9 Expedited Reporting

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

7.3.10 Assessment of Causal Relationship to the Study Drug

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

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

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

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

7.4 ADVERSE EVENTS REPORTING PROCEDURES

7.4.1 Reporting Adverse Events

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

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

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

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

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

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

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

7.4.2 Reporting Serious Adverse Events

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

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

SAEs occurring during the screening phase (from ICF signature to randomization), SAEs that may occur off-study, or in case the electronic system fails or is not available, will be reported within 24 hours to the Pharmacovigilance Department using the paper SAE form by fax (+34 91 846 6004), e-mail (phv@pharmamar.com) or telephone (+34 91 823 4617).

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 alternative methods (not electronically), must be followed by a completed electronic SAE reporting on e-CRF from the investigational staff within one working day.

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

7.4.3 Reporting Pregnancy Cases Occurred within the Clinical Trial

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

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

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

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

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

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

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

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

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

7.5 ADVERSE EVENTS MONITORING

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

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

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

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

7.6 PATIENT-REPORTED OUTCOMES

To measure the quality of life of patients, the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires will be assessed every six weeks (± one week) until EOT.

7.7 PHARMACOKINETICS

7.7.1 Plasma Sampling

Blood samples (detailed in Table 14) will be collected from all patients enrolled exclusively in the experimental arm to analyze PM01183, DOX and its metabolite doxorubicinol. The samples will be obtained in two cycles: Cycle 1, and a second cycle between Cycles 2 and 4. The second cycle with PK sampling will be assigned once the patient has been randomized into the experimental arm.

Table 14. Samples for pharmacokinetic evaluations.

Sample No.	Time	Acceptable window times	Sampling time	
			For DOX	For PM01183
#1	0	1 to 5 min before treatment start	Predose	Preinfusion
#2	5 min	± 2 min	5 min after EOA	-
#3	1 h	± 4 min	-	5 min before EOI
#4	2 h	± 10 min	2 h after EOA	1 h after EOI
#5	96 h	± 24 h	96 h after EOA	95 h after EOI

DOX, doxorubicin; EOA, end of administration; EOI, end of infusion; h, hour; min, minute.

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. Use the PM01183 reference sampling times for samples #3 to #5 to manage any delays between DOX administration and PM01183 infusion.

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 five samples of about 9 ml each will be collected for the determination of plasma concentrations of PM01183 on Cycle 1 and in another cycle randomly between Cycle 2 and Cycle 4 (about 90 ml of whole blood) at the predefined times depicted in the above table. A Laboratory Manual will be provided with details on collection and storage of PK samples. Please read it carefully before PK sampling. In short, after collection, each sample will be centrifuged and the resulting plasma layer split into two new tubes for the determination of PM01183 concentration, and of DOX and doxorubicinol concentrations. The plasma-containing tubes will be stored frozen until their shipment to the Central Laboratory for PK Samples (see details in the Study Contacts). All the material for PK procedures will be provided by the Sponsor(s).

7.7.2 Analytical Procedures

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

7.7.3 Pharmacokinetic Parameters

Pharmacokinetic analysis will be the responsibility of the Sponsor in accordance with the current Clinical Pharmacokinetics guidelines on population pharmacokinetic analyses [54, 55]. Clearance and volume of distribution will be the primary parameters of interest for the population PK analysis. Additional PK parameters will be calculated, if deemed appropriate.

7.8 PHARMACOGENETIC EVALUATIONS

To explore factors that may help to explain individual variability in the main PK parameters, the presence or absence of germline mutations or polymorphisms will be analyzed in leukocyte DNA extracted from one blood sample obtained at any time

during the study in the experimental arm. A selection of genes involved in PM01183 metabolism or transport will be investigated in order to identify genetic variants associated with PM01183 clearance (see APPENDIX 6 for details).

The collection and management of the polymorphisms samples for pharmacogenetics are quite different than those for PK assessment (please, refer to the Laboratory Manual for details). The assessment of genetic polymorphisms is not affected by treatment. Therefore, the Sponsor may require the collection of additional polymorphisms samples for pharmacogenetics later on, if the first assessment has not been performed accurately. Only patients treated with PM01183 and DOX in the experimental arm who voluntarily sign the ICF for this pharmacogenetic sub-study will participate in the pharmacogenetic evaluation. Refusal to participate in this sub-study will not affect patient participation in the clinical study PM1183-C-003-14. Patients with available PK and pharmacogenetic samples from this and other clinical trials with PM01183 will be included. Briefly, the pharmacogenetic analysis will investigate the impact of genetic variants in genes relevant for PM01183 disposition on unexplained between subjects variability in PK parameters obtained by the population PK model incorporating non genetic covariates using data aggregated from across the PM01183 clinical development program.

