PM1183-A-003-10 (NCT01970540)

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

STATISTICAL ANALYSIS PLAN

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List of Abbreviations

AE(s)	Adverse Event(s)
AFP	Alpha-fetoprotein
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline phosphatase
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BSA	Body Surface Area
BPD	Blood Diastolic Pressure
BPS	Blood Systolic Pressure
CA-125	Carbohydrate Antigen-125
CA15-3	Carbohydrate Antigen 15-3
CA19-9	Carbohydrate Antigen 19-9
CEA	Carcinoembryonic Antigen
CI	Confidence Interval
CL	Clearance
Cmax	Maximum Plasma Concentration
CPK	Creatine Phosphokinase
CPK-MB	Creatine Phosphokinase Muscle-Brain (serum CPK isoenzymes found in cardiac muscle)
CR	Complete Response/Complete Regression
CrCl	Creatinine Clearance
CRF	Case Report Form
CTFI	Chemotheraphy Free-Interval
CT-scan	Computed Tomography Scan
DAC	Data Analysis Conventions
d/D	Day(s)
DI	Dose Intensity
DL	Dose Level
DLT	Dose-Limiting Toxicity
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG-PS	Performance Status according to Eastern Cooperative Oncology Group
FD	Flat Dose
FUP	Follow-up
G-CSF	Granulocyte Colony-stimulating Factor
CSF	Colony-stimulating Factor
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
GGT	Gama-glutamyltransferasa
HR	Heart Rate
i.v.	Intravenous (intravenously)
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committees
INR	International Normalized Ratio
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
min	Minutes
ml	Milliliter
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple-gated Acquisition Scan
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events (version 4 will be used for this trial)
NSCLC	Non-small Cell Lung Cancer
OS	Overall Survival
PFS	Progression Free Survival
PD	Progressive Disease
PGx	Pharmacogenomic(s)
PK	Pharmacokinetic(s)
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
q3wk	Every 3 Weeks
RD	Recommended Dose
QT	QT Interval (measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle)
QTcF	Louis Sigurd Fridericia's formula for the correction of the QT interval
RECIST	Response Evaluation Criteria In Solid Tumors (version 1.1 will be used for this trial)
RT	Radiotherapy
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
Sec	Seconds
SD	Stable Disease
TA	Tumor Assessment
STD	Standard Deviation
TFI	Systemic Chemotheraphy Free Interval
TTP	Time to Progression
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO	World Health Organization

1. Introduction.

This document [Statistical Analysis Plan (SAP)] explains in detail the statistical analyses that will be carried out for the PharmaMar PM1183-A-003-10 study.

The analyses described in this SAP are based upon and supplement those described in the study protocol version 1.0, version 2.0 and version 3.0 and the protocol amendments No.1, dated 21 November 2011, No.2, dated 10 July 2013, No.3, dated 17 October 2014 and No.1 Non substantial amendment, dated 30 January 2015.

2. Study Objectives.

The clinical trial protocol states the following:

2.1. Primary Objective.

- To determine the maximum tolerated dose (MTD) and the recommended dose (RD) of PM01183 in combination with doxorubicin in patients with selected advanced solid tumors.

2.2. Secondary Objectives.

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

3. Study Design.

Prospective, open-label, dose-ranging, uncontrolled phase I study with escalating doses of PM01183 in combination with fixed doses of doxorubicin (see escalation dose scheme in section 4.2).

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

Cohorts of three to six patients will be included at each dose level (DL). If no DLT occurs in more than one patient within each cohort, escalation will proceed to the following dose level. If one of the first three evaluable patients experiences a DLT, the dose level should be expanded up to six patients.

The MTD will be the lowest dose level explored during the dose escalation at which more than one evaluable patient experience a DLT in Cycle 1. All evaluable patients within a dose level will be followed for at least one cycle (i.e., three weeks) before dose escalation may proceed. Dose escalation will be terminated once the MTD or the last dose level (DL4) is reached, whichever occurs first, except if all DLTs occurring at a given dose level are related to neutropenia (e.g., febrile neutropenia, grade 4 neutropenia lasting more than seven days or neutropenic sepsis) in which case dose escalation may be resumed, starting at the lowest dose level where exclusively neutropenia-related DLTs have occurred, and will follow the same original schedule but with compulsory primary G-CSF prophylaxis. An expansion cohort to complete a minimum of nine evaluable patients will be recruited at the immediate lower dose level, or at the last dose level (DL4) if the MTD is not defined yet. This level will be confirmed as the RD if less than one third of the first nine evaluable patients experience DLT during Cycle 1.

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

In addition, a new cohort B of 20 evaluable patients with small cell lung cancer (SCLC) who failed treatment after first-line standard cytotoxic-containing therapy and at least nine evaluable patients with endometrial cancer will be included to further define the efficacy, safety and feasibility of a doxorubicin dose adaptation (doxorubicin 40 mg/m^2 and PM01183 2.0 mg/m^2). The administered doses of both PM01183 and doxorubicin will be capped at 2.0 m^2 of body surface area (BSA) for any patients exceeding this BSA value. Patients in this cohort who have received ten cycles of the doxorubicin/PM01183 combination or have to discontinue doxorubicin due to a cardiac AE may continue receiving treatment with single-agent PM01183 at 4.0 mg/m^2 q3wk if patient benefit is perceived according to the Investigator. These patients will be followed every three months until death or the date of study termination, whichever occurs first.

Patients will be divided into two cohorts. Cohort A will consist of all patients included before the implementation of protocol amendment #3, and Cohort B will consist of all patients included after the implementation of protocol amendment #3.

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

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

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

Patients will receive PM01183 and doxorubicin until progression, unacceptable toxicity, consent withdrawal or while it is considered to be in their best interest. More specifically, doxorubicin will be administered in the absence of disease progression or unacceptable toxicity before a maximal total cumulative dose of 450 mg/m^2 is reached. Thus, a maximum of ten cycles of the combination will be administered to patients with SCLC and endometrial cancer included in the new cohort B. Once this dose has been reached, the patients may continue treatment with PM01183 alone at the established single-agent RD, 7.0 mg FD q3wk and for patients included in the new cohort B they may continue treatment with PM01183 alone at 4.0 mg/m^2 q3wk.

Tumor assessments will be done every six weeks while on treatment. After treatment discontinuation, patients will be followed every four weeks until resolution or stabilization of all toxicities, if any. Patients discontinuing treatment without progression will be followed every two months until disease progression, other antitumor therapy, death or the date of study termination, whichever occurs first (see study protocol, section 5.9).

In the new cohort B, patients with SCLC and endometrial cancer will be followed every three months until death or the date of study termination, whichever occurs first. Antitumor response will be assessed using the RECIST v.1.1 and/or serum tumor markers as appropriate (e.g., ovarian cancer markers).

No serum markers will be evaluated in patients with SCLC and endometrial cancer included in the new cohort B. Patients will be evaluated at scheduled visits on three study periods: Pre-treatment, Treatment and Follow-up (see study protocol, section 5.2).

4. Sample Size and Dose Escalation.

4.1. Sample Size.

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

4.2. Dose Escalation Schedule.

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

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

The dose escalation schedule is summarized in the following table:

Dose escalation schedule (cohort A).

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

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

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

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

New cohort (cohort B) after implementation of protocol amendment #3 (Cohort B):

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

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

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

PM01183 doses will be rounded to the first decimal, if necessary. Doxorubicin doses will be rounded according to institutional guidelines/standard practices.

5. Population and Endpoints.

Patients must fulfill all the inclusion/exclusion criteria to be eligible for admission to the study. See clinical trial protocol, sections 4.1 Inclusion Criteria and 4.2 Exclusion Criteria.

5.1. Patient Evaluability Criteria.

The analysis sets are defined as follows:

The "All Included Patients" analysis set is defined as all patients who are included in the study, regardless of whether they have received any study drug or not.

The "All Treated Patients" analysis set is defined as all included patients who have received at least part of one infusion of PM01183.

The "All Evaluable Patients for the Assessment of the Primary Endpoint" analysis set is defined as all included patients who have received at least one complete cycle (including observation period), except if early discontinuations or missed doses or delays and/or assessments were the consequence of drug-related toxicity (excluding hypersensitivity reactions and/or extravasations).

The "All Evaluable for Efficacy Patients" analysis set is defined as all evaluable patients measured according to the RECIST v.1.1 at least six weeks after treatment initiation in all patients with measurable disease, and/or by CA-125 levels if applicable, i.e. ovarian cancer with at least 2 x upper limit of normal (ULN) at baseline [according to the Gynecologic Cancer Intergroup (GCIG/Rustin) specific criteria]. No serum markers will be evaluated in patients with SCLC and endometrial cancer included in the new cohort B.

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

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

All analyses will be performed as per protocol rather than on an intention-to-treat-basis. Any departure from the planned treatment according to the study schedule will be listed and documented in the clinical study report.

5.2. Endpoints.

5.2.1. Primary Endpoint.

- The MTD will be the lowest dose level explored during the dose escalation at which more than one evaluable patient experience a DLT in Cycle 1.
- The RD will be the highest dose level explored in which less than one third of evaluable patients experience a DLT during Cycle 1.

If the DLTs of the doxorubicin and PM01183 combination without G-CSF prophylaxis are exclusively related to neutropenia, the MTD and RD will also be determined with primary G-CSF prophylaxis.

5.2.1.1. Determination of MTD and RD.

A minimum of three patients will be included at each dose level. If no patients experience a DLT during the first cycle, the dose will be escalated. If one of three patients experiences a DLT, three additional patients will be included at that level. If >1 evaluable patient during dose escalation at a given dose level experience a DLT during the first cycle, that level will be considered the MTD and dose escalation will be terminated except if all DLTs occurring at a given dose level are related to neutropenia (e.g., febrile neutropenia, grade 4 neutropenia lasting more than 7 days or neutropenic sepsis) in which case dose escalation may be resumed, starting at the lowest dose level where exclusively neutropenia-related DLTs have occurred, and will follow the same original schedule but with compulsory primary G-CSF prophylaxis The DL immediately below the MTD, or DL4 if the MTD is not reached during dose escalation and the last dose level (DL4) is reached, was to be initially expanded up to a minimum of nine evaluable patients. If less than three among the first nine evaluable patients treated within the expansion cohort experience a DLT during Cycle 1 this DL will be the RD.

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

Determination of the maximum tolerated dose.

No. of patients evaluable* for DLT	**No. of patients with DLTs in Cycle 1**	**Action**
3	0	Escalate DL until DL4 is reached
	1	Add 3 patients
	>1	MTD
6	1	Escalate DL until DL4 is reached
	>1	MTD
DL, dose level; DLT, dose-limiting toxicities; MTD, maximum tolerated dose. * Patients not evaluable for DLT during dose optimization must be replaced. ** For replacement of patients and replacement of patients after implementation of Amendment #3 (see Protocol section 5.3).		

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

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

5.2.1.2. DLT Criteria.

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

- Grade 4 neutropenia [absolute neutrophil count (ANC) < 0.5 x 10^9/l] lasting > 7 days.
- Grade ≥ 3 febrile neutropenia of any duration or neutropenic sepsis.
- Grade 4 thrombocytopenia (platelet count < 25 x 10^9/l) or grade 3 with any major bleeding episode requiring a platelet transfusion.
- Grade 4 alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) increase, or grade 3 lasting > 14 days.
- Treatment-related grade ≥ 2 ALT or AST increase concomitantly with ≥ 2 xULN total bilirubin increase and normal alkaline phosphatase (AP).
- Grade ≥ 3 creatine phosphokinase (CPK) increase.
- Any other grade 3/4 non-hematological AE that is suspected to be related to study drug(s), except nausea/vomiting (unless the patient is receiving an optimal anti-emetic regimen), hypersensitivity reactions, extravasations, grade 3 asthenia lasting less than one week, and non-clinically relevant isolated biochemical abnormalities [e.g., isolated increase in gamma-glutamyltransferase (GGT)]. In any case, the clinical relevance should be discussed between the Investigators and Sponsor's representatives.
- Delay in the administration of Cycle 2 of the combination exceeding 15 days of the theoretical date (i.e., Day 22), due to any AEs related to study drug(s).
- The following circumstances will be discussed between the Principal Investigator and the Sponsor, and the final consensus will be documented:
  - DLTs with delayed onset (i.e., that occur after Cycle 1).

5.2.2. Secondary Endpoints.

5.2.2.1. Safety.

Safety parameters include:

- Adverse events.
- Hematology.
- Clinical chemistry.
- Coagulation tests.
- Vital signs.
- Electrocardiogram (ECG) and Left Ventricular Ejection Fraction (LVEF).
- Physical examinations.
- Delays and reductions.
- Withdrawals.

AEs will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4 and coded using the Medical Dictionary for Regulatory Activities (MedDRA).

5.2.2.2. Efficacy.

Although it is not the main objective of this study, antitumor activity will be measured according to the RECIST v.1.1 at least six weeks after treatment initiation in all patients with measurable disease, or by evaluation of tumor markers if applicable (e.g., ovarian cancer). Patients included at the RD in the expansion cohort must be evaluable per RECIST v.1.1 or by evaluation of tumor markers (see Section 7.4 for efficacy evaluation).

No serum markers will be evaluated in patients with SCLC and endometrial cancer included in the new cohort B.

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

In the new cohort B, exploratory assessment for progression-free survival (PFS) and overall survival (OS) will be performed.

The best overall response is defined as the best response achieved during the study according to RECIST v.1.1 and/or GCIG, whenever is applicable, before disease progression, administration of subsequent anticancer treatment or study discontinuation.

The response rate is defined as the ratio of patients with any response [complete response (CR) or partial response (PR)] by the total number of patients included in the efficacy population. The number of patients with stable disease SD $\geq$ 3 and/or 4 months will also be shown.

Duration of response (DR), defined as the time between the date when the response criteria (PR or CR, the first that is reached) are fulfilled and the first date when disease progression, recurrence or death is objectively documented (taking the smallest measurements documented since the treatment started as reference for progressive disease).

Progression-free survival (PFS), defined as the time from the first day of study treatment to the day of negative assessment (progression or death) or last tumor evaluation.

In addition, patients with SCLC and endometrial cancer included in the cohort B will be followed for survival for up to 18 months after the first study dose.

5.2.2.3. Pharmacokinetics.

Pharmacokinetic (PK) analyses will be described and reported in a different document out of the scope of this SAP.

5.2.2.4. Pharmacogenomics.

Pharmacogenomic (PGx) analyses will be described and reported in a different document out of the scope of this SAP.

6. General analysis methods.

6.1. Statistical Software.

Oracle Clinical will be used for double data entry and clinical data management.

SAS® Software v.9.2 or higher will be used for all statistical analyses.

6.2. Data Analysis Conventions.

All data analysis conventions, derived data calculations and grouping needed to perform the statistical analysis will come in separate document not included in this SAP.

7. Statistical analysis.

7.1. Patient Disposition and Protocol Deviations.

Patients and dose levels will be summarized and listed by the populations used in the study:

- All Included Patients.
- All Treated Patients.
- All Evaluable Patients for the Assessment of the Primary Endpoint.
- All Evaluable for Efficacy Patients.

Reasons for not belonging to any population will be detailed.

The accrual and study discontinuation details will be presented descriptively.

Reasons for treatment discontinuation by number of cycles received will be described by counts and percentages. Reasons of treatment discontinuation other than disease progression will be detailed.

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

determined), and also to other procedures described in the protocol that concern the Good Clinical Practice (GCP) guidelines or ethical issues (e.g., issues related to obtaining the patients' Informed Consent, data reporting, the responsibilities of the Investigator, etc.).

Protocol deviations will be categorized by the PharmaMar's responsible physician and summarized for all patients. A summary table with the number of patients with inclusion/exclusion deviations will be presented per criterion. These patients will be listed with the unmet criteria. Deviations with no effects on the risk/benefit ratio of the clinical trial (such as minimal delays in assessments or visits) will be distinguished from those that might have an effect on this risk/benefit ratio.

A summary including but not necessarily restricted to the following categories will be presented:

- Ineligible patients as per protocol.
- Patient not withdrawn as per protocol.
- Excluded concomitant medication.
- Incorrect dose or schedule, including patients not meeting re-treatment criteria on Day 1 of subsequent cycles.

7.2. Baseline Characteristics.

7.2.1. Demographics.

Demographics and baseline characteristics will be summarized for all treated patients. All patient characteristics will be described by dose level (or most adequate dose grouping/cohort/Tumor type or other clinical relevant variable).

Continuous variables will be summarized and presented with summary statistics, i.e., mean, median, range and standard deviation.

Categorical variables will be summarized in frequency tables. Percentages in the summary tables will be rounded and may therefore not always add up to exactly 100%.

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

Baseline Eastern Cooperative Oncology Group (ECOG) performance status will be summarized with frequency counts.

For the cancer history, histologic diagnosis, time from diagnosis, number of baseline lesions, and involvement in the different sites will be summarized. Time from initial diagnosis to the start of study treatment and time from the latest disease progression to the start of study treatment will be calculated in months and summarized descriptively. If incomplete dates are recorded, the rules described in section 8.5 will be used for imputation.

The primary tumor sites and baseline lesions will be recoded by PharmaMar's physicians in order to categorize them accurately in the analysis.

The previous relevant medical history (other than cancer) will be listed by dose level (or most adequate dose grouping/cohort/Tumor type or other clinical relevant variable) and patient.

A frequency tabulation of the different types of previous oncologic surgery (excluding only diagnostic or palliative procedures), radiotherapy, or anticancer systemic therapy (number of lines for advanced and number of agents) will be given. Chemotherapy agents and lines will be recoded by PharmaMar's physicians in order to categorize them accurately in the analysis.

The signs and symptoms, hematology and serum biochemistry abnormalities at baseline will be displayed by tabulation of frequencies according to NCI-CTCAE v.4.0 toxicity grades. The signs and symptoms and laboratory abnormalities of grade ≥2 at baseline will be listed by dose level (or most adequate dose grouping/cohort/Tumor type or other clinical relevant variable) and patient.

7.3.Statistical Analysis for Safety.

All analysis of safety variables will be descriptive. Data retrieved at both scheduled and unscheduled visits will be tabulated and listed.

The safety population is composed by all patients that receive at least part of a PM01183 infusion. The safety patient population will be used for the general safety presentations.

The "All Evaluable Patients for the Assessment of the Primary Endpoint" population will be used for primary analysis.

For the evaluation of the main endpoint, the total number of patients included, the number of patients evaluable for determination of DLTs, and the number of patients with any DLT (and their categorization) will be summarized by dose level (or most adequate dose grouping/cohort/Tumor type or other clinical relevant variable). The toxicities meeting the DLT criteria in Cycle 1 and toxicities in subsequent cycles, if any, will be listed separately, and the description of laboratory abnormalities (hematology/ biochemistry) will be supported by graphs depicting the evolution in time of laboratory values (including nadir calculation and median time to recovery from baseline values).

7.3.1. Treatment Administration and Exposure.

Exposure to each treatment will be described by dose level (or most adequate dose grouping/cohort/tumor type or other clinical relevant variable) for all patients who have received at least one of the study treatments.

Total cumulative dose, expressed in mg for PM01183 and in mg for doxorubicin and defined as the sum of all the product doses from the 1st dose received until the last dose received.

Intended dose intensity is the planned dose of the cycle divided by planned duration of a cycle in weeks.

Absolute dose intensity: is the total cumulative dose divided by the duration of the treatment. As a convention, the duration of the last cycle is considered to be 21 days (planed cycle duration).

Relative dose intensity (%): is the ratio of absolute dose intensity divided by the intended dose intensity.

Time on treatment: is the interval expressed in weeks, between the first infusion date and the last infusion date plus 30 days or start of new treatment or date of death (whichever occurs first).

The number of cases, median, standard deviations, 95% confidence interval (CI), minimum and maximum values for the parameters defined above will be tabulated by dose level (or most adequate dose grouping/cohort/Tumor type or other clinical relevant variable) and drug (PM01183 and doxorubicin).

7.3.2. Cycle Delays and Omissions.

The item "Infusion delayed: No/Yes" in the case report from (CRF) will be used to calculate the delay. For doses considered as delayed by the investigator, the delay will be calculated as:

Delay (in days) will be equal to the date of start of current cycle minus the date of start of previous cycle minus 21 days (planed cycle duration, in days).

Dose delay is defined by a delay in the administration of the first infusion of one cycle (Day 1 infusion).

Cycle 1 will be excluded from all calculations of cycle delay (and the denominator used for calculations will be equal to the number of cycles susceptible to be delayed).

The distribution of delays according to the infusion administered will be studied by means of counts and percentages. The reasons for infusion delay will be detailed, specifying how many were due to treatment-related toxicity and how many were not (administrative reasons will be analyzed separately and additional tables will be prepared after exclusion of these delays). Within delays attributable to treatment, hematological and/or non-hematological reasons will be outlined, and the specific reasons will be detailed, if possible.

Skipped dose or dose omission is defined as every doxorubicin infusion not administrated on Day 1 of the cycle. The distribution of skipped doses will be studied by means of counts and percentages (the denominator used for calculations will be equal to the number of patients/cycles susceptible to have an omission) and a detailed listing of patients with skipped dose and reason will be showed. Also reasons for dose omission will be detailed, specifying how many were due to treatment, how many were not and how many reached a maximal total cumulative dose of 450 mg/m^2.

All cycles in which a maximal total cumulative dose of 450 mg/m^2 is not reached are susceptible of doxorubicin omission (the denominator used for calculations will be equal to the number of cycles susceptible to be omitted).

7.3.3. Dose Reductions.

All dose reductions will be considered and described (per cycle and patient), specifying the magnitude and the reason(s) for reduction treatment-related (hematological toxicity, non-hematological toxicity or both), or if any, other causes unrelated to treatment.

7.3.4. Adverse Events.

All adverse events will be coded using the MedDRA coding dictionary.

The toxicity evaluation will be made according to the National Cancer Institute- Common Toxicity Criteria (NCI-CTCAE) v.4 and the events will be coded and classified using the MedDRA dictionary.

As far as all the toxicities are concerned, the NCI-CTCAE grade will be used wherever an NCI-CTCAE grading exists. Otherwise, the severity will be noted. As a convention, the term "Grade" will always be used. Toxicities will be described according to the worst NCI-CTCAE grade or, for toxicities which do not form the subject of NCI-CTCAE classification, according to the worst severity.

Descriptive statistics will be used for the evaluation of safety. The incidence and grade of adverse events and laboratory abnormalities will be calculated considering the most severe grade per patient and cycle and will be displayed in frequency tables using counts and percentages.

The shift of severity grades from baseline to the worst occurrence during treatment will be tabulated.

Deaths, serious adverse events and events resulting in study discontinuation will be tabulated.

Additional safety analyses may be determined at any time, in order to most clearly enumerate rates of toxicities and to further define the safety profile of PM01183 in combination with doxorubicin. In order to categorize accurately the safety information, additional classifications other than system organ class (SOC)/preferred term (PT) could be populated in order to understand better the safety drug profile.

7.3.5. Serious Adverse Events (SAEs).

Database listings of deaths and serious adverse events will be provided, including at least date of onset and resolution (if applicable), severity, relationship to study drug, most important significant consequence and main action taken.

7.3.6. Laboratory Evaluations.

7.3.6.1. Hematology.

Hematological toxicities classified according to the NCI-CTCAE v.4 will be calculated in all cycles by dose level (or most adequate dose grouping/cohort/Tumor type or other clinical relevant variable). Separate analyses will be carried out for the first cycle of treatment. The worst grade reached by each patient during treatment and Cycle 1 will also be determinated.

If serious toxicities occur, a special follow-up will be done to determine the pattern of thrombocytopenia and neutropenia within and between the different cycles. This follow-up will include the calculation of median and the range of nadir values and of the median time to recovery to baseline values and also descriptive tables.

If appropriate, these tables might be complemented with graphic representations of the nadir of neutrophil and platelets count by cycle during treatment by dose level (or most adequate dose grouping/cohort/Tumor type or other clinical relevant variable). Furthermore, graphs of the inter-cycle time course of neutropenia, thrombocytopenia or any other considered

parameter will be provided. If applicable, graphs comparing the time course of these parameters during the first and second cycles will be created.

7.3.6.2. Serum Biochemistry and Coagulation Tests.

The non-hematological laboratory abnormalities (i.e., NCI-CTCAE grades) of transaminases, creatinine, CPK**,** bilirubin, AP**,** etc. will be calculated by patient and cycle as explained for hematological toxicities. Separate analyses will be carried out for the first cycle of treatment. The worst grade reached by each patient during treatment and Cycle 1 will also be calculated.

If serious toxicities occur, a special follow-up that will include calculation of median and range of peak values and of median time to recovery to baseline values and, together with descriptive tables will be done to determine the pattern of these toxicities within and between cycles.

If appropriate, these tables might be complemented with boxplots for the peaks of transaminases, creatinine, CPK, bilirubin, AP, etc. by cycle along the treatment by dose level (or most adequate dose grouping/cohort/Tumor type or other clinical relevant variable). Furthermore, graphs of the inter-cycle time course of any considered parameter will be provided. If applicable, graphs comparing the time course during the first and second cycles will be created.

7.3.7. Physical Examination.

The evaluation of physical examination (i.e., normal/abnormal) will be summarized with frequency counts. All data will be listed by dose level (or most adequate dose grouping/cohort/Tumor type or other clinical relevant variable).

7.3.8. ECG / LVEF.

Baseline ECG evaluation (normal/abnormal) will be summarized with frequency counts.

Continuous variables (PR Interval, QT Interval, QRS Complex, Ventricular Rate, LVEF and LVEF Normal Range) will be summarized and summary statistics will be provided (i.e., mean, standard deviation, median and range). Baseline values and their evolution during treatment will be tabulated with summary statistics.

$$QTcF = \frac{QT}{\sqrt[3]{\mathrm{RR}}}$$

QTcF (Fridericia's formula) will be graded using the NCI-CTCAE v.4

7.3.9. Vital Signs.

PS and weight gain / loss during the study will be summarized by frequency tabulation.

7.3.10. Concomitant Medication.

Concomitant therapies will be coded using the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) classification system dictionary and categorized according to the ATC (levels 1, 2 and 4) class. The number of patients receiving each type of therapy will be tabulated in two separated frequency tables: one for therapies that started pre-study, and for those administrated during the study. The accompanying listing will include all concomitant therapies.

Additional listings for patients taking prohibited medications / therapies according to protocol will be provided.

7.4. Statistical analysis for efficacy.

7.4.1. Exploratory Analysis of Antitumor Activity.

The "All Evaluable for Efficacy Patients" population will be used for the analysis of the efficacy and also "All Treated Patients" population will be used for the overall response analysis.

Response rates will be characterized using descriptive statistics (95% confidence interval). If applicable, overall response rate (percentage of patients with PR or CR), percentages for PR or CR separately and percentage of patients with SD $\geq$ 4 months will be analyzed.

Time-related parameters (DR and PFS) will be analyzed according to the Kaplan-Meier methodology, if applicable.

The characteristics of the patients achieving an objective response or SD $\geq$ 4 months by RECIST v.1.1, or a clinically significant improvement measured by tumor markers, will be displayed.

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

7.4.2. Level of Significance.

Confidence intervals will be constructed using the 95% level. No formal statistical tests are defined, but if needed, all will be done at a significance level of 5% and will be considered exploratory.

8. Other statistical analysis.

8.1.Stratification and Covariate Analysis.

No stratification by prognostic factors or tumor types is planned. If a disease is adequately represented, response rates might be analyzed descriptively, and time-related parameters might be analyzed according to the Kaplan-Meier method. Efficacy parameters could also be subjected to further analysis (if appropriate), considering correlation with factors of known prognostic value such as patient ECOG performance status at entry, disease burden, prior therapies, other disease-specific known prognostic factor, or population characteristics, etc. using the appropriate test (Fisher's exact test, Spearman test, etc.).

8.2.Multivariate Analysis.

Exploratory *Cox* regression for multivariate analysis will be used for time-dependent efficacy parameters, and logistic regression for the evaluation of covariates associated with best overall response, if appropriate.

8.3.Subgroup Analysis.

If any cancer subtype or any other baseline characteristics of patients are adequately represented, a separate analysis by tumor type and efficacy as per RECIST v.1.1, will be performed.

If there is a representative number of patients who receive a maximal total cumulative dose of 450 mg/m^2 of doxorubicin and continue treatment with PM01183 alone, a separate analysis will be performed and tables, listings and graphic representations for this population will be provided when applicable.

8.4.Interim Analysis.

Non-scheduled interim analyses might be performed exclusively for enhancing patient’s safety.

8.5.Missing Values Management.

Missing laboratory values will be subtracted from the denominator of the tables.

Imputation of incomplete dates

Dates before randomization

If the day of a date is unknown, the imputed day will be 15. If the month is also unknown, the imputed date will 01/July/year. This assumption will be valid if the imputed date is earlier than the informed consent's date; otherwise the imputed date will be the first day of the informed consent's month date (i.e., 01/ informed consent's month date/year).

Dates after end of treatment

To ensure the most conservative approach for the efficacy time-to-event variables (i.e., PFS) that can be affected by missing values the following rules will be implemented: if the day of a date is unknown, then the imputed day will be 01; if the month is also unknown, then the imputed date will be 01/July/year. 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 the planed cycle duration (21 days) or the last day of the reported month, whichever occurs first.

8.6. Decimals Places.

By default, all numeric results will be rounded to one decimal, except in the case where variables are integer; in that case, they will be reported without decimals, for example, age in years, number of sites, etc.

9. Tables, Listings and Figures.

After the implementation of protocol amendment #3, a new cohort B of patients with SCLC and endometrial cancer has been included. All statistical outputs will be displayed according to dose level (grouped)/cohort/tumor type or primary site/ CSF use or not/other relevant clinical variable, whenever applicable and if an adequate number of patients is represented. Summary tables will have source data footnotes that will refer to the relevant listings. The tables' layout may change to adequately accommodate cohort/group size as appropriate.

If the number of categories or items would not yield appropriate tabular or graphic representations, detailed listings will be shown instead.

The abbreviation DL shown in the mock tables might refer to dose level (grouped <RD, RD, etc…)/cohort (i.e. Cohort A and B)/tumor type or primary site (i.e. Ovarian, SCLC (2nd line), etc…)/CSF use or not/other clinical relevant variable).The following is a list of tables, listings and figures that will be produced:

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10. Appendix I. Patients Disposition.

All statistical outputs will be displayed according to Dose level (grouped)/Cohort/Cancer type or primary site/CSF use or not/other clinical relevant variable, whenever applicable and if an adequate number of patients is represented. Summary tables will have source data footnotes that will refer to the relevant listings. The tables' layout may change to adequately accommodate cohort/group size as appropriate.

10.1.General Characteristics.

10.1.1. Patients Treated, Eligible and Evaluable.

Table 10.1.1.1 Patient Accrual by Institution and Dose Level.

	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Institution 1										
Institution 2										
···										
Total										

Note: Percentages based on number of patients by dose level.

Table 10.1.1.2 Disposition of Patients.

	Date information
Date of first consent	
Date of first dose	
Date of last consent	
Date of first dose of last patient	
Date of last dose	
Date of last follow up*	

Note: (*) Last follow up date, examination date or procedure before study closure.

Table 10.1.1.3 Time on Treatment by Dose Level.

Median and Range of Time on treatment (weeks)	DL I	DL II	···	DL n	Total
N					
Mean					
Median					
Min					
Max					
STD					

Table 10.1.1.4 Number of Patients Evaluable for Analysis.

Number of included patients	Treated Patients				Evaluable for DLT				Evaluable for Safety				Evaluable for Efficacy*	
	Yes		No		Yes		No		Yes		No		Yes	No
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
DL I														
···														
DL n														
Total														

Notes: (*) Efficacy by RECIST. A listing of patients not-evaluable by RECIST v.1.1 will be provided.

Table 10.1.1.5 Listing of Not Evaluable Patients.

Not Evaluable for	Dose level	Patient	Reason(s)
DLT			
Safety			
Efficacy			

Not Evaluable for	Dose level	Patient	Reason(s)
...			

10.1.2. Treatment Discontinuations.

Table 10.1.2.1 Treatment Discontinuation by Dose Level*.

	DL I		DL II		...		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Progressive disease										
Treatment non-related AE										
Treatment related AE										
Patient refusal										
Death										
Investigator's decision										
Other **										
Total										

Notes: Percentages based on number of patients by dose level. (*) Reasons for treatment discontinuation for patients who discontinued while the combination or PM alone will be provided, if required. (**) If applicable, a supporting listing 10.1.2.1.a will be provided and reasons for treatment discontinuation may suffer re-categorization after clinical review.

Table 10.1.2.2 Treatment Discontinuation Details.

Dose level	Patient No	Last cycle infused	Treatment discontinuation reason	Details

Table 10.1.2.3 Reasons for Treatment Discontinuations by Cycle and Dose Level.

Treatment discontinuation		DL I		DL II		...		DL n		Total	
		N	%	N	%	N	%	N	%	N	%
Progressive disease	Cycle 1										
	Cycles 2-3										
	Cycles ≥4										
Patient refusal	Cycle 1										
	Cycles 2-3										
	Cycles ≥4										
Non treatment-related AE	Cycle 1										
	Cycles 2-3										
	Cycles ≥4										
…..*	Cycle 1										
	Cycles 2-3										
	Cycles ≥4										
Total	Cycle 1										
	Cycles 2-3										
	Cycles ≥4										

Notes: Percentages based on number of patients by dose level. Cycle grouping is only shown as an example.

Table 10.1.2.4 Listing of patients with Discontinuation with PM01183 alone.

Dose level	Patient No	Last cycle infused	Treatment discontinuation reason	Details

Table 10.1.2.5 Treatment Discontinuation Due to Adverse Events.

Dose level	Patient	SOC / Group	Event	…*

Note: (*) Adverse event, Cycle, Grade, NCI-CTCAE v.4., Relationship, Action taken, Seriousness criteria, Prior PM01183 dose reduction.

Table 10.1.2.6 Reasons for Treatment Discontinuation Other than Progressive Disease.

Dose level	Patient No	Last cycle infused	Off Study reason	Specify

Table 10.1.2.7 Reasons for Study Discontinuation by Dose Level.

Treatment discontinuation	DL I		DL II		•••		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Study completion										
Patient follow-up completed										
Patient refusal										
Death										
Never treated										
Lost to follow up										
Other*										
Total										

Notes: Percentages based on number of patients by dose level. (*) If applicable, a supporting listing 10.1.2.6.a will be showed.

10.1.3. Protocol Deviations.

Table 10.1.3.1 Supportive Listing Relevant Protocol Deviations.

Dose level	Patient No	Protocol deviation type	Specify

10.2.Patient Characteristics.

All statistical outputs will be displayed according to Dose level (grouped)/Cohort/Cancer type or primary site/CSF use or not/other clinical relevant variable, whenever applicable and if an adequate number of patients is represented. Summary tables will have source data footnotes that will refer to the relevant listings. The tables' layout may change to adequately accommodate cohort/group size as appropriate.

10.2.1. Patient Characteristics at Baseline.

Table 10.2.1.1 Age at Entry by Dose Level.

Age at entry	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%

Age at entry	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
18-45 years										
46-55 years										
···										
< 76* years										
Total										

Note: Percentages based on number of patients by dose level. (*) Example categories.

Table 10.2.1.2 Age Median and Range by Dose Level.

Age median and range	DL I	DL II	···	DL n	Total
N					
Median					
Min					
Max					
STD					

Table 10.2.1.3 Gender by Dose Level.

Gender	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Male										
Female										
Total										

Note: Percentages based on number of patients by dose level.

Table 10.2.1.4 Race by Dose Level.

Gender	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Caucasian										
…										
Total										

Note: Percentages based on number of patients by dose level.

Table 10.2.1.5 Pregnancy Tests by Dose Level.

Result	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Not applicable*										
Negative										
Positive										
Total										

Note: Percentages based on number of premenopausal patients by dose level. (*) A supporting listing 10.1.2.5.a with reasons will be showed.

Table 10.2.1.6 Physical Examination Result by Dose Level.

Physical Examination	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Normal										
Abnormal										
Total										

Notes Percentages based on number of patients by dose level.

Table 10.2.1.7 Physical Examination Parameters by Dose Level.

	DL I	DL II	···	DL n	Total
Weight (kg).					
N					
Mean					
Median					
Min					
Max					
STD					
……*					
N					
Mean					
Median					
Min					
Max					
STD					

Notes: (*) Height (cm) and body surface area (BSA) (DuBois formula).

Table 10.2.1.8 ECOG Performance Status by Dose Level at Baseline.

PS (ECOG)	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
0										
1										
···										
Total										

Note: Percentages based on number of patients by dose level.

Table 10.2.1.9 Vital Signs Parameters by Dose Level.

Vital signs	DL I	DL II	···	DL n	Total
Heart rate (beats / minute)					
N					
Mean					
Median					
Min					
Max					
STD					
BPS (mmHg)					
N					
Median					
Min					
Max					
STD					
BPD (mmHg)					
N					
Mean					
Median					
Min					
Max					
STD					
Temperature (ºC)					
N					
Mean					

Vital signs	DL I	DL II	···	DL n	Total
Median					
Min					
Max					
STD					

Table 10.2.1.10 ECG Result by Dose Level.

Physical Examination	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Normal										
Abnormal*										
Total										

Notes: Percentages based on number of patients by dose level. (*) If abnormal, a supportive listing will show detailed information.

Table 10.2.1.11 ECG Parameters by Dose Level.

ECG	DL I	DL II	···	DL n	Total
PR interval (msec)					
N					
Mean					
Median					
Min					
Max					
STD					
QT interval (msec)					
N					
Mean					
Median					
Min					
Max					
STD					
RR interval (msec)					
N					
Mean					
Median					
Min					
Max					
STD					
QRS interval (msec)					
N					
Mean					
Median					
Min					
Max					
STD					
QTcF * (msec)					
N					
Mean					
Median					
Min					
Max					
STD					

Note: (*) Fridericia method.

Table 10.2.1.12 Median LVEF for Patients with Previous Treatment with Anthracyclines by Dose Level.

LVEF	DL I	DL II	···	DL n	Total
Anthracyclines					
N					
Mean					
Median					
Min					
Max					
STD					
Non Anthracyclines					
N					
Mean					
Median					
Min					
Max					
STD					
Total					
N					
Mean					
Median					
Min					
Max					
STD					

10.2.2. Cancer History.

Table 10.2.2.1 Time from Diagnosis to First Infusion.

Time from Diagnosis to First Infusion	DL I		DL II		···		DL n		Total	
(years)	N	%	N	%	N	%	N	%	N	%
N										
Mean										
Median										
Min										
Max										
STD										

Table 10.2.2.2 Time from last PD to First Infusion.

Time from Last PD to First Infusion	DL I		DL II		···		DL n		Total	
(months)	N	%	N	%	N	%	N	%	N	%
N										
Mean										
Median										
Min										
Max										
STD										

Table 10.2.2.3 TTP of Last Prior Therapy.

TTP in months of last Prior Therapy	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%

TTP in months of last Prior Therapy	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
N										
Mean										
Median										
Min										
Max										
STD										

Table 10.2.2.4 Tumor type by Dose Level.

Tumor type*	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Breast										
. . . *										
Total										

Notes: Percentages based on number of patients by dose level. (*) CRF categories will be shown and categories will be susceptible of clinical coding, if requested. A supportive table 10.2.2.6.a will be provided for subcategories. (e.g: sarcomas).

Table 10.2.2.5 Summary of Cancer History per Patient and Tumor type.

Dose level	Patient No	Primary tumor site	Histology	……..*

Notes: (*) Stage at diagnosis, Histology grade , Date of first diagnosis, Current stage (date), date of last PD before study entry, TTP to prior therapy, best response to last prior therapy. Also characteristics of patients by specific tumor type, e.g: smoker, etc… If required, tabulations for specific categories will be shown as Supportive tables.

10.2.3. Sites Involved.

Table 10.2.3.1 No of Sites Involved by Tumor type and Dose Level.

Tumor Type*	No of Sites	DL I		DL II		···		DL n		Total	
		N	%	N	%	N	%	N	%	N	%
Breast	1 Sites										
	2 Sites										
	>2										
…..*	1 Sites										
	2 Sites										
	>2										
	Total										

Notes: Percentages based on number of patients by dose level. (*) Coded tumor types.

Table 10.2.3.2 Summary Statistics. No of Sites Involved by Tumor type Dose Level.

Tumor Type*	Median, range and STD for No. of sites involved	DL I	DL II	···	DL n	Total
Breast	N**					
……*						

Notes: (*) Coded tumor types. (**) N, mean, STD, median and range.

Table 10.2.3.3 Frequency of Patients Classified by Sites Involved by Tumor type and Dose Level.

Tumor Type*	Site**	DL I		DL II		···		DL n		Total	
		N	%	N	%	N	%	N	%	N	%
Breast	CNS										
	Liver										
…..*	....										

Notes: Percentages based on number of patients by dose level. (* and **) Coded tumor types and sites will be recoded, if required.

Table 10.2.3.4 Listing of Sites per Patient.

Dose level	Patient No	Tumor type*	Target/Non target	Method	Diameter (mm)

Note: (*) Coded tumor types.

Table 10.2.3.5 Bulky disease by Tumor type and Dose Level.

Tumor type*	Maximum diameter	DL I		DL II		···		DL n		Total	
		N	%	N	%	N	%	N	%	N	%
Breast	≥ 50 mm										
	< 50 mm										
.....											

Notes: Percentages based on number of patients by dose level. (*) Coded tumor types.

Table 10.2.3.6 Median sum of diameter of target lesions (mm).

Tumor type*	Median and range for sum of target lesions (mm)	DL I	DL II	···	DL n	Total
Breast	N**					
……						

Notes: (*) Coded tumor types (**) N, mean, STD, median and range.

10.2.4. Previous Treatment Summary.

Table 10.2.4.1 Previous Treatment Summary by Dose Level.

Previous Treatment	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Systemic Therapy										
Surgery*										
Radiotherapy										
Systemic Therapy + Surgery*										
Systemic Therapy + Radiotherapy										
Systemic Therapy + Surgery*+ Radiotherapy										
Total										

Notes: Percentages based on number of patients by dose level. (*) Curative / Palliative.

Table 10.2.4.2 Previous Systemic Therapy by Dose Level/Tumor type.

Tumor type	Previous Treatment	DL I	DL II	···	DL n	Total

		N	%	N	%	N	%	N	%	N	%
Breast	Chemotherapy										
	Biological therapy										
	Hormonal therapy										
	…..										
…..	Total										

Note: (*)Adjuvant and /or neoadjuvant therapies are not included in this table, if required a supportive table for this therapies will be shown.

10.2.5. Previous Surgery.

Table 10.2.5.1 Previous Surgery by Dose Level (Curative/Palliative).

Previous Surgery	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
No										
Yes										
Total										

Note: Percentages based on number of patients by dose level.

10.2.6. Previous Radiotherapy.

Table 10.2.6.1 Previous Radiotherapy by Dose Level.

Previous Radiotherapy	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
No										
Yes										
Total										

Note: Percentages based on number of patients by dose level.

10.2.7. Previous Anticancer Medical Therapy.

Table 10.2.7.1 Agents of Previous Anticancer Therapy (ATC level 1 & 4) by Dose Level/Tumor type.

Medication*	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
ATC level 1										
ATC level 4										
···										
ATC level 4										

Notes: Percentages based on number of patients by dose level. (*) A supportive table of Agents of Previous Chemotherapy will be displayed. Adjuvant and/or neoadjuvant therapies are not included in this table; if required, a supportive table for these therapies will be shown.

Table 10.2.7.2 No of Lines of Prior Anticancer Therapy for Advanced Disease by Dose Level/Tumor type.

No of lines*	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
0 lines										
1 line										
…..										
≥ N lines										

No of lines*	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Total										

Notes: Percentages based on number of patients by dose level. (*) Adjuvant and /or neoadjuvant therapies are not included in this table and a supportive table of Agents of Previous Chemotherapy-containing Therapies for Advanced Disease will be displayed.

Table 10.2.7.3 Summary Statistics. No of Lines of Prior Anticancer Therapy by Dose Level/Tumor type.

Median and range for No of lines*	DL I	DL II	···	DL n	Total
N					
Mean					
Median					
Min					
Max					
STD					

Note: (*) Adjuvant and /or neoadjuvant therapies are not included in this table and a supportive table of Agents of Previous Chemotherapy-containing Therapies for Advanced Disease will be displayed.

Table 10.2.7.4 No of Agents of Prior Anticancer Therapy by Dose Level/Tumor type.

No of agents	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
0 agents										
1 agent										
2 agents										
….										
≥N agents										
Total										

Note: Percentages based on number of patients by dose level. Any agents used more than once will only add 1 to the total.

Table 10.2.7.5 No of Agents of Last Prior Anticancer Therapy before PM01183 treatment by Dose Level/Tumor type.

No of agents	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
0 agents										
1 agent										
2 agents										
….										
≥N agents										
Total										

Note: Percentages based on number of patients by dose level. Any agents used more than once will only add 1 to the total.

Table 10.2.7.6 Summary Statistics. No of Agents of Prior Anticancer Therapy by Dose Level/Tumor type.

Median and range for No of agents	DL I	DL II	···	DL n	Total
N					
Mean					
Median					
Min					
Max					
STD					

Table 10.2.7.7 Listing of Agents of Prior Anticancer Therapy by Dose Level.

Dose level	Patient No	Setting	Type	……..*	Progression date

(*) Dose and units; Schedule, Start –End date and Best Response.

Table 10.2.7.8 Agents of Prior Anticancer Therapy by Dose Level/Tumor type.

Agents*	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Platinum										
…..										

Notes: Percentages based on number of patients by dose level or by tumor type. Any agents used more than once will only add 1 to the total. (*) Indicated by clinical request e.g: Anti-EGFR targeted therapies, Taxanes, Other investigational drugs, etc…

Table 10.2.7.9 CTFI by Dose Level/Cohort/Tumor type

CTFI/TFI*	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Resistant										
Sensitive										
…..										
Total										

Note: (*) CTFI (Chemotheraphy Free Interval)/for SCLC patients and TFI (Systemic Chemotherapy Free Interval) for Endometrial patients. Calculated from the last therapy previous therapy with ATC coded "L01XA" and calculated as the difference from the end of therapy to the PD, e.g: for SCLC patients Categories R (resistant) and S (sensitive).

Table 10.2.7.10 Summary Statistics: CTFI by Dose Level/Cohort/Tumor type.

Tumor type*/Median and range	DL I	DL II	···	DL n	Total
N					
Mean					
Median					
Min					
Max					
STD					

Note: (*) Tumor type, if apply

Table 10.2.7.11 Patients Previously Treated with Anthracyclines by Dose Level.

Anthracyclines*	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Yes										
No										
Total										

Note: (*) For those patients previously treated with anthracyclines a supportive listing 10.2.7.7.a will be given.

Table 10.2.7.12 Summary Statistics: Cumulative Dose in Patients Previously Treated with Anthracyclines by Dose Level.

Median and range	DL I	DL II	···	DL n	Total
N					
Mean					
Median					
Min					
Max					

Median and range	DL I	DL II	···	DL n	Total
STD					

10.2.8. Hematological Evaluation at Baseline.

Table 10.2.8.1 Hematological Abnormalities at Baseline by Dose Level.

Abnormality*	DL I	DL II	···	DL n	Total
Anemia					
Grade 1 - 4, n (%)					
Grade 1					
Grade 2					
Grade 3					
Grade 4					
….…*					
Grade 1 - 4, n (%)					
Grade 1					
Grade 2					
Grade 3					
Grade 4					

Notes: Baseline values obtained from last value recorded before or on the date of first infusion .Percentages based on number of patients by dose level/cohort. (*) Also Leukopenia, Lymphopenia, Neutropenia, and Thrombocytopenia.

Table 10.2.8.2 Median and Range for Hematological Parameters at Baseline by Dose Level.

Parameters*	DL I	DL II	···	DL n	Total
Hemoglobin (g/dL)					
N					
Mean					
Median					
Min					
Max					
STD					
…..*					

Notes: Baseline values obtained from last value recorded before or on the date of first infusion. Percentage based on number of patients by dose level. (*) Also Lymphocytes, WBC, Neutrophils, Platelets in 10^9/L.

Table 10.2.8.3 Supportive Listing: Patients with grade >1 Hematological Abnormalities at Baseline.

Dose level	Patient	Lab. test	Cycle	Examination date	Std. value	Grade NCI-CTCAE v.4

Table 10.2.8.4 Patients with Missing Hematological Evaluations at Baseline.

Dose level	Patient	Lab. test

10.2.9. Biochemical Evaluation at Baseline.

Table 10.2.9.1 Biochemical Abnormalities at Baseline by Dose Level.

Abnormality*	DL I	DL II	···	DL n	Total
AP increase					
Grade 1 - 4, n (%)					
Grade 1					
Grade 2					
Grade 3					
Grade 4					
……*					
Grade 1 - 4, n (%)					
Grade 1					
Grade 2					
Grade 3					
Grade 4					

Notes: Baseline values obtained from last value recorded before or on the date of first infusion. Percentages based on number of patients by dose level. (*) All biochemical abnormalities susceptible to be graded with NCI-CTCAE v.4.

Table 10.2.9.2 Median and Range for Biochemical Parameters at Baseline by Dose Level.

Parameters*	DL I	DL II	···	DL n	Total
AP					
N					
Mean					
Median					
Min					
Max					
STD					
…..*					
N					
Mean					
Median					
Min					
Max					
STD					

Note: (*) Baseline values obtained from last value recorded before or on the date of first infusion AP, AST, ALT, LDH, CPK, CPK MB and Amylase in IU/L. Total and direct bilirubin, creatinine, Alpha-1 acid glycoprotein, and LDL in mg/dl. Total proteins in g/dl and C-reactive protein in mg/l.

Table 10.2.9.3 Supportive Listing: Patients with Grade >1 Biochemical Abnormalities at Baseline.

Dose level	Patient	Lab. test	Cycle	Examination date	Std. value	Grade NCI-CTCAE v.4

Table 10.2.9.4 Patients with Missing Biochemical Evaluations at Baseline.

Dose level	Patient	Lab. test

10.2.10. Coagulation Evaluations at Baseline.

Table 10.2.10. 1 Coagulation Abnormalities at Baseline by Dose Level.

Abnormality	DL I	DL II	···	DL n	Total
INR increase					
Grade 1 - 4, n (%)					
Grade 1					
Grade 2					
Grade 3					
Grade 4					
PTT					
Grade 1 - 4, n (%)					
Grade 1					
Grade 2					
Grade 3					
Grade 4					

Note: Baseline values obtained from last value recorded before or on the date of first infusion. Percentages based on number of patients by dose level.

Table 10.2.10. 2 Median and Range for Coagulation Parameters at Baseline by Dose Level.

Parameters*	DL I	DL II	···	DL n	Total
INR					
N					
Mean					
Median					
Min					
Max					
STD					
….*					

Notes: (*) Baseline values obtained from last value recorded before or on the date of first infusion . INR: no units. PTT and PT in seconds.

Table 10.2.10. 3 Supportive Listing: Patients with Grade >1 Coagulation Abnormalities at Baseline.

Dose level	Patient	Lab. test	Cycle	Examination date	Std. value	Grade NCI-CTCAE v.4

Table 10.2.10. 4 Patients with Missing Coagulation Evaluations at Baseline.

Dose level	Patient	Lab. test

10.2.11. Other Metabolic Evaluations at Baseline.

Table 10.2.11. 1 Metabolic Abnormalities at Baseline by Dose Level.

Abnormality*	DL I	DL II	···	DL n	Total
Hypercalcemia					
Grade 1 - 4, n (%)					
Grade 1					
Grade 2					

Abnormality*	DL I	DL II	···	DL n	Total
Grade 3					
Grade 4					
…..*					
Grade 1 - 4, n (%)					
Grade 1					
Grade 2					
Grade 3					
Grade 4					

Notes: Baseline values obtained from last value recorded before or on the date of first infusion. Percentages based on number of patients by dose level. (*) All metabolic abnormalities susceptible to be graded with the NCI-CTCAE v.4.

Table 10.2.11. 2 Median and Range for Metabolic Parameters at Baseline by Dose Level.

Parameters*	DL I	DL II	···	DL n	Total
Calcium					
N					
Mean					
Median					
Min					
Max					
STD					
…..*					

Notes: (*) Baseline values obtained from last value recorded before or on the date of first infusion. Sodium, potassium, chloride, glucose, magnesium and calcium in mmol/L, triglycerides and total cholesterol in mg/dL and albumin in g/dL.

Table 10.2.11. 3 Supportive Listing: Patients with grade >1 Metabolic Abnormalities at Baseline.

Dose level/	Patient	Lab. test	Cycle	Examination date	Std. value	Grade NCI-CTCAE v.4

Table 10.2.11. 4 Patients with Missing Metabolic Evaluations at Baseline.

Dose level	Patient	Lab. test

10.2.12. Signs and Symptoms at Baseline.

Table 10.2.12. 1 Signs and Symptoms by Dose Level.

MedDRA System	DL I								···				Total			
Organ Class	Gr. 1*		Gr. 2		Gr. 3		Gr. 4		Gr. 1		Gr. 2		Gr. 3		Gr. 4	
Preferred Term	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%

Notes: Percentages based on number of patients by dose level. (*) Grades may suffer modification (e.g. G 1 and G > 1), if requested.

Table 10.2.12. 2 Listing of Adverse Events at Baseline Grade >1.

Dose level	Patient No	Literal	MedDRA Preferred Term	NCI-CTCAE v.4 grade	Start date	Relationship	Treated

Dose level	Patient No	Literal	MedDRA Preferred Term	NCI-CTCAE v.4 grade	Start date	Relationship	Treated

10.2.13. Concomitant and Prophylactic Medication Starting Pre-Study.

Table 10.2.13. 1 Concomitant Medication Starting Pre-Study (ATC Levels 1 and 4) by Dose Level.

Medication Term (ATC level 1)	Medication Term (ATC level 2)	Medication Term (ATC level 4)	DL I		DL II		···		DL n		Total	
			N	%	N	%	N	%	N	%	N	%

Note: Percentages based on number of patients by dose level.

Table 10.2.13. 2 Concomitant Medication Starting Pre-Study (RBC and Platelet transfusions/EPO).

Medication Term (ATC level 1)	Medication Term (ATC level 2)	Medication Term (ATC level 4)	DL I		DL II		···		DL n		Total	
			N	%	N	%	N	%	N	%	N	%
Platelet transfusion												
RBC transfusion												
…												

Note: Percentages based on number of patients by dose level.

Table 10.2.13. 3 Supportive Listing: RBC and Platelet transfusions/EPO (Pre-Study).

Dose Level	Patient No	Cycle	Type	Literal Term	ATC4	ATC2	ATC1	Route	….	Start date	End date	Reason for Use

Table 10.2.13. 4 No of patients with Opioids Treatment at Baseline by Dose Level.

Opioids*	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
….										
…										

Note: (*) ATC classification including opioids and terms will be selected and provided by clinical request.

Table 10.2.13. 5 Median number of No of Opioids per patient by Dose Level.

Opioids*	DL I	DL II	···	DL n	Total
N					
Mean					
Median					
Min					
Max					
STD					

(*) The ATC classification including opioids and terms will be selected and provided by clinical request.

Table 10.2.13. 6 No of patients with Steroids treatment at baseline by dose Level

Steroids*	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
….										

Steroids*	DL I		DL II		…		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
…										

Note: (*) The ATC classification, including steroids and terms, will be selected and provided by clinical request.

Table 10.2.13. 7 Known CYP 3A4 Inducers/Inhibitors/Substrates Concomitant Therapies at BL.

CYP 3A4*	DL I		DL II		…		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Inhibitor										
….										
…										

Notes: (*) Also the possibility of displaying one table for each category Inducers/Inhibitors or substrates. Some medication will be excluded by clinical request (e.g. Dexamethasone).

Table 10.2.13. 8 Listing of CYP 3A4 Inducers/Inhibitors/Substrates Concomitant Therapies at BL.

Dose Level	Patno	Type*	Literal Term	ATC4	ATC2	ATC1	…	Start date	End date	Reason for Use	SS/AE	Specify

Notes: (*) Also the possibility of display onetable for each category Inducers/Inhibitors or substrates. Some medication will be excluded by clinical request (e.g. Dexamethasone).

11. Appendix II. Safety Evaluation.

All statistical outputs in this section, whenever applicable, will be displayed according to the discontinuation of the combination treatment. Treatment exposure, delays, omissions and reductions will be shown considering the whole study treatment and/or before and after discontinuation, if appropriate.

Dose level may suffer categorization (e.g: RD ≤ or RD, Cohorts/Cancer type or primary site/CSF use or not/other clinical relevant variable), if required and if an adequate number of patients is represented.

Each specific table and listing will have a comprehensive header identifying the group/cohort of treatment, whenever necessary.

Summary tables will have source data footnotes that will refer to the relevant listings. The tables' layout may change to adequately accommodate cohort/group size as appropriate.

11.1.Extent of Exposure.

11.1.1. Cumulative Dose, Dose Intensity and Relative Dose Intensity.

Table 11.1.1.1 No of Cycles Administered by Dose Level.

		Patients		
Dose level	No. of cycles infused	No. of patients with PM01183+Doxo	No. of patients with PM01183 alone
I	1 Cycle 2 Cycles ….			
II **…**	1 Cycle 2 Cycles …			
N	1 Cycle 2 Cycles …			
Total	1 Cycle 2 Cycles …. N Cycles			

Table 11.1.1.2 Median and Range of Cycles Administered by Dose Level.

Drug	Median range and STD of cycles administered	DL I	DL II	···	DL n	Total
PM01183 + Doxorubicin	N*					
PM01183 alone	N*					
Total	N*					

Note: (*) N, median, mean, range, and STD.

Table 11.1.1.3 Cumulative Dose by Dose Level.

Drug	Cumulative dose	DL I	DL II	···	DL n	Total
PM01183 (mg)	N					
	Mean					
	Median					
	Min					
	Max					
	STD					
Doxorubicin (mg/m^2)	N					
	Mean					
	Median					
	Min					
	Max					
	STD					

Table 11.1.1.4 Dose Intensity by Dose Level.

Drug	Dose intensity	DL I	DL II	···	DL n	Total
PM01183* (mg/week)	N					
	Mean					
	Median					
	Min					
	Max					
	STD					
PM01183* (mg/m^2/week)	N					
	Mean					
	Median					
	Min					
	Max					
	STD					
Doxorubicin (mg/m^2/week)	N					
	Mean					
	Median					
	Min					
	Max					
	STD					

(*) Results of dose intensity maybe grouped and presented in mg/m^2/week for patients treated in the Cohort A, if appropriate.

Table 11.1.1.5 Relative Dose Intensity by Dose Level.

Drug	Relative dose intensity (%)	DL I	DL II	···	DL n	Total
PM01183	N					
	Mean					
	Median					
	Min					
	Max					
	STD					
Doxorubicin	N					
	Mean					
	Median					
	Min					
	Max					
	STD					

Table 11.1.1.6 Drug Administration: Patients that Reached the Maximal Cumulative Dose of 450 mg/m^2.

Dose level	Patient No	No. of Cycles PM01183	No. of Cycles Doxorubicin	Delay	Delay specify	…..*

Note: (*) Delays, omissions, reductions and specify.

11.1.2. Cycle Delays and Omissions.

Table 11.1.2.1 No of Patients with Delayed Cycles by Dose Level.

No of patients with delayed	DL I		DL II		···		DL n		Total	
cycles	N	%	N	%	N	%	N	%	N	%
No										
Yes										
Any DR*										
All NDR**										
Total										

Notes: Percentages based on number of patients by dose level. (*) Drug related (**) Non -drug related.

Table 11.1.2.2 No of Patients with Dose Delayed by Dose Level According to Relationship.

No of cycles delayed		DL I		DL II		···		DL n		Total	
		N	%	N	%	N	%	N	%	N	%
No											
Yes	Drug Related										
	Hematological										
	Non Hematological										
	Both										
	Non Drug Related										
Total											

Note: Percentages based on number of cycles susceptible of delay by dose level.

Table 11.1.2.3 No of Cycles Delayed Per Patient by Dose Level.

No patients with :	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
No cycle delayed										
01 cycle delayed										
02 cycles delayed										
···										
N cycles delayed										
Total										

Note: Percentages based on number of patients by dose level.

Table 11.1.2.4 No of Cycles Delayed Per Patient by Dose Level. Summary Statistics.

No patients with delays	DL I	DL II	···	DL n	Total
N					
Median					
Min					
Max					
STD					

Table 11.1.2.5 Number of Cycles with Drug Related Delay per Patient by Dose Level.

No cycles with :	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
No cycle delayed										
01 cycle delayed										
02 cycles delayed										
···										
N cycles delayed										
Total										

Table 11.1.2.6 Number of Cycles with Drug Related Delay per Patient by Dose Level. Summary Statistics.

No cycles with delays	DL I	DL II	···	DL n	Total
N					
Median					
Min					
Max					
STD					

Table 11.1.2.7 Length of Delay According to relationship by Dose Level. Summary Statistics.

Relationship	DL I	DL II	···	DL n	Total
Hematological					
N					
Mean					
Median					
Min					
Max					
STD					
Non Hematological					
N					
Mean					
Median					
Min					
Max					
STD					
Both					
N					
Mean					
Median					
Min					
Max					
STD					
Total					
N					
Mean					
Median					
Min					
Max					
STD					

Table 11.1.2.8 Listing of Patient with Dose Delays.

Dose level	Patient No	Cycle	Date	Intended dose	Total dose	Length of Delay	Delay Reason	Delay specify

Table 11.1.2.9 Supportive Listing: Dose Delays Excluding Administrative Reasons.

Dose level	Patient No	Cycle	Date	Intended dose	Total dose	Length of Delay	Delay Reason	Delay specify

Note: (*) Excluding administrative reasons.

Table 11.1.2.10 No. of Patients with Doxorubicin Omissions by Dose Level.

No of patients with any dosage omitted	DL I		DL II		...		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Omitted										
Maintained										
Total										

Note: Percentages based on number of patients by dose level.

Table 11.1.2.11 No of Patients with Doxorubicin Cycles Omission by Dose Level.

No of patients with cycles omitted	DL I		DL II		...		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
No omission										
1 cycle										
2 cycles										
...										
Total										

Note: Percentages based on number of patients by dose level.

Table 11.1.2.12 Listing of Doxorubicin Dose Omissions.

Dose level	Patient No	Cycle	DA Start Date	DA infusion omitted?	DA Omission reason	Specify

Table 11.1.2.13 Listing of Cycles Delays due to Hematological Abnormalities.

Dose level	Patient No	Total number of cycles received	Cycle numbers with dose delay due to …*	Cycle numbers with dose delay not due to …*	Cycle numbers with …**

Notes: (*/**) Also Leukopenia /CSF, Anemia / EPO, Thrombocytopenia / platelet transfusions. Narratives with the information contained in the tables will be provided instead of tables only if a low number of dose delays occur.

Table 11.1.2.14 Listing of Cycles Delays due to Non-Hematological Adverse Events.

Dose level	Patient No	Total number of cycles received	Cycle numbers with dose delays due to …*	Cycle numbers with dose delays not due to …*	Cycle numbers without adequate prophylaxis

Notes: (*)Adverse event. Narratives with the information contained in the tables will be provided instead of tables only if a low number of dose delays are found.

11.1.3. Dose Reductions.

Table 11.1.3.1 No of Patients with PM01183 Dose Reduction by Dose Level.

No of patients with any dose modified	DL I		DL II		…		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Reduced										
No reduced										
Total										

Note: Percentages based on number of patients by dose level.

Table 11.1.3.2 No of Patients with PM01183 Cycles Dose Reduction by Dose Level.

No of patients with cycles reduced	DL I		DL II		…		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
1 reduction										
2 reductions										
…										
Total										

Note: Percentages based on number of patients by dose level.

Table 11.1.3.3 Reasons for PM01183 Dose Reduction by Dose Level.

No of patients with cycles reduced	DL I		DL II		…		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
No dose reduction										
Hematological										
Non-hematological										
Both (hematological and non-hematological)										
Other										
Total										

Note: Percentages based on number of patients by dose level.

Table 11.1.3.4 Listing of PM01183 Dose Reductions.

Dose level	Patient No	Cycle	DA Start Date	DA infusion reduced?	% of reduction	DA Reduce reason	Specify

Table 11.1.3.5 Listing of Dose Reductions due to Hematological Abnormalities.

Dose level	Patient No	Total number of cycles received	Cycle numbers with dose reduction due to …*	Cycle numbers with dose reduction not due to …*	Cycle numbers with …**

Notes: (*/**) Also Leukopenia/CSF, Anemia / EPO, Thrombocytopenia / platelet transfusions.

Table 11.1.3.6 Listing of Dose Reductions due to Non-Hematological Adverse Events.

Dose level	Patient No	Total number of cycles received	Cycle numbers with dose reduction due to …*	Cycle numbers with dose reduction not due to …*	Cycle numbers without adequate prophylaxis

Note: (*) Adverse event.

11.1.4. Dose Interruption and Re-administration.

Table 11.1.4. 1 Listing of Patients with Dose Interruption and Re-administration.

Dose level	Patient No	Cycle	Infusion Day 1/Day 8	Drug	Was infusion interrupted? Reason	Date	Intended dose	Total dose	Total Volume

11.2.Dose-Limiting Toxicities.

11.2.1. Dose-Limiting Toxicities.

Table 11.2.1.1 Summary of Patients with DLT by Dose Level.

G-CSF factors	Dose level	N	Patients with DLT

Table 11.2.1.2 Characteristics of Patients with DLT by Dose Level.

G-CSF factors	Dose level	Patient Id	Cycle	DLT Description	NCI-CTCAE v.4.0 Grade	……..*

Note: (*) Onset –Resolved date, Relation (Specify), Action taken and Main Consequences.

11.3.Adverse Events (AEs).

11.3.1. Display of Adverse Events.

All adverse events tables will be listed by cohort and dose level (or most adequate dose grouping/tumor type/other clinical relevant variable or according to the discontinuation of the combination treatment, if required).

Table 11.3.1.1 Combination (PM01183-Doxorubicin) Related (or Relationship Unknown) Adverse Events. Worst Grade by Patient and Dose Level.

Table 11.3.1.2 PM01183-Only Related (or Relationship Unknown) Adverse Events. Worst Grade by Patient and Dose Level.

Table 11.3.1.3 Doxorubicin-Only Related (or Relationship Unknown) Adverse Events. Worst Grade by Patient and Dose Level.

Table 11.3.1.4 Combination (PM01183-Doxorubicin) Related (or Relationship Unknown) Adverse Events in the First Cycle by Patient and Dose Level.

Table 11.3.1.5 PM01183-Only Related (or Relationship Unknown) Adverse Events in the First Cycle by Patient and Dose Level.

Table 11.3.1.6 Doxorubicin-Only Related (or Relationship Unknown) Adverse Events in the First Cycle by Patient and Dose Level.

Table 11.3.1.7 Combination (PM01183-Doxorubicin) Related (or Relationship Unknown) Adverse Events. Worst Grade Per Cycle by Dose Level.

Table 11.3.1.8 PM01183-Only Related (or Relationship Unknown) Adverse Events. Worst Grade Per Cycle by Dose Level.

Table 11.3.1.9 Doxorubicin-Only Related (or Relationship Unknown) Adverse Events. Worst Grade Per Cycle by Dose Level.

Table 11.3.1.10 Combination (PM01183-Doxorubicin) Related (or Relationship Unknown) Adverse Events Observed in ≥10% of Patients Treated by Dose Level.

Table 11.3.1.11 PM01183-Only Related (or Relationship Unknown) Adverse Events Observed in ≥10% of Patients Treated by Dose Level.

Table 11.3.1.12 Doxorubicin-Only Related (or Relationship Unknown) Adverse Events Observed in ≥10% of Patients Treated by Dose Level.

Table 11.3.1.13 Combination (PM01183-Doxorubicin) Related (or Relationship Unknown) Adverse Events Observed in ≥ 10% of Patients Treated. Worst grade per Cycle by Dose Level.

Table 11.3.1.14 PM01183-Only Related (or Relationship Unknown) Adverse Events Observed in ≥10% of Patients Treated. Worst grade per Cycle by Dose Level.

Table 11.3.1.15 Doxorubicin-Only Related (or Relationship Unknown) Adverse Events Observed in ≥10% of Patients Treated. Worst grade per Cycle by Dose Level.

Table 11.3.1.16 Adverse Events Regardless of Relationship. Worst Grade by Patient by Dose Level.

Table 11.3.1.17 Adverse Events Regardless of Relationship in the First Cycle by Patient and Dose Level.

Table 11.3.1.18 Adverse Events Regardless of Relationship. Worst Grade per Cycle by Dose Level.

Table 11.3.1.19 Adverse Events Observed in ≥ 10% of Patients Treated by Dose Level.

Table 11.3.1.20 Adverse Events Observed in ≥ 10% of Patients Treated. Worst grade per Cycle by Dose Level.

Tables 11.3.1.1-.20 will have the following pattern but DL and Grade column might be grouped if required.

MedDRA System Organ Class	DL I				...				DL n				Total			
Preferred Term	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
	n %	n %	n %	n %	n %	n %	n %	n %	n %	n %	n %	n %	n %	n %	n %	n %

Note: Percentages based on number of patients/cycles by dose level.

Table 11.3.1.21 Supportive Listing: Drug Related (or Relationship Unknown) Adverse Events Grade 3-4 by Dose Level.

Dose level	Patient	SOC	MedDRA Preferred Term	Literal term	Grade	SAE (Y/N)	Onset Date	Resolved Date	Relationship to Study Drug	Action Taken	Main Consequence

Table 11.3.1.22 Time to course to Alopecia Grade >1.

Dose level	Patient	Grade at Baseline	Grade	Onset Date	Resolved Date	Time in days *	Action Taken	Main Consequence

(*) Time in days calculated as the difference between Onset date and DA first drug administration.

11.4.Deaths and Other Serious Adverse Events.

11.4.1. Deaths.

Table 11.4.1.1 Patients who Died While on Treatment.

Dose level	Patient No	Last cycle received	Last infusion date	Death date	Time from last infusion date (days)	Cause	Comments	Time on treatment (weeks)

Note: Patients with death reported as end of treatment reason.

Table 11.4.1.2 Patients Who Died Within 30 Days of Last Drug Administration.

Dose level	Patient No	Last cycle received	Last infusion date	Death date	Time from last infusion date (days)	Cause	Comments	Time on treatment (weeks)

Table 11.4.1.3 Listing of All Deaths.

Dose level	Patient No	Last cycle received	Last infusion date	Death date	Cause	Comments	Autopsy	Time on treatment (weeks)	Time from last infusion date (days)

11.4.2. Serious Adverse Events.

All serious adverse events will be listed only for the purpose of reconciliation with the database of pharmacovigilance. The listings provided by the Product Safety department will be used for the clinical study report.

Table 11.4.2.1 All SAEs.

Dose level	Patient	Cycle	MedDRA System Organ Class	Preferred Term	Grade	AE Status	AE relationship	AE consequences	SAE	Onset date	Resolved date

11.5. Clinical Laboratory Evaluation.

11.5.1. Hematological Abnormalities.

Table 11.5.1.1 Hematological Abnormalities: Worst Grade per Patient by Dose Level.

Table 11.5.1.2 Hematological Abnormalities: Worst Grade per Cycle by Dose Level.

Table 11.5.1.3 Hematological Abnormalities: Worst Grade per patient in the First Cycle by Dose Level.

Tables 11.5.1.1-.3 will have the following pattern but DL and Grade columns might be grouped if required.

Abnormality*	DL I	DL II	···	DL n	Total
Anemia					
Grade 1-4, n (%)					
Grade 1					
Grade 2					
Grade 3					
Grade 4					
…..*					
Grade 1-4, n (%)					
Grade 1					
Grade 2					
Grade 3					
Grade 4					

Notes: Percentages based on number of patients by dose level. (*) Also Leukopenia, Lymphopenia, Neutropenia, and Thrombocytopenia.

Table 11.5.1.4 Supportive Listing: Patients with Grade 4 Hematological Abnormalities.

Dose level	Patient	Lab. test	Cycle	Examination date	…….*

Notes: (*) Include the following: Value at BL, Grade at BL, Onset day, Onset grade, Nadir day, Nadir value, Nadir grade, Recovery day, Recovery value, Recovery grade, Days Grade 4.

Table 11.5.1.5 Patients with Missing Hematological Evaluations.

Dose level/CSF	Patient	Cycle	Lab. test

Dose level/CSF	Patient	Cycle	Lab. test

Table 11.5.1.6 Shift of Hematological Abnormalities. Baseline Grade vs. Worst Grade on First Cycle.

Dose level/Parameter*		Baseline Grade	Worst Grade on First Cycle							
			Gr. 1		Gr. 2		Gr. 3		Gr. 4	
			N	%	N	%	N	%	N	%
DLI	Anemia	0								
		…								
		4								
	……	0								
		…								
		4								
…	Anemia	0								
		…								
		4								
	…	0								
		…								
		4								
Total	Anemia	0								
		…								
		4								
	…	0								
		…								
		4								

Notes: Percentages based on number of patients by dose level. (*) Also Leukopenia, Lymphopenia, Neutropenia and Thrombocytopenia.

Table 11.5.1.7 Shift of Hematological Abnormalities. Baseline Grade vs. Worst Grade on Treatment.

Dose level/Parameter*		Baseline Grade	Worst Grade during on Treatment							
			Gr. 1		Gr. 2		Gr. 3		Gr. 4	
			N	%	N	%	N	%	N	%
DLI	Anemia	0								
		…								
		4								
	……	0								
		…								
		4								
…	Anemia	0								
		…								
		4								
	…	0								
		…								
		4								
Total	Anemia	0								
		…								
		4								
	…	0								
		…								
		4								

Notes: Percentages based on number of patients by dose level. (**) Leukopenia, Lymphopenia, Neutropenia and Thrombocytopenia.

Table 11.5.1.8 Listing of Patients with Hematological Abnormalities >G2 and Experience Grade Increase (wpp) from Baseline.

Dose level	Patient	Event*	NCI-CTCAE v.4 at baseline	NCI-CTCAE v.4 at Cycle	Cycle

Table 11.5.1.9 Summary of Characteristics of wpp Hematological Abnormailities G3-4.

Dose Level	Parameter	N/(%)*	Mean**	Median**	Range**

Notes: (*) Percentages based on number of patients by dose level with grade 3-4. (**) Cycle occurrence.

Table 11.5.1.10 Summary of Hematological Abnormalities Grade 4 and specific Transfusions/treatment.

Dose level	Patient	Cycles received	Cycle number with hematological abnormality * grade 4	Cycle numbers with ….**	Cycle numbers with dose reduction

Note: (*) Neutropenia/CSF administration. Thrombocytopenia / Platelets transfusion and Anemia / EPO.

Table 11.5.1.11 Anemia wpp/wpc and Use of EPO per Dose Level in Cycle >1.

EPO/Dose Level		Worst Grade on Treatment*/Cycle*							
		Gr. 1-2		Gr. 3		Gr. 4		Total	
		N	%	N	%	N	%	N	%
EPO	DL I								
	…..·								
No EPO	DL I								
	…….								

Table 11.5.1.12 Patients with Anemia Grade 3/4 and Use of EPO in Cycle >1.

Dose Level	Tumor type	Patno	Cycle	Prophylaxis CSF (Y/N)	*

Notes: (*) Grade, nadir day to grade 3/4, recovery day to grade ≤3,** duration in days to grade 3**, (**) Grade 2 or 1 also if clinically indicated (***) Numeric intervals in days might change upon request.

Table 11.5.1.13 Platelet Count Time Course Pattern (summary).

	Parameter*	DL I	· · ·	DL n

Parameter*			DL I			···			DL n		
Platelet transfusion											
			N	Median	Range	N	Median	Range	N	Median	Range
Baseline grade 0	Onset day grade 4	1st cycle									
		Cycle >1									
		Total									
Baseline grade >0	Onset day grade 4	1st cycle									
		Cycle >1									
		Total									
No Platelet transfusion											
			N	Median	Range	N	Median	Range	N	Median	Range
Baseline grade 0	Onset day grade 4	1st cycle									
		Cycle >1									
		Total									
Baseline grade >0	Onset day grade 4	1st cycle									
		Cycle >1									
		Total									
Totals											
			N	Median	Range	N	Median	Range	N	Median	Range
Baseline grade 0	Onset day grade 4	1st cycle									
		Cycle >1									
		Total									
Baseline grade >0	Onset day grade 4	1st cycle									
		Cycle >1									
		Total									

Notes: (*) Also nadir day grade 4, nadir value grade 4, recovery day to grade ≤3, duration in days to grade 3, recovery day to grade ≤2, duration in days to grade 2, recovery day to grade ≤1 and duration in days to grade 1. Grade limits may change under request.

Table 11.5.1.14 Platelet Count Time Course Pattern.

Parameter*			DL I		···		DL n	
Platelet transfusion								
		Onset day grade 4	N	%	N	%	N	%
Baseline grade 0	1st cycle	≤7***						
		8-14						
		≥15						
	Cycle >1	≤7						
		8-14						
		≥15						
Baseline grade >0	1st cycle	≤7						
		8-14						
		≥15						
	Cycle >1	≤7						
		8-14						
		≥15						
No Platelet transfusion								
		Onset day grade 4	N	%	N	%	N	%
……	…..	≤7						
		8-14						
		≥15						

Parameter*		DL I	···	DL n
	…..	≤7 8-14 ≥15		

Totals

	Onset day grade 4	N	%	N	%	N	%
……	…..	≤7 8-14 ≥15					
	…..	≤7 8-14 ≥15					
……..*							

Note: (*) Also nadir day to grade 4, recovery day to grade ≤3**, duration in days to grade 3**, (**) Grade 2 or 1 also if clinically indicated, (***) Numeric intervals in days might change upon request.

Table 11.5.1.15 Thrombocytopenia wpp/wpc and Use of Transfusions per Dose Level in Cycle>1.

Tansfusion/Dose Level		Worst Grade on Treatment*/Cycle*							
		Gr. 1-2		Gr. 3		Gr. 4		Total	
		N	%	N	%	N	%	N	%
Transfusion	DL I								
	…..·								
No Transfusion	DL I								
	…….								

Table 11.5.1.16 Patients with Thrombocytopenia Grade 3/4 and Use of Transfusions in Cycle >1.

Dose Level	Tumor type	Patno	Cycle	Prophylaxis CSF (Y/N)	*

Notes: (*) Grade, nadir day to grade 3/4, recovery day to grade ≤3, (**) duration in days to grade 3**, (**) Grade 2 or 1 also if clinically indicated (***) Numeric intervals in days might change upon request.

Table 11.5.1.17 Summary of Hematological Abnormalities Grade 4 and Specific Transfusions.

Dose level	Patient	Cycles received	Cycle number with hematological abnormality * grade 4	Cycle numbers with ….**	Cycle numbers with dose reduction

Note: (*) Also Neutropenia,/CSF administration. Thrombocytopenia/ Platelets transfusion and Anemia / EPO transfusions.

Table 11.5.1.18 Neutrophil Count Time Course Pattern (summary).

Parameter*			DL I			···			DL n		
CSF use											
			N	Median	Range	N	Median	Range	N	Median	Range
Baseline grade 0	Onset day grade 4	1st cycle									
		Cycle >1									
		Total									
Baseline grade >0	Onset day grade 4	1st cycle									
		Cycle >1									
		Total									
No CSF											
			N	Median	Range	N	Median	Range	N	Median	Range
Baseline grade 0	Onset day grade 4	1st cycle									
		Cycle >1									
		Total									
Baseline grade >0	Onset day grade 4	1st cycle									
		Cycle >1									
		Total									
Totals											
			N	Median	Range	N	Median	Range	N	Median	Range
Baseline grade 0	Onset day grade 4	1st cycle									
		Cycle >1									
		Total									
Baseline grade >0	Onset day grade 4	1st cycle									
		Cycle >1									
		Total									

Note: (*) Also nadir day grade 4, nadir value grade 4, recovery day to grade ≤3, duration in days to grade 3, recovery day to grade ≤2, duration in days to grade 2, recovery day to grade ≤1 and duration in days to grade 1.

Table 11.5.1.19 Platelet Count Time Course Pattern.

Parameter*			DL I		···		DL n	
Platelet transfusion								
Onset day grade 4			N	%	N	%	N	%
Baseline grade 0	1st cycle	≤7***						
		8-14						
		≥15						
	Cycle >1	≤7						
		8-14						
		≥15						
Baseline grade >0	1st cycle	≤7						
		8-14						
		≥15						
	Cycle >1	≤7						
		8-14						
		≥15						
No Platelet transfusion								
Onset day grade 4			N	%	N	%	N	%
……	…..	≤7						
		8-14						
		≥15						

Parameter*		DL I	···	DL n
	…..	≤7		
		8-14		
		≥15		
Totals				
……	….	≤7		
		8-14		
		≥15		
	….	≤7		
		8-14		
		≥15		
……..*				

Notes: (*) Also nadir day to grade 4, recovery day to grade ≤3**, duration in days to grade 3**, (**) Grade 2 or 1 also if clinically indicated, (***) Numeric intervals in days might change upon request.

Table 11.5.1.20 Neuthropenia wpp/wpc and Use of Prophylactic CSF per Dose Level in Cycle>1.

Tansfusion/Dose Level		Worst Grade on Treatment*/Cycle*							
		Gr. 1-2		Gr. 3		Gr. 4		Total	
		N	%	N	%	N	%	N	%
CSF	DL I								
	……								
No CSF	DL I								
	……								

Table 11.5.1.21 Patients with Neutrophenia Grade 3/4 and Use of Prophylactic CSF in Cycle >1.

Dose Level	Tumor type	Patno	Cycle	Prophylaxis CSF (Y/N)	*

(*) Grade, nadir day to grade 3/4, recovery day to grade ≤3, (**) duration in days to grade 3**, (**) Grade 2 or 1 also if clinically indicated (***) Numeric intervals in days might change upon request.

11.5.2. Biochemical Abnormalities.

Table 11.5.2.1 Biochemical Abnormalities: Worst Grade per Patient by Dose Level.

Table 11.5.2.2 Biochemical Abnormalities: Worst Grade per Cycle by Dose Level.

Table 11.5.2.3 Biochemical Abnormalities: Worst Grade per Patient in the first Cycle by Dose Level.

Tables 11.5.2.1-.3 will have the following pattern but Grade column might be grouped if required.

Abnormality*	DL I	DL II	···	DL n	Total
AP					

Abnormality*	DL I	DL II	···	DL n	Total
Grade 1 - 4, n (%)					
Grade 1					
Grade 2					
Grade 3					
Grade 4					
….*					
Grade 1 - 4, n (%)					
Grade 1					
Grade 2					
Grade 3					
Grade 4					

Notes: Percentages based on number of patients by dose level. (*) All biochemical abnormalities susceptible to be graded with NCI-CTCAE v.4.

Table 11.5.2.4 Patients with Missing Biochemical Evaluation.

Dose level	Patient	Cycle	Lab. test

Table 11.5.2.5 Shift of Biochemical Abnormalities. Baseline Grade vs. Worst Grade on First Cycle.

Dose level/Parameter		Baseline Grade	Worst Grade on Cycle 1							
			Gr. 1		Gr. 2		Gr. 3		Gr. 4	
			N	%	N	%	N	%	N	%
DL I	AP increase	0								
		…								
		4								
	……	0								
		…								
		4								
…	AP increase	0								
		…								
		4								
	…	0								
		…								
		4								
Total	AP increase	0								
		…								
		4								
	…	0								
		…								
		4								

Notes: Percentages based on number of patients by dose level. (*) All biochemical abnormalities susceptible to be graded with NCI-CTCAE v.4.

Table 11.5.2.6 Shift of Biochemical Abnormalities. Baseline Grade vs. Worst Grade on Treatment.

Dose level/Parameter		Baseline Grade	Worst Grade on Treatment							
			Gr. 1		Gr. 2		Gr. 3		Gr. 4	
			N	%	N	%	N	%	N	%
DL I	AP increase	0								
		…								
		4								
	……	0								

		… 4
…	AP increase	0 … 4
	…	0 … 4
Total	AP increase	0 … 4
	…	0 … 4

Notes: Percentages based on number of patients by dose level. (*) All biochemical abnormalities susceptible to be graded with NCI-CTCAE v.4.

Table 11.5.2.7 Listing of patients with Biochemical Abnormalities >G2 and Experience Grade Increase (wpp) from Baseline.

Dose level	Patient	Event*	NCI-CTCAE v4 at baseline	NCI-CTCAE v4 at Cycle	Cycle

Note: (*) For nausea and vomiting events, other table will be provided and use or not of antiemetic will be added.

Table 11.5.2.8 Summary of Characteristics of wpp Biochemical Abnormalities G3-4.

Dose Level	Parameter	N*	Mean**	Median**	Range**

Notes: (*) Percentages based on number of patients by dose level. with grade 3-4. (**) Cycle occurrence.

Table 11.5.2.9 AST/ALT Count Time Course Pattern (summary).

	Parameter*		DL I	…	DL n
			N Median Range	N Median Range	N Median Range
Baseline grade 0	Onset day grade 3-4	1st cycle			
		Cycle >1			
		Total			
Baseline grade >0	Onset day grade 3-4	1st cycle			
		Cycle >1			
		Total			
			Totals		
			N Median Range	N Median Range	N Median Range
Baseline grade 0	Onset day grade 3-4	1st cycle			
		Cycle >1			
		Total			
Baseline grade >0	Onset day grade 3-4	1st cycle			
		Cycle >1			
		Total			

Note: (*) Also Onset day grade 3-4, Peak day grade 3-4, Peak value grade 3-4, Recovery* day to grade ≤2, Duration in days to grade 2, Recovery day to grade ≤1, Duration in days to grade 1. Grade limits may change under request.

Table 11.5.2.10 AST/ALT Count Time Course Pattern.

Parameter			DL I		···		DL n	
	Onset day grade 3-4		N	%	N	%	N	%
Baseline grade 0	1st cycle	≤7***						
		8-14						
		≥15						
	Cycle >1	≤7						
		8-14						
		≥15						
Baseline grade >0	1st cycle	≤7						
		8-14						
		≥15						
	Cycle >1	≤7						
		8-14						
		≥15						
Totals								
Onset day grade 3-4			N	%	N	%	N	%
……	…...	≤7						
		8-14						
		≥15						
	…...	≤7						
		8-14						
		≥15						

Notes: (*) Also Peak day to grade 3-4, recovery day to grade ≤2**, duration in days to grade 2**, (**) Grade 1 also if clinically indicated (***) Numeric intervals in days might change upon request.

11.5.3. Other Metabolic Abnormalities.

Table 11.5.3. 1 Other Metabolic Abnormalities: Worst Grade per Patient by Dose Level.

Table 11.5.3. 2 Other Metabolic Abnormalities: Worst Grade per Cycle by Dose Level.

Table 11.5.3. 3 Other Metabolic Abnormalities: Worst Grade per Patient in the first Cycle by Dose Level.

Tables 11.5.3.1-.3 will have the following pattern but Grade column might be grouped if required.

Abnormality*	DL I	DL II	···	DL n	Total
Metabolic abnormality					
Grade 1 - 4, n (%)					
Grade 1					
Grade 2					
Grade 3					
Grade 4					
….*					
Grade 1 - 4, n (%)					
Grade 1					
Grade 2					
Grade 3					
Grade 4					

Notes: Percentages based on number of patients by dose level. (*) All biochemical abnormalities susceptible to be graded with NCI-CTCAE v.4.

Table 11.5.3. 4 Patients with missing Metabolic Evaluations.

Dose level	Patient	Cycle	Lab. test

Table 11.5.3. 5 Shift of Metabolic Abnormalities. Baseline Grade vs. Worst Grade on First Cycle.

Dose level/Parameter		Baseline Grade	Worst Grade on Cycle 1							
			Gr. 1		Gr. 2		Gr. 3		Gr. 4	
			N	%	N	%	N	%	N	%
DLI	Hypercalcemia	0								
		…								
		4								
	…..	0								
		…								
		4								
…	Hypercalcemia	0								
		…								
		4								
	…	0								
		…								
		4								
Total	Hypercalcemia	0								
		…								
		4								
	…	0								
		…								
		4								

Notes: Percentages based on number of patients by dose level. (*) All metabolic abnormalities susceptible to be graded with NCI-CTCAE v.4.

Table 11.5.3. 6 Shift of Metabolic Abnormalities. Baseline Grade vs. Worst Grade on Treatment.

Dose level/Parameter		Baseline Grade	Worst Grade on Treatment							
			Gr. 1		Gr. 2		Gr. 3		Gr. 4	
			N	%	N	%	N	%	N	%
DLI	Hypercalcemia	0								
		…								
		4								
	…..	0								
		…								
		4								
…	Hypercalcemia	0								
		…								
		4								
	…	0								
		…								
		4								
Total	Hypercalcemia	0								
		…								
		4								
	…	0								

	…	
	4	

Notes: Percentages based on number of patients by dose level. (*) All metabolic abnormalities susceptible to be graded with NCI-CTCAE v.4.

Table 11.5.3. 7 Listing of Patients with Metabolic Abnormailities >G2 and Experience Grade Increase (wpp) from Baseline.

Dose level	Patient	Event	NCI-CTCAE v.4 at baseline	NCI-CTCAE v.4 at Cycle	Cycle

Table 11.5.3. 8 Supportive Listing: Patients with Grade ≥3 Metabolic Abnormalities

Dose level	Patient	Lab. test	Cycle	Examination date	……..*

Note: (*) It will include the following: Value at BL, Grade at BL, Onset day, Onset grade, Nadir day, Nadir value, Nadir grade, Recovery day, Recovery value, Recovery grade, Days Grade 3-4.

11.5.4. Coagulation Abnormalities.

Table 11.5.4. 1 Coagulation Abnormalities: Worst Grade per Patient by Dose Level.

Table 11.5.4. 2 Coagulation Abnormalities: Worst Grade per Cycle by Dose Level.

Table 11.5.4. 3 Coagulation Abnormalities: Worst Grade per Patient in the first Cycle by Dose Level.

Tables 11.5.4.1-.3 will have the following pattern but Grade column might be grouped if required.

Abnormality	DL I	DL II	· · ·	DL n	Total
INR					
Grade 1 - 4, n (%)					
Grade 1					
Grade 2					
Grade 3					
Grade 4					
PTT					
Grade 1 - 4, n (%)					
Grade 1					
Grade 2					
Grade 3					
Grade 4					

Table 11.5.4. 4 Shift of Coagulation Abnormalities. Baseline Grade vs. Worst Grade on First Cycle.

Dose level/Parameter*		Baseline Grade	Worst Grade on Treatment					
			Gr. 1		Gr. 2		Gr. 3	
			N	%	N	%	N	%
DL I	INR increase	0						
		…						
		3						

	…..	0 … 3
…	INR increase	0 … 3
	…	0 … 3
Total	INR increase	0 … 3
	…	0 … 3

Notes: Percentages based on number of patients by dose level. (*) INR and PTT. If data available.

Table 11.5.4. 5 Shift of Coagulation Abnormalities. Baseline Grade vs. Worst Grade on Treatment.

Dose level/Parameter*		Baseline Grade	Worst Grade on Treatment					
			Gr. 1		Gr. 2		Gr. 3	
			N	%	N	%	N	%
DL I	INR increase	0 … 3						
	…..	0 … 3						
…	INR increase	0 … 3						
	…	0 … 3						
Total	INR increase	0 … 3						
	…	0 … 3						

Notes: Percentages based on number of patients by dose level. (*) INR and PTT. If data available.

Table 11.5.4. 6 Listing of Patients with Coagulation Abnormalities >G2 and Experience Grade Increase from Baseline.

Dose level	Patient	Event	NCI-CTCAE v4 at baseline	NCI-CTCAE v4 at Cycle	Cycle

Table 11.5.4. 7 Patients with missing Metabolic Evaluations.

Dose level	Patient	Cycle	Lab. test

Dose level	Patient	Cycle	Lab. test

11.6. Vital Signs, Physical Findings, ECG, LVEF and Pregnancy tests.

All statistical outputs in this section, whenever applicable, will be displayed according to assignment to prophylactic CSF use or not as well as per Dose level/Dose group or by cancer type or primary site if adequate number of patients is represented. Total numbers will be displayed independently, if applicable.

11.6.1. Vital Signs and Physical Findings.

Table 11.6.1.1 Physical examination during the Study by Cycle and Dose Level.

		Baseline	**Cycle 1**	**Cycle 2**	**…**	**Cycle N**
Dose level	Patient No	Normal/Abnormal	Normal/Abnormal	Normal/Abnormal	Normal/Abnormal	Normal/Abnormal
I						
…						
N						

Table 11.6.1.2 Performance Status during the Study by Cycle and Dose Level.

		Baseline	**Cycle 1**	**Cycle 2**	**…**	**Cycle N**
Dose level	Patient No	PS	PS	PS	PS	PS
I						
…						
N						

Table 11.6.1.3 Weight Change during the Study by Dose Level.

Dose level	Patient No	Weight at baseline (kg)	**Cycle 1**	**Cycle 2**	**…**	**Cycle N**
			% change	% change	% change	% change
I						

Dose level	Patient No	Weight at baseline (kg)	**Cycle 1**	**Cycle 2**	**…**	**Cycle N**
			% change	% change	% change	% change
…						
N						

11.6.2. Electrocardiogram.

Table 11.6.2 1 ECG during the Study by Dose Level.

Dose level	Patient No	**Baseline**	**Cycle 1**	**Cycle 2**	**…**	**Cycle N**
		Normal/Abnormal	Normal/Abnormal	Normal/Abnormal	Normal/Abnormal	Normal/Abnormal
I						
…						
N						

Table 11.6.2 2 ECG during the Study by Dose Level.

	No cycles with delays	DL I	DL II	…	DL n	Total
PR interval	N Mean Median Min Max STD					
QT interval	N Mean Median Min Max STD					
…..*	N Mean Median Min Max STD					

Note: (*) Also RR interval, QRS interval, QTcF.

Table 11.6.2 3 QTcF Values during the Study by Dose Level.

Dose level	Patient No	Baseline QTcF (msec)	Cycle 1	Cycle 2	···	Cycle N
			% change	% change	% change	% change
I						
···						
N						

Table 11.6.2 4 QTcF (msec) Change per Patient during the Study by Dose Level.

Dose level	Patient No	Baseline QTcF (msec)	Cycle 1 QTcF (msec)	Cycle 2 QTcF (msec)	··· QTcF (msec)	Cycle N QTcF (msec)
I						
···						
N						

Table 11.6.2 5 Shift of QTc. Baseline Grade vs. Worst Grade on Treatment.

Dose level/Parameter		Baseline Grade	Worst Grade on Treatment.							
			Gr. 1		Gr. 2		Gr. 3		Gr. 4	
			N	%	N	%	N	%	N	%
DL I	QTc corrected	0								
		…								
		4								
…	QTc corrected	0								
		…								
		4								
Total	QTc corrected	0								
		…								
		4								

Table 11.6.2 6 QTcF Values during the Study by Doxorubicin Cumulative Dose.

	QTcF (msec)	0-xx (mg/m^2)	xx-xx	xx-xx	xx-xx	xx-450 (mg/m^2)	Total
Previous to treatment or at BL	N						
	Mean						
	Median						
	Min						
	Max						
	STD						

	QTcF (msec)	0-xx (mg/m^2)	xx-xx	xx-xx	xx-xx	xx-450 (mg/m^2)	Total
Accumulated during treatment	N Mean Median Min Max STD						

Table 11.6.2 7 Listing of Patients with Grade ≥ 2 QTc Interval Prolonged.

Dose level	Patient	Cycle	QTc value (msec)	Grade NCI-CTC v.4	QTc at Baseline	% of increase from BL	Total cumulative dose of anthracyclines

11.6.3. LVEF.

Table 11.6.3 1 LVEF (%) Change per Patient during the Study by Dose Level.

		Baseline	**Cycle 1**	**Cycle 2**	**…**	**Cycle N**
Dose level	Patient No	Normal/Abnormal	Normal/Abnormal	Normal/Abnormal	Normal/Abnormal	Normal/Abnormal
I						
…						
N				.		.

Table 11.6.3 2 Median LVEF Values (%) during the Study by Doxorubicin Cumulative Dose.

	QTcF (msec)	0-xx (mg/m^2)	xx-xx	xx-xx	xx-xx	xx-450 (mg/m^2)	Total
Previous to treatment or at BL	N Mean Median Min Max STD						
Accumulated during treatment	N Mean Median Min Max STD						

Table 11.6.3 3 Shift of LVEF. Baseline vs. Worst Grade on Treatment.

Dose level	Baseline Grade	Worst Grade on Treatment.		
		Gr. 1	Gr. 2	Gr. 3

		N	%	N	%	N	%
DL I	0 …						
…	0 …						
Total	0 …						

Table 11.6.3 4 Listing of Patients with Grade ≥ 2 LVEF Decrease.

Dose level	Patient	Cycle	LVEF value (%)	Grade NCI-CTCAE v.4	LVEF at Baseline	% of decrease from BL

11.7. Concomitant and Prophylactic Medication.

11.7.1. Concomitant and Prophylactic Medication During Study.

Table 11.7.1.1 Concomitant Medication during Study (ATC Level 1 and 4) by Dose Level.

Medication Term (ATC level 1)	Medication Term (ATC level 2)	Medication Term (ATC level 4)	DL I		DL II		…		DL n		Total	
			N	%	N	%	N	%	N	%	N	%

Note: Percentages based on number of patients by dose level.

Table 11.7.1.2 EPO/RBC and PlateletsTransfusions/CSF.

Medication Term (ATC level 1)	Medication Term (ATC level 2)	Medication Term (ATC level 4)	DL I		DL II		…		DL n		Total	
			N	%	N	%	N	%	N	%	N	%
EPO												
RBC transfusion												
Platelet transfusion												
CSF*												
…												

Notes: Percentages based on number of patients by dose level. (*) Non-prophylactic CSF use.

Table 11.7.1.3 Patients with EPO/RBC and Platelets Transfusions/CSF.

Dose Level	Patient No	Cycle	Not done	Type*	Literal	Route	Specify of route	Dose	Unit	Start date (text)	Start date ongoing	End date (text)	End date ongoing	Reason

Note: (*) Non-prophylactic CSF use.

Table 11.7.1.4 Prophylactic Medication during Study.

Medication Term (ATC level 1)*	DL I N	DL I %	DL II N	DL II %	··· N	··· %	DL n N	DL n %	Total N	Total %
Cycle 1										
Steroids										
5-HT antagonist										
Prokinetics										
Aprepitant										
Other										
Total										
Cycle >1										
Steroids										
5-HT antagonist										
Prokinetics										
Aprepitant										
Other										
Total										
All										
Steroids										
5-HT antagonist										
Prokinetics										
Aprepitant										
Other										
Total										

Notes: Percentages based on number of patients by dose level. (*) Antiemetic use may include more categories as extended and extensive, or a frequency table just for antiemetic medication will be added, if clinically indicated.

Table 11.7.1.5 Patients with Nausea and /or Vomiting G3/4 and Use of Antiemetics in Cycle >1.

Dose Level	Tumor type	Patno	Cycle	AE prefered Term	NCI-CTCAE v.4	Antiemetics* (Y/N)	Medication Term	…**

Notes:(*) Antiemetics e.g: Dexamethasone + 5HT3. (**) AE onset date/resolved date. Antiemetics dates, etc…

Table 11.7.1.6 No of Patients with Opioids Treatment During Treatment by Dose Level.

Opioids*	DL I N	DL I %	DL II N	DL II %	··· N	··· %	DL n N	DL n %	Total N	Total %
….										
…										

(*) The ATC classification including opioids and terms will be selected and provided by clinical request.

Table 11.7.1.7 Median Number of No of Opioids per Patient During Treatment by Dose Level.

Opioids*	DL I	DL II	···	DL n	Total
N					
Mean					
Median					
Min					
Max					
STD					

(*) The ATC classification including opioids and terms will be selected and provided by clinical request.

Table 11.7.1.8 No of Patients with Steroids Treatment During Treatment by Dose Level.

Steroids*	DL I		DL II		…		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
….										
…										

(*) The ATC classification including steroids and terms will be selected and provided by clinical request.

Table 11.7.1.9 Known CYP 3A4 Inducers/Inhibitors/Substrates Concomitant Therapies at BL.

CYP 3A4*	DL I		DL II		…		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Inhibitor										
….										
…										

Note: (*) Also the possibility of displaying one table for each category of Inducers/Inhibitors or substrates. Some medication will be excluded by clinical request (e.g. Dexamethasone).

Table 11.7.1.10 Listing of CYP 3A4 Inducers/Inhibitors/Substrates Concomitant Therapies During Treatment.

Dose Level	Pat No	Type*	Literal Term	ATC4	ATC2	ATC1	…	Start date	End date	Reason for Use	SS/AE	Specify

Note: (*) Also the possibility of displaying one table for each category of Inducers/Inhibitors or substrates. Some medication will be excluded by clinical request (e.g. Dexamethasone).

12. Appendix III. Efficacy Evaluation.

All statistical outputs will be displayed according to Dose level (grouped)/Cohort/Cancer type or primary site/CSF use or not/other clinical relevant variable (e.g. 2nd line SCLC by CTFI), whenever applicable and if an adequate number of patients is represented. Summary tables will have source data footnotes that will refer to the relevant listings. The tables' layout may change to adequately accommodate cohort/group size as appropriate.

12.1.Efficacy Analysis.

12.1.1. Response.

Table 12.1.1.1 Overall response by Dose Level: Treated Patients.

Overall response	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
RECIST v.1.1										
CR										
PR										
SD<4 months										
SD≥4 months										
PD										
NE										
Total										
Other evaluation criteria (if needed)										
CR										
PR										
SD<4 months										
SD≥4 months										
PD										
NE										
Total										

Note: Percentages based on number of patients by dose level.

Table 12.1.1.2 Overall response by Tumor type and Dose Level: Treated Patients.

Tumor type	Overall response	DL I		DL II		···		DL n		Total	
		N	%	N	%	N	%	N	%	N	%
Breast	CR										
	PR										
	SD<4 months										
	SD≥4 months										
	PD										
……*											
……	Total										

Notes: Percentages based on number of patients by dose level. (*) Coded tumor types.

Table 12.1.1.3 Overall response by Dose Level: Evaluable Patients.

Overall response	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
CR										
PR										
SD < 4 months										
SD ≥ 4 months										
PD										
Total										

Note: Percentages based on number of evaluable patients by dose level.

Table 12.1.1.4 Overall Response by Tumor type and Dose Level: Evaluable Patients.

Tumor type	Overall response	DL I		DL II		···		DL n		Total	
		N	%	N	%	N	%	N	%	N	%
Breast	CR										
	PR										
	SD < 4 months										
	SD ≥ 4 months										
	PD										
……*											
……	Total										

Notes: Percentages based on number of evaluable patients by dose level. (*) Coded tumor types.

Table 12.1.1.5 SD ≥ 4 months by Dose Level: Evaluable Patients.

SD ≥ 4 months	DL I		DL II		···		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
No										
Yes										
Total										

Note: Percentages based on number of evaluable patients by dose level.

Table 12.1.1.6 Tumor Marker Evolution During Study.

			Baseline	**Cycle 1**	···	**Cycle N**
Dose level	Patient No	Tumor type/ Tumor marker*	Tumor marker value	Tumor marker value / (%) change from BL	Tumor marker value / (%) change from BL	Tumor marker value / (%) change from BL
I						
…						
N						

(*) If available data

Table 12.1.1.7 Characteristics of Patients with Clinical Benefit*.

Dose level	Patient No	Sex/ Age/	Tumor type	Number of	Agents (previous	Best Response	TTP Previous	Cycles Received	Overall Response	TTP (months)	OS (months)	Treatment Discontinuation

	PS	lines of previous treatment	treatment)	Previous CT	CT	PM01183				Reason

Note: (*) "Evidence of Clinical Benefit" when response is CR, PR or SD≥4 months and/or no evidence of PD with increase tumor markers, if non-evaluable as per RECIST v.1.1.

Table 12.1.1.8 Characteristics of Patients with Clinical Benefit based on any Specific Tumor Marker Criteria.

Dose level	Patient No	Sex/ Age/ PS	Tumor type	Number of lines of previous treatment	Agents (previous treatment)	Best Response Previous CT	TTP Previous CT	Cycles Received PM01183	Overall Response for tumor marker	…..*

Notes: (*Also overall response by RECIST v1.1, TTP, OS, Treatment discontinuation reason, e.g: CA-125 value at BL, Nadir value CA-125. In patients for whom response to treatment are evaluated by both RECIST v.1.1 and any specific tumor marker criteria, the date of response and progression will be the earliest date of the two methods.

Table 12.1.1.9 Progression-Free Survival: Evaluable Patients.

Summary*
N=XX
Events X (XX.X%)
Censored X (XX.X%)
Median X.X 95% CI (X.X-X.X)
PFS at 3 months XX.X% 95% CI XX.X%-XX.X%)
PFS at 6 months XX.X% 95% CI XX.X%-XX.X%)

Note: (*) If any particular tumor type or any other clinically relevant variable is adequately represented and PFS at 12, and 24 months also if available data.

Table 12.1.1.10 Duration of Response.

Summary*
N=XX
Events X (XX.X%)
Censored X (XX.X%)
Median X.X 95% CI (X.X-X.X)
Duration of Response at 3 months XX.X% 95% CI XX.X%-XX.X%)
Duration of Response at 6 months XX.X% 95% CI XX.X%-XX.X%)

(*) If any particular tumor type or any other clinically relevant variable is adequately represented and DR at 12 and 24 months also if available data.

Table 12.1.1.11 Overall survival.

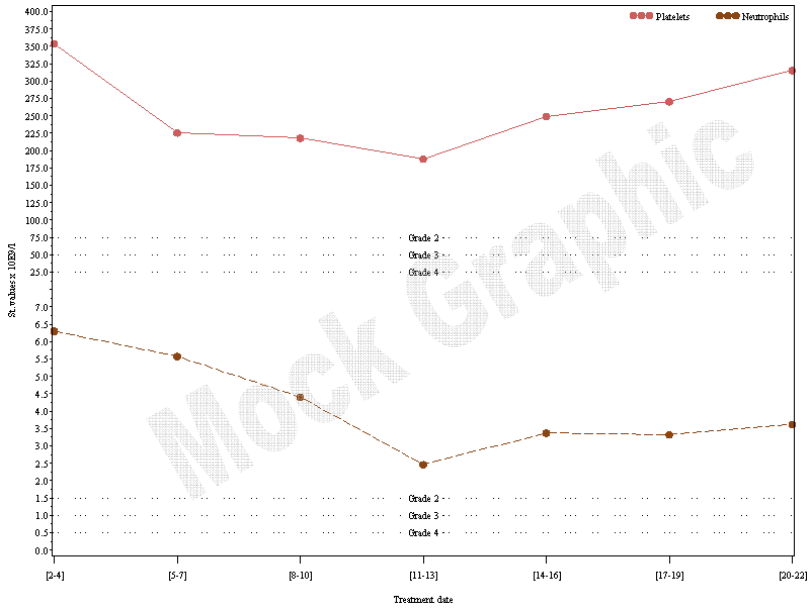
Summary*
N=XX
Events X (XX.X%)
Censored X (XX.X%)
Median X.X 95% CI (X.X-X.X)
OS at 6 months XX.X% 95% CI XX.X%-XX.X%)
OS at 12 months XX.X% 95% CI XX.X%-XX.X%)
OS at 18 months XX.X% 95% CI XX.X%-XX.X%)

(*) Only for Cohort B but if requested also for cohort A.

13. Figures.

All statistical outputs will be displayed according to Dose level (grouped)/Cohort/Cancer type or primary site/CSF use or not/other clinical relevant variable (e.g. 2nd line SCLC by CTFI), whenever applicable and if an adequate number of patients is represented. The figures' layout may change to adequately accommodate cohort/group size as appropriate

Figure 13.1 1 Pattern of Hematological/non Hematological DLTs in Individual Patients.



Also if applicable pattern for Neutropenia for patients with prophylactic CSF vs. No CSF.

Figure 13.1 2 Transaminase Series in Individual Patients.

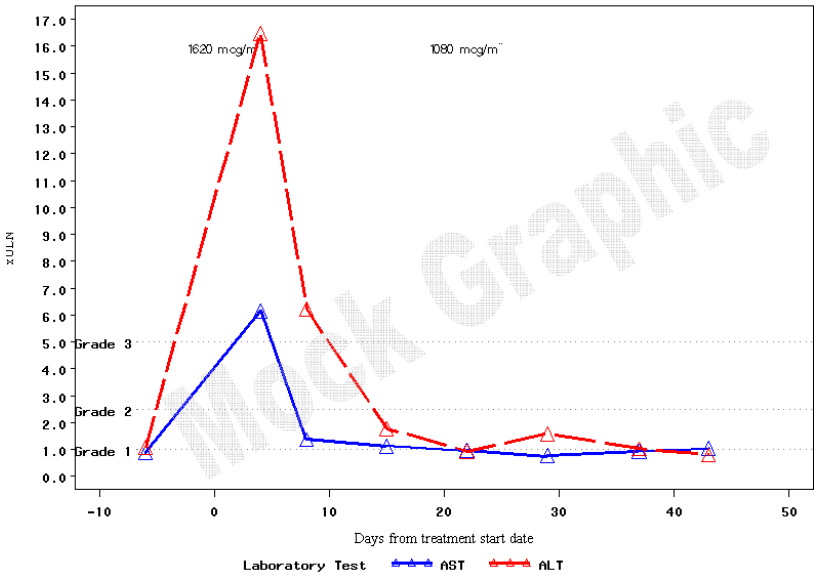


Figure 13.1 3 Barcharts of Adverse Events or Laboratory Abnormalities by Dose Level/Cohort.

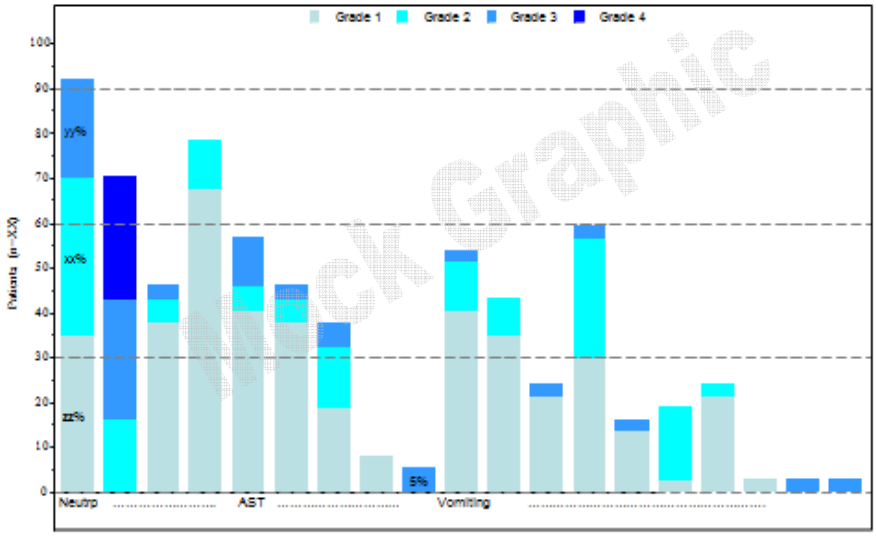


Figure 13.1 4 Barcharts of Adverse Events or Laboratory Abnormalities by Dose Level/Cohort/Tumor type/ or Other Clinical Relevant Variable.

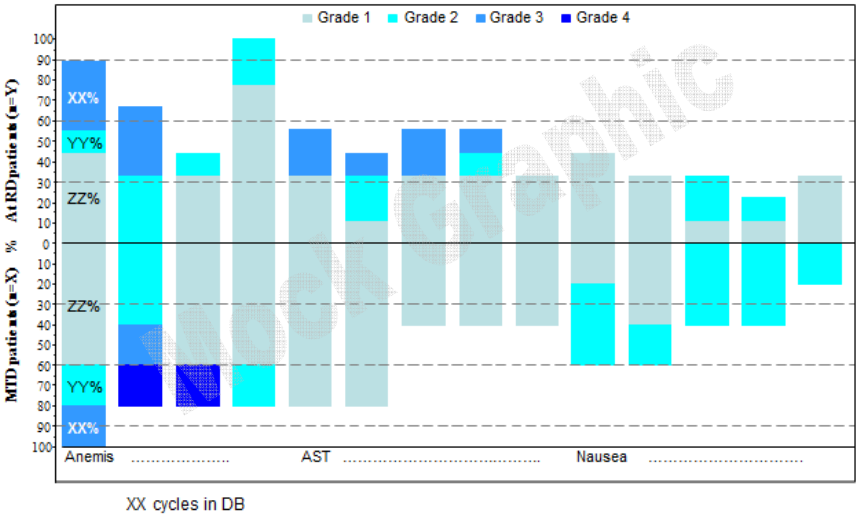


Figure 13.1 5 Hematology/Transaminase Worst Severity by Cycle.

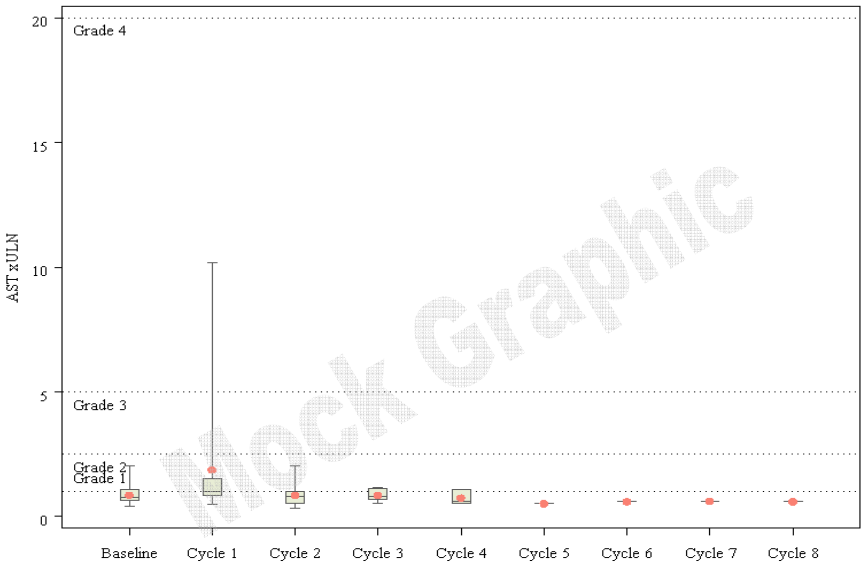


Figure 13.1 6 LVEF/QTcF Boxplot by Dose Level.

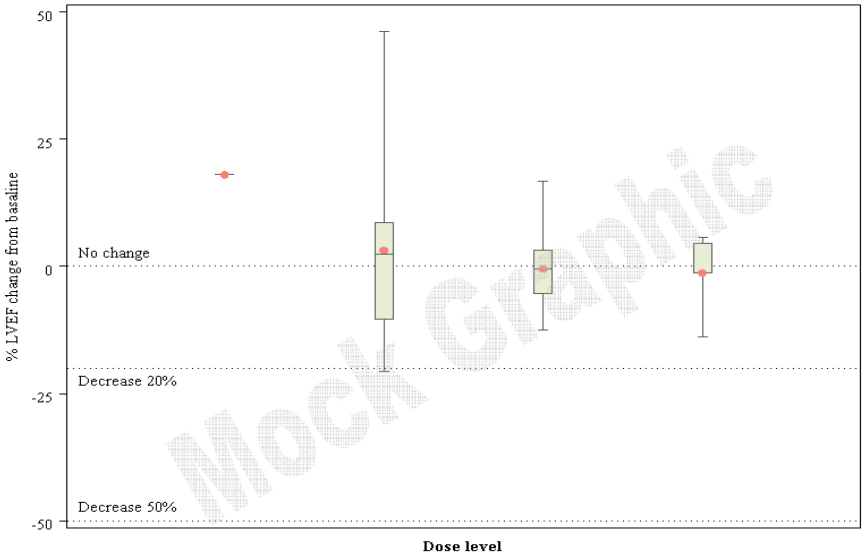


Figure 13.1 7 Boxplot QTcF Worst Value by Cycle.

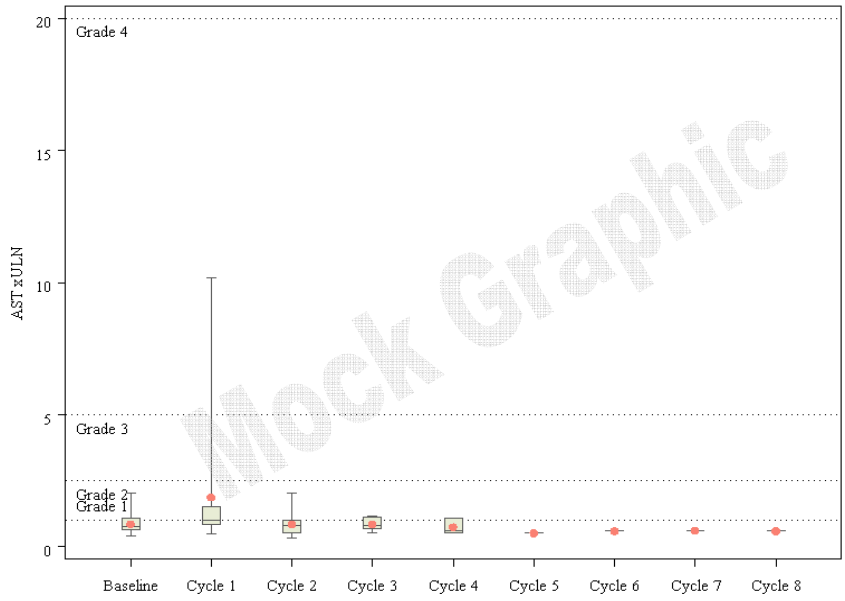
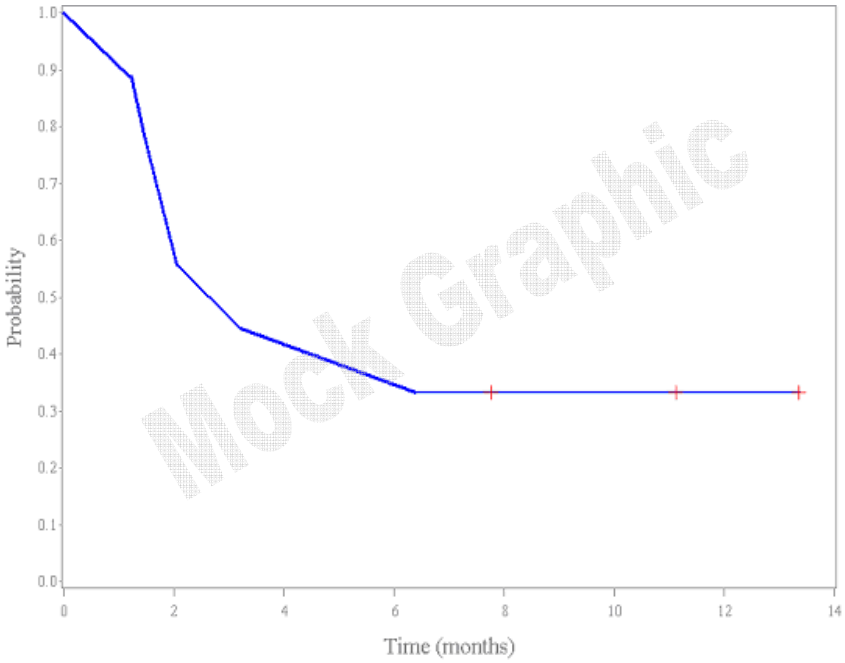


Figure 13.1 8 Duration of Response.



Kaplan-Meier curve of duration of response (If any response is observed).

Figure 13.1 9 Progression-free Survival by Dose level/Cohort/Tumor type/ or Other Clinical Relevant Variable.

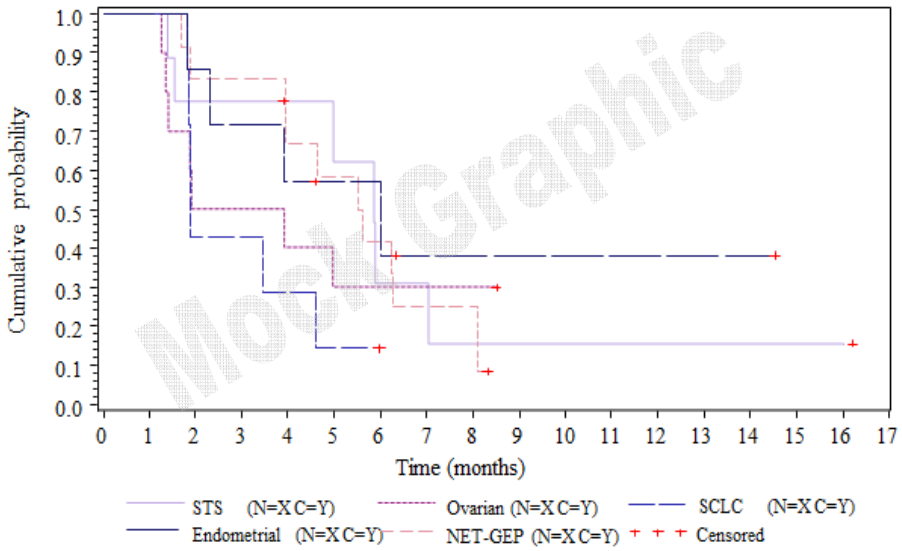


Figure 13.1 10 Overall Survival.

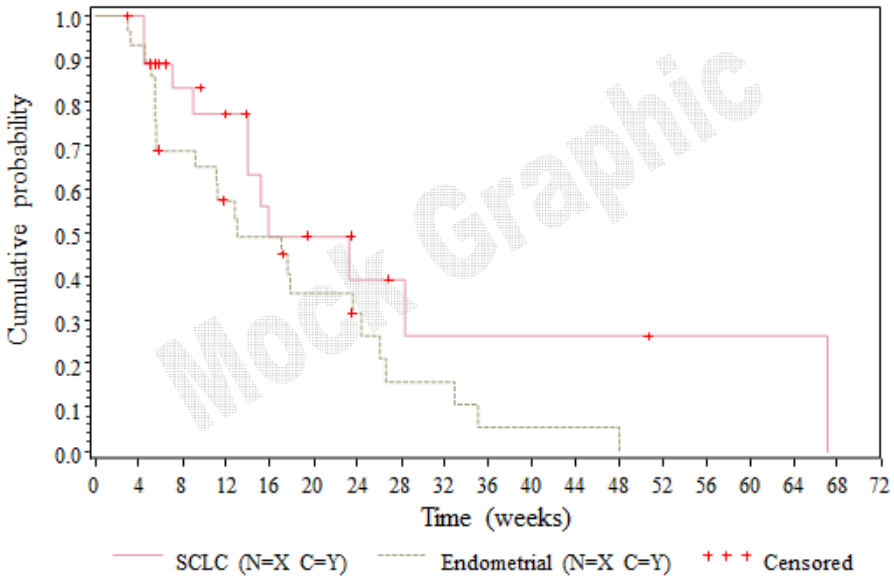
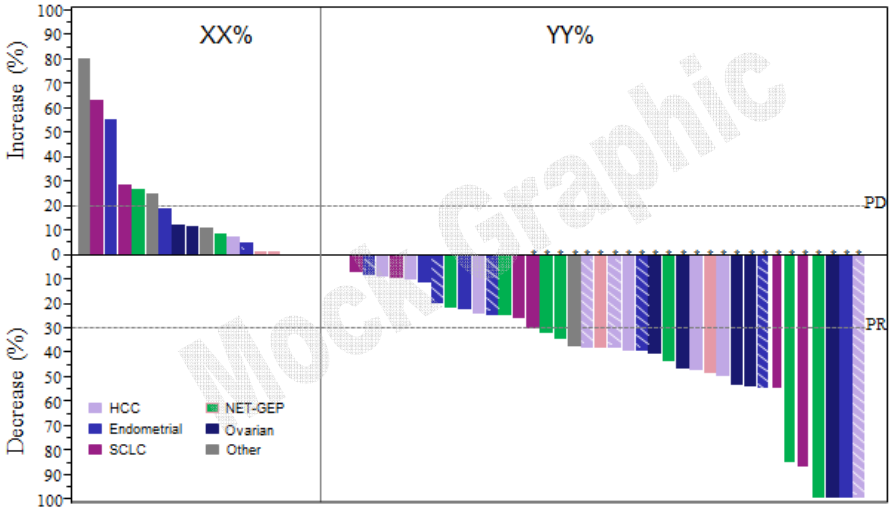
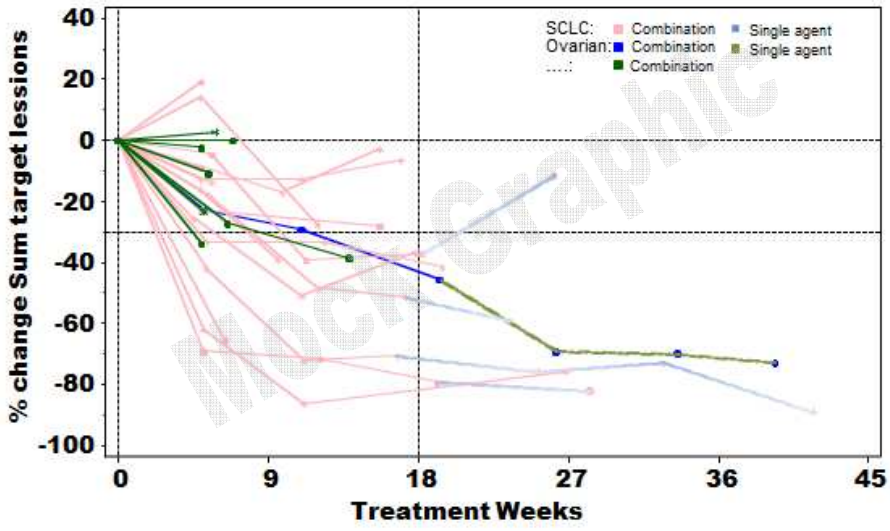


Figure 13.1 11 Waterfall Graphs.



Waterfall graphs will be displayed in measurable lesions by RECIST v.1.1Also graphs for each tumor type/cohort and for responders.

Figure 13.1 12 Spider plot: Evolution of RECIST v.1.1 Assessments.



Spider plot will be displayed individually for each tumor type/cohort / or Other clinical relevant variable, if required.

Figure 13.1 13 Best RECIST v.1.1 Efficacy Assessment in Evaluable pts per Tumour Type.

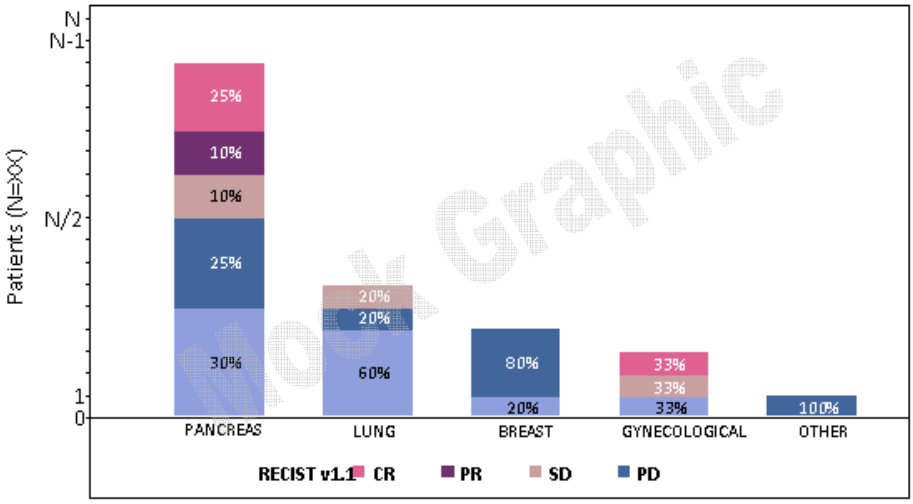


Figure 13.1 14 Treatment Exposure and Reasons for Discontinuation per Tumour Type.

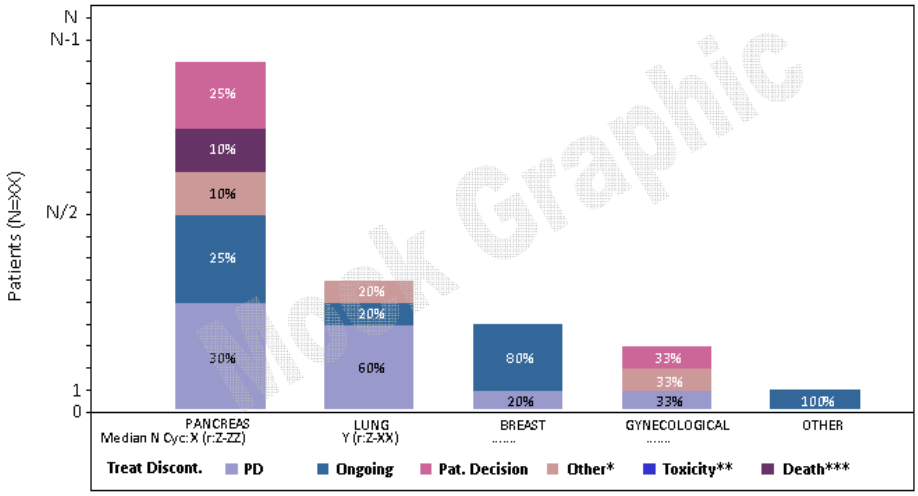


Figure 13.1 15 Best RECIST v.1.1 Response According to Line of Treatment.

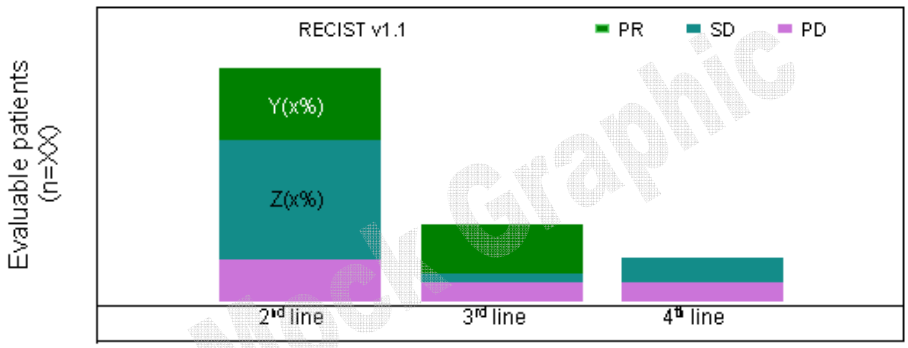


Figure 13.1 16 Last Prior Treatment Response (TTP) vs PM001183/Combo response (TTP).

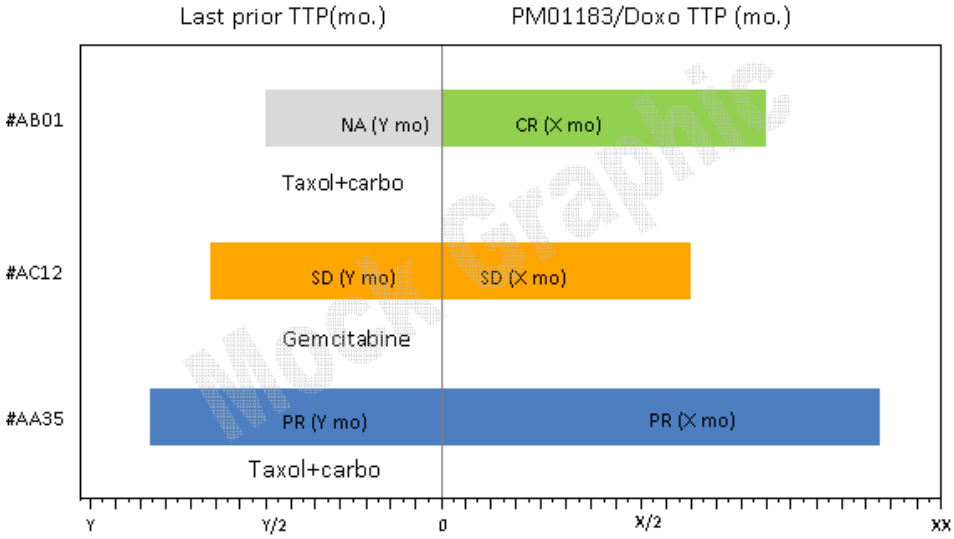


Figure 13.1 17 Number of Cycles, Reason for Treatment Discontinuation for Patients with Response or Clinical Benefit.

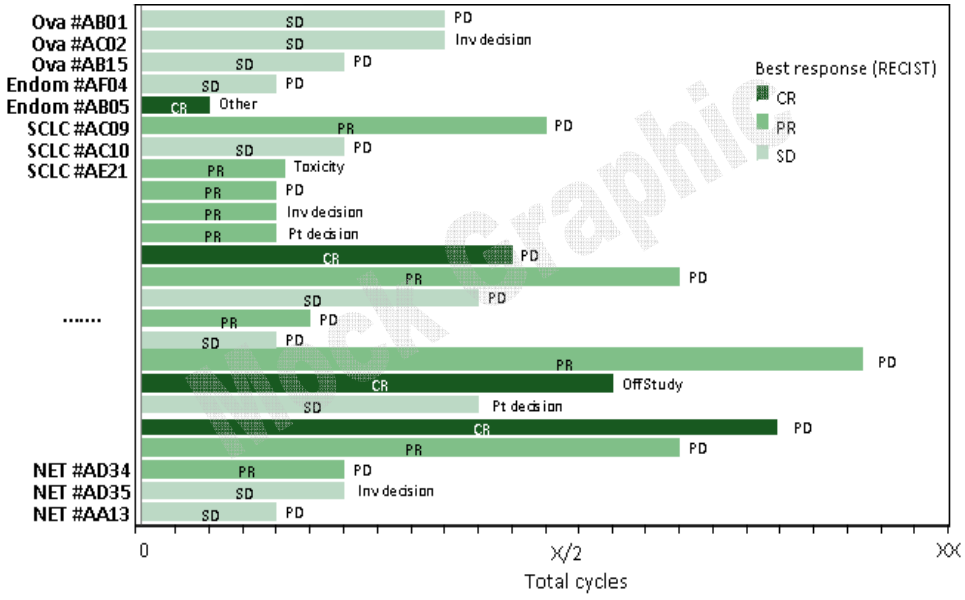


Figure 13.1 18 Efficacy and Individual TTP in Selected Patients by BSA/CTFI and Treatment Discontinuation.

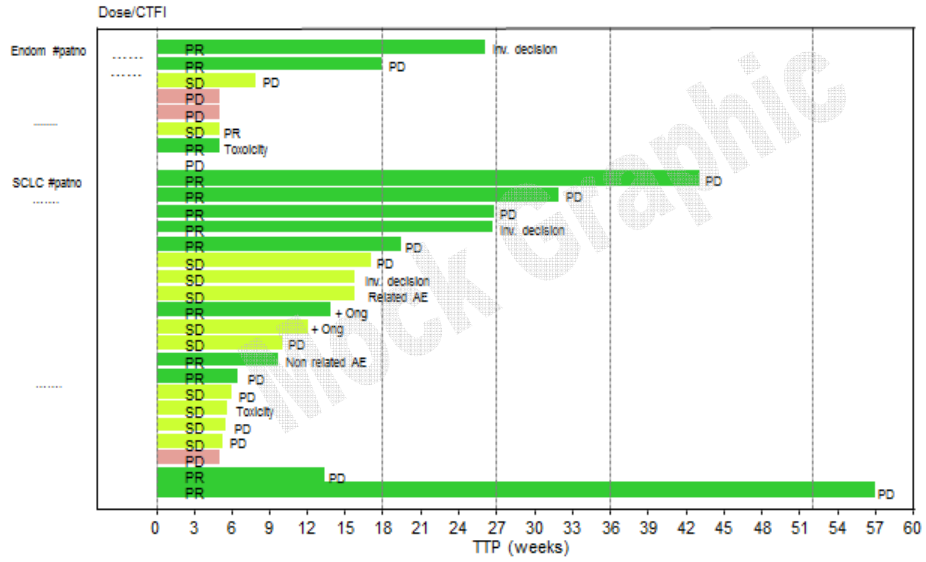
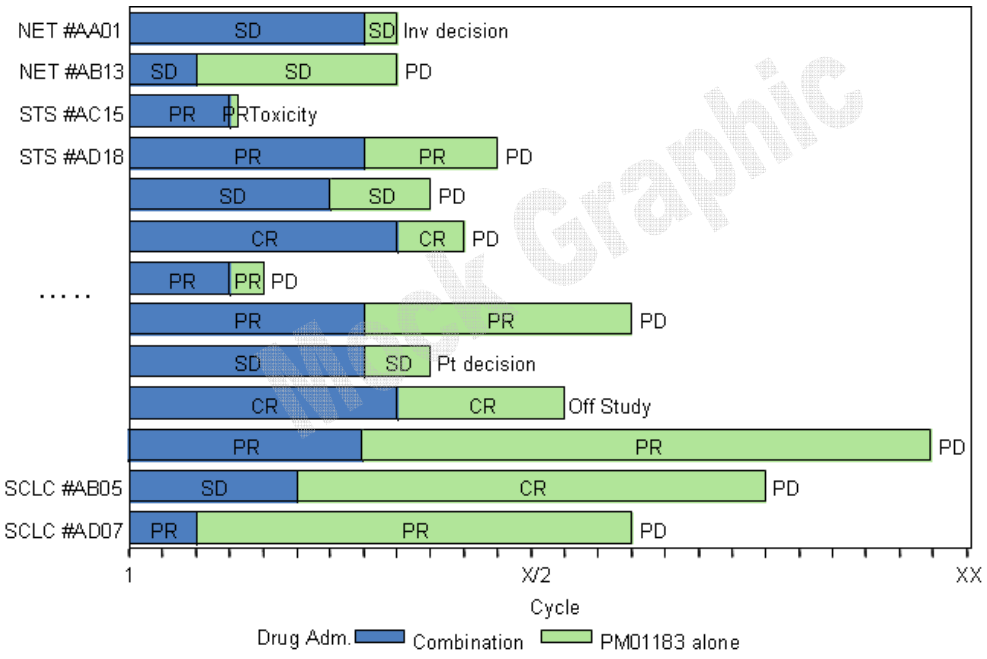


Figure 13.1 19 Number of Cycles, Reason for Treatment Discontinuation and Response in Patients who Received PM001183 Alone.



14. Database Listings.

Listing 14.1 Patient Registration.
Listing 14.2 Demography.
Listing 14.3 Patient Disposition.
Listing 14.4 Protocol Deviations.
Listing 14.5 Patient Populations.
Listing 14.6 Selection Criteria.
Listing 14.7 Medical History.
Listing 14.8 Cancer History.
Listing 14.9 Current Disease.
Listing 14.10 Prior Surgery.
Listing 14.11 Prior Radiotherapy.
Listing 14.12 Prior Anticancer Therapy.
Listing 14.13 Signs and Symptoms.
Listing 14.14 Tumor Assessment (Target Lesions).
Listing 14.15 Tumor Assessment (Non - Target Lesions).
Listing 14.16 Tumor Assessment (New Lesions).
Listing 14.17 Radiological Response (RECIST v.1.1).
Listing 14.18 Clinical Evaluation Response.
Listing 14.19 Tumor Marker Evaluation Response.
Listing 14.20 Overall Cycle Response.
Listing 14.21 Treatment Exposure.
Listing 14.22 Hematology Laboratory Results.
Listing 14.23 Clinical Chemistry and Coagulation Laboratory Results.
Listing 14.24 Physical Examination and Performance Status (PS).
Listing 14.25 Vital Signs.
Listing 14.26 ECG Results.
Listing 14.27 Left Ventricular Ejection Fraction (LVEF) Results.
Listing 14.28 Other Tests and Procedures Results.
Listing 14.29 Adverse Events.
Listing 14.30 Concomitant Therapy.

Listing 14.31 End of Treatment.
Listing 14.32 Follow-up.
Listing 14.33 Follow-up: Antitumor therapy.
Listing 14.34 Death Report.
Listing 14.35 Best Study Overall Response.
Listing 14.36 Off Study.
Listing 14.37 Signature Report.

15. SAP Version History.

15.1.SAP Version History v1.

After the first version of the SAP was approved by the responsible physician, the medical writer and the biostatistics manager, a new protocol "substantial amendment No. 1" was included; therefore the SAP has been updated (highlighted in ***italic bold***) in accordance with the new version (version 2) of the protocol as follows:

- Changes in Study design/dose escalation and G-CSF/CSF primary prophylaxis and MTD definition has been rephrased in order to maintain consistency between DLT and MTD definitions.
- Changes in Inclusion/exclusion criteria have been done: a maximum age limit of 75 years old has been set and the inclusion of patients with mesothelioma has been allowed.
- Some minor changes and corrections have been done in the text and the mock shells to allow a clear and unambiguous communication of the science and statistics of the trial.

Summary of proposed changes from section 2.1 to 8:

Section 2.1 Primary Objective:

Original text:

- To determine the maximum tolerated dose (MTD) and the recommended dose (RD) of PM01183 in combination with doxorubicin in patients with selected advanced solid tumors.

Change to:

- ***To determine the MTD and the RD of PM01183 in combination with doxorubicin with primary prophylaxis with G-CSF in patients with selected advanced solid tumors (if DLTs of the combination without G-CSF prophylaxis are exclusively related to neutropenia).***

Section 3. Study design:

Original text:

….. All evaluable patients within a dose level will be followed for at least one cycle (i.e., three weeks) before dose escalation may proceed. Dose escalation will be terminated once the MTD or the last dose level (DL4) is reached, whichever occurs first.

Change to:

… All evaluable patients within a dose level will be followed for at least one cycle (i.e., three weeks) before dose escalation may proceed. ***Dose escalation will be terminated once the MTD or the last dose level (DL4) is reached, whichever occurs first, except if all DLTs***

occurring at a given dose level are related to neutropenia (e.g., febrile neutropenia, grade 4 neutropenia lasting more than 7 days or neutropenic sepsis) in which case dose escalation may be resumed, starting at the lowest dose level where exclusively neutropenia-related DLTs have occurred, and will follow the same original schedule but with compulsory primary G-CSF prophylaxis.

Section 5.2.1.1 Determination of MTD and RD

Original text:

…….If >1 evaluable patient during dose escalation at a given DL experience a DLT during Cycle 1, that DL will be considered the MTD and dose escalation will be terminated. The DL immediately below the MTD, or DL4 if the MTD is not yet defined during dose escalation before the last DL (i.e., DL4) is reached, will be expanded up to a minimum of nine evaluable patients. If less than three among the first nine evaluable patients treated within the expansion cohort experience a DLT during Cycle 1, this DL will be the RD.

Change to:

……..***If >1 evaluable patient during dose escalation at a given DL experience a DLT during the first cycle, that level will be considered the MTD and dose escalation will be terminated except if all DLTs occurring at a given dose level are related to neutropenia (e.g., febrile neutropenia, