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)

STATISTICAL ANALYSIS PLAN

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

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ABBREVIATIONS AND GLOSSARY

AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
AST (SGOT)	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BSA	Body Surface Area
CAV	Cyclophosphamide, Doxorubicin and Vincristine
CBR	Clinical Benefit Rate
CHT	Chemotherapy
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine Phosphokinase
CR	Complete Response
CRF	Case Report Form
CSF	Colony Stimulating Factor
CT	Computed Tomography
CTFI	Chemotherapy Free Interval
CTX	Cyclophosphamide
D	Day
DCR	Disease Control Rate
DF	Degrees of Freedom
DNA	Deoxyribonucleic Acid
DOX	Doxorubicin
DR	Duration of Response
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
EPO	Erythropoietin
FU	Follow-up
HR	Hazard Ratio
IA	Investigator Assessment
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IRC	Independent Review Committee
ITT	Intention-to-treat
LDH	Lactate Dehydrogenase
LR	Log Rank Test
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
mo	Months
MRI	Magnetic Resonance Imaging
NA	Not Available

NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not Evaluable
NOS	Not Otherwise Specified
ORR	Overall Response Rate
OS	Overall Survival
PCI	Prophylactic Cranial Irradiation
PD	Progressive Disease
PD-1	Programmed Cell Death Protein-1
PD-L1	Programmed Death Ligand-1
PDy	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PR	Partial Response
PRO	Patient-Reported Outcomes
PS	Performance Status
PT	Preferred Term
q3wk	Every Three Weeks
QOL	Quality of Life
R	Resistant
RECIST	Response Evaluation Criteria In Solid Tumors
S	Sensitive
SAE	Serious Adverse Event
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SOC	System Organ Class
STD	Standard Deviation
TTF	Time to Treatment Failure
UK	Unknown
ULN	Upper Limit of Normal
USA	United States of America
VCR	Vincristine
VS	Very Sensitive
vs.	versus
WBC	White Blood Cells
WHO	World Health Organization
wk	Week

1 STUDY RATIONALE

Patients with relapsed small cell lung cancer (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 deoxyribonucleic acid (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 the expanded cohort of second-line SCLC patients treated in an uncontrolled phase Ib study with the doxorubicin (DOX) combination showed a high activity in terms of objective responses and a relatively prolonged progression-free survival consistent with the synergistic effects found *in vitro/in vivo.*

Therefore, a randomized trial has been proposed to compare the combination of lurbinectedin (PM01183) and doxorubicin *vs.* cyclophosphamide (CTX), DOX and vincristine (VCR) (CAV) or topotecan in the treatment of relapsed SCLC patients.

A full rationale for the study may be found in the appropriate sections of the study Clinical Protocol.

2 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 with disease progression after 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 (Arm B), the assigned treatment will be based on the reported Investigator's preference between CAV or topotecan.

A minimum recruitment of 165 patients (>45% of patients in the control arm) will be ensured in the anthracycline containing regimen, CAV, in order to have sufficient data to study the contribution of PM01183 to the PM01183/DOX combination compared to the CAV.

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)], eastern cooperative oncology group performance status (ECOG PS) (0 *vs.* 1-2), baseline central nervous system (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 for the control arm (Topotecan *vs.* CAV).

Approximately 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 the Response Evaluation Criteria in

Solid Tumors (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. 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/progression free survival (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 investigator assessment (IA), best antitumor response as per RECIST v.1.1 and DR (both assessed by IA), patient reported outcomes (PRO), subgroup analyses, pharmacokinetics (PK), PK/pharmacodynamic (PDy) correlations, and pharmacogenetics.

In order to check 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 reviewed at this time, as follow-up will not have reached maturity at this point; therefore, no type I/II error corrections will be applied. Further safety and efficacy analyses could be performed upon request from the IDMC.

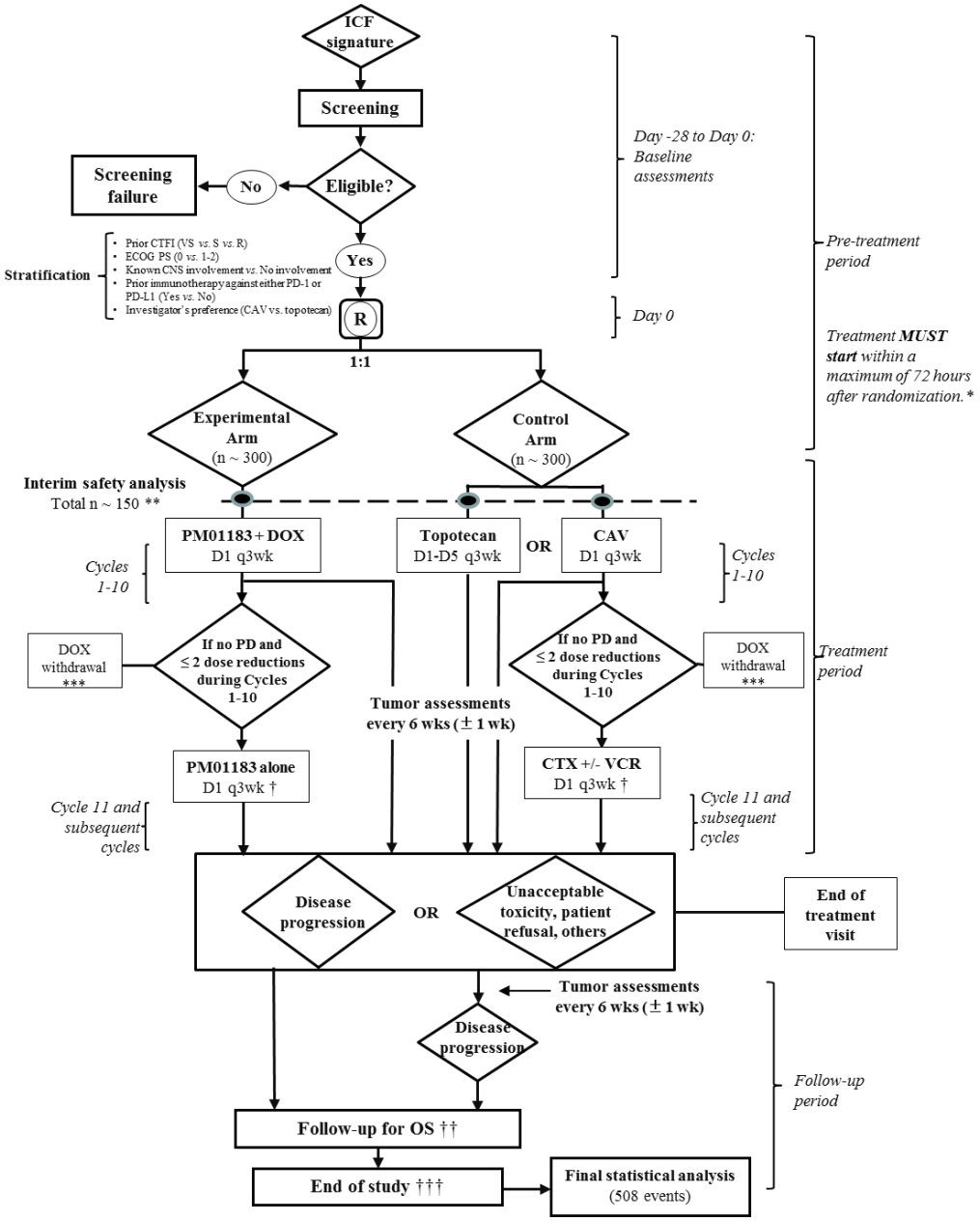
There is no intention to claim superiority before the necessary number of events for the OS analysis has been reached. However, if formal interim analyses are requested by the IDMC, Lan and DeMets error spending function that corresponds to the O'Brien-Fleming boundary will be used, calculated during 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.

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 treatment 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 progressive disease (PD) or unacceptable toxicity.

A summary of the study design is shown in the below figure.

ATLANTIS Trial - SCLC after failure of one prior platinum-containing line



* 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 withdrawal.

† See Clinical Protocol 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. This clinical trial is expected to finish (clinical cutoff) at approximately 18 months after the last patient is randomized.

3 PATIENTS EVALUABILITY CRITERIA

Patients must fulfill all the inclusion/exclusion criteria to be eligible to participate in the study. Randomized patients will not be replaced.

3.1 Intention-to-Treat (ITT) Population

All patients randomized to either treatment arm independent of whether they received study drug or not, and analyzed in the group where they were allocated.

3.2 Safety Population

Safety population or "all treated patients" population will be defined as patients who have received at least part of one infusion of the investigational agents, and analyzed in the group where they were treated.

4 OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

- 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 cyclophosphamide (CTX), doxorubicin (DOX) and vincristine (VCR) (CAV) or topotecan, as treatment in SCLC patients after failure of one prior platinum-containing line.

4.2 Secondary Objectives

- 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 Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1.
- Safety profile.

4.3 Tertiary Objectives

- 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.

4.4 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 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. Those for whom the investigator's preference is topotecan will be also analyzed independently. Consequently, to avoid potential imbalance in the patient allocations, investigator's preference for the control arm will be a stratification factor and the results will be shown between either option.
- **Progression-free survival (PFS) per RECIST v.1.1 by IA.**
- **Best antitumor response by IA** will be the best response obtained in any evaluation according to RECIST v.1.1.
- **Duration of response (DR) by IA** will be calculated from the date of first documentation of response per RECIST v.1.1 (complete or partial response, whichever comes first) to the date of documented PD or death. The censoring rules defined above for PFS will be used for DR.
- **Patient-reported outcomes (PRO):** To measure the quality of life of patients, the European Organization for Research and Treatment of Cancer (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.

5 SAMPLE CONSIDERATIONS

5.1 Randomization and Stratification

Central dynamic 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 (Arm B), the assigned treatment will be based on the reported Investigator's preference between CAV or topotecan.

Stratification will be performed according to 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 for the control arm (Topotecan *vs.* 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 accepted windows must be repeated and eligibility criteria must be reassessed, if applicable.

5.2 Sample Size

This phase III clinical trial is designed to determine 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 (CHT) line.

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 25% reduction in the relative risk of death (hazard ratio; HR=0.75) to be achieved with the experimental arm, at a one-sided 2.5% significance level with at least 90% power, following exponential distributions and fulfilling the proportional hazard assumption. Median OS with CAV or topotecan is expected to be around 7.5 months[(1)]. It is forecasted that an observed HR of approximately 0.84 will have enough power to reject the null hypothesis.

To obtain the required 508 events, approximately 600 patients with SCLC who failed one prior platinum-containing CHT 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 (~25 patients/month) and a total study duration of about three and a half years for the final OS analysis is planned.

With the prospective assumptions above mentioned, about 265 OS events are expected in the control arm and 243 in the treatment arm.

5.2.1 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 reviewed at this time, as follow-up will not have reached maturity at this point; therefore, no type I/II error corrections will be applied.

As previously explained, there is no intention to claim superiority before the necessary number of events for the OS analysis has been reached. However, 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.

6 STATISTICAL METHODOLOGY FOR EFFICACY

6.1 Efficacy Definitions

Primary endpoint.

Overall survival (OS) is defined as the time 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). Final OS analysis is planned 18 months after randomization of last patient (planned end of study date).

After radiological 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. For survival follow-up (FU) purposes, after radiological PD is documented or new therapy is started, a documented telephone call from the investigational sites will be adequate. Once the whole recruitment is completed, the survival follow-up procedure will change and 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.

Secondary/tertiary endpoints.

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.

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) of the pelvis, abdomen and chest].

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

Adequate CNS imaging (contrast enhanced-CT or MRI, if applicable) will be performed at baseline to document any disease involvement. This assessment will not be repeated routinely regardless of treatment arm, unless it is 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.

Patients who have withdrawn from the treatment without PD documentation will continue with the tumor assessments every six weeks (± one week) until PD, start of a new antitumor therapy, death or date of study termination (clinical cut-off), whichever occurs first.

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.

Crossover is not allowed.

Progression-free survival (PFS) by IA will be calculated using the same methodology as explained above for IRC assessment but following Investigator assessments.

Landmark analyses of OS at 12/18/24 months will be the Kaplan-Meier estimates of the probability of being alive at these time points.

Difference in OS between PM01183/DOX and CAV, in patients with CAV as best Investigator's choice will be measured using OS data derived for the primary endpoint calculation and selecting investigator's preference ticked in the electronic case report form (eCRF).

OS/PFS in patients with and without baseline CNS involvement will be measured using derived data and selecting the CNS involvement status reported in the eCRF. Afterwards, subgroup analyses of CNS involvement restricted to the sensitive and resistant populations will also be performed.

Subgroup analyses of the PM01183/DOX arm *vs.* CAV or topotecan based on investigator's preference.

Best antitumor response by IRC/IA will be the best response obtained in any evaluation according to RECIST v.1.1.

Duration of response (DR) will be calculated from the date of first documentation of response per RECIST v.1.1 (complete or partial response, whichever comes first) to the date of documented PD or death. The censoring rules defined above for PFS will be used for duration of response.

Assessments must be done consistently in both treatment arms to ensure a symmetrical assessment of tumor response and progression. Every effort should be made to ensure that these assessments are done on the required date. Time to n^{th} (i.e. 1, 2, 3…) disease assessment is defined as weeks between randomization and the recorded date of the n^{th} assessment after randomization.

Other supportive endpoints:

Disease control rate (DCR) by IRC/IA, defined as percentage of patients with best response CR, PR or SD.

Clinical benefit rate (CBR) by IRC/IA, defined as percentage of patients with best response CR, PR or SD ≥4 months.

Time to treatment failure (TTF) by IA, defined as time from randomization to progression, EOT due to AE, EOT due to symptomatic deterioration or death will be calculated.

Time to onset of first brain metastases by IA, defined as time from randomization to clinical diagnosis of brain mets will be calculated.

6.2 Efficacy Analysis Methods

Time-to-event variables (OS, PFS DR, TTF and time to onset of first brain metastases) and their set time estimates (e.g., OS 12/18/24) will be analyzed according to the Kaplan-Meier method.

The stratified log-rank (LR) test, selecting CNS and CTFI values of the stratification factors, on the ITT population will be primarily used to compare the time-to-event variables. A sensitivity analysis will be performed using all randomization strata variables.

Unstratified log-rank tests will also be calculated as supportive analyses.

If the result of the primary endpoint analysis is statistically significant, the hierarchical step-up Hochberg procedure[(2)] 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. The p-values for this procedure will be calculated using the corresponding unstratified log-rank test in each subgroup.

The symmetry of tumor evaluations between treatment arms will be examined. The Wilcoxon test to compare time to disease assessments between treatment arms will be used to assess symmetry of evaluations. Moreover, Kaplan-Meier curves of the time from randomization and the first and second disease assessments will be plotted.

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.

Mean Kaplan-Meier estimates will be used to compare areas under the curves for OS and PFS.

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

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

Multivariate models (main effects or including interaction terms, if appropriate) will include all stratification factors and/or prognostic factors/covariates widely reported and recognized by the scientific community: treatment (PM01183/DOX *vs.* control), CTFI after first-line treatment [as strata categories ≥180 days (VS) *vs*. 90-179 days (S) *vs*. <90 days (R) or as usually reported ≥90 days *vs*. <90 days], ECOG PS (0 *vs.* 1-2 or coded as 0 *vs.* 1 *vs.* 2), baseline CNS involvement (yes *vs.* no), prior immunotherapy against either PD-1 or PD-L1 (yes *vs.* no) [or independently by each group if enough representative cases, prior PD-1 (yes *vs.* no) and prior PD-L1 (yes *vs.* no)], investigator's preference for the control arm (Topotecan *vs.* CAV), geographical area (USA *vs.* Europe *vs.* rest of the world), sex (male *vs.* female), age, age at diagnosis, race (caucasian *vs.* other), smoking status (current *vs.* former *vs.* never), disease stage at study entry (limited *vs.* extensive), PD-L1 expression (if enough cases; <1% *vs.* ≥1% or <50% *vs.* ≥50%), prior lines (1 *vs.* >1 lines or coded as ordinal) , time from diagnosis to randomization, time elapsed from last dose of prior chemotherapy regimen to randomization, response to prior chemotherapy (yes *vs.* no), time to progression to prior chemotherapy, prior prophylactic cranial irradiation (PCI) (yes *vs.* no), prior consolidation with thoracic radiotherapy (yes *vs.* no), visceral metastases (yes *vs.* no), number of metastatic sites at baseline, body mass index (BMI), height, weight, body surface area (BSA), presence of any bulky (< 50 mm *vs.* ≥ 50 mm) lesion at baseline, measurable disease by RECIST v1.1 (yes *vs.* no), hypertension (yes *vs.* no), cardiac disease (yes *vs.* no) , diabetes (yes *vs.* no) , chronic obstructive pulmonary disease (COPD) (yes *vs.* no), secondary tumors (yes *vs.* no), steroids at baseline (yes *vs.* no), opioids at baseline (yes *vs.* no), paraneoplastic syndrome at baseline (yes *vs.* no), baseline lactate dehydrogenase (LDH) value (≤ upper limit of normal (ULN) *vs.* >ULN), hemoglobin value at baseline (g/dl), albumin value at baseline (g/dl), C-reactive protein value at baseline (mg/dl), C-reactive protein/albumin baseline ratio and baseline global quality of life (QoL). In addition, continuous variables categorized as discrete variables will also be investigated in the continuum range and if they fit better then the continuous variable will be selected in the model.

All variables with a good percentage of valid cases (approximately ≥ 90%) will be included in the multivariate analysis, although if any prognostic value lacks more than

10% of values, sensitivity analyses considering multiple imputation methods will be performed. Within the multivariate stepwise Logistic/Cox regression analysis, the chosen significance level for entering an explanatory variable into the model will be 0.05 (for all variables not in the model, the one with the smallest p-value will be entered if the p-value is less than or equal to the specified significance level). The significance level for removing an explanatory variable from the model will be 0.05 (for all variables in the model, the one with the largest p-value will be removed if the p-value exceeds the specified significance level). The parameter estimates, hazard ratios/odds ratios and p-values of the variables retained in the model will be presented.

Forest plots will be plotted for PFS and OS summarizing main results, stratification and factors/covariates used in multivariate analyses[3]. Continuous variables not categorized by prior definition will be coded into two categories taking as reference the median value, below or equal the median value and above the median value.

Median follow-up (FU) time for OS and PFS will be calculated in a descriptive way, taking only into account the censored values and using the Kaplan-Meier method for reversing the censoring values as described by Parmar[4].

Concordance between IRC and IA PFS assessments will be evaluated by means of Kaplan-Meier curves. Forest plots for response will also be performed adapting them to show relevant information (e.g. percentages will be shown instead of medians).

Sensitivity analyses for different PFS censoring will be performed. The following approaches will be calculated: 1) Date of progression based on scheduled time instead of recorded date (e.g. if progression occurs in the ninth week and assessment would have to be done in the sixth week then the expected date is used instead of the actual date); 2) First date of progression combining IRC and IA assessments (e.g. the lowest date between IRC and IA is used); 3) Date of progression moved to the prior tumor assessment date (e.g. if progression has not been documented in the second assessment and is documented in the third assessment then progression date is moved to the second assessment); 4) First date of progression or death not censoring data if further antitumor therapy is received before the documented progression.

Proportional hazard assumption for OS and PFS will be checked by means of a Cox regression including treatment and its interaction with survival time[5]. In case of strong rejection of proportionality, then restricted mean survival estimates will also be calculated in addition to HR[6,7].

Main summary of efficacy analyses

Order	Endpoint	Population	Statistics
Primary endpoint	OS	ITT population	-Stratified log rank test (primary analysis) -Unstratified log rank test -Kaplan Meier estimates -Univariate Cox regression -Multivariate Cox regression
Secondary endpoints	PFS by IRC	ITT population	-Stratified log rank test -Unstratified log rank test -Kaplan Meier estimates -Univariate Cox regression -Multivariate Cox regression
	DOR by IRC	ITT population: Responder patients	-Kaplan Meier estimates
	Response rate by IRC	ITT population	-Fisher exact test -Logistic regression
	Subgroup analyses*	ITT population (based on investigator's preference)	-Stratified log rank test -Unstratified log rank test -Kaplan Meier estimates -Univariate Cox regression -Multivariate Cox regression
	OS/PFS by no CNS involvement*	ITT population (patients with no CNS)	-Stratified log rank test -Unstratified log rank test -Kaplan Meier estimates -Univariate Cox regression -Multivariate Cox regression

* If the result of the primary endpoint analysis is statistically significant, the Hochberg procedure will be used at the overall two-sided significance level of 0.05 to test the difference between PM01183/DOX and CAV in OS in patients with CAV as best Investigator's choice, and the difference in OS in the subgroup of patients without baseline CNS involvement. The unstratified log-rank tests will be used to calculate p-values. IA, Investigator Assessment; IRC, Independent Review Committee; ITT, intention-to-treat; PFS, progression-free survival; OS, overall survival.

7 STATISTICAL METHODOLOGY FOR SAFETY

7.1 Toxicity and Adverse Events

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 AEs will be coded using to the Medical Dictionary for Regulatory Activities (MedDRA). Any treatment-related AEs will be followed until recovery to at least grade 1 or stabilization of symptoms, whenever is possible.

Summary of overall AEs will be done by system organ class (SOC) and preferred term (PT), by severity (worst toxicity grade) and by relationship. Tables will be sorted by body system/preferred term.

A frequency table will be made for the AEs leading to cycle delay, dose reduction, dose omissions (if applicable), or withdrawal of study medication. AEs leading to permanent treatment stop and AEs with outcome of death will also be presented by relationship to drug.

Exploratory Fisher's exact tests will be performed to compare the incidence of grade 4 or grade 3/4 AEs between treatment arms.

7.2 Clinical Laboratory Evaluation

Laboratory results will be classified according to the NCI-CTCAE v.4. All laboratory visits reported as "End of treatment" visit will be mapped to the last cycle visit for each patient.

The worst grade per patient will be tabulated during overall treatment and per cycle for hematology values [white blood cells (WBC), absolute neutrophil count (ANC), lymphocyte count, platelet count and hemoglobin] and for the following biochemistry tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (AP), creatine phosphokinase (CPK), creatinine, glucose, sodium, potassium and albumin.

Exploratory Fisher's exact tests will be performed to compare the incidence of grade 4 or grade 3/4 laboratory evaluations between treatment arms.

7.3 Physical Examination Findings

Tables summarizing the performance status (PS), height, body weight and BSA (according to the Dubois and Dubois formula) at baseline will be prepared.

In addition, changes in the ECOG PS and body weight of each patient during the treatment compared to baseline will be presented.

7.4 Deaths and other Serious Adverse Events

Deaths, and other serious adverse events (SAEs) will be tabulated following the same pattern than AEs.

8 OTHER ANALYSES

Non-continuous variables will be described in frequency tables using counts and percentages. Continuous variables will be described by median, mean, standard deviation (STD), minimum and maximum.

8.1 Baseline and Demographic Data

Baseline data such as demographics, cancer history, number of organs involved and sites of disease, prior therapy, laboratory values at baseline, prior relevant history, signs and symptoms, electrocardiogram, and concomitant medication [Anatomical Therapeutic Chemical – World Health Organization (ATC-WHO) coded] will be described following standard tables (detailed in Appendix I).

CTFI is defined as the time from the last dose of the platinum drugs in the last platinum regimen to the occurrence of progressive disease.

Prior immunotherapy to PD-1 or PD-L1 data will be collected from the screening page.

For pre-treatment characteristics with multiple measurements per patient before the start of treatment (e.g. laboratory assessments, vital signs), the baseline measurement will be considered the last value prior to or on the first day of treatment.

8.2 Protocol Deviations

Analysis of protocol deviations following 'Protocol Deviation and Non-Compliance Management Plan' will be done as described in Appendix I.

8.3 Treatment Administration

Total cumulative dose, time on treatment, dose intensity and relative dose intensity, administration delay, and dose reductions/omissions will be described following standard tables (detailed in Appendix I) and the reported cycle information on the case report form (CRF) pages will be used for the analyses.

Time on treatment, expressed in weeks, is defined as last infusion date minus first infusion date plus 30 days, except if the patient dies or starts a new antitumor therapy within 30 days from the last infusion date, in which case the time on treatment will be the date of death or the date of the start of a new antitumor therapy minus the date of the first infusion.

Total cumulative dose by drug, expressed in mg, is the sum of all the product doses from the first cycle until the last cycle, including the dose received in the last cycle.

Intended dose intensity is the planned dose per cycle divided by the planned number of weeks by cycle (e.g. 2.0 mg/m^2 for PM01183 when it is combined with DOX).

Absolute dose intensity is the actual cumulative dose divided by the number of weeks of treatment. As a convention, for this calculation, the duration of the last cycle will be the predefined cycle length (e.g, 21 days). Relative dose intensity (%) is the ratio of absolute dose intensity divided by the intended dose intensity.

The items « Infusion delayed: yes/no» and « Dose reduced: yes/no» present on the treatment exposure CRF pages will be used to calculate delays and dose reductions, respectively. For cycles considered as delayed by the Investigator, the length of the delay will be calculated as:

Duration of cycle delay: Date of the current drug administration – Date of the previous drug administration – the predefined cycle length (i.e., 21 days).

According to the protocol, non-progressing patients in the PM01183 + DOX may continue treatment with PM01183 alone on Day 1 q3wk after reaching 10 cycles of combination. Consequently, for PM01183 dose calculations two distinct summaries, if applicable, have to be performed. One when it is administered combined with DOX and another one when it is administered as single agent, once DOX has to be withdrawn. If necessary, same approach would be implemented in the control arm patients if DOX is withdrawn and the other intended doses are modified.

8.4 Patient-reported Outcomes (PRO)

To measure the quality of life of patients, EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires will be analyzed every six weeks (± one week) from randomization until EOT. All visits reported as "End of treatment" visit will be mapped to the last cycle visit for each patient.

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

Scale scores were calculated by averaging items within scales and transforming average scores linearly. All of the scales range in score from 0 to 100. A high score for a functional scale represents a high/healthy level of functioning whereas a high score for a symptom scale or item represents a high level of symptomatology or problems.

8.5 Subsequent Therapies

A table summarizing the subsequent therapies received after treatment discontinuation will be shown and subgroup analyses will be implemented.

8.6 Imputation in Incomplete Dates

Dates of certain historical or current clinical activities are key component for statistical analysis. An incomplete date results from a missing day, month or year; in that case, the missing figure can be imputed allowing for the calculation of variables, such duration and time to certain event. However, when all of them, day, month and year, are missing no imputation will be done.

Before randomization/treatment start date

All variables needed to summarize for example prior information (e.g. first diagnosis date) where partial information is available will be subject of imputation by means of SAS programming. If the day of a date is unknown then the imputed day will be 1, if the month is also unknown then the imputed date will 1/July. This assumption will be valid if the imputed date is earlier than the randomization date; otherwise, the imputed date will be the first day of the month of the randomization date (i.e. 01/Randomization month date/year).

Between treatment start and end of treatment

All date variables during treatment where information is needed and is not fully available, for example adverse events or concomitant medications, will be subject of imputation by means of SAS programming. If the day of a date is unknown then the imputed day will be 1, if the month and/or year is also unknown then the imputed date will 1/January (this assumption will be valid if the imputed date is earlier than the treatment start date; otherwise, the imputed date will be the treatment start date).

After end of treatment

A conservative approach for the variables collecting information after end of treatment where partial information is available (e.g., main time-to-event variables; PFS and OS) will be imputed by means of SAS programming. The following rules will be implemented: if the day of a date is unknown then the imputed day will be 1; if the month is also unknown, then the imputed date will be 1/July. This assumption will be valid if the imputed date occurs later than the last drug administration date; otherwise, the imputed date will be the last drug administration date plus 1 day.

Once the OS follow-up assessments will be implemented following the calendar time if a patient deceased but his/her complete death date is missing then if month/year is known then death date will be imputed as 01/Month/Year, otherwise the death date will be imputed as last time to the patient was known to be alive plus 1 day.

8.7 Variable Unit Standardization

Variables reported with different units will be homogenized to standardized variables following the International System of Units (e.g. laboratory tests, biometrical assessments...) unless otherwise specified in the following sections.

8.8 Decimal Places, Missing Values and Allowed Assessment Windows

By default, all results will be rounded to one decimal place, except when variables are integer, which will be reported without decimals (e.g., age in years, number of sites, etc.). For representing p-values four decimals will be selected as default but they could be rounded to fewer decimals if necessary. Hazard ratios will be presented with three decimal places.

Missing values will not be included in the calculation of outputs. Assessment windows as specified in the clinical protocol will be respected.

8.9 Subgroup Analyses

Some preplanned efficacy analyses are the following: subgroup analyses based on comparison of PM01183/DOX with CAV or topotecan, subgroup analyses for stratification factors (mainly CNS and CTFI), subgroup analyses for patients with primary site different to lung, subgroup analyses if enough cases for baseline PD-L1 expression (<1% *vs.* ≥1%) or PD-L1 expression (<50% *vs.* ≥50%), and the analysis of the subset of patients who received subsequent therapies.
Special attention will be put in the subgroup analysis comparing treatment arms in the CTFI after first line subsets. Subsets will be defined as [≥90 days (sensitive) vs. <90 days (resistant; R)] and adjusted p-values, one on patients with sensitive disease and one on patients with resistant disease, will be calculated by means of Bootstrap replication.
Other subgroup analyses that are implemented *a posteriori* based on clinically findings will have an exploratory nature.

Pre-specified safety subgroup analyses are: by sex (male *vs.* female), by age (<65 years-old *vs.* ≥65 years-old), by race (white *vs.* other), by number of prior lines (1 *vs.* >1 line), by BSA (<2 *vs.* ≥2) and by geographical area (USA *vs.* Europe *vs.* rest of the world).

8.10 Pharmacokinetic and Pharmacogenetic Analyses

These analyses will be detailed and reported in separate documents.

8.11 Generalised Pairwise comparison assessment

A risk-benefit measure will be calculated using the generalised pairwise comparison[8]. A favourable benefit outcome will be determined by differences in OS exceeding 2, 3 or 4 months. An unfavourable risk outcome will be determined by the occurrence of any G3-4 adverse reaction or a clinically important adverse event:

A clinically important adverse event will be defined as:

- Any AE causing death or treatment discontinuation
- Febrile neutropenia/neutropenic sepsis
- Grade 4 neutropenia lasting > 3 days
- Grade 4 thrombopenia or grade 3 thrombopenia concomitant with bleeding events.
- Grade 4 AST/ALT or grade 3 lasting >14 days.
- Treatment-related grade ≥ 2 ALT or AST increase concomitantly with ≥ 2 times the upper limit of normal (ULN) total bilirubin increase and normal alkaline phosphatase (AP).
- Grade ≥ 3 creatine phosphokinase (CPK) increase.
- Grade 3 fatigue lasting > 3 days.

- Any other grade 3/4 non-hematological AE that is suspected to be related to study drug(s), except nausea/vomiting (unless the patient is receiving an optimal anti- emetic regimen), hypersensitivity reactions, extravasations and non-clinically relevant isolated biochemical abnormalities [e.g., isolated increase in gamma-glutamyltransferase (GGT)].

9 STATISTICAL SOFTWARE

Medidata Rave® EDC will be used for data entry and clinical data management.

Medidata Balance® will be used for dynamic randomization design and management.

EAST® v.6.4 has been used to calculate sample size[9].

SAS® v.9.4 or superior will be used for all statistical analysis outputs[10].

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3. Qinghua (Kathy) Chen. Incorporating Graphics into Summary Report Tables using ODS and GTL. PharmaSUG2011 – Paper SP02.

4. Parmar M. Machin D. Survival analysis. A practical approach. Wiley, Chichester, 1995.

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7. Klein et al. SAS and R Functions to Compute Pseudo-values for Censored Data Regression. Comput Methods Programs Biomed. 2008 March ; 89(3): 289–300.

8. Buyse M. Generalized pairwise comparisons for prioritized outcomes in the two-sample problem. Statist Med 29: 3245-57, 2010.

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APPENDIX I

Applicable outputs will also be created at the time of the interim safety analysis. They will be specified as an appendix to the IDMC charter.

10 Study Patients

Study patient analysis will be carried out on the ITT population except for screening failures where no randomization is performed.

10.1 Patient Disposition

Main characteristics concerning inclusion in the study, end of treatment, withdrawal of the study and protocol deviations will be displayed in this section.

Table 10.1.1 Disposition of screened patients

Screening failure	Total	
	N	%
Yes		
No (Patient randomized)		

Listing 10.1.2 Screening failures

Patient	Inclusion/Exclusion criteria not met

Table 10.1.3 Disposition of patients

	PM01183+DOX		Control		Total	
	N	%	N	%	N	%
Randomized patients (ITT population)						
Treated patients (Safety population)						

Table 10.1.4 Disposition of patients in the control arm

	CAV		Topotecan		Total	
	N	%	N	%	N	%
Randomized patients (ITT population)						
Treated patients (Safety population)						

Listing 10.1.5 Randomized patients who were not treated

Treatment arm*	Patient	Reason

*PM01183+DOX/Topotecan/CAV

Table 10.1.6 Patients accrual by institution

			PM01183+DOX	Control	Total
No. randomized	Country 1	Institution 1			
		…			
		Total			
	…	Institution 1			
		…			
		Total			
	Total	Institution 1			
		…			
		Total			
No. treated	Country 1	Institution 1			
		…			
		Total			
	…	Institution 1			
		…			
		Total			
	Total	Institution 1			
		…			
		Total			

Table 10.1.7 Study dates

	Date
Date of first consent	
Date of first randomization	
Date of first dose of first patient	
Date of last consent	
Date of last randomization	
Date of first dose of last patient	
Date of last dose	
Last follow-up date	

Listing 10.1.8 Patients assigned to incorrect strata at the time of randomization

Treatment arm*	Patient	Actual stratum (Screening form)	Strata reported at randomization (Randomization form)

*PM01183+DOX/Topotecan/CAV

Table 10.1.9 Investigator's preference for the control arm

	PM01183+DOX		Topotecan		CAV	
	N	%	N	%	N	%
Topotecan						
CAV						

10.2 Reasons for Treatment Discontinuation

Table 10.2.1 Treatment discontinuation

Reason	PM01183+DOX		Control	
	N	%	N	%
Progressive disease (PD)				
Patient refusal to treatment				
Death				
Investigator's decision				
Study drug-related AE				
Non study drug-related AE				
Symptomatic deterioration				
Other				
Total*				

*Denominator is number of treated patients

When reason for discontinuation is study drug-related AE or study drug-related death, identify patients and describe them in depth here.

Listing 10.2.2 Reasons for treatment discontinuation other than progressive disease

Treatment arm*	Patient ID.	Reason	Last cycle	Dose in the last cycle	Date	Specify (if applicable)

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

Listing 10.2.3 AEs with reported action taken equal to 'treatment withdrawn'

Treatment arm*	Patient ID.	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	SAE	Onset date	Resolved date	Outcome

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

Table 10.2.4 Reasons for off study

Reason	PM01183+DOX		Control	
	N	%	N	%
Study termination (clinical cut-off)				
Withdrawal of consent				
Death				
Lost to follow-up				
Other				
Total				

10.3 Protocol Deviations

Classification will follow definitions made in Protocol Deviation and Non-Compliance Management Plan.

Listing 10.3.1 Protocol deviations

Treatment arm*	Patient	Classification	Deviation Category	Deviation

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

11 Efficacy Evaluation

11.1 Demographic and other Baseline Characteristics

Baseline/screening characteristics will be carried out on the ITT population.

11.1.1 Patient Characteristics at Baseline

Table 11.1.1.1 Baseline characteristics

	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
Number of patients								
Sex Male Female								
Age (years) Median (range) Mean (std)								
Age group 18-49 50-65 ≥65								
Childbearing potential?* Yes No								
Race American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander White Other (specify) Not applicable								
ECOG PS 0 1 2 …								
Smoking status Current Former Never								
Time from first diagnosis to randomization Median (range) Mean (std)								
Disease stage Limited Extensive								
Ki-67/MIB-1 expression (Small Cell non Lung patients) Median (range) Mean (std)								
Baseline CNS involvement Yes No								

	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
Disease involvement at baseline Bone Lung Lymph node Liver Brain …								
Visceral metastasis Yes No								
Number of sites involved** 1 2 … Median (range) Mean (std)								
Measurable lesion/s at baseline Yes No								
Presence of any bulky (< 50 mm *vs.* ≥ 50 mm) lesion at baseline Yes No								
Paraneoplastic syndrome at baseline Yes Cushing syndrome SIADH … No								
Physical examination by Body System examined Abnormalities found Yes No Clinically significant Not Clinically significant								
Weight (kg) Median (range) Mean (std)								
Height (cm) Median (range) Mean (std)								
Body surface area (m^2) Median (range) Mean (std) ≤ 2 m^2 > 2 m^2								

	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
BMI (kg/m^2) Median (range) Mean (std)								
BMI categories ≤ 20 20-25 25-30 > 30								
LVEF Normal Significant abnormalities Non significant abnormalities								
ECG results **PR interval (msec)** Median (range) Mean (std) **Heart Rate (bpm)** Median (range) Mean (std) **QT interval (raw) (msec)** Median (range) Mean (std) **QRS complex duration (msec)** Median (range) Mean (std) **Fridericia corrected QT** Median (range) Mean (std)								
LVEF results (MUGA) Median (range) Mean (std) **LVEF results (ECHO)** Median (range) Mean (std)								
Vital signs **Heart rate (beats/minute)** Median (range) Mean (std) **Systolic blood pressure (mmHg)** Median (range) Mean (std) **Diastolic blood pressure (mmHg)** Median (range) Mean (std) **Temperature (ºC)** Median (range) Mean (std)								

N(%) for categorical variables; Median (range)/Mean (std) for continuous variables

*Denominator is number of female patients

**Counted from Cancer History Form

Table 11.1.1.2 Severity grade for hematological tests at baseline

	Total	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4		Grade 1-4	
	N	N	%	N	%	N	%	N	%	N	%	N	%
PM01183+DOX													
Leukopenia													
Anemia													
Thrombocytopenia													
Neutropenia													
Lymphopenia													
Control													
Leukopenia													
Anemia													
Thrombocytopenia													
Neutropenia													
Lymphopenia													

Table 11.1.1.3 Hematology values at baseline

	PM01183+DOX	Control
	n Median (range) Mean (std)	n Median (range) Mean (std)
WBC		
Neutrophils		
Hemoglobin		
Platelets		
Lymphocytes		

Listing 11.1.1.4 Hematological tests not assessed at baseline

Treatment arm*	Patient ID.	Lab. test
	…	
	…	

*PM01183+DOX/Topotecan/CAV

Listing 11.1.1.5 Hematological abnormalities grade≥1 at baseline

Treatment arm*	Patient ID.	Test	Grade
	…		
	…		

*PM01183+DOX/Topotecan/CAV

Table 11.1.1.6 Severity grade de for biochemical tests at baseline

	Total	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4		Grade 1-4	
	N	N	%	N	%	N	%	N	%	N	%	N	%
PM01183+DOX													
Creatinine increase													
CPK increase													
Bilirubin increase													
AP increase													
AST increase													
ALT increase													
Control													
Creatinine increase													
CPK increase													
Bilirubin increase													
AP increase													
AST increase													
ALT increase													

Table 11.1.1.7 Biochemistry values at baseline

	PM01183+DOX	Control
	n Median (range) Mean (std)	n Median (range) Mean (std)
Creatinine		
Creatinine clearance		
CPK		
Total bilirubin		
AP		
AST		
ALT		
LDH ≤ULN >ULN		

Listing 11.1.1.8 Biochemical tests not assessed at baseline

Treatment arm*	Patient ID.	Lab. test
	…	
	…	

*PM01183+DOX/Topotecan/CAV

Listing 11.1.1.9 Biochemical abnormalities grade≥1 at baseline

Treatment arm*	Patient ID.	Test	Grade
	…		
	…		

*PM01183+DOX/Topotecan/CAV

Table 11.1.1.10 Severity grade for other metabolic tests at baseline

	Total	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4		Grade 1-4	
	N	N	%	N	%	N	%	N	%	N	%	N	%
PM01183+DOX													
Hyperglycemia													
Hypernatremia													
Hyperkalemia													
Hypercalcemia													
Hypoglycemia													
Hyponatremia													
Hypokalemia													
Hypocalcemia													
Hypoalbuminemia													
Control													
Hyperglycemia													
Hypernatremia													
Hyperkalemia													
Hypercalcemia													
Hypoglycemia													
Hyponatremia													
Hypokalemia													
Hypocalcemia													
Hypoalbuminemia													

Table 11.1.1.11 Other metabolic values at baseline

	PM01183+DOX	Control
	n Median (range) Mean (std)	n Median (range) Mean (std)
Glucose		
Sodium		
Potassium		
Calcium		
Albumin		
CRP		

Listing 11.1.1.12 Metabolic tests not assessed at baseline

Treatment arm*	Patient ID.	Lab. test
	…	
	…	

*PM01183+DOX/Topotecan/CAV

Listing 11.1.1.13 Other metabolic abnormalities grade≥1 at baseline

Treatment arm*	Patient ID.	Test	Grade
	…		
	…		

*PM01183+DOX/Topotecan/CAV

11.1.2 Prior Anticancer Therapy

Table 11.1.2.1 Prior therapy

	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
Radiotherapy Yes No								
Prior prophylactic cranial irradiation (PCI) Yes No								
Prior surgery excluding diagnostic Yes No								

Table 11.1.2.2 Prior anticancer medical therapy

	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
Number of prior regimens 1 2 … Median (range) Mean (std)								
Type Chemotherapy Inmunotherapy … **Maintenance** Yes No								
Number of prior chemotherapy lines 1 2 … Median (range) Mean (std)								
Number of prior chemotherapy agents 1 2 … Median (range) Mean (std)								
Prior agents of chemotherapy (ATC coded)* Carboplatin Cisplatin Etoposide …								
Prior inmunotherapies agents (ATC coded)* Nivolumab …								

	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
Prior immunotherapy against either PD-1 or PD-L1 Yes No								
Prior immunotherapy against either PD-1 or PD-L1 Yes (Both) Yes (PD-1) Yes (PD-L1) No								
PD-L1 expression <1% 1%-50% ≥50%								
Prior investigational agents **Others**								
CTFI after first-line treatment (calculated from dates reported and as reported in screening form) Median (range) Mean (std) ≥180 days (calculated) 90-179 days (calculated) <90 days (calculated) ≥180 days (screening form) 90-179 days (screening form) <90 days (screening form)								
Time from last prior progression to randomization Median (range) Mean (std)								
TTP to prior chemotherapy* Median (range) Mean (std)								
Time from end date of last prior chemotherapy to randomization Median (range) Mean (std)								
Best response to last prior chemotherapy therapy CR PR SD PD NE/UK/NA								
Best response to last prior immunotherapy against either PD-1 or PD-L1 CR PR SD PD NE/UK/NA								

* Sites have been instructed in the database completion guidelines to report one drug per record, but in the summary it may be requested to group some combinations, e.g. CAV

**If total number of patients with maintenance is less than 15% then take out them from calculus, if percentage is higher then censored them at the initial time of the maintenance

11.1.3 Prior Relevant Medical History

A table with the description of the most relevant abnormalities found at baseline will be provided in this section. Special attention will be given to the most relevant comorbidities (see section 6.2).

Table 11.1.3.1 Medical history

SOC	Preferred term	PM01183+DOX		Control					
				Total		Topotecan		CAV	
		N	%	N	%	N	%	N	%
Gastrointestinal disorders	Constipation								
	Diarrhoea NOS								
	…								
…	…								
	…								

11.1.4 Signs and Symptoms at Baseline

Signs and symptoms refer to any AE with onset date before the first treatment dose.

Table 11.1.4.1 Patients with signs and symptoms at baseline

	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
No. of signs and symptoms per patient								
0								
1								
2								
≥ 3								
Median (range)								
Mean (std)								

Table 11.1.4.2 Signs and symptoms at baseline (MedDRA coded)

SOC	Preferred term	Total	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1-4	
		N	N	%	N	%	N	%	N	%	N	%
PM01183+DOX												
Gastrointestinal disorders	Constipation											
	…											
	…											
Control												
Gastrointestinal disorders	Constipation											
	…											

Listing 11.1.4.3 Signs and symptoms at baseline

Treatment arm*	Patient ID.	Sign/symptom	Grade	Onset date

*PM01183+DOX/Topotecan/CAV

11.1.5 *Concomitant Medication at Baseline*

Concomitant medication at baseline according to the ATC classification.

Table 11.1.5.1 Concomitant medication at baseline (ATC1/ATC2/ATC4)

	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
Alimentary tract and Antiacids Magnesium compounds ….								
Blood and blood forming Antithrombotic agents Vitamin K antagonists …								
… …								

11.1.6 PRO scores at baseline

Table 11.1.6.1 PRO scores at baseline

Item	PM01183+DOX			Control								
				Total			Topotecan			CAV		
	N	Median (range)	Mean (std)	N	Median (range)	Mean (std)	N	Median (range)	Mean (std)	N	Median (range)	Mean (std)
EORTC QLQ-C30												
Item 1												
Item 2												
…												
Item 30												
EORTC QLQ-LC13												
Item 31												
…												
Item 43												

11.2 Measurements of Treatment Compliance

Compliance of individual patients with the treatment regimen under study will be measured and tabulated in section 12.1 and listed in appendix 16.2.5 (ICH listings).

11.3 Efficacy Analysis

Efficacy analysis will be carried out on the ITT population.

Overall survival

Table 11.3.1.1 OS (Stratified log rank test)

Variable	Stratification factors	p-value*
Treatment arm (main analysis)	Actual values (CNS and CTFI)	
Treatment arm (sensitivity)	Values reported for randomization (CNS and CTFI)	
Treatment arm (sensitivity)	Actual values (all stratification factors)	
Treatment arm (sensitivity)	Values reported for randomization (all stratification factors)	

*Stratified log rank test.

Table 11.3.1.2 Median FU for OS

	Total (PM01183+DOX and Control)	
Follow-up (descriptive way)	Median (range)	
Follow-up (reversing censor method)	Median (95%CI)	

Table 11.3.1.3 OS

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median OS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
Mean OS				-
OS at 12 months (95% CI)			Diff:	
OS at 18 months (95% CI)				
OS at 24 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.3) will be shown too.

Table 11.3.1.4 Multivariate analysis of OS (Stratification factors and treatment arm only)

Analysis of Maximum Likelihood Estimates								
Variable label	Variable values	DF	Parameter estimate	Standard error	Chi-square	Pr > ChiSq	Hazard ratio	95% Hazard ratio confidence limits

Table 11.3.1.5 Multivariate analysis of OS

Analysis of Maximum Likelihood Estimates								
Variable label	Variable values	DF	Parameter estimate	Standard error	Chi-square	Pr > ChiSq	Hazard ratio	95% Hazard ratio confidence limits

(see list of covariates in section 6.2).

Table 11.3.1.6 Proportional hazard assumption and restricted mean survival for OS

Variable	PM01183+DOX	Control	Interaction p-value
Restricted mean survival*			

*It will be calculated if proportional hazard assumption is not met.

Forest plot (Figure 11.3.1.7) summarizing main results, stratification factors and covariates in terms of OS will be prepared.

Overall survival (CAV comparison)

Table 11.3.1.8 OS *vs* CAV (Stratified log rank test)

Variable	Stratification factors	p-value*
Treatment arm	Actual values (CNS and CTFI)	
Treatment arm	Values reported for randomization (CNS and CTFI)	
Treatment arm	Actual values (all stratification factors)	
Treatment arm	Values reported for randomization (all stratification factors)	

*Stratified log rank test.

Table 11.3.1.9 OS *vs* CAV

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median OS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
Mean OS				-
OS at 12 months (95% CI)			Diff:	
OS at 18 months (95% CI)				
OS at 24 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.9) will be shown too.

Forest plot (Figure 11.3.1.10) summarizing main results, stratification factors and covariates in terms of OS will be prepared.

Overall survival (non CNS comparison)

Table 11.3.1.11 OS in non CNS (Stratified log rank test)

Variable	Stratification factors	p-value*
Treatment arm	Actual values (CNS and CTFI)	
Treatment arm	Values reported for randomization (CNS and CTFI)	
Treatment arm	Actual values (all stratification factors)	
Treatment arm	Values reported for randomization (all stratification factors)	

*Stratified log rank test.

Table 11.3.1.12 OS in non CNS

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median OS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
Mean OS				-
OS at 12 months (95% CI)			Diff:	
OS at 18 months (95% CI)				
OS at 24 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.12) will be shown too.

Forest plot (Figure 11.3.1.13) summarizing main results, stratification factors and covariates in terms of OS will be prepared.

Progression-free survival by IRC

Table 11.3.1.14 PFS by IRC (primary analysis)

Variable	Stratification factors	p-value*
Treatment arm	Actual values (CNS and CTFI)	
Treatment arm	Values reported for randomization (CNS and CTFI)	
Treatment arm	Actual values (all stratification factors)	
Treatment arm	Values reported for randomization (all stratification factors)	

*Stratified log rank test.

Table 11.3.1.15 Median FU for PFS by IRC

	Total (PM01183+DOX and Control)	
Follow-up (descriptive way)	Median (range)	
Follow-up (reversing censor method)	Median (95%CI)	

Table 11.3.1.16 PFS by IRC

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
Mean PFS				-
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.16) will be shown too.

Table 11.3.1.17 Multivariate analysis of PFS by IRC (Stratification factors and treatment arm only)

Analysis of maximum likelihood estimates								
Variable label	Variable values	DF	Parameter estimate	Standard error	Chi-square	Pr > ChiSq	Hazard ratio	95% Hazard ratio confidence limits

Table 11.3.1.18 Multivariate analysis of PFS by IRC

Analysis of maximum likelihood estimates								
Variable label	Variable values	DF	Parameter estimate	Standard error	Chi-square	Pr > ChiSq	Hazard ratio	95% Hazard ratio confidence limits

(see list of covariates in section 6.2).

Table 11.3.1.19 Proportional hazard assumption and restricted mean survival for PFS by IRC

Variable	PM01183+DOX	Control	Interaction p-value
Restricted mean survival*			

*It will be calculated if proportional hazard assumption is not met.

Forest plot (Figure 11.3.1.20) summarizing main results, stratification factors and covariates in terms of PFS by IRC will be prepared.

Progression-free survival by IA

Table 11.3.1.21 PFS by IA (Stratified log rank test)

Variable	Stratification factors	p-value*
Treatment arm	Actual values (CNS and CTFI)	
Treatment arm	Values reported for randomization (CNS and CTFI)	
Treatment arm	Actual values (all stratification factors)	
Treatment arm	Values reported for randomization (all stratification factors)	

*Stratified log rank test.

Table 11.3.1.22 Median FU for PFS by IA

	Total (PM01183+DOX and Control)	
Follow-up (descriptive way)	Median (range)	
Follow-up (reversing censor method)	Median (95%CI)	

Table 11.3.1.23 PFS by IA

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
Mean PFS				-
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.23) will be shown too.

Table 11.3.1.24 Multivariate analysis of PFS by IA (Stratification factors and treatment arm only)

Analysis of Maximum Likelihood Estimates								
Variable label	Variable values	DF	Parameter estimate	Standard error	Chi-square	Pr > ChiSq	Hazard ratio	95% Hazard ratio confidence limits

Table 11.3.1.25 Multivariate analysis of PFS by IA

Analysis of Maximum Likelihood Estimates								
Variable label	Variable values	DF	Parameter estimate	Standard error	Chi-square	Pr > ChiSq	Hazard ratio	95% Hazard ratio confidence limits

(see list of covariates in section 6.2).

Table 11.3.1.26 Proportional hazard assumption and restricted mean survival for PFS by IA

Variable	PM01183+DOX	Control	Interaction p-value
Restricted mean survival*			

*It will be calculated if proportional hazard assumption is not met.

Forest plot (Figure 11.3.1.27) summarizing main results, stratification factors and covariates in terms of PFS by IA will be prepared

Table 11.3.1.28 Time to disease assessments

Disease assessment	Treatment arm	n	Median (days)	Wilcoxon p-value
1	PM01183+DOX			
	Control			
2	PM01183+DOX			
	Control			
…	PM01183+DOX			
	Control			

-ITT population, Kaplan Meier plot (Figure 11.3.1.28) will be shown too.

Concordance PFS IRC and PFS IA

Table 11.3.1.29 Concordance PFS

	PM01183+DOX (IRC)	PM01183+DOX (IA)	Control (IRC)	Control (IA)	Parameter	p-value
N						
Events						
Censored						
Median PFS (95% CI)					Log-Rank:	LR:
PFS at 6 months (95% CI)						
PFS at 12 months (95% CI)						

Kaplan Meier plot (Figure 11.3.1.29) will be shown too.

Sensitivity PFS analyses

-Date of progression based on scheduled time instead of recorded date.

Table 11.3.1.30 PFS based on scheduled time by IRC

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.30) will be shown too.

Table 11.3.1.31 PFS based on scheduled time by IA

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.31) will be shown too.

-First date of progression combining IRC and IA assessments.

Table 11.3.1.32 PFS based on first date of progression

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.32) will be shown too.

- Date of progression moved to the prior tumor assessment.

Table 11.3.1.33 PFS moved to the prior tumor assessment by IRC

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.33) will be shown too.

Table 11.3.1.34 PFS moved to the prior tumor assessment by IA

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.34) will be shown too.

- First date of progression or death not censoring data if further antitumor therapy.

Table 11.3.1.35 PFS not censoring if further antitumor by IRC

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.35) will be shown too.

Table 11.3.1.36 PFS not censoring if further antitumor by IA

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.36) will be shown too.

Objective response and duration of response by IRC

Table 11.3.1.37 Response rate by IRC

Response	PM01183+DOX		Control		p-value
	N	%	N	%	
CR PR SD PD Unknown*					
CR+PR; n (%) and binomial exact 95% confidence interval					
DCR; n (%) and binomial exact 95% confidence interval					
CBR; n (%) and binomial exact 95% confidence interval					

(*) Including NE, non-responders and insufficient data available.

Table 11.3.1.38 Multivariate analysis of response rate by IRC (Stratification factors and treatment arm)

Analysis of Maximum Likelihood Estimates								
Variable label	Variable values	DF	Estimate	Standard error	Wald chi-square	Pr > ChiSq	Odds ratio estimate	95% Wald confidence limits

Table 11.3.1.39 Multivariate analysis of response rate by IRC

Analysis of Maximum Likelihood Estimates								
Variable label	Variable values	DF	Estimate	Standard error	Wald chi-square	Pr > ChiSq	Odds ratio estimate	95% Wald confidence limits

(See list of covariates in section 6.2).

Forest plot (Figure 11.3.1.40) summarizing main results, stratification factors and covariates in terms of response by IRC will be prepared.

A waterfall plot (Figure 11.3.1.41) describing the best variation of the sum of target lesions during the treatment will be prepared.

Table 11.3.1.42 DR by IRC

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median DR (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:

Objective response and duration of response by IA

Table 11.3.1.43 Response rate by IA

Response	PM01183+DOX		Control		p-value
	N	%	N	%	
CR PR SD PD Unknown*					
CR+PR; n (%) and binomial exact 95% confidence interval					
DCR; n (%) and binomial exact 95% confidence interval					
CBR; n (%) and binomial exact 95% confidence interval					

(*) Including NE, non-responders and insufficient data available.

Table 11.3.1.44 Multivariate analysis of response rate by IA (Stratification factors and treatment arm)

Analysis of maximum likelihood estimates								
Variable label	Variable values	DF	Estimate	Standard error	Wald chi-square	Pr > ChiSq	Odds ratio estimate	95% Wald confidence limits

Table 11.3.1.45 Multivariate analysis of response rate by IA

Analysis of maximum likelihood estimates								
Variable label	Variable values	DF	Estimate	Standard error	Wald chi-square	Pr > ChiSq	Odds ratio estimate	95% Wald confidence limits

(See list of covariates in section 6.2).

A forest plot (Figure 11.3.1.46) summarizing main results, stratification factors and covariates in terms of response by IA will be prepared.

A waterfall plot (Figure 11.3.1.47) describing the best variation of the sum of target lesions during the treatment will be prepared.

Table 11.3.1.48 DR by IA

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median DR (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:

Progression and censoring reasons by IRC/IA

Table 11.3.1.49 Progression type by IRC/IA

Reason	IRC				IA			
	PM01183+DOX		Control		PM01183+DOX		Control	
	N	%	N	%	N	%	N	%
Target lesion Non-target lesion Death due to malignant disease Other*								

(*)Please specify.

Table 11.3.1.50 Censoring reason by IRC/IA

Reason	IRC				IA			
	PM01183+DOX		Control		PM01183+DOX		Control	
	N	%	N	%	N	%	N	%
Free of progression last tumor assessment Subsequent therapy before documented progression Not treated Other*								

(*)Please specify.

A sensitivity analysis by IA will be performed on patients who have CNS progression and continue on treatment excluding the CNS progression. These patients will be followed until the next progression or censoring in the last tumor assessment; if the patient is discontinued from treatment, he/she will be censored on that date.

Table 11.3.1.51 Sensitivity PFS according to CNS progressions by IA

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.51) will be shown too.

Time to treatment failure

Table 11.3.1.52 Time to treatment failure by IA

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.52) will be shown too.

Time to brain mets

Table 11.3.1.53 Time to clinical diagnosis of brain mets by IA

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.53) will be shown too.

Subgroup analyses

Forest plots summarizing main results, stratification factors and covariates.

Comparison between PM01183+DOX and CAV according to Investigator's preference will be plotted.

- Figure 11.3.1.54 PFS by IRC (PM01183 *vs.* CAV)
- Figure 11.3.1.55 PFS by IA (PM01183 *vs.* CAV)
- Figure 11.3.1.56 OS (PM01183 *vs.* CAV)
- Figure 11.3.1.57 RR by IRC (PM01183 *vs.* CAV)
- Figure 11.3.1.58 RR by IA (PM01183 *vs.* CAV)
- Figure 11.3.1.59 DR by IRC (PM01183 *vs.* CAV)
- Figure 11.3.1.60 DR by IA (PM01183 *vs.* CAV)

Comparison between PM01183+DOX and Topotecan according to Investigator's preference will be plotted.

- Figure 11.3.1.61 PFS by IRC (PM01183 *vs.* Topotecan)
- Figure 11.3.1.62 PFS by IA (PM01183 *vs.* Topotecan)
- Figure 11.3.1.63 OS (PM01183 *vs.* Topotecan)
- Figure 11.3.1.64 RR by IRC (PM01183 *vs.* Topotecan)
- Figure 11.3.1.65 RR by IA (PM01183 *vs.* Topotecan)
- Figure 11.3.1.66 DR by IRC (PM01183 *vs.* Topotecan)
- Figure 11.3.1.67 DR by IA (PM01183 *vs.* Topotecan)

Comparison in patients with no CNS involvement.

- Figure 11.3.1.68 Patients with no CNS. PFS by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.69 Patients with no CNS. PFS by IA (PM01183 *vs.* Control)
- Figure 11.3.1.70 Patients with no CNS. OS (PM01183 *vs.* Control)
- Figure 11.3.1.71 Patients with no CNS. RR by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.72 Patients with no CNS. RR by IA (PM01183 *vs.* Control)
- Figure 11.3.1.73 Patients with no CNS. DR by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.74 Patients with no CNS. DR by IA (PM01183 *vs.* Control)

Comparison in patients with CNS involvement.

- Figure 11.3.1.75 Patients with CNS. PFS by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.76 Patients with CNS. PFS by IA (PM01183 *vs.* Control)
- Figure 11.3.1.77 Patients with CNS. OS (PM01183 *vs.* Control)
- Figure 11.3.1.78 Patients with CNS. RR by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.79 Patients with CNS. RR by IA (PM01183 *vs.* Control)

- Figure 11.3.1.80 Patients with CNS. DR by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.81 Patients with CNS. DR by IA (PM01183 *vs.* Control)

Comparison in patients with no CNS involvement and CTFI≥90 days (sensitive).

- Figure 11.3.1.82 Patients with no CNS in sensitive. PFS by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.83 Patients with no CNS in sensitive. PFS by IA (PM01183 *vs.* Control)
- Figure 11.3.1.84 Patients with no CNS in sensitive. OS (PM01183 *vs.* Control)
- Figure 11.3.1.85 Patients with no CNS in sensitive. RR by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.86 Patients with no CNS in sensitive. RR by IA (PM01183 *vs.* Control)
- Figure 11.3.1.87 Patients with no CNS in sensitive. DR by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.88 Patients with no CNS in sensitive. DR by IA (PM01183 *vs.* Control)

Comparison in patients with no CNS involvement and CTFI<90 days (resistant).

- Figure 11.3.1.89 Patients with no CNS in resistant. PFS by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.90 Patients with no CNS in resistant. PFS by IA (PM01183 *vs.* Control)
- Figure 11.3.1.91 Patients with no CNS in resistant. OS (PM01183 *vs.* Control)
- Figure 11.3.1.92 Patients with no CNS in resistant. RR by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.93 Patients with no CNS in resistant. RR by IA (PM01183 *vs.* Control)
- Figure 11.3.1.94 Patients with no CNS in resistant. DR by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.95 Patients with no CNS in resistant. DR by IA (PM01183 *vs.* Control)

Comparison in patients with CTFI≥90 days (sensitive).

- Figure 11.3.1.96 Patients with CTFI≥90 (sensitive). PFS by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.97 Patients with CTFI≥90 (sensitive). PFS by IA (PM01183 *vs.* Control)
- Figure 11.3.1.98 Patients with CTFI≥90 (sensitive). OS (PM01183 *vs.* Control)
- Figure 11.3.1.99 Patients with CTFI≥90 (sensitive). RR by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.100 Patients with CTFI≥90 (sensitive). RR by IA (PM01183 *vs.* Control)
- Figure 11.3.1.101 Patients with CTFI≥90 (sensitive). DR by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.102 Patients with CTFI≥90 (sensitive). DR by IA (PM01183 *vs.* Control)

Comparison in patients with CTFI<90 days (resistant).

- Figure 11.3.1.103 Patients with CTFI<90 (resistant). PFS by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.104 Patients with CTFI<90 (resistant). PFS by IA (PM01183 *vs.* Control)
- Figure 11.3.1.105 Patients with CTFI<90 (resistant). OS (PM01183 *vs.* Control)
- Figure 11.3.1.106 Patients with CTFI<90 (resistant). RR by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.107 Patients with CTFI<90 (resistant). RR by IA (PM01183 *vs.* Control)
- Figure 11.3.1.108 Patients with CTFI<90 (resistant). DR by IRC (PM01183 *vs.* Control)
- Figure 11.3.1.109 Patients with CTFI<90 (resistant). DR by IA (PM01183 *vs.* Control)

Patients with primary site different to lung will be plotted.

- Figure 11.3.1.110 Primary site different to lung. PFS by IRC (PM01183+DOX *vs.* Control)
- Figure 11.3.1.111 Primary site different to lung. PFS by IA (PM01183+DOX *vs.* Control)
- Figure 11.3.1.112 Primary site different to lung. OS (PM01183+DOX *vs.* Control)
- Figure 11.3.1.113 Primary site different to lung. RR by IRC (PM01183+DOX *vs.* Control)
- Figure 11.3.1.114 Primary site different to lung. RR by IA (PM01183+DOX *vs.* Control)
- Figure 11.3.1.115 Primary site different to lung. DR by IRC (PM01183+DOX *vs.* Control)
- Figure 11.3.1.116 Primary site different to lung. DR by IA (PM01183+DOX *vs.* Control)

For baseline PD-L1 expression (<1% *vs.* ≥1%).

- Figure 11.3.1.117 Baseline PD-L1 expression. PFS by IRC (PM01183+DOX *vs.* Control)
- Figure 11.3.1.118 Baseline PD-L1 expression. PFS by IA (PM01183+DOX *vs.* Control)
- Figure 11.3.1.119 Baseline PD-L1 expression. OS (PM01183+DOX *vs.* Control)
- Figure 11.3.1.120 Baseline PD-L1 expression. RR by IRC (PM01183+DOX *vs.* Control)
- Figure 11.3.1.121 Baseline PD-L1 expression. RR by IA (PM01183+DOX *vs.* Control)
- Figure 11.3.1.122 Baseline PD-L1 expression. DR by IRC (PM01183+DOX *vs.* Control)
- Figure 11.3.1.123 Baseline PD-L1 expression. DR by IA (PM01183+DOX *vs.* Control)

For baseline PD-L1 expression (<50% *vs.* ≥50%).

- Figure 11.3.1.124 Baseline PD-L1 expression. PFS by IRC (PM01183+DOX *vs.* Control)
- Figure 11.3.1.125 Baseline PD-L1 expression. PFS by IA (PM01183+DOX *vs.* Control)
- Figure 11.3.1.126 Baseline PD-L1 expression. OS (PM01183+DOX *vs.* Control)
- Figure 11.3.1.127 Baseline PD-L1 expression. RR by IRC (PM01183+DOX *vs.* Control)
- Figure 11.3.1.128 Baseline PD-L1 expression. RR by IA (PM01183+DOX *vs.* Control)
- Figure 11.3.1.129 Baseline PD-L1 expression. DR by IRC (PM01183+DOX *vs.* Control)
- Figure 11.3.1.130 Baseline PD-L1 expression. DR by IA (PM01183+DOX *vs.* Control)

Subsequent therapies.

- Figure 11.3.1.131 Time to first subsequent therapy (PM01183+DOX *vs.* Control)
- Figure 11.3.1.132 OS from first subsequent therapy (PM01183+DOX *vs.* Control)
- Figure 11.3.1.133 OS censoring at first subsequent therapy (PM01183+DOX *vs.* Control)
- Figure 11.3.1.134 OS in patients without subsequent therapy (PM01183+DOX *vs.* Control)
- Figure 11.3.1.135 Time to first PD-1/PD-L1 subsequent therapy (PM01183+DOX *vs.* Control)
- Figure 11.3.1.136 OS from first PD-1/PD-L1 therapy (PM01183+DOX *vs.* Control)

In the Forest plots, continuous variables not categorized in the definition will be classified into two categories taking as reference the median value. The groups will be created as below or equal the median value, and above the median value.

Subgroup analysis comparing PFS by IRC in the CTFI after first line subsets.

Table 11.3.1.137 PFS by IRC according to prior CTFI

Subset	p-value*
≥90 days (sensitive)	
<90 days (resistant; R)	

*Adjusted p-value by Bootstrap replication.

Generalised Pairwise comparison

Table 11.3.1.138 Generalised Pairwise comparison

	Arm A	Arm B	-	p-value
2 months OS and any G3-4 adverse reaction				
2 months OS and important AE				
3 months OS and any G3-4 adverse reaction				
3 months OS and important AE				
4 months OS and any G3-4 adverse reaction				
4 months OS and important AE				

Characteristics of responders

A summary of the main characteristics of patients showing clinical benefit, defined as patients with response or PFS≥4 months by IRC/IA, will be shown.

Listing 11.3.1.139 Characteristics of patients with clinical benefit

Treatment arm*	Patient ID.	Age	Strata	Prior therapy**	Cycles received	RR by IRC/IA	PFS by IRC/IA	DR by IRC/IA	OS

*PM01183+DOX/Topotecan/CAV
**Last prior therapy data; Setting, Best response and prior PFS.

12 Safety Analysis

Safety analysis will be carried out on the safety population.

12.1 Extent of Exposure

12.1.1 Treatment Administration

Table 12.1.1.1 Number of cycles administered and time on treatment

	PM01183+DOX*		Control					
			Total		Topotecan		CAV	
No. of cycles administered per patient	N	%	N	%	N	%	N	%
1 2 3 …								
Median (range) / Mean (std)								
Time on treatment (weeks) Median (range) / Mean (std)								

*Including when PM01183 is administered alone

Table 12.1.1.2 Summary of dose received

	PM01183+DOX			Control			
	PM01183 (combination)	PM01183 (alone)	DOX	Topotecan	Cy	DOX	VCR
Cumulative dose (mg/m²) Median (range) / Mean (std)							
Dose intensity (mg/m²/wk) Median (range) / Mean (std)							
Relative dose intensity (%) Median (range) / Mean (std)							

12.1.2 Cycle Delays

12.1.2.1 Number of Patients and Cycles with Dosing Delay, any Relationship

Table 12.1.2.1.1 Number of patients and cycles with dosing delay, any relationship

	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
No. of patients treated								
No. of patients susceptible to be delayed*								
No. of patients with any dose delay								
No. of patients with any drug related dose delay								
Hematological reason								
Non-hematological reason								
Both reasons								
No. of cycles administered								
No. of cycles susceptible to be delayed**								
No. of cycles with dosing delay***								
No. of patients with No cycles delayed 1 cycle delayed 2 cvcles delaved ≥ 3 cycles delayed								

* Excluding patients who received only the first cycle.
** All cycles excluding first cycle.
*** Denominator= Number of cycles susceptible to be delayed.

Table 12.1.2.1.2 Number of patients and cycles with dosing delay according to the relationship

	PM01183+DOX				Control											
					Total				Topotecan				CAV			
	Rel**		No		Rel**		No		Rel**		No		Rel**		No	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
No. of patients with No cycles delayed 1 cycle 2 cycles ≥ 3 cycles																
No. of cycles with dosing delay*																

* Denominator= Number of cycles susceptible to be delayed.
**Related: Hematological reason, non-hematological reason or both. If the cause is related and not related the most conservative approach will be used (i.e. counted only once as related).

Table 12.1.2.1.3 Duration of dosing delay

Length of delay	PM01183+DOX						Control															
							Total						Topotecan				CAV					
	Rel*		No		All		Rel*		No		All		Rel*		No		All		Rel*		No		All	
Median (range) Mean (std)																						
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
<=7 days																						
(7,14] days																						
>14 days																						

*Related: Hematological reason, non-hematological reason or both. If the cause is related and not related the most conservative approach will be used (i.e. counted only once as related).

12.1.2.2 Number of Delays According to Cycle Number

Table 12.1.2.2.1 Number and reasons of delays according to cycle number

	PM01183+DOX						Control																	
							Total						Topotecan						CAV					
	Cycle 2		Cycle n^{th}		All		Cycle 2		Cycle n^{th}		All		Cycle 2		Cycle n^{th}		All		Cycle 2		Cycle n^{th}		All	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Number of delays																								
Related*																								
Hema.																								
Non hema.																								
Both																								
Non related*																								

* Denominator= Number of cycles susceptible to be delayed.

The distribution of delays according to the cycle administered will be studied by means of counts and percentages. The reasons for cycle delay will be detailed, specifying how many were due to treatment and how many were not.

Listing 12.1.2.2.2 Patients and cycles with dosing delays

Treatment arm*	Patient ID.	Cycle	Reason of delay	Delay (days)

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

Listing 12.1.2.2.3 AEs associated with a cycle delay as action taken

Treatment arm*	Patient ID.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Outcome

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

12.1.3 Dose Reductions

Table 12.1.3.1 Number of patients and cycles with dose reduction, any relationship

	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
No. of patients treated								
No. of patients susceptible to be dose reduced*								
No. of patients with dose reductions								
No. of patients with any drug related dose								
Hematological reason								
Non-hematological reason								
Both reasons								
No. of cycles administered								
No. of cycles susceptible to be dose reduced**								
No. of cycles with dose reduction***								
No. of patients with No reductions 1 reduction 2 reductions								

* Excluding patients who received only the first cycle.
** All cycles excluding the first cycle.
*** Denominator= Number of cycles susceptible to be reduced.

Table 12.1.3.2 Number of patients and cycles with dose reduction according to relationship

	PM01183+DOX				Control											
					Total				Topotecan				CAV			
	Rel**		No		Rel**		No		Rel**		No		Rel**		No	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
No. of patients with No reductions 1 reduction 2 reductions ≥ 3 reductions																
No. of cycles with dose reduction*																

* Denominator= Number of cycles susceptible to be reduced.
**Hematological reason, non-hematological reason or both. If the cause is related and not related the most conservative approach will be used (i.e. counted only once as related).

Table 12.1.3.3 Number and reasons of reductions according to cycle number

	PM01183+DOX						Control															
							Total						Topotecan						CAV			
	Cycle 2		Cycle n^{th}		All		Cycle 2		Cycle n^{th}		All		Cycle 2		Cycle n^{th}		All		Cycle 2		Cycle n^{th}		All	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Number of reductions																								
Related*																								
Hema.																								
Non hema.																								
Both																								
Non related*																								

* Denominator= Number of cycles susceptible to be reduced.

Listing 12.1.3.4 Dose reductions

Treatment arm*	Patient ID.	Cycle	Dose	Reason

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

Listing 12.1.3.5 AEs associated with a dose reduction as action taken

Treatment arm*	Patient ID.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Serious Outcome

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

12.2 Adverse Events (AEs)

12.2.1 Adverse Events

AE refers to any event with onset date after the first treatment dose. AEs will be described irrespective of their relationship to the drug and as drug-related events stated as Related to Study Drug or Unknown. Safety will be described according to the NCI-CTCAE v.4. AEs consisting of laboratory abnormalities (e.g., neutropenia) may be under-reported as AEs. Since these events are better evaluated using objective laboratory results, laboratory abnormalities will be discussed in Section 12.4.

The type of toxicity and worst grade or severity by cycle and by patient will be summarized according to System Organ Class (SOC) and Preferred Term (PT) as per the MedDRA dictionary. Subsequent grouping of similar or clinically related items might be appropriate at the time of the analysis. Tables will be organized by category of events using SOC and in descending frequencies (e.g. higher to lower).

12.2.2 Display of Adverse Events

Table 12.2.2.1 Summary of adverse events

Category	PM01183+DOX	Control
	N (%)	N (%)
Number of patients with any AE		
Number of patients with any drug-related AE		
Number of patients with any grade 3/4 AE		
Number of patients with any grade 4 AE		
Number of patients with any grade 3/4 drug-related AE		
Number of patients with any grade 4 drug-related AE		
Number of patients with any SAE in clinical database		
Number of patients with any drug-related SAE in clinical database		
Number of patients with any grade 3/4 SAE in clinical database		
Number of patients with any grade 4 SAE in clinical database		
Number of patients with any grade 3/4 drug-related SAE in clinical database		
Number of patients with any grade 4 drug-related SAE in clinical database		
Number of patients with death associated with AEs		
Number of patients with death associated with drug-related AEs		
Number of patients with treatment discontinuations associated with AEs		
Number of patients with treatment discontinuations associated with drug-related AEs		
Number of patients with delays associated with AEs		
Number of patients with delays associated with drug-related AEs		
Number of patients with reductions associated with AEs		
Number of patients with reductions associated with drug-related AEs		

Table 12.2.2.2 Drug-related adverse events. Worst grade by patient

Category/MedDRA Code		Grade																			
		PM01183+DOX										Control									
		1		2		…		G≥1		G≥3		1		2		…		G≥1		G≥3	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Blood and lymphatic system disorders																					
	Anaemia NOS																				
	…																				
Cardiac disorders																					
	Arrhythmia NOS																				
	…																				
...																					

Table 12.2.2.3 Drug-related adverse events. Worst grade by cycle

Category/MedDRA Code		Grade																			
		PM01183+DOX										Control									
		1		2		…		G≥1		G≥3		1		2		…		G≥1		G≥3	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Blood and lymphatic system disorders																					
	Anaemia NOS																				
	…																				
Cardiac disorders																					
	Arrhythmia NOS																				
	…																				
...																					

Table 12.2.2.4 Adverse Events regardless of relationship. Worst grade by patient

Category/MedDRA Code		**Grade**																			
		PM01183+DOX										**Control**									
		1		**2**		**…**		**G≥1**		**G≥3**		**1**		**2**		**…**		**G≥1**		**G≥3**	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Blood and lymphatic system disorders																					
	Anaemia NOS																				
	…																				
Cardiac disorders																					
	Arrhythmia NOS																				
	…																				
...																					

Table 12.2.2.5 Adverse Events regardless of relationship. Worst grade by cycle

Category/MedDRA Code		**Grade**																			
		PM01183+DOX										**Control**									
		1		**2**		**…**		**G≥1**		**G≥3**		**1**		**2**		**…**		**G≥1**		**G≥3**	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Blood and lymphatic system disorders																					
	Anaemia NOS																				
	…																				
Cardiac disorders																					
	Arrhythmia NOS																				
	…																				
...																					

Listing 12.2.2.6 Drug-related grade 3/4 adverse events. Worst grade by cycle

Treatment arm*	Patient ID.	Cycle	SOC Name	PTCode	Grade

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

Listing 12.2.2.7 Grade 3/4 adverse events regardless of relationship. Worst grade by cycle

Treatment arm*	Patient ID.	Cycle	SOC Name	PTCode	Grade

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

12.2.3 Evolution of Signs and Symptoms during the Treatment

Worst grade of signs and symptoms present at baseline in a percentage≥10% or grade ≥3 and their evolution during treatment will be shown regardless of relationship.

Table 12.2.3.1 Shift of signs and symptoms during treatment

MedDRA PT	Baseline grade	Worst grade per patient during treatment							
		Grade 1		Grade 2		Grade 3		Grade 4	
		N	%	N	%	N	%	N	%
PM01183+DOX									
Constipation	1								
	2								
	…								
...	1								
	…								
Control									
Constipation	1								
	…								

12.2.4 Shift of AEs between combination and single agent administration

In patients randomized to PM01183+Doxorubicin who will be treated with single agent PM01183 the worst grade of AEs related present in a percentage≥10% or with grade ≥3 and their evolution during single arm treatment will be shown.

Table 12.2.4.1 Shift of AEs in PM01183

MedDRA PT	Worst grade per patient during combination treatment	Worst grade per patient during single agent treatment							
		Grade 1		Grade 2		Grade 3		Grade 4	
		N	%	N	%	N	%	N	%
PM01183+DOX									
Constipation	1								
	2								
	…								
...	1								
	…								

12.3 Serious Adverse Events and Deaths.

12.3.1 Serious Adverse Events

Table 12.3.1.1 Drug-related serious adverse events. Worst grade by patient

Category/MedDRA Code		**Grade**																			
		PM01183+DOX										**Control**									
		1		**2**		**…**		**G≥1**		**G≥3**		**1**		**2**		**…**		**G≥1**		**G≥3**	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Blood and lymphatic system disorders																					
	Anaemia NOS																				
	…																				
Cardiac disorders																					
	Arrhythmia NOS																				
	…																				

Table 12.3.1.2 Drug-related serious adverse events. Worst grade by cycle

Category/MedDRA Code		Grade																			
		PM01183+DOX										Control									
		1		2		…		G≥1		G≥3		1		2		…		G≥1		G≥3	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Blood and lymphatic system disorders																					
	Anaemia NOS																				
	…																				
Cardiac disorders																					
	…																				
	...																				

Table 12.3.1.3 Serious adverse events regardless of relationship. Worst grade by patient

Category/MedDRA Code		Grade																			
		PM01183+DOX										Control									
		1		2		…		G≥1		G≥3		1		2		…		G≥1		G≥3	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Blood and lymphatic system disorders																					
	Anaemia NOS																				
	…																				
Cardiac disorders																					
	Arrhythmia NOS																				
	…																				
...																					
	...																				

Table 12.3.1.4 Serious adverse events regardless of relationship. Worst grade by cycle

Category/MedDRA Code		**Grade**																			
		PM01183+DOX										**Control**									
		1		**2**		**…**		**G≥1**		**G≥3**		**1**		**2**		**…**		**G≥1**		**G≥3**	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Blood and lymphatic system disorders																					
	Anaemia NOS																				
	…																				
Cardiac disorders																					
	Arrhythmia NOS																				
	…																				
...																					

Listing 12.3.1.5 Drug-related grade 3/4 serious adverse events. Worst grade by cycle

Treatment arm*	Patient ID.	Cycle	SOC Name	PTCode	Grade

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

Listing 12.3.1.6 Grade 3/4 serious adverse events regardless of relationship. Worst grade by cycle

Treatment arm*	Patient ID.	Cycle	SOC Name	PTCode	Grade

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

12.3.2 Deaths

Table 12.3.2.1 Cause of death

Reason[#]	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
Malignant disease								
Study drug-related AE								
Non study drug-related AE								
Other								
Total								

(#) Denominator=Number of patients who died

Listing 12.3.2.2 Deaths

Treatment arm[*]	Patient ID.	Death date	Cause	Number of cycles administered	Last infusion date	Time on treatment[**]	Time from Last dose[***]

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

**Time on treatment: defined as the date of the last infusion minus the first infusion date plus 30 days; or the date of death minus the first infusion date; or the date of start of new antitumor therapy minus the first infusion date (whichever comes first).

***Time from the last dose: defined as the date of death minus the last infusion date.

Listing 12.3.2.3 AEs reported as Fatal**

Treatment arm[*]	Patient ID.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV. **Outcome=death

12.4 Clinical Laboratory Evaluation

12.4.1 Hematological Abnormalities

Hematological toxicities classified according to NCI-CTCAE v.4 will be calculated for all cycles. The worst grade reached by each patient during treatment will also be calculated.

Table 12.4.1.1 Hematological abnormalities, worst grade per patient

	Grade																			
	PM01183+DOX										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Leukopenia																				
Anemia																				
Thrombocytopenia																				
Neutropenia																				
Lymphopenia																				

Listing 12.4.1.2 Hematological tests not assessed at any treatment visit by patient

Treatment arm*	Patient ID.	Lab. test
	…	
	…	

*PM01183+DOX/Topotecan/CAV

Table 12.4.1.3 Hematological abnormalities, worst grade per cycle

	Grade																			
	PM01183+DOX										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Leukopenia																				
Anemia																				
Thrombocytopenia																				
Neutropenia																				
Lymphopenia																				

Table 12.4.1.4 Hematological abnormalities, worst grade per cycle by cycle

	Grade																			
	PM01183+DOX										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Cycle 1																				
Leukopenia																				
Anemia																				
Thrombocytopenia																				
Neutropenia																				
Lymphopenia																				
Cycle ...																				

Listing 12.4.1.5 Hematological tests not assessed by patient and cycle

Treatment arm*	Patient ID.	Cycle	Lab. test
	…		
	…		

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

Listing 12.4.1.6 Grade 3/4 hematological abnormalities. Worst grade by cycle

Treatment arm*	Patient ID.	Cycle	Test	Grade

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

12.4.2 Biochemical Abnormalities

Table 12.4.2.1 Biochemical abnormalities, worst grade per patient

	Grade																			
	PM01183+DOX										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Creatinine increase																				
CPK increase																				
Bilirubin increase																				
AP increase																				
AST increase																				
ALT increase																				

Listing 12.4.2.2 Biochemical tests not assessed at any treatment visit by patient

Treatment arm*	Patient ID.	Lab. test
	…	
	…	

*PM01183+DOX/Topotecan/CAV

Table 12.4.2.3 Biochemical abnormalities, worst grade per cycle

	Grade																			
	PM01183+DOX										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Creatinine increase																				
CPK increase																				
Bilirubin increase																				
AP increase																				
AST increase																				
ALT increase																				

Table 12.4.2.4 Biochemical abnormalities, worst grade per cycle by cycle

	Grade																			
	PM01183+DOX										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Cycle 1																				
Creatinine increase																				
CPK increase																				
Bilirubin increase																				
AP increase																				
AST increase																				
ALT increase																				
Cycle ...																				

Listing 12.4.2.5 Biochemical tests not assessed by patient and cycle

Treatment arm*	Patient ID.	Cycle	Lab. test
	…		
	…		

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

Listing 12.4.2.6 Grade 3/4 biochemical abnormalities. Worst grade by cycle

Treatment arm*	Patient ID.	Cycle	Test	Grade

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

12.4.3 Other Metabolic Parameters

Table 12.4.3.1 Metabolic abnormalities, worst grade per patient

	Grade																			
	PM01183+DOX										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Hyperglycemia																				
Hypernatremia																				
Hyperkalemia																				
Hypercalcemia																				
Hypoglycemia																				
Hyponatremia																				
Hypokalemia																				
Hypocalcemia																				
Hypoalbuminemia																				

Listing 12.4.3.2 Metabolic tests not assessed at any treatment visit by patient

Treatment arm*	Patient ID.	Lab. test
	…	

*PM01183+DOX/Topotecan/CAV

Table 12.4.3.3 Metabolic abnormalities, worst grade per cycle

	Grade																			
	PM01183+DOX										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Hyperglycemia																				
Hypernatremia																				
Hyperkalemia																				
Hypercalcemia																				
Hypoglycemia																				
Hyponatremia																				
Hypokalemia																				
Hypocalcemia																				
Hypoalbuminemia																				

Table 12.4.3.4 Metabolic abnormalities, worst grade per cycle by cycle

	Grade																			
	PM01183+DOX										**Control**									
	0		**1**		**…**		**G≥1**		**G≥3**		**0**		**1**		**…**		**G≥1**		**G≥3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Cycle 1																				
Hyperglycemia																				
Hypernatremia																				
Hyperkalemia																				
Hypercalcemia																				
Hypoglycemia																				
Hyponatremia																				
Hypokalemia																				
Hypocalcemia																				
Hypoalbuminemia																				
Cycle ...																				

Listing 12.4.3.5 Metabolic tests not assessed by patient and cycle

Treatment arm*	Patient ID.	Cycle	Lab. test
	…		
	…		

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

Listing 12.4.3.6 Grade 3/4 metabolic abnormalities. Worst grade by cycle

Treatment arm*	Patient ID.	Cycle	Test	Grade

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

12.4.4 Laboratory Values over Time

A summary of the laboratory values found in all patients will be shown.

Laboratory abnormality categories will be defined as:

-Hematological abnormalities, including leukopenia, neutropenia, anemia, thrombocytopenia and lymphopenia.

-Biochemical abnormalities, including creatinine increase, CPK increase, total bilirubin increase, AP increase, AST increase and ALT increase.

-Other metabolic abnormalities, including hyperglycemia, hypernatremia, hyperkalemia, hypercalcemia, hypoglycemia, hyponatremia, hypokalemia, hypocalcemia and hypoalbuminemia.

Table 12.4.4.1 Summary of laboratory values

Category	PM01183+DOX	Control
	N (%)	N (%)
Any abnormality (G1/4) in laboratory value (hema, bio or metabolic)		
Any abnormality (G3/4) in laboratory value (hema, bio or metabolic)		
Any abnormality (G4) in laboratory value (hema, bio or metabolic)		
Any abnormality (G1/4) in hematological value		
Any abnormality (G3/4) in hematological value		
Any abnormality (G4) in hematological value		
Any abnormality (G1/4) in biochemical value		
Any abnormality (G3/4) in biochemical value		
Any abnormality (G4) in biochemical value		
Any abnormality (G1/4) in other metabolic value		
Any abnormality (G3/4) in other metabolic value		
Any abnormality (G4) in other metabolic value		

The worst grade during treatment and in the first cycle compared to baseline will be shown for hematological and biochemical parameters.

Table 12.4.4.2 Shift of hematological abnormalities, worst grade per patient *vs.* baseline

	Baseline grade*	Worst grade per patient during treatment							
		Grade 0		Grade 1		Grade …		Grade 4	
		N	%	N	%	N	%	N	%
PM01183+DOX									
Leukopenia	0								
	1								
	…								
Neutropenia	0								
	…								
…**	0								
	…								
Control									
Leukopenia	0								
	1								
	…								
Neutropenia	0								
	…								
…**	0								

*Defined as the last value recorded before or on the date of first infusion.
** Anemia, thrombocytopenia and lymphopenia.

Table 12.4.4.3 Shift of hematological abnormalities (PM01183), worst grade during combination *vs.* single agent

	Worst grade per patient during combination treatment	Worst grade per patient during single agent treatment							
		Grade 0		Grade 1		Grade …		Grade 4	
		N	%	N	%	N	%	N	%
Leukopenia	0								
	1								
	…								
Neutropenia	0								
	…								
…*	0								

*Anemia, thrombocytopenia and lymphopenia.

Table 12.4.4.4 Shift of biochemical abnormalities, worst grade per patient *vs.* baseline

	Baseline grade*	Worst grade per patient during treatment							
		Grade 0		Grade 1		Grade …		Grade 4	
		N	%	N	%	N	%	N	%
PM01183+DOX									
ALT	0								
	1								
	…								
AST	0								
	…								
…**	0								
	…								
Control									
ALT	0								
	1								
	…								
AST	0								
	…								
…**	0								
	…								

*Defined as the last value recorded before or on the date of first infusion.
** Total bilirubin, AP, CPK, creatinine, hyperglycemia, hypernatremia, hyperkalemia, hypoglycemia, hyponatremia, hypokalemia and hypoalbuminemia.

Table 12.4.4.5 Shift of biochemical abnormalities (PM01183), worst grade during combination *vs.* single agent

	Worst grade per patient during combination treatment	Worst grade per patient during single agent treatment							
		Grade 0		Grade 1		Grade …		Grade 4	
		N	%	N	%	N	%	N	%
ALT	0								
	1								
	…								
AST	0								
	…								
…*	0								
	…								

* Total bilirubin, AP, CPK, creatinine, hyperglycemia, hypernatremia, hyperkalemia, hypoglycemia, hyponatremia, hypokalemia and hypoalbuminemia.

Median intercycle figures showing PM01183+DOX and Control arms for laboratory values will be added.

- Figure 12.4.4.6 Median nadir values for platelets
- Figure 12.4.4.7 Median nadir values for neutrophils
- Figure 12.4.4.8 Median peak values for AST
- Figure 12.4.4.9 Median peak values for ALT

Example intercycle graph

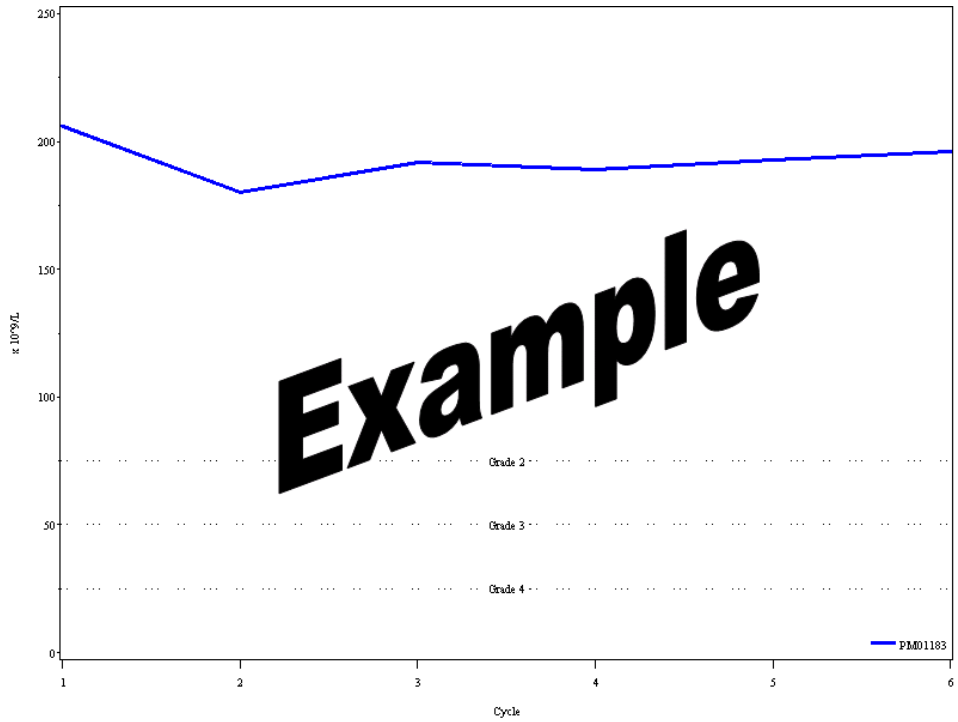


Table 12.4.4.10 Fisher exact test. Worst grade <3 *vs.* grade ≥3 by patient

	PM01183+DOX		Control		p-value
	Grade <3	Grade ≥3	Grade <3	Grade ≥3	
Thrombocytopenia					
Neutropenia					
Febrile Neutropenia					
Neutropenic Sepsis					
Neutropenic Infection					
AP					
Bilirubin					
AST					
ALT					
CPK					
Nausea					
Vomiting					
Fatigue					
Other*					

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.4.4.11 Fisher exact test. Worst grade <4 *vs.* grade ≥4 by patient

	PM01183+DOX		Control		p-value
	Grade <4	Grade ≥4	Grade <4	Grade ≥4	
Thrombocytopenia					
Neutropenia					
Febrile Neutropenia					
Neutropenic Sepsis					
Neutropenic Infection					
Other*					

*Any other clinical laboratory test or drug-related toxicity present in >=5% of patients in any group.

12.5 Subgroup Analyses Related to Safety

Information for laboratory abnormalities comes from hematology/biochemistry forms and not from the AE form.

Table 12.5.1 Worst grade 3/4 by patient in special subgroups (Sex)

Laboratory abnormalities/ drug-related AEs	Male			Female		
	No. of patients evaluated	Grade 3/4	%	No. of patients evaluated	Grade 3/4	%
PM01183+DOX						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						
Control						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.5.2 Worst grade 3/4 by cycle in special subgroups (Sex)

Laboratory abnormalities/ drug-related AEs	Male			Female		
	No. of cycles evaluated	Grade 3/4	%	No. of cycles evaluated	Grade 3/4	%
PM01183+DOX						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						
Control						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

*Any drug-related toxicity present in >=3% of cycles in any group.

Table 12.5.3 Worst grade 3/4 by patient in special subgroups (Age)

Laboratory abnormalities/ drug-related AEs	≤65 years-old			>65 years-old		
	No. of patients evaluated	Grade 3/4	%	No. of patients evaluated	Grade 3/4	%
PM01183+DOX						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						
Control						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.5.4 Worst grade 3/4 by cycle in special subgroups (Age)

Laboratory abnormalities/ drug-related AEs	≤65 years-old			>65 years-old		
	No. of cycles evaluated	Grade 3/4	%	No. of cycles evaluated	Grade 3/4	%
PM01183+DOX						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						
Control						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

*Any drug-related toxicity present in >=3% of cycles in any group.

Table 12.5.5 Worst grade 3/4 by patient in special subgroups (Race)

Laboratory abnormalities/ drug-related AEs	White			Other		
	No. of patients evaluated	Grade 3/4	%	No. of patients evaluated	Grade 3/4	%
PM01183+DOX						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						
Control						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.5.6 Worst grade 3/4 by cycle in special subgroups (Race)

Laboratory abnormalities/ drug-related AEs	White			Other		
	No. of cycles evaluated	Grade 3/4	%	No. of cycles evaluated	Grade 3/4	%
PM01183+DOX						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						
Control						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

*Any drug-related toxicity present in >=3% of cycles in any group.

Table 12.5.7 Worst grade 3/4 by patient in special subgroups (Number of prior lines)

Laboratory abnormalities/ drug-related AEs	1			>1		
	No. of cycles evaluated	Grade 3/4	%	No. of cycles evaluated	Grade 3/4	%
PM01183+DOX						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						
Control						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.5.8 Worst grade 3/4 by cycle in special subgroups (Number of prior line)

Laboratory abnormalities/ drug-related AEs	1			>1		
	No. of cycles evaluated	Grade 3/4	%	No. of cycles evaluated	Grade 3/4	%
PM01183+DOX						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						
Control						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

*Any drug-related toxicity present in >=3% of cycles in any group.

Table 12.5.9 Worst grade 3/4 by patient in special subgroups (BSA)

Laboratory abnormalities/ drug-related AEs	<2			≥2		
	No. of cycles evaluated	Grade 3/4	%	No. of cycles evaluated	Grade 3/4	%
PM01183+DOX						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						
Control						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.5.10 Worst grade 3/4 by cycle in special subgroups (BSA)

Laboratory abnormalities/ drug-related AEs	<2			≥2		
	No. of cycles evaluated	Grade 3/4	%	No. of cycles evaluated	Grade 3/4	%
PM01183+DOX						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						
Control						
Thrombocytopenia						
Neutropenia						
AP						
Bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

*Any drug-related toxicity present in >=3% of cycles in any group.

Table 12.5.11 Worst grade 3/4 by patient in special subgroups (Geographical area)

Laboratory abnormalities/ drug-related AEs	USA			Europe			Rest of the world		
	No. of patients evaluated	Grade 3/4	%	No. of patients evaluated	Grade 3/4	%	No. of patients evaluated	Grade 3/4	%
PM01183+DOX									
Thrombocytopenia									
Neutropenia									
AP									
Bilirubin									
AST									
ALT									
CPK									
Nausea									
Vomiting									
Fatigue									
Other*									
Control									
Thrombocytopenia									
Neutropenia									
AP									
Bilirubin									
AST									
ALT									
CPK									
Nausea									
Vomiting									
Fatigue									
Other*									

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.5.12 Worst grade 3/4 by cycle in special subgroups (Geographical area)

Laboratory abnormalities/ drug-related AEs	USA			Europe			Rest of the world		
	No. of patients evaluated	Grade 3/4	%	No. of patients evaluated	Grade 3/4	%	No. of patients evaluated	Grade 3/4	%
PM01183+DOX									
Thrombocytopenia									
Neutropenia									
AP									
Bilirubin									
AST									
ALT									
CPK									
Nausea									
Vomiting									
Fatigue									
Other*									
Control									
Thrombocytopenia									
Neutropenia									
AP									
Bilirubin									
AST									
ALT									
CPK									
Nausea									
Vomiting									
Fatigue									
Other*									

*Any drug-related toxicity present in >=3% of cycles in any group.

Table 12.5.13 Worst grade by patient comparison *vs.* Topotecan

Laboratory abnormalities/ drug-related AEs	Grade																			
	PM01183										Topotecan									
	0		1		…		G≥1		G≥3		0		1		…		G≥1		G≥3	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Thrombocytopenia																				
Neutropenia																				
AP																				
Bilirubin																				
AST																				
ALT																				
CPK																				
Nausea																				
Vomiting																				
Fatigue																				
Other*																				

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.5.14 Worst grade by cycle comparison *vs.* Topotecan

Laboratory abnormalities/ drug-related AEs	Grade																			
	PM01183										Topotecan									
	0		1		…		G≥1		G≥3		0		1		…		G≥1		G≥3	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Thrombocytopenia																				
Neutropenia																				
AP																				
Bilirubin																				
AST																				
ALT																				
CPK																				
Nausea																				
Vomiting																				
Fatigue																				
Other*																				

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.5.15 Worst grade by patient comparison *vs.* CAV

Laboratory abnormalities/ drug-related AEs	Grade																			
	PM01183										CAV									
	0		1		…		G≥1		G≥3		0		1		…		G≥1		G≥3	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Thrombocytopenia																				
Neutropenia																				
AP																				
Bilirubin																				
AST																				
ALT																				
CPK																				
Nausea																				
Vomiting																				
Fatigue																				
Other*																				

*Any drug-related toxicity present in >=5% of patients in any group.

Table 12.5.16 Worst grade by cycle comparison *vs.* CAV

Laboratory abnormalities/ drug-related AEs	Grade																			
	PM01183										CAV									
	0		1		…		G≥1		G≥3		0		1		…		G≥1		G≥3	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Thrombocytopenia																				
Neutropenia																				
AP																				
Bilirubin																				
AST																				
ALT																				
CPK																				
Nausea																				
Vomiting																				
Fatigue																				
Other*																				

*Any drug-related toxicity present in >=5% of patients in any group.

LVEF and QT analyses will be performed comparing the PM01183+DOX arm *vs.* the Control arm, but an intrapatient comparison will also be conducted on patients who received combination and single-agent treatment in the PM01183+DOX arm.

Table 12.5.17 LVEF decrease from baseline

	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
MUGA								
Absolute decrease ≥15%								
Absolute decrease ≥10%-15%								
Less than lower limit of normal and absolute								
ECHO								
Absolute decrease ≥15%								
Absolute decrease ≥10%-15%								
Less than lower limit of normal and absolute								

Figure 12.5.18 LVEF value during treatment

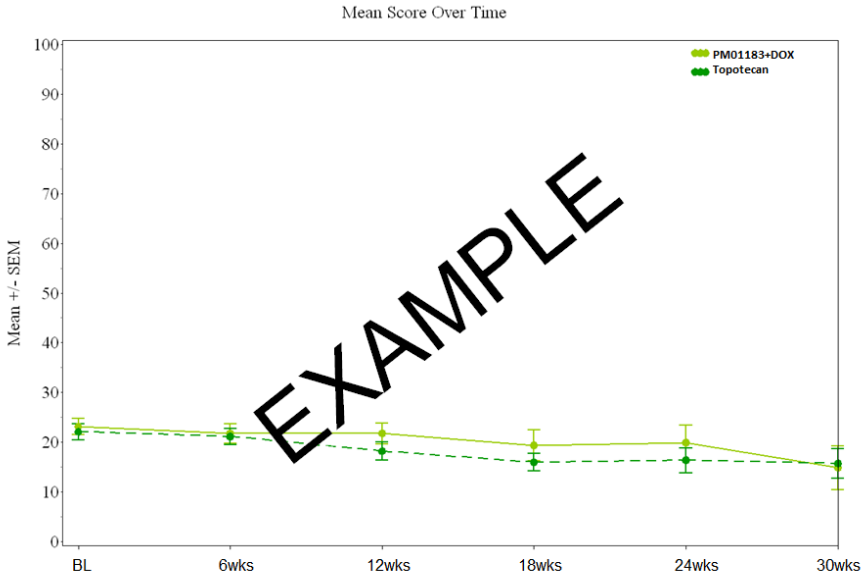


Table 12.5.19 PM01183+DOX arm. LVEF decrease with combination or with single-agent treatment

	Combination		PM01183 alone	
	N	%	N	%
MUGA				
Absolute decrease ≥15%				
Absolute decrease ≥10%-15%				
Less than lower limit of normal and absolute decrease ≥5%				
ECHO				
Absolute decrease ≥15%				
Absolute decrease ≥10%-15%				
Less than lower limit of normal and absolute decrease >5%				

Table 12.5.20 QTcF worst value on treatment

	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
≥501ms								
≥481ms								
≥451ms								

Figure 12.5.21 QTcF value across treatment

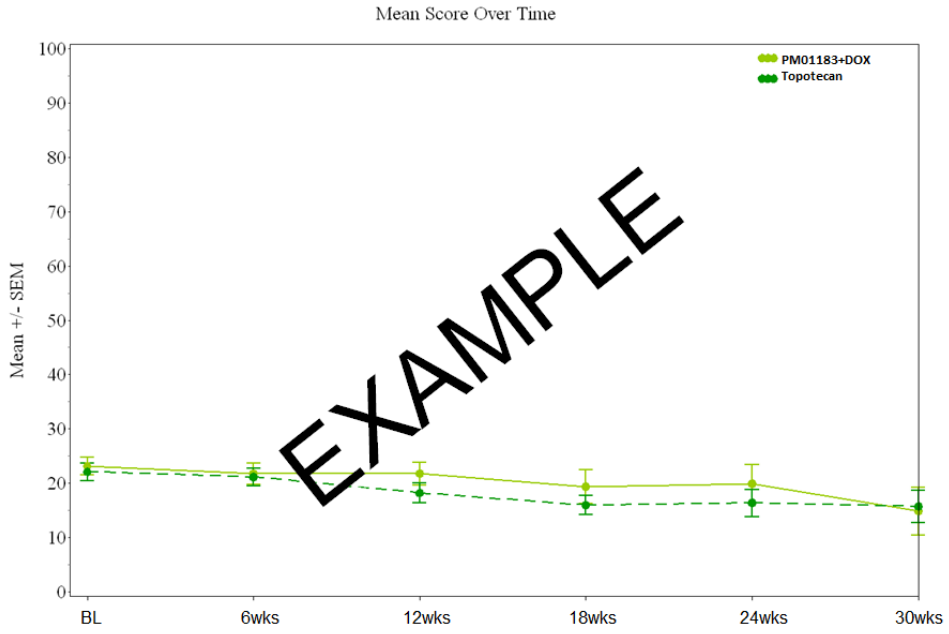


Table 12.5.22 PM01183+DOX arm. QTcF worst value with combination or single-agent treatment.

	Combination		PM01183 alone	
	N	%	N	%
≥501ms				
≥481ms				
≥451ms				

12.6 Concomitant Medication during Treatment

Table 12.6.1 Concomitant medication during treatment (ATC1/ATC2/ATC4)

Concomitant medication	PM01183+DOX		Control	
	N	%	N	%
Alimentary tract and metabolism Antiacids Magnesium compounds ….				
Blood and blood forming organs Antithrombotic agents Vitamin K antagonists …				

Table 12.6.2 Transfusions or EPO

	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
Platelets transfusions RBC transfusions EPO								

Listing 12.6.3 Patients who have been treated with transfusions or EPO

Treatment arm*	Patient ID.	Type	Agent	Route	Dose	Unit	Start date	Stop date	Reason	Indication

*PM01183+DOX (Combination or PM01183 Alone)/Topotecan/CAV

12.7 Subsequent Therapy

Table 12.7.1 Subsequent therapy

	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
Type Chemotherapy Surgery Inmunotherapy …								
Subsequent therapy agents* Platinum Taxanes Nivolumab Investigational agent …								

* Sites have been instructed in the database completion guidelines to report one drug per record, but in the summary it may be requested to group some combinations, e.g. CAV

12.8 PRO during Treatment

Completion rate will be defined as the number of patients with answer to item X in the numerator and the number of available patients in each time moment as denominator.

Missing data will not be taken into account in the analyses; anyway, if the quantity is considered relevant then supportive analyses will be performed applying a conservative approach of assuming missing data as failures.

Table 12.8.1 Completion rate

Item	**Cycle**	PM01183+DOX		Control	
		Missing (%)	Completed (%)	Missing (%)	Completed (%)
EORTC QLQ-C30					
Item 1	Baseline				
	Week 6				
	…				
….	Baseline				
	…				
Any item	Baseline				
	Week 6				
	…				
EORTC QLQ-LC13					
Item 31	Baseline				
	Week 6				
	…				
….	Baseline				
	…				
Any item	Baseline				
	Week 6				
	…				
EORTC QLQ-C30 and QLQ-LC13					
Any item	Baseline				
	…				

Table 12.8.2 T-test change *vs.* baseline

Item	**Cycle**	PM01183+DOX		Control*		p-value
		N	Mean (std)	N	Mean (std)	
*Control refers to topotecan and/or CAV						
Item 1	Week 6					
	Week 12					
	…					
….	Week 6					
	Week 12					
	…					
Item 43	Week 6					
	Week 12					
	…					
*Control refers to topotecan						

Item	**Cycle**	PM01183+DOX		Control*		p-value
		N	Mean (std)	N	Mean (std)	
Item 1	Week 6					
	Week 12					
	…					
….	Week 6					
	Week 12					
	…					
Item 43	Week 6					
	Week 12					
	…					
*Control refers to CAV						
Item 1	Week 6					
	Week 12					
	…					
….	Week 6					
	Week 12					
	…					
Item 43	Week 6					
	Week 12					
	…					

Table 12.8.3 Percentage of patients with an improvement ≥10% *vs.* baseline

Item	**Cycle**	PM01183+DOX		Control*		p-value
		N	%	N	%	
*Control refers to topotecan and/or CAV						
Item 1	Week 6					
	Week 12					
	…					
….	Week 6					
	Week 12					
	…					
Item 43	Week 6					
	Week 12					
	…					
*Control refers to topotecan						
Item 1	Week 6					
	Week 12					
	…					
….	Week 6					
	Week 12					
	…					
Item 43	Week 6					
	Week 12					
	…					

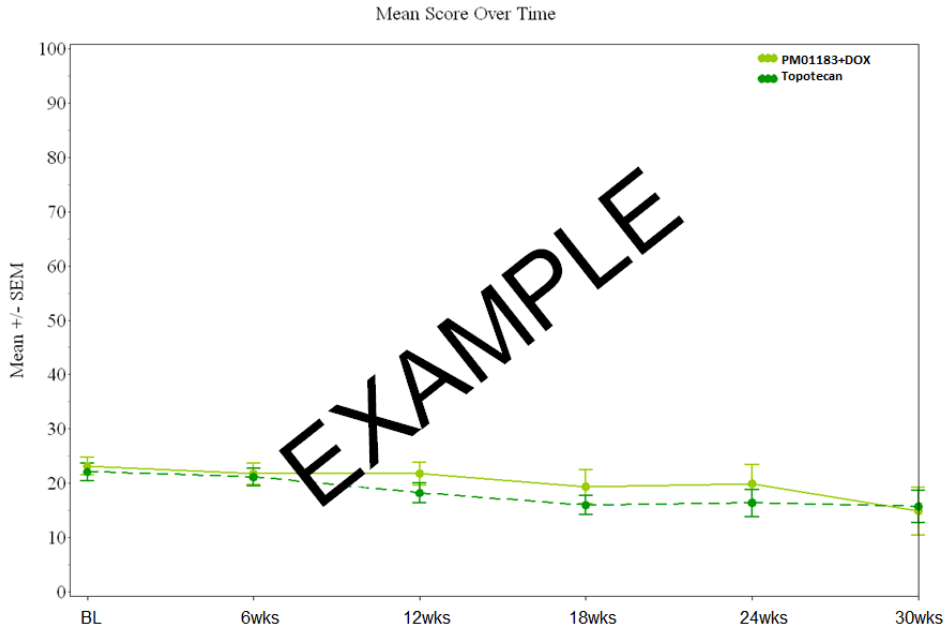
Item	**Cycle**	PM01183+DOX		Control*		p-value
		N	%	N	%	
*Control refers to CAV						
Item 1	Week 6					
	Week 12					
	…					
….	Week 6					
	Week 12					
	…					
Item 43	Week 6					
	Week 12					
	…					

Longitudinal analyses will be performed assuming a mixed-effect model with treatment (Y), time effect (days after baseline), and a time-treatment interaction as covariates, using a covariance structure of autoregressive order 1.

Table 12.8.4 Mixed effect model

Item	**Estimated point change per day**	**p-value**	**Mean change during treatment**
*Control refers to topotecan and/or CAV			
Item 1			
….			
Item 43			
*Control refers to topotecan			
Item 1			
….			
Item 43			
*Control refers to CAV			
Item 1			
….			
Item 43			

Figures 12.8.5-12.8.47 Means plot by each item



12.9 Time to different deterioration in QoL assessments

Time to deterioration to ≥10 points in the Global Health Status and the additional indirect QoL assessment of time to PS deterioration will be performed. Patients not reaching the event will be censored in the last available assessment.

Table 12.9.1.1 Time to deterioration to ≥10 points in the Global Health Status

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median time (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
Mean time				-

Kaplan Meier plot (Figure 12.9.1.1) will be shown too.

Table 12.9.1.2 Time to PS deterioration

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median time (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
Mean time				-

Kaplan Meier plot (Figure 12.9.1.2) will be shown too. PS deterioration is defined as PS>2 or increase in two levels from baseline value (e.g from 0 to 2).

APPENDIX II

13 Clinical Database Listings

Database listings including key variables showing all the recorded information following CRF's Form name will be shown.

-Listing 13.1.1: Subject

Treatment arm	Patient id.	Country / Site Number	Country	Investigator First Name	Investigator Last name	Institution	Address

-Listing 13.1.2: Visit Date

Treatment arm	Patient id.	Date of Visit

-Listing 13.1.3: Screening

Treatment arm	Patient id.	Protocol Version	Informed consent date/ Planned date of treatment initiation	SCLC confirmed diagnosis date	Extensive stage disease	ECOG PS/ CCL/ BSA	Last dose of CT	Date of CT PD /If Non-PD, specify	CTFI	Additional treatment/ PD1 or PDL-1	CNS involvement	Control arm preference	Subject Met All Eligibility Requirements (If not, specify)	Is patient a screening failure	Screen Failure Date

-Listing 13.1.4: Randomization Details

Treatment arm	Patient id.	Ready to randomization?	Randomization ID	Date and time of randomization	Date of Patient randomization in the study	Stratum name	CTFI	PS	CNS	PD-1 or PD-L1	Actual treatment to be given	Now

-Listing 13.1.5: Study Registration

Treatment arm	Patient id.	Pharmacogenetics Substudy Registration		
		PGt consent	Date of PGt/PGx sample	Date of blood sample

-Listing 13.1.6: Demographics

Treatment arm	Patient id.	Date of birth	Age (years)	Gender	Race (Other, specify)	Is the patient of childbearing potential? (If No, reason/Other)	Adequate contraception (If NA, specify)

-Listing 13.1.7: Pregnancy Test

Treatment arm	Patient id.	Visit	Not done	Which type of test was performed?	Date of sample	Result

-Listing 13.1.8: Medical History

Treatment arm	Patient id.	Medical History	Description	Verbatim	Onset date	Resolved date	Ongoing?

-Listing 13.1.9: Cancer History

							Brain metastases						Smoking			
Treatment arm	Patient id.	Date of diagnosis	Ki-67 /MIB-1 Expression	PD-L1 overexpression (If positive, please specify overexpression)	Date of last progression before study entry	Site (s) of current disease (If other, specify)	Known	Date of diagnosis	Symptomatic	Steroid	within 2 weeks was	Paraneoplastic syndrome (If Yes, specify which)	Status	Date started	Ongoing (If no, date stopped)	Pack years

-Listing 13.1.10: Prior Anticancer Therapy: Surgical Procedures

Treatment arm	Patient id.	Prior surgery	Procedures	Date	Surgery Result

-Listing 13.1.11: Prior AntiCancer Therapy: RadioTherapy

Treatment arm	Patient id.	Radiotherapy	Site Anatomic	Total Dose (Gy)	First Dose	Last Dose	Indication

-Listing 13.1.12: Prior AntiCancer Medical Therapy for Study Disease

Treatment arm	Patient id.	Prior therapy	Regimen number	Type	Agent	Start date	Stop date	Best Response	Progression Date	Non PD

-Listing 13.1.13: Hematology

Treatment arm	Patient id.	Visit	Not done	Date	WBC	Neutrophils	Lymphocytes	Platelets	Hemoglobin

-Listing 13.1.14: Biochemistry

Treatment arm	Patient id.	Visit	Not done	Date	ALT	AST	AP	Total Bilirubin	Direct Bilirubin	Albumin	Creatinine	Creatinine Clearance	CPK	Glucose	Na	K	Total Calcium	CRP	LDH

-Listing 13.1.15: Physical Examination

Treatment arm	Patient id.	Visit	Not done	Date	Abnormalities	Body System	Findings	Weight	Height	BSA

-Listing 13.1.16: Performance Status

Treatment arm	Patient id.	Visit	Not Done	Date	PS (ECOG)

-Listing 13.1.17: Vital Signs

Treatment arm	Patient id.	Visit	Not done	Date	Heart rate	BPS	BPD	Temperature

-Listing 13.1.18: Electrocardiogram

Treatment arm	Patient id.	Visit	Not done	Date	Reason for clinically indicated	Result	Abnormal, specify	PR	Heart rate	QT interval (raw)	QRS complex duration	QTcF

-Listing 13.1.19: Left Ventricular Ejection Fraction (LVEF)

Treatment arm	Patient id.	Visit	Not done	Date	Reason for clinically indicated	Method	LVEF (%)	Lower limit of normality	Result	Abnormal, specify

-Listing 13.1.20: Anti-emetic Prophylactic Medication (Per Protocol)

Treatment arm	Patient id.	Visit	Not Done	Drug Type	Specify	Route	Daily Dose	Units	Start date	Stop date	Taken per protocol	Specify (not per protocol)

-Listing 13.1.21: CSF Prophylactic Medication

Treatment arm	Patient id.	Visit	Not Done/Not Applicable	Drug	Route	Daily Dose	Units	Start date	Stop date

-Listing 13.1.22: PM01183 Administration

Treatment arm	Patient id.	Visit	Date	Route	Start time	End time	Intended dose	Total intended dose	Total dose	Total volume given	Reduction	Reduction reason	Delay	Delay reason	Interruption	Interruption reason

-Listing 13.1.23: PM01183 Re-Administration

Treatment arm	Patient id.	Visit	Not done	Date	Route	Start time	End time	Total dose	Total volume given

-Listing 13.1.24: Doxorubicin Administration

Treatment arm	Patient id.	Visit	Date	Route	Start time	End time	Intended dose	Total intended dose	Total dose	Total volume given	Reduction	Reduction reason	Delay	Delay reason	Interruption	Interruption reason

-Listing 13.1.25: Doxorubicin Re-Administration

Treatment arm	Patient id.	Visit	Not done	Date	Route	Start time	End time	Total dose	Total volume given

-Listing 13.1.26: Topotecan Administration

Treatment arm	Patient id.	Visit	Not Done	Delay (reason)	Day	Date	Route	Start time	End time	Intended dose level	Total intended dose	Total dose	Omission (reason)	Reduction (reason)	Interruption (reason)

-Listing 13.1.27: Topotecan Re-Administration

Treatment arm	Patient id.	Visit	Day	Not done	Date	Route	Start time	End time	Total dose

-Listing 13.1.28: Cyclophosphamide Administration

Treatment arm	Patient id.	Visit	Date	Route	Start time	End time	Intended dose	Total intended dose	Total dose	Total volume given	Reduction	Reduction reason	Delay	Delay reason	Interruption	Interruption reason

-Listing 13.1.29: Cyclophosphamide Re-Administration

Treatment arm	Patient id.	Visit	Not done	Date	Route	Start time	End time	Total dose	Total volume given

-Listing 13.1.30: Vincristine Administration

Treatment arm	Patient id.	Visit	Date	Route	Start time	End time	Intended dose	Total dose	Total volume given	Reduction	Reduction reason	Delay	Delay reason	Interruption	Interruption reason

-Listing 13.1.31: Vincristine Re-Administration

Treatment arm	Patient id.	Visit	Not done	Date	Route	Start time	End time	Total dose	Total volume given

-Listing 13.1.32: Adverse Events YN?

Treatment arm	Patient id.	AEs

-Listing 13.1.33: Adverse Events

Treatment arm	Patient id.	Adverse Event	Grade	Start Date (Ongoing)	End Date (Duration/ongoing)	Relationship (PM1183/Topotecan/CAV/Specify)	Action	Serious Event (Death/Life Threat./Hospi./Disa./Conge./Other Impor./Infectious.)	Outcome	SAE associated to QC?	Case ID	Derived Subject number

-Listing 13.1.34: SAE Summary

Treatment arm	Patient id.	Adverse Event	Outcome	Start Date	Case ID	Death	Life Threat.	Hospi.	Admission Date	Discharge Date	Disa.	Conge.	Other Medi.	Infec.	Narrative	Nulli.	Related docs?	Serious Event	#Submi. to PHV

-Listing 13.1.35: SAE Attachments

Treatment arm	Patient id.	Attachment

-Listing 13.1.36: Concomitant Medication YN?

Treatment arm	Patient id.	Concomitant medication?

-Listing 13.1.37: Concomitant Medication

Treatment arm	Patient id.	Type of Therapy	Drug Name	Route	Dose	Unit	Frequency	No. of doses	No. of time units	Time units	Start Date	End Date	Ongoing	Reason	Indication	AEs	MH

-Listing 13.1.38: Concomitant Procedures

Treatment arm	Patient id.	None	Procedure	Indication	Date of Procedure	AE	MH	Result / Comments

-Listing 13.1.39: Other Tests/Procedures

Treatment arm	Patient id.	Not Done	Test Name	Test Date	Result	Unit

-Listing 13.1.40: Target Lesions

Treatment arm	Patient id.	Were Target Lesions assessed	Target Lesions	Lesion Number	Organ	Specify	Lesion Description	Date	Method (specify)	Longest diameter	Sum of Diameters

-Listing 13.1.41: Non Target Lesions

Treatment arm	Patient id.	Were Non Target Lesions assessed.	Non Target Lesions	Organ	Specify	Lesion Description	Date	Method (specify)	Response

-Listing 13.1.42: New Lesions

Treatment arm	Patient id.	New Lesions	Organ	Specify	Lesion Description	Date	Method (specify)

-Listing 13.1.43: Radiological Evaluation of Response

Treatment arm	Patient id.	Evaluation (Not Done)	Date	Target lesions	Non-Target lesions	New lesion	Not Done	Overall cycle response

-Listing 13.1.44: End of Treatment

Treatment arm	Patient id.	Reason	Specify (Investigator's decision)	Specify (AE)	Specify (Other)	Symptomatic deterioration date	Symptomatic deterioration, please specify

-Listing 13.1.45: Follow Up

Treatment arm	Patient id.	Date	Survival	Disease Status	PD or any further therapy	TA done	TA not done	Specify (not done)

-Listing 13.1.46: Surgery Procedures for Study Disease (after End of Treatment)

Treatment arm	Patient id.	Further surgery	Procedure	Date	Surgery Result

-Listing 13.1.47: Radiotherapy (after End of Treatment)

Treatment arm	Patient id.	Further radiotherapy	Site	Total dose (Gy)	Start date	End date	Ongoing	Indication

-Listing 13.1.48: Medical Treatment (after End of Treatment)

Treatment arm	Patient id.	Further therapy	Agent	Start date	End date	Ongoing	Best response

-Listing 13.1.49: Death Report Form

Treatment arm	Patient id.	Date	Cause	Specify (Other)	Autopsy	Attachment

-Listing 13.1.50: Off Study

Treatment arm	Patient id.	Off Study	Date	Primary reason

-Listing 13.1.51: Pharmacokinetics

Treatment arm	Patient id.	PK Samples	Sample No.	Day	Sampling time	Acceptable window times	Sampling time relative to the Doxorubicin infusion	Sampling time relative to the PM01183 infusion	Not Done	Date	Actual time	Derived DateTime	Comments	Cycle the next Pharmacokinetics is due at:

-Listing 13.1.52: Polymorphisms

Treatment arm	Patient id.	Cycle	Date	Time	Derived date time	Not Done	Comments

-Listing 13.1.53: Alpha-1 Acid Glycoprotein

Treatment arm	Patient id.	AAGP sample taken?	Date	Comments

-Listing 13.1.54: EORTC Quality of Life Questionnaire

Treatment arm	Patient id.	Not Done	Date	Q1 to Q5	Specify if not performed	Q6 to Q28	Specify if not performed	Q29-Q30	Specify if not performed	Q31-Q41	Q42 (if yes where)	Q43 (If yes, how much did it help?)	Specify if not performed

-Listing 13.1.55: Treatment Continuation

Treatment arm	Patient id.	Add Next Cyle?

-Listing 13.1.56: Investigator Comments

Treatment arm	Patient id.	Visit	Form	Date	Comment

-Listing 13.1.57: Unscheduled

Treatment arm	Patient id.	Visit	LVEF	ECG

-Listing 13.1.58: IRC data

Treatment arm	Patient id.	Visit	Reviewer identification	Target Response	Non Target Response	New Lesions	Best response	Progression Date	First Response Date

APPENDIX III

14 ICH Listings

Following ICH E-3 guideline, patient listings specified as section 16.2 will be performed.

- 16.2.1 Discontinued Patients

Treatment arm	Patient id.	Country	Institution	Subject Met All Eligibility Requirements (If not, specify)	Is patient a screening failure	Screen Failure Date	Randomization date	Treated (Yes/No)	Drug adm. Start date (First cycle)	Cycles received	End of Treatment (specify)	Off Study (reason)

- 16.2.2 Protocol Deviations

Treatment arm	Patient id.	Severity	Type	Deviation

- 16.2.3 Patients Not Included in the Efficacy Analysis

Treatment arm	Patient id.	Reason

- 16.2.4 Demographic Data

Treatment arm	Patient id.	Investigator's preference for the control arm	Gender	Age (years)	Race (Other, specify)	ECOG PS	Smoking status	Disease stage	Ki-67/ MIB-1 expression	Baseline CNS involvement	Site (s) of current disease (If other, specify)	BSA (m^2)	Prior Surgery/ Prior Radiotherapy	CTFI (months)	Prior PD-1/ PD-L1	#Prior chemotherapy /Prior Agents

- 16.2.5 Compliance and/or Drug Concentration Data

Treatment arm	Patient id.	Cycles received	Cumulative dose (mg/m^2)	Dose intensity ($mg/m^2/wk$)	Relative dose intensity (%)	Visit	Treatment	Date	Intended dose level	Reduction (reason)	Delay (reason)	Interruption (reason)	Omission (reason)

- 16.2.6 Individual Efficacy Response Data

Treatment arm	Patient id.	IRC					IA						OS (mo.)	Event /Censored
		Overall response	PFS (mo.)	Event /Censored	DR (mo.)	Event /Censored reason	Overall response	CA125 response	PFS (mo.)	Event /Censored	DR (mo.)	Event /Censored reason		

- 16.2.7 Adverse Event Listing (each patient)

Treatment arm	Patient id.	SOC	PT	Adverse Event	Grade	Start Date (Ongoing)	End Date (Duration/ongoing)	Relationship (PM1183/Topotecan/CAV/Specify)	Action	Serious Event (Death/Life Threat./Hospi./Disa./Conge./Other Impor./Infectious.)	Outcome

- 16.2.8 Listing of Individual Laboratory Measurements by Patient

Treatment arm	Patient id.	Visit	Date	Test	Standard Value	Normal lab. range	Grade

15 History of Changes

15.1 SAP amendment from v2.0 to v3.0

Some issues/clarifications have appeared during programming tasks performed by an external contract research organization that have been added to the SAP v2.0 dated 03/October/2018.

A brief summary of these issues/clarifications is provided below.

- Addition of summary for patients with disease control rate (CR+PR+SD) and clinical benefit rate (CR+PR+SD≥4 months).
- Clarification of CTFI calculation and prior immunotherapy data source.
- Clarification that two analyses are performed for Bootstrap replication
- The prior and subsequent therapies are recorded with one drug per row in accordance with database completion guidelines, but in the reporting it may be requested to group some combinations like CAV.
- Correction of typos in title section for figures 103 to 109 and category split for table 12.5.3-12.5.4

Detailed changes are presented in the next pages. Changes are highlighted in ***Italic bold*** and text removed has been ~~crossed out~~.

6.1 Efficacy Definitions

….
Other supportive endpoints:

Disease control rate (DCR) by IRC/IA, defined as percentage of patients with best response CR, PR or SD.

Clinical benefit rate (CBR) by IRC/IA, defined as percentage of patients with best response CR, PR or SD ≥4 months.

Time to treatment failure (TTF) by IA, defined as time from randomization to progression, EOT due to AE, EOT due to symptomatic deterioration or death will be calculated.

Time to onset of first brain metastases by IA, defined as time from randomization to clinical diagnosis of brain mets will be calculated.

8.1 Baseline and Demographic Data

Baseline data such as demographics, cancer history, number of organs involved and sites of disease, prior therapy, laboratory values at baseline, prior relevant history, signs and symptoms, electrocardiogram, and concomitant medication [Anatomical

Therapeutic Chemical – World Health Organization (ATC-WHO) coded] will be described following standard tables (detailed in Appendix I).

CTFI is defined as the time from the last dose of the platinum drugs in the last platinum regimen to the occurrence of progressive disease.

Prior immunotherapy to PD-1 or PD-L1 data will be collected from the screening page.

For pre-treatment characteristics with multiple measurements per patient before the start of treatment (e.g. laboratory assessments, vital signs), the baseline measurement will be considered the last value prior to or on the first day of treatment.

8.9 Subgroup Analyses

Some preplanned efficacy analyses are the following: subgroup analyses based on comparison of PM01183/DOX with CAV or topotecan, subgroup analyses for stratification factors (mainly CNS and CTFI), subgroup analyses for patients with primary site different to lung, subgroup analyses if enough cases for baseline PD-L1 expression (<1% *vs.* ≥1%) or PD-L1 expression (<50% *vs.* ≥50%), and the analysis of the subset of patients who received subsequent therapies.
Special attention will be put in the subgroup analysis comparing treatment arms in the CTFI after first line subsets. Subsets will be defined as [≥90 days (sensitive) vs. <90 days (resistant; R)] and adjusted p-values***, one on patients with sensitive disease and one on patients with resistant disease,*** will be calculated by means of Bootstrap replication.
Other subgroup analyses that are implemented *a posteriori* based on clinically findings will have an exploratory nature.

Pre-specified safety subgroup analyses are: by sex (male *vs.* female), by age (<65 years-old *vs.* ≥65 years-old), by race (white *vs.* other), by number of prior lines (1 *vs.* >1 line), by BSA (<2 *vs.* ≥2) and by geographical area (USA *vs.* Europe *vs.* rest of the world).

Table 11.1.2.2 Prior anticancer medical therapy

	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
…								
Prior agents of chemotherapy (ATC coded)*								
Carboplatin								
Cisplatin								
Etoposide								
…								
Prior inmunotherapies agents (ATC coded)*								
Nivolumab								
…								
…								
TTP to prior chemotherapy**								
Median (range)								
Mean (std)								
…								

**** Sites have been instructed in the database completion guidelines to report one drug per record, but in the summary it may be requested to group some combinations, e.g. CAV***

**If total number of patients with maintenance is less than 15% then take out them from calculus, if percentage is higher then censored them at the initial time of the maintenance

Table 11.3.1.37 Response rate by IRC

Response	PM01183+DOX		Control		p-value
	N	%	N	%	
CR PR SD PD Unknown*					
CR+PR; n (%) and binomial exact 95% confidence interval					
DCR; n (%) and binomial exact 95% confidence interval					
CBR; n (%) and binomial exact 95% confidence interval					

Table 11.3.1.43 Response rate by IA

Response	PM01183+DOX		Control		p-value
	N	%	N	%	
CR PR SD PD Unknown*					
CR+PR; n (%) and binomial exact 95% confidence interval					
DCR; n (%) and binomial exact 95% confidence interval					
CBR; n (%) and binomial exact 95% confidence interval					

Table 12.7.1 Subsequent therapy

	PM01183+DOX		Control					
			Total		Topotecan		CAV	
	N	%	N	%	N	%	N	%
Type Chemotherapy Surgery Inmunotherapy …								
Subsequent therapy agents* Platinum Taxanes Nivolumab Investigational agent …								

**** Sites have been instructed in the database completion guidelines to report one drug per record, but in the summary it may be requested to group some combinations, e.g. CAV***

Comparison in patients with ~~no CNS involvement and~~ CTFI<90 days (resistant).

- Figure 11.3.1.103 Patients with CTFI<90 (resistant). PFS by IRC (PM01183 vs. Control)
- Figure 11.3.1.104 Patients with CTFI<90 (resistant). PFS by IA (PM01183 vs. Control)
- Figure 11.3.1.105 Patients with CTFI<90 (resistant). OS (PM01183 vs. Control)
- Figure 11.3.1.106 Patients with CTFI<90 (resistant). RR by IRC (PM01183 vs. Control)
- Figure 11.3.1.107 Patients with CTFI<90 (resistant). RR by IA (PM01183 vs. Control)
- Figure 11.3.1.108 Patients with CTFI<90 (resistant). DR by IRC (PM01183 vs. Control)
- Figure 11.3.1.109 Patients with CTFI<90 (resistant). DR by IA (PM01183 vs. Control)

Table 12.5.3 Worst grade 3/4 by patient in special subgroups (Age)

Laboratory abnormalities/ drug-related AEs	≤65 years-old			>65 years-old		
	No. of patients evaluated	Grade 3/4	%	No. of patients evaluated	Grade 3/4	%

Table 12.5.4 Worst grade 3/4 by cycle in special subgroups (Age)

Laboratory abnormalities/ drug-related AEs	≤65 years-old			>65 years-old		
	No. of cycles evaluated	Grade 3/4	%	No. of cycles evaluated	Grade 3/4	%

15.2 SAP amendment from v1.0 to v2.0

Clarifications/modifications after the implementation of the 3rd substantial amendment to the protocol have been added to the SAP v1.0 dated on 03/October/2016.

A brief summary is included below.

- Primary endpoint change from PFS by IRC to OS and all the associated statistical updates (e.g. sample size, assumptions, analyses…).
- Deletion of cap definition.
- Clarification of the way the stratification factors should be handled in the analyses. A listing of patients assigned to the wrong strata at the time of randomization will also be included.
- Inclusion of more detailed secondary endpoint analyses and the way multiplicity adjustment will be calculated.
- If formal interim analyses are conducted, the procedure that alpha-spending will be corrected is explained.
- Inclusion of time to treatment failure, time to brain metastasis and generalised pairwise comparison.
- Modifications/clarifications of list of covariates, missing imputation and how EOT visit will be managed for laboratory/QoL analyses.
- Inclusion of a new section of time to QoL deterioration.
- Inclusion of shell listings for section 13 DB Listings and for section 14 ICH Listings.
- Other not relevant minor comments/clarifications (not specified in the document to maintain the simplicity).

Detailed changes are presented in the next pages. Changes are highlighted in ***Italic bold*** and text removed has been ~~crossed out~~.
Any changes in the automatic numbering of tables, sections and references in the SAP are not listed but will be implemented in the new version.

Section 2 (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~~ ***with disease progression after*** 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 (Arm B), the assigned treatment will be based on the reported Investigator's preference between CAV or topotecan. ~~However, whenever the number of patients randomized to either CAV or topotecan reaches 55% of the total number of patients expected in the control arm, i.e., 165 patients, then the assigned treatment will be restricted to the remaining option, i.e., that which has not reached 165 patients, until the end of accrual.~~

A minimum recruitment of 165 patients (>45% of patients in the control arm) will be ensured in the anthracycline containing regimen, CAV, in order to have sufficient data to study the contribution of PM01183 to the PM01183/DOX combination compared to the CAV.

…

~~Up to~~ ***Approximately*** 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.

…

The primary endpoint of the trial is the ~~progression free~~ ***overall*** survival (~~PFS) per RECIST v.1.1 assessed by the IRC.~~***OS).*** Secondary endpoints comprise ~~overall survival (OS), mid- and long-term survival assessed by measuring OS at 12/18/24 months, PFS per RECIST v.1.1 by investigator assessment (IA),~~***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 ~~IA),~~ safety profile~~, patient reported outcomes (~~***. Tertiary endpoints comprise mid- and long-term survival assessed by measuring OS at 12/18/24 months, PFS per RECIST v.1.1 by investigator assessment (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 check 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 reviewed at this time, as follow-up will not have reached maturity at this point; therefore, no type I/II error corrections will be applied. ***Further safety and efficacy analyses could be performed upon request from the IDMC.***

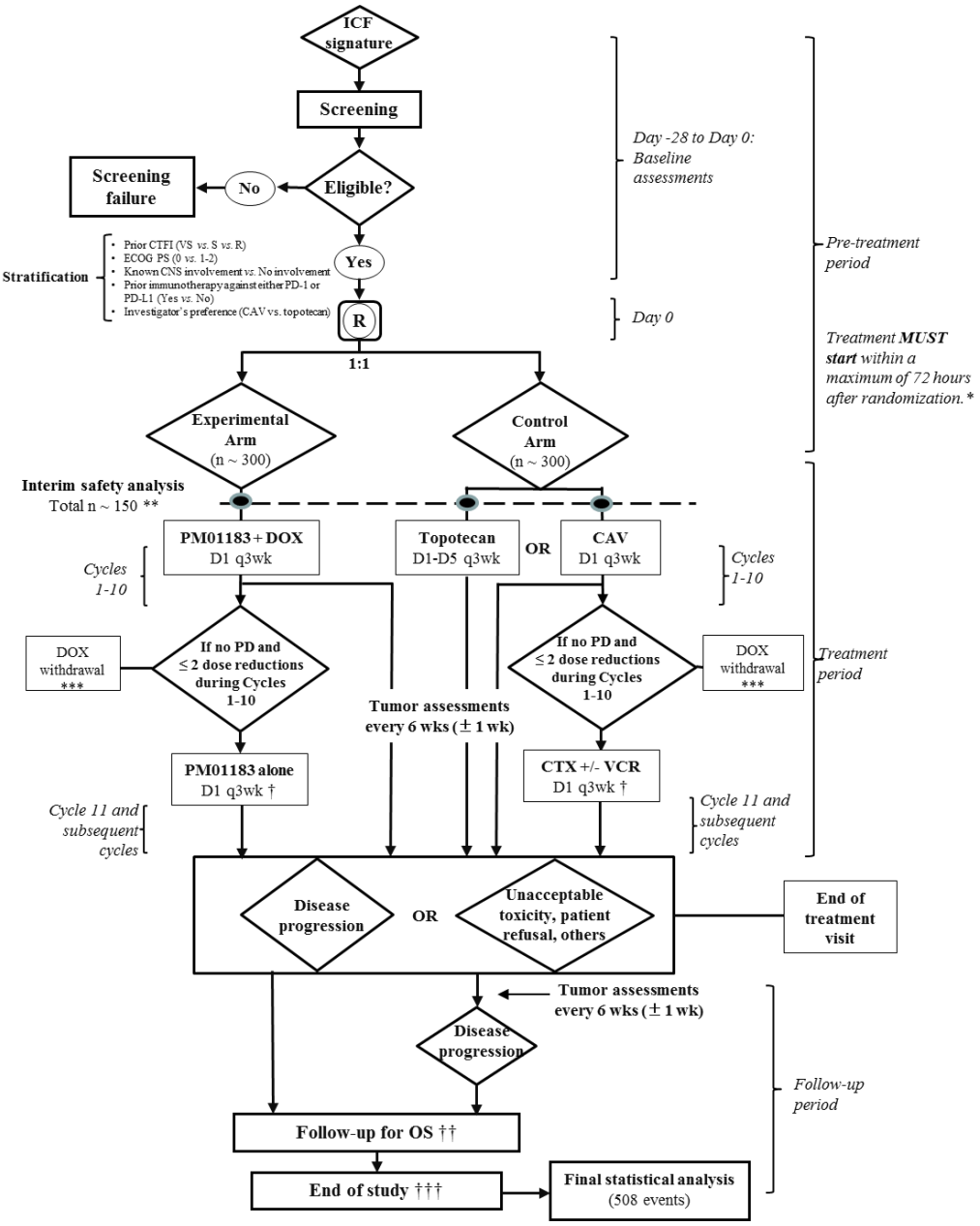
There is no intention to claim superiority before the necessary number of events for the ~~PFS~~ ***OS*** analysis has been reached. However, if ***formal interim analyses are*** requested by the IDMC, ~~the significance level will be determined by the observed number of~~

~~events and will be controlled by the~~ Lan and DeMets error spending function that corresponds to the O'Brien-Fleming ~~boundaries~~ ***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.***

…

Figure is updated

ATLANTIS Trial - SCLC after failure of one prior platinum-containing line



…

~~§ Whenever the number of patients randomized to either CAV or topotecan reaches 55% of the total number of patients expected in the control arm, i.e., 165 patients, then the assigned treatment will be restricted to the remaining option, i.e., that which has not reached 165 patients, until the end of accrual.~~

…

†† 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.***

…

Section 4 (OBJECTIVES AND ENDPOINTS)

4.1 Primary Objective

- To determine ***whether there is*** a difference in ~~PFS by an Independent Review Committee (IRC~~ ***overall survival (OS***) between lurbinectedin (PM01183)/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.

4.2 Secondary Objectives

- ***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*** ~~overall~~ survival (~~OS~~***PFS) by an Independent Review Committee (IRC).***
- ***Antitumor activity by IRC according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1.***
- ***Safety profile.***

4.3 Tertiary Objectives

…

- Antitumor activity ***by IA*** according to the RECIST v.1.1.
- ~~Safety profile.~~

…

4.4 Endpoints

Primary endpoint:

- ~~Progression-free survival (PFS) by IRC is defined as the time from the date of randomization to the date of documented progression per RECIST v.1.1 or death (regardless of the cause of death). If the patient receives further antitumor therapy or is lost to follow-up before PD, PFS will be censored at the date of last tumor assessment before the date of subsequent antitumor therapy.~~
- ***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:

…

- **Best antitumor response by ~~IRC/~~IA** will be the best response obtained in any evaluation according to RECIST v.1.1.
- **Duration of response (DR) by ~~IRC/~~IA** will be calculated from the date of first documentation of response per RECIST v.1.1 (complete or partial response, whichever comes first) to the date of documented PD or death. The censoring rules defined above for PFS will be used for 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.~~

Section 5.1 (Randomization and Stratification)

Central dynamic 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 (Arm B), the assigned treatment will be based on the reported Investigator's preference between CAV or topotecan. ~~However, whenever the number of patients randomized to either CAV or topotecan reaches 55% of the total number of patients expected in the control arm, i.e., 165 patients, then the assigned treatment will be restricted to the remaining option, i.e., that which has not reached 165 patients, until the end of accrual.~~

…

Section 5.2 (Sample Size)

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

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 ~25% reduction in the relative risk of ~~progression or~~ death (hazard ratio; HR=0.***75***) to be achieved with the experimental arm, at a one-sided 2.5% significance level with at least 90% power, following exponential distributions and fulfilling the proportional hazard assumption. Median ~~PFS~~***OS*** with CAV or topotecan is expected to be around ~~3~~***7***.5 months[(1)]. It is forecasted that an observed HR of approximately 0.84 will have enough power to reject the null hypothesis.

To obtain the required ~~484~~***508*** events, approximately 600 patients with SCLC who failed one prior platinum-containing CHT line will be stratified and randomized at a 1:1 ratio. With the aforementioned prospective assumptions, recruitment is foreseen to be completed in ~~17~~***24*** months (~~35~~***25*** patients/month)~~, the required PFS events are expected to occur around three months after randomization of the last patient. Therefore the IDMC meeting after the IRC review to test PFS is expected to occur about six months after randomization of the last patient. For a final OS analysis~~ ***and*** a total study duration of about three ***and a half*** years ***for the final OS analysis*** is planned.

With the prospective assumptions above mentioned, about ~~253 PFS~~***265 OS*** events are expected in the control arm and ~~231~~***243*** in the treatment arm.

~~The IDMC will review the results and 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.~~Section 5.2.1 (Interim Safety Analysis)

…

As previously explained, there is no intention to claim superiority before the necessary number of events for the ~~PFS~~***OS*** analysis has been reached. However, if ~~requested~~***formal interim analyses are conducted*** by the IDMC, ~~the significance level will be determined by the observed number of events and will be controlled by the~~***a*** Lan and DeMets error spending function that corresponds to the O'Brien-Fleming ~~boundaries~~***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.***

~~15.1.1 OS Analysis~~

~~OS has been selected as a secondary endpoint. A sample size of 600 patients is expected to have enough power to detect a clinically and statistically relevant treatment effect in OS. Assuming a median OS of ~7.5 months in the control arm (1) the Sponsor believes that the sample size would have enough power to test a HR~ 0.75.~~

~~An interim OS analysis is planned for the time of the final PFS analysis. The significance level will be determined by the observed number of events and will be controlled by the Lan and DeMets error spending function that corresponds to the O'Brien-Fleming boundaries.~~

~~The OS statistical analyses will be performed following the same approach as for PFS analyses. Consequently, the stratified log-rank test (primary analysis), the unstratified log-rank test and Cox regression on the ITT population will be calculated.~~

~~The end of the study is set at 18 months after the randomization of the last patient; currently, and with the pre-established assumptions, ~500 events are expected to occur.~~

Section 6.1 (Efficacy Definitions)
Primary endpoint.

Overall survival (OS) is defined as the time 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). Final OS analysis is planned 18 months after randomization of last patient (planned end of study date).

After radiological 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. For survival follow-up (FU) purposes, after radiological PD is documented or new therapy is started, a documented telephone call from the investigational sites will be adequate. Once the whole recruitment is completed, the survival follow-up procedure will change and 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.

Secondary/tertiary endpoints.

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~~After radiological 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. For survival follow-up (FU) purposes, after radiological PD is documented or new therapy is started, a documented telephone call from the investigational sites will be adequate.~~

…

~~Secondary endpoints.~~

~~The hierarchical step-up Hochberg procedure will be used to test the secondary endpoints (i.e. OS and ORR) at the overall two-sided significance level of 0.05 in the event the primary endpoint is significant.~~

~~Subgroup analyses of the PM01183/DOX arm vs. CAV or topotecan based on investigator's preference.~~

~~Overall survival (OS) is defined as the time 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). Counting out subsequent therapies impact, sample size is powered to detect OS differences in the 15-25% range. Final OS analysis is planned 18 months after randomization of last patient (planned end of study date). As previously mentioned, for interim OS analysis type I error will be controlled by the Lan and DeMets error spending function that corresponds to the O'Brien-Fleming boundaries.~~

~~Landmark analyses of OS at 12/18/24 months will be the Kaplan-Meier estimates of the probability of being alive at these time points.~~

…

Landmark analyses of OS at 12/18/24 months will be the Kaplan-Meier estimates of the probability of being alive at these time points.

Difference in OS between PM01183/DOX and CAV, in patients with CAV as best Investigator's choice will be measured using OS data derived for the primary endpoint calculation and selecting investigator's preference ticked in the eCRF.

OS/PFS in patients with and without baseline CNS involvement will be measured using derived data and selecting the CNS involvement status reported in the eCRF. Afterwards, subgroup analyses of CNS involvement restricted to the sensitive and resistant populations will also be performed.

Subgroup analyses of the PM01183/DOX arm vs. CAV or topotecan based on investigator's preference.

…

Other supportive endpoints:

Time to treatment failure (TTF) by IA, defined as time from randomization to progression, EOT due to AE, EOT due to symptomatic deterioration or death will be calculated.

Time to onset of first brain metastases by IA, defined as time from randomization to clinical diagnosis of brain mets will be calculated.

Section 6.2 (Efficacy Analysis Methods)

Time-to-event variables (***OS,*** PFS, ~~OS~~ ***DR, TTF*** and ~~DR~~***time to onset of first brain metastases***) 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, ~~using all randomization strata variables~~***selecting CNS and CTFI values of the stratification factors***, on the ITT population will be primarily used to compare the time-to-event variables. ***A sensitivity analysis will be performed using all randomization strata variables.***

Unstratified log-rank tests will also be calculated as supportive analyses.

If the result of the primary endpoint analysis is statistically significant, the hierarchical step-up Hochberg procedure[(2)] 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. The p-values for this procedure will be calculated using the corresponding unstratified log-rank test in each subgroup.

The symmetry of tumor evaluations between treatment arms will be examined. The Wilcoxon test to compare time to disease assessments between treatment arms will be used to assess symmetry of evaluations. Moreover, Kaplan-Meier curves of the time from randomization and the first and second disease assessments will be plotted.

Cox regression will be used to calculate the risk reduction (***OS,*** PFS~~, OS~~ and DR) and to evaluate the influence of the stratification variables and other potential prognostic factors on the time-to-event efficacy endpoints.

Mean Kaplan-Meier estimates will be used to compare areas under the curves for OS and PFS.

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

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

Multivariate models (main effects or including interaction terms, if appropriate) will include all stratification factors and/or prognostic factors/covariates widely reported and recognized by the scientific community: treatment (PM01183/DOX *vs.* control), CTFI after first-line treatment [as strata categories ≥180 days (VS) *vs*. 90-179 days (S) *vs*. <90 days (R) or as usually reported ≥90 days *vs*. <90 days], ECOG PS (0 *vs.* 1-2 or coded as 0 *vs.* 1 *vs.* 2), baseline CNS involvement (yes *vs.* no), prior immunotherapy against either PD-1 or PD-L1 (yes *vs.* no) [or independently by each group if enough representative cases, prior PD-1 (yes *vs.* no) and prior PD-L1 (yes *vs.* no)], investigator's preference for the control arm (Topotecan *vs.* CAV), geographical area (USA *vs.* Europe *vs.* rest of the world), sex (male *vs.* female), age, age at diagnosis, race (caucasian *vs.* other), smoking status (current *vs.* former *vs.* never), ~~actual~~ disease stage ***at study entry*** (limited *vs.* extensive), PD-L1 expression (if enough cases; <1% *vs.* ≥1% or <50% *vs.* ≥50%), prior lines (1 *vs.* >1 lines or coded as ordinal) , time from diagnosis to randomization, time elapsed from last dose of prior chemotherapy regimen to randomization, response to prior chemotherapy (yes *vs.* no), time to progression to prior chemotherapy, prior prophylactic cranial irradiation (PCI) (yes *vs.* no)***, prior consolidation with thoracic radiotherapy (yes vs. no)***, visceral metastases (yes *vs.* no), number of metastatic sites at baseline, body mass index (BMI), height, weight, body surface area (BSA), presence of any bulky (< 50 mm *vs.* ≥ 50 mm) lesion at baseline, measurable disease by RECIST v1.1 (yes *vs.* no), hypertension (yes *vs.* no), cardiac disease (yes *vs.* no) , diabetes (yes *vs.* no) , ***chronic obstructive pulmonary disease (***COPD***)*** (yes *vs.* no), secondary tumors (yes *vs.* no), steroids at baseline (yes *vs.* no), opioids at baseline (yes *vs.* no), paraneoplastic syndrome at baseline (yes *vs.* no), baseline ***lactate dehydrogenase (***LDH***)*** value (≤ ***upper limit of normal (***ULN***)*** *vs.* >ULN), hemoglobin value at baseline (g/dl), albumin value at baseline (g/dl)***, C-reactive protein value at baseline (mg/dl), C-reactive protein/albumin baseline ratio*** and baseline global ***quality of life (***QoL***)***. In addition, continuous variables categorized as discrete variables will also be investigated in the continuum range and if ~~the adjustment is~~***they fit*** better then the ~~continual~~***continuous*** variable will be selected in the model.

All variables with a good percentage of valid cases (approximately ≥ 90%) will be included in the multivariate analysis***, although if any prognostic value lacks more than 10% of values, sensitivity analyses considering multiple imputation methods will be performed***…

…

Median follow-up (FU) time for ~~PFS~~***OS*** and ***PFS***~~OS~~ will be calculated in a descriptive way, taking only into account the censored values and using the Kaplan-Meier method for reversing the censoring values as described by Parmar[(4)].

…

Sensitivity analyses for different PFS censoring will be performed. The following approaches will be calculated: 1) Date of progression based on scheduled time instead of recorded date (e.g. if progression occurs in the ninth week and assessment would have to be done in the sixth week then the expected date is used instead of the actual date); 2) First date of progression combining IRC and IA assessments (e.g. the lowest date between IRC and IA is used);~~and~~ 3) Date of progression moved to the prior tumor assessment date (e.g. if progression has not been documented in the second assessment and is documented in the third assessment then progression date is moved to the second assessment)***; 4) First date of progression or death not censoring data if further***

antitumor therapy is received before the documented progression.
Proportional hazard assumption for ~~PFS~~***OS*** and ***PFS***~~OS~~ will be checked by means of a Cox regression including treatment and its interaction with survival time[5]. In case of strong rejection of proportionality, then restricted mean survival estimates will also be calculated in addition to HR[6,7].

Main summary of efficacy analyses

Order	Endpoint	Population	Statistics
Primary endpoint	~~PFS by IRC~~***OS***	ITT population	-Stratified log rank test ***(primary analysis)*** ***-Unstratified log rank test*** ***-Kaplan Meier estimates*** ***-Univariate Cox regression*** ***-Multivariate Cox regression***
Secondary endpoints~~*~~	~~OS~~***PFS by IRC***	ITT population	-Stratified log rank test -Unstratified log rank test -Kaplan Meier estimates -Univariate Cox regression -Multivariate Cox regression
	~~OS at 12/18/24 months~~ ***DOR by IRC***	ITT population***: Responder patients***	-Kaplan Meier estimates
	Response rate by IRC	ITT population	-Fisher exact test -Logistic regression
	Subgroup analyses*****	ITT population (based on investigator's preference)	-Stratified log rank test -Unstratified log rank test -Kaplan Meier estimates -Univariate Cox regression -Multivariate Cox regression
	OS/PFS by no CNS involvement*	***ITT population (patients with no CNS)***	***-Stratified log rank test*** ***-Unstratified log rank test*** ***-Kaplan Meier estimates*** ***-Univariate Cox regression*** ***-Multivariate Cox regression***

* ~~The~~***If the result of the primary endpoint analysis is statistically significant, the*** Hochberg procedure will be used at the overall two-sided significance level of 0.05 ***to test the difference between PM01183/DOX and CAV in OS in patients with CAV as best Investigator's choice, and the difference in OS in the subgroup of patients without baseline CNS involvement. The unstratified log-rank tests will be used to calculate p-values.*** IA, Investigator Assessment; IRC, Independent Review Committee; ITT, intention-to-treat; PFS, progression-free survival; OS, overall survival.

Section 7.2 (Clinical Laboratory Evaluation)

Laboratory results will be classified according to the NCI-CTCAE v.4. ***All laboratory visits reported as "End of treatment" visit will be mapped to the last cycle visit for each patient.***

…

Section 8.4 (Patient-reported Outcomes (PRO))

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

EOT. ***All visits reported as "End of treatment" visit will be mapped to the last cycle visit for each patient.***

Section 8.6 (Imputation in Incomplete Dates)

…

After end of treatment

…

Once the OS follow-up assessments will be implemented following the calendar time if a patient deceased but his/her complete death date is missing then if month/year is known then death date will be imputed as 01/Month/Year, otherwise the death date will be imputed as last time to the patient was known to be alive plus 1 day.

Section 8.8 (Decimal Places, Missing Values and Allowed Assessment Windows)

By default, all results will be rounded to one decimal place, except when variables are integer, which will be reported without decimals (e.g., age in years, number of sites, etc.). For representing p-values four decimals will be selected as default but they could be rounded to fewer decimals if necessary. ***Hazard ratios will be presented with three decimal places.***

…

Section 8.9 (Subgroup Analyses)

Some preplanned ~~upfront~~ efficacy analyses are the following: subgroup analyses based on comparison of PM01183/DOX with CAV or topotecan, subgroup analyses for stratification factors ***(mainly CNS and CTFI),*** subgroup analyses for patients with primary site different to lung, subgroup analyses if enough cases for baseline PD-L1 expression (<1% *vs.* ≥1%) or PD-L1 expression (<50% *vs.* ≥50%), and the analysis of the subset of patients who received subsequent therapies.

…

Section 8.11 (Generalised Pairwise comparison assessment)

8.11 Generalised Pairwise comparison assessment

A risk-benefit measure will be calculated using the generalised pairwise comparison[8]. A favourable benefit outcome will be determined by differences in OS exceeding 2, 3 or 4 months. An unfavourable risk outcome will be determined by the occurrence of any G3-4 adverse reaction or a clinically important adverse event:

A clinically important adverse event will be defined as:

- ***Any AE causing death or treatment discontinuation***
- ***Febrile neutropenia/neutropenic sepsis***
- ***Grade 4 neutropenia lasting > 3 days***
- ***Grade 4 thrombopenia or grade 3 thrombopeniaconcomitant with bleeding events.***
- ***Grade 4 AST/ALT or grade 3 lasting >14 days.***
- ***Treatment-related grade ≥ 2 ALT or AST increase concomitantly with ≥ 2 times the upper limit of normal (ULN) total bilirubin increase and normal alkaline phosphatase (AP).***

- ***Grade ≥ 3 creatine phosphokinase (CPK) increase.***
- ***Grade 3 fatigue lasting > 3 days.***
- ***Any other grade 3/4 non-hematological AE that is suspected to be related to study drug(s), except nausea/vomiting (unless the patient is receiving an optimal anti- emetic regimen), hypersensitivity reactions, extravasations and non-clinically relevant isolated biochemical abnormalities [e.g., isolated increase in gamma-glutamyltransferase (GGT)].***

Section 9 (STATISTICAL SOFTWARE)

…

EAST® v.6.~~3~~*4* has been used to calculate sample size[9].

…

Section REFERENCES

…

2 Multiple Endpoints in Clinical Trials Guidance for Industry, Draft (January 2017)

…

8 Buyse M. Generalized pairwise comparisons for prioritized outcomes in the two-sample problem. Statist Med 29: 3245-57, 2010.

…

Section 10.1 (Patient Disposition)

…

Listing 10.1.8 Patients assigned to incorrect strata at the time of randomization

*Treatment arm**	*Patient*	*Actual stratum (Screening form)*	*Strata reported at randomization (Randomization form)*

PM01183+DOX/Topotecan/CAV

Table 10.1.9 Investigator's preference for the control arm

	PM01183+DOX		*Topotecan*		*CAV*	
	N	*%*	*N*	*%*	*N*	*%*
Topotecan						
CAV						

Section 11.1.1 (Patient Characteristics at Baseline)

Table 11.1.1.1 Baseline characteristics

~~**Primary site**~~ ~~**SCLC**~~ ~~**Small cell from extrapulmonary primary site**~~	

Section 11.3 (Efficacy Analysis)

Overall survival

Table 11.3.1.1 OS (Stratified log rank test)

Variable	Stratification factors	p-value*
Treatment arm (main analysis)	**Actual values (CNS and CTFI)**	
Treatment arm (sensitivity)	**Values reported for randomization (CNS and CTFI)**	
Treatment arm (sensitivity)	**Actual values (all stratification factors)**	
Treatment arm (sensitivity)	**Values reported for randomization (all stratification factors)**	

***Stratified log rank test.**

…

Table 11.3.1.3 OS

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median OS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
Mean OS				**-**
OS at 12 months (95% CI)			Diff:	
OS at 18 months (95% CI)				
OS at 24 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.3) will be shown too.

…

Overall survival (CAV comparison)

Table 11.3.1.8 OS vs CAV (Stratified log rank test)

Variable	Stratification factors	p-value*
Treatment arm	**Actual values (CNS and CTFI)**	
Treatment arm	**Values reported for randomization (CNS and CTFI)**	
Treatment arm	**Actual values (all stratification factors)**	
Treatment arm	**Values reported for randomization (all stratification factors)**	

***Stratified log rank test.**

Table 11.3.1.9 OS vs CAV

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median OS (95% CI)			**Log-Rank: HR (95% CI) :**	**LR: HR:**
Mean OS				**-**
OS at 12 months (95% CI)			**Diff:**	
OS at 18 months (95% CI)				
OS at 24 months (95% CI)			**Diff:**	

Kaplan Meier plot (Figure 11.3.1.9) will be shown too.

Forest plot (Figure 11.3.1.10) summarizing main results, stratification factors and covariates in terms of OS will be prepared.

Overall survival (non CNS comparison)

Table 11.3.1.11 OS in non CNS (Stratified log rank test)

Variable	Stratification factors	p-value*
Treatment arm	**Actual values (CNS and CTFI)**	
Treatment arm	**Values reported for randomization (CNS and CTFI)**	
Treatment arm	**Actual values (all stratification factors)**	
Treatment arm	**Values reported for randomization (all stratification factors)**	

***Stratified log rank test.**

Table 11.3.1.12 OS in non CNS

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median OS (95% CI)			**Log-Rank: HR (95% CI) :**	**LR: HR:**
Mean OS				**-**
OS at 12 months (95% CI)			**Diff:**	
OS at 18 months (95% CI)				
OS at 24 months (95% CI)			**Diff:**	

Kaplan Meier plot (Figure 11.3.1.12) will be shown too.

Forest plot (Figure 11.3.1.13) summarizing main results, stratification factors and covariates in terms of OS will be prepared.

Progression-free survival by IRC

Table 11.3.14 PFS by IRC (primary analysis)

Variable	***Stratification factors***	***p-value****
Treatment arm	***Actual values (CNS and CTFI)***	
Treatment arm	***Values reported for randomization (CNS and CTFI)***	
Treatment arm	***Actual values (all stratification factors)***	
Treatment arm	***Values reported for randomization (all stratification factors)***	

****Stratified log rank test.***

…

Table 11.3.1.16 PFS by IRC

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
Mean PFS				**-**
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.16) will be shown too.

…

Progression-free survival by IA

Table 11.3.1.21 PFS by IA (Stratified log rank test)

Variable	***Stratification factors***	***p-value****
Treatment arm	***Actual values (CNS and CTFI)***	
Treatment arm	***Values reported for randomization (CNS and CTFI)***	
Treatment arm	***Actual values (all stratification factors)***	
Treatment arm	***Values reported for randomization (all stratification factors)***	

****Stratified log rank test.***

…

Table 11.3.1.23 PFS by IA

	PM01183+DOX	Control	Parameter	p-value
N				
Events				
Censored				
Median PFS (95% CI)			Log-Rank: HR (95% CI) :	LR: HR:
Mean PFS				**-**
PFS at 6 months (95% CI)			Diff:	
PFS at 12 months (95% CI)			Diff:	

Kaplan Meier plot (Figure 11.3.1.23) will be shown too.

…

- First date of progression or death not censoring data if further antitumor therapy.

Table 11.3.1.35 PFS not censoring if further antitumor by IRC

	PM01183+DOX	***Control***	***Parameter***	***p-value***
N				
Events				
Censored				
Median PFS (95% CI)			***Log-Rank: HR (95% CI) :***	***LR: HR:***
PFS at 6 months (95% CI)			***Diff:***	
PFS at 12 months (95% CI)			***Diff:***	

Kaplan Meier plot (Figure 11.3.1.35) will be shown too.

Table 11.3.1.36 PFS not censoring if further antitumor by IA

	PM01183+DOX	***Control***	***Parameter***	***p-value***
N				
Events				
Censored				
Median PFS (95% CI)			***Log-Rank: HR (95% CI) :***	***LR: HR:***
PFS at 6 months (95% CI)			***Diff:***	
PFS at 12 months (95% CI)			***Diff:***	

Kaplan Meier plot (Figure 11.3.1.36) will be shown too.

…

Time to treatment failure

Table 11.3.1.52 Time to treatment failure by IA

	PM01183+DOX	*Control*	*Parameter*	*p-value*
N				
Events				
Censored				
Median PFS (95% CI)			***Log-Rank: HR (95% CI) :***	***LR: HR:***
PFS at 6 months (95% CI)			***Diff:***	
PFS at 12 months (95% CI)			***Diff:***	

Kaplan Meier plot (Figure 11.3.1.52) will be shown too.

Time to brain mets

Table 11.3.1.53 Time to clinical diagnosis of brain mets by IA

	PM01183+DOX	*Control*	*Parameter*	*p-value*
N				
Events				
Censored				
Median PFS (95% CI)			***Log-Rank: HR (95% CI) :***	***LR: HR:***
PFS at 6 months (95% CI)			***Diff:***	
PFS at 12 months (95% CI)			***Diff:***	

Kaplan Meier plot (Figure 11.3.1.53) will be shown too.

…

Comparison in patients with no CNS involvement.

- Figure 11.3.1.68 Patients with no CNS. PFS by IRC (PM01183 vs. Control)
- Figure 11.3.1.69 Patients with no CNS. PFS by IA (PM01183 vs. Control)
- Figure 11.3.1.70 Patients with no CNS. OS (PM01183 vs. Control)
- Figure 11.3.1.71 Patients with no CNS. RR by IRC (PM01183 vs. Control)
- Figure 11.3.1.72 Patients with no CNS. RR by IA (PM01183 vs. Control)
- Figure 11.3.1.73 Patients with no CNS. DR by IRC (PM01183 vs. Control)
- Figure 11.3.1.74 Patients with no CNS. DR by IA (PM01183 vs. Control)

Comparison in patients with CNS involvement.

- Figure 11.3.1.75 Patients with CNS. PFS by IRC (PM01183 vs. Control)
- Figure 11.3.1.76 Patients with CNS. PFS by IA (PM01183 vs. Control)
- Figure 11.3.1.77 Patients with CNS. OS (PM01183 vs. Control)
- Figure 11.3.1.78 Patients with CNS. RR by IRC (PM01183 vs. Control)
- Figure 11.3.1.79 Patients with CNS. RR by IA (PM01183 vs. Control)
- Figure 11.3.1.80 Patients with CNS. DR by IRC (PM01183 vs. Control)
- Figure 11.3.1.81 Patients with CNS. DR by IA (PM01183 vs. Control)

Comparison in patients with no CNS involvement and CTFI≥90 days (sensitive).

- Figure 11.3.1.82 Patients with no CNS in sensitive. PFS by IRC (PM01183 vs. Control)
- Figure 11.3.1.83 Patients with no CNS in sensitive. PFS by IA (PM01183 vs. Control)
- Figure 11.3.1.84 Patients with no CNS in sensitive. OS (PM01183 vs. Control)
- Figure 11.3.1.85 Patients with no CNS in sensitive. RR by IRC (PM01183 vs. Control)
- Figure 11.3.1.86 Patients with no CNS in sensitive. RR by IA (PM01183 vs. Control)
- Figure 11.3.1.87 Patients with no CNS in sensitive. DR by IRC (PM01183 vs. Control)
- Figure 11.3.1.88 Patients with no CNS in sensitive. DR by IA (PM01183 vs. Control)

Comparison in patients with no CNS involvement and CTFI<90 days (resistant).

- Figure 11.3.1.89 Patients with no CNS in resistant. PFS by IRC (PM01183 vs. Control)
- Figure 11.3.1.90 Patients with no CNS in resistant. PFS by IA (PM01183 vs. Control)
- Figure 11.3.1.91 Patients with no CNS in resistant. OS (PM01183 vs. Control)
- Figure 11.3.1.92 Patients with no CNS in resistant. RR by IRC (PM01183 vs. Control)
- Figure 11.3.1.93 Patients with no CNS in resistant. RR by IA (PM01183 vs. Control)
- Figure 11.3.1.94 Patients with no CNS in resistant. DR by IRC (PM01183 vs. Control)
- Figure 11.3.1.95 Patients with no CNS in resistant. DR by IA (PM01183 vs. Control)

Comparison in patients with CTFI≥90 days (sensitive).

- Figure 11.3.1.96 Patients with CTFI≥90 (sensitive). PFS by IRC (PM01183 vs. Control)
- Figure 11.3.1.97 Patients with CTFI≥90 (sensitive). PFS by IA (PM01183 vs. Control)
- Figure 11.3.1.98 Patients with CTFI≥90 (sensitive). OS (PM01183 vs. Control)
- Figure 11.3.1.99 Patients with CTFI≥90 (sensitive). RR by IRC (PM01183 vs. Control)
- Figure 11.3.1.100 Patients with CTFI≥90 (sensitive). RR by IA (PM01183 vs. Control)
- Figure 11.3.1.101 Patients with CTFI≥90 (sensitive). DR by IRC (PM01183 vs. Control)
- Figure 11.3.1.102 Patients with CTFI≥90 (sensitive). DR by IA (PM01183 vs. Control)

Comparison in patients with no CNS involvement and CTFI<90 days (resistant).

- Figure 11.3.1.103 Patients with CTFI<90 (resistant). PFS by IRC (PM01183 vs. Control)
- Figure 11.3.1.104 Patients with CTFI<90 (resistant). PFS by IA (PM01183 vs. Control)
- Figure 11.3.1.105 Patients with CTFI<90 (resistant). OS (PM01183 vs. Control)
- Figure 11.3.1.106 Patients with CTFI<90 (resistant). RR by IRC (PM01183 vs. Control)
- Figure 11.3.1.107 Patients with CTFI<90 (resistant). RR by IA (PM01183 vs. Control)
- Figure 11.3.1.108 Patients with CTFI<90 (resistant). DR by IRC (PM01183 vs. Control)
- Figure 11.3.1.109 Patients with CTFI<90 (resistant). DR by IA (PM01183 vs. Control)

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Generalised Pairwise comparison

Table 11.3.1.138 Generalised Pairwise comparison

	Arm A	Arm B	-	p-value
2 months OS and any G3-4 adverse reaction				
2 months OS and important AE				
3 months OS and any G3-4 adverse reaction				
3 months OS and important AE				
4 months OS and any G3-4 adverse reaction				
4 months OS and important AE				

…

12.9 Time to different deterioration in QoL assessments

Time to deterioration to ≥10 points in the Global Health Status and the additional indirect QoL assessment of time to PS deterioration will be performed. Patients not reaching the event will be censored in the last available assessment.

Table 12.9.1.1 Time to deterioration to ≥10 points in the Global Health Status

	PM01183+DOX	*Control*	*Parameter*	*p-value*
N				
Events				
Censored				
Median time (95% CI)			***Log-Rank: HR (95% CI) :***	***LR: HR:***
Mean time				***-***

Kaplan Meier plot (Figure 12.9.1.1) will be shown too.

Table 12.9.1.2 Time to PS deterioration

	PM01183+DOX	*Control*	*Parameter*	*p-value*
N				
Events				
Censored				
Median time (95% CI)			***Log-Rank: HR (95% CI) :***	***LR: HR:***
Mean time				***-***

Kaplan Meier plot (Figure 12.9.1.2) will be shown too. PS deterioration is defined as PS>2 or increase in two levels from baseline value (e.g from 0 to 2).

Adds to (13 DB Listings)

Shell listings based on the unique forms for eCRF dated on 20APR2016 have been added to the main body of the SAP where they were not present previously. To avoid unnecessary multiplicity, they have not been repeated in this summary section.

Adds to (14 ICH Listings)

Shell listings have been added to the main body of the SAP where they were not present previously. To avoid unnecessary multiplicity, they have not been repeated in this summary section.