8. STATISTICAL METHODS

This phase III clinical trial is designed to determine whether there is a statistically significant difference in the OS between PM01183/DOX *vs.* CAV or topotecan as second-line treatment in SCLC patients after failure of one platinum-containing chemotherapy line.

The primary study analysis (OS) will be performed by means of the stratified log-rank test selecting the actual CNS and CTFI values of the stratification factors on the intention-to-treat (ITT) population, defined as all randomized patients analyzed in the group where they were allocated.

An IDMC will oversee the conduct of the study.

8.1 SAMPLE SIZE

Patients will be randomized to receive DOX at 40 mg/m^2 followed by PM01183 at 2.0 mg/m^2 (experimental arm), and either CAV or topotecan (control arm).

The prospective assumptions are a one-sided 2.5% significance level with at least 90% power to detect a 25% decrease in the risk of death to be achieved with the experimental arm (HR=0.75). OS with either CAV or topotecan is expected to be 7.5 months [25].

To obtain the required 508 events, approximately 600 patients with SCLC who failed one prior platinum-containing chemotherapy line will be stratified and randomized at a 1:1 ratio. With the aforementioned prospective assumptions, recruitment is foreseen to be completed in 24 months, and a total study duration for final OS analysis of about three and a half years is planned.

Stratification will be performed according to the CTFI after first line [≥180 days (VS) *vs.* 90-179 days (S) *vs.* <90 days (R)], ECOG PS (0 *vs.* 1-2), baseline CNS involvement *vs.* no such involvement, prior immunotherapy against either PD-1 or PD-L1 (Yes *vs.* No) and Investigator's preference (best Investigator's choice prior to randomization) between topotecan and CAV.

In order to evaluate the overall safety in both arms, an interim safety analysis is planned after the recruitment of 150 patients (i.e., ~75 patients into each arm) (see Section 8.3). Recruitment will not be put on hold while the interim safety analysis is being performed.

8.2 STATISTICAL ANALYSIS

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

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

8.2.1 Efficacy Analyses

Time-to-event variables (OS, PFS and DR) and their set time estimates (e.g., OS 12/18/24) will be analyzed according to the Kaplan-Meier method. The stratified log-rank test (primary analysis) and the unstratified log-rank test on the ITT population will be used to compare the time-to-event variables.

Cox regression will be used to calculate the risk reduction (OS, PFS and DR) and to evaluate the influence of the stratification variables and other potential prognostic factors on the time-to-event efficacy endpoints. Continuous variables that would have been categorized as discrete variables will also be investigated in the continuum range, and if the adjustment is better, then the continuous variable will be kept in the regression model.

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

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

If the result of the primary endpoint analysis is statistically significant, the hierarchical step-up Hochberg procedure will be used to test the most relevant secondary efficacy endpoints (i.e., difference in OS in patients with CAV as best Investigator's choice, and OS in the subgroup of patients without baseline CNS involvement) at the overall two-sided significance level of 0.05.

8.2.2 Safety Analyses

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

Patients having any grade ≥3 laboratory abnormalities and/or treatment-related AEs must have the relevant tests re-assessed at least every 48-72 hours until recovery to at least grade 2 has been documented.

The IDMC may request to review other preliminary safety/efficacy parameters, but no claim of superiority will be made.

8.2.3 Patient-reported Outcomes (PRO) Analyses

PRO will be analyzed to determine if efficacy and side effects are accompanied by measurable changes. The analysis will be performed on summary scores of the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires, as well as on subscales, and individual symptoms.

8.2.4 Pharmacokinetic Analyses

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

Population PK analysis of plasma concentration-time data of PM01183, DOX and doxorubicinol will be performed using non-linear mixed-effects modeling. Data may be combined with additional trials to support a relevant structural model. Available patient characteristics (demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan, and results will be presented in a separate report.

8.2.5 Pharmacokinetic/pharmacodynamic Correlation

Population PK correlations of drug exposure with safety and efficacy will be explored. Details will be given in specific population PK/PDy analysis plans, and results will be presented in separate reports.

8.2.6 Pharmacogenetic Analyses

The influence of genetic polymorphisms on main PK parameters will not be assessed or reported for individual clinical trials. Pharmacogenetic analysis will instead be performed using data aggregated from across the PM01183 clinical development program and presented in a separate report.

8.3 INTERIM SAFETY ANALYSIS

In order to evaluate the overall safety in both arms, an interim safety analysis is planned after the recruitment of 150 patients (i.e., ~75 patients into each arm). Recruitment will not be put on hold while the interim safety analysis is being performed. Efficacy parameters will not be formally analyzed in this interim evaluation. Further safety and efficacy analyses could be performed upon request from the IDMC.

As previously explained, if any formal interim OS/PFS analysis is performed, unblinded only to the IDMC, a type I error correction according to the Lan and DeMets error spending function that corresponds to the O'Brien-Fleming boundary will be used, calculated during the interim analyses to preserve an overall (one-sided) 0.005 false positive error rate; if early termination does not occur, the alpha level of the

final analysis will be chosen to preserve an overall (one-sided) 0.025 false positive error rate.

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

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

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

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

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

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

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

9.2 MONITORING, AUDITING AND INSPECTING

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

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

Adequate time for these visits should be allocated by the Investigator. The Investigator should also ensure that the monitor is given direct access [as per International Conference on Harmonization (ICH) Topic E6 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 ICFs. This copy must provide written full information about the clinical trial, in a language that is non-technical and easily understood, as well as on the pharmacogenetic sub-study. The Investigator should allow the necessary time for the patient or his/her legally acceptable representative, when required, to inquire about the details of the clinical trial; then, the ICFs must be freely signed and personally dated by the patient and by the person who conducted the Informed Consent discussion before the beginning of the study. The patient should receive a copy of the signed ICFs and any other written information provided to study patients prior to participation in the trial.

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

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

9.4 CONFIDENTIALITY/ PATIENTS IDENTIFICATION

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

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

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

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

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

Pharma Mar S.A. shall comply with the Directive 95/46/EEC of the European Parliament and of the Council of 24 October 1995 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

Electronic CRFs will be used to record all data for each patient. It is the responsibility of the Investigator to ensure that the CRFs are properly and completely filled in, in

English. CRFs must be completed for all patients who have given their informed consent.

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

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

9.6 INSURANCE

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

9.7 RETENTION OF RECORDS

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

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

9.8 USE OF INFORMATION AND PUBLICATION

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

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

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

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11. APPENDICES

APPENDIX 1: ECOG PERFORMANCE STATUS ASSESSMENT SCALE

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

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

APPENDIX 2: 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 17 March 2016).

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 suspected pregnancy in a patient, the decision on her continued participation in the clinical trial will be jointly taken by the patient, the Investigator and the Sponsor, with the patient's best interest in mind. A decision to continue the pregnancy will require immediate 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. A combination 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: CALCULATION OF THE BODY SURFACE AREA. THE DUBOIS FORMULA

For calculating the patient's body surface area (BSA):

$$BSA\ (m^2) = 0.007184 \times Height\ (cm)^{0.725} \times Weight\ (kg)^{0.425}$$

Reference:

DuBois D, DuBois E.F. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med* 1916;17:863–71.

APPENDIX 4: LIST OF CYP1/CYP2/CYP3 INHIBITORS, INDUCERS AND SUBSTRATES

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

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

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

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

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

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

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

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

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

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 5: EVALUATION OF RESPONSE. THE RECIST.

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

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

LIST OF ABBREVIATIONS

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

LIST OF TABLES

Table 1. Summary of major changes from RECIST 1.0 to RECIST 1.1[3].

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

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

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

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

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

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

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

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

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

RECIST 1.0	RECIST 1.1	Rationale

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

1. MEASURABILITY OF TUMOR LESIONS AT BASELINE

1.1 Definitions

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

1.1.1 Measurable

Tumor Lesions:

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

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

Malignant Lymph Nodes:

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

1.1.2 Non-measurable

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

1.1.3 Special Considerations Regarding Lesion Measurability

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

Bone Lesions:

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

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

- Blastic bone lesions are non-measurable.

Cystic Lesions:

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

Lesions with Prior Local Treatment:

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

1.2. Specifications by Methods of Measurement

1.2.1 Measurement of Lesions

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

1.2.2 Method of Assessment

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

Clinical Lesions:

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

Chest X-Ray:

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

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

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

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

Ultrasound:

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

Endoscopy, Laparoscopy:

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

2. TUMOR RESPONSE EVALUATION

2.1 Assessment of Overall Tumor Burden and Measurable Disease

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

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

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

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

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

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

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

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

2.3 Response Criteria

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

2.3.1 Evaluation of Target Lesions

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

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

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

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

2.3.2 Special Notes on the Assessment of Target Lesions

Lymph Nodes:

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

Target Lesions that Become 'Too Small to Measure':

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

Lesions that Split or Coalesce on Treatment:

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

2.3.3 Evaluation of Non-target Lesions

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

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

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

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

When the Patient Also Has Measurable Disease:

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

When the Patient Has only Non-measurable Disease:

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

2.3.5 New Lesions

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

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

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

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

2.4 Evaluation of Best Overall Response

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

2.4.1 Time Point Response

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

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

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

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

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

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

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

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

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

2.4.2 Missing Assessments and Inevaluable Designation

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

2.4.3 Best Overall Response: All Time Points

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

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

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

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

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

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

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

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

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

APPENDIX 6: LIST OF GENES TO BE INVESTIGATED IN THE PM01183 PHARMACOGENETIC ANALYSIS

Table 1. List of genes.

Gene group	Gene subgroup	Gene symbol (HGNC)	Gene name
Metabolism	Drug metabolizing enzymes (DMEs)	*CYP3A4*	Cytochrome P450 family 3 subfamily A member 4
		CYP3A5	Cytochrome P450 family 3 subfamily A member 5
		CYP3A7	Cytochrome P450 family 3 subfamily A member 7
		CYP3A43	Cytochrome P450 family 3 subfamily A member 43
		CYP2D6	Cytochrome P450 family 2 subfamily D member 6
	DME electron donors	*POR*	Cytochrome P450 oxidoreductase
		CYB5A	Cytochrome B5 type A
		PGRMC1	Progesterone receptor membrane component 1
		PGRMC2	Progesterone receptor membrane component 2
	Regulators of DME expression*	Ligand-dependent nuclear receptors	
		NR1I2	Nuclear receptor subfamily 1 group I member 2
		NR1I3	Nuclear receptor subfamily 1 group I member 3
		VDR	Vitamin D (1,25- dihydroxyvitamin D3) receptor
		NR1H4	Nuclear receptor subfamily 1 group H member 4
		PPARA	Peroxisome proliferator activated receptor alpha
		RARA	Retinoic acid receptor alpha
		RXRA	Retinoid X receptor alpha
		NR1H3	Nuclear receptor subfamily 1 group H member 3
		NR1H2	Nuclear receptor subfamily 1 group H member 2
		NR3C1	Nuclear receptor subfamily 3 group C member 1
		ARNT	Aryl hydrocarbon receptor nuclear translocator
		AHR	Aryl hydrocarbon receptor
		NR5A2	Nuclear receptor subfamily 5 group A member 2
		NR0B2	Nuclear receptor subfamily 0 group B member 2
		Constitutive transcription factors	
		HNF4A	Hepatocyte nuclear factor 4 alpha
		NR2F2	Nuclear receptor subfamily 2 group F member 2
		CEBPB	CCAAT/enhancer binding protein beta
		CEBPA	CCAAT/enhancer binding protein alpha
		USF1	Upstream transcription factor 1
		HNF1A	HNF1 homeobox A
		FOXA3	Forkhead box A3
		FOXA2	Forkhead box A2
		PPARGC1A	PPARG coactivator 1 alpha
		NCOA1	Nuclear receptor coactivator 1
		Transcription factors signaling regulators	
		NFKB1	Nuclear factor kappa B subunit 1
		NFKB2	Nuclear factor kappa B subunit 2
		NFKBIA	NFKB inhibitor alpha
		IL6R	Interleukin 6 receptor
		IL6ST	Interleukin 6 signal transducer
Transport	Drug transporters	*ABCB1*	ATP binding cassette subfamily B member 1
	Plasma binding proteins (PBP)	*ALB*	Albumin
		ORM1	Orosomucoid 1
		ORM2	Orosomucoid 2

* Also involved in the regulation of drug transporter and plasma binding protein genes expression.

APPENDIX 7: 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.

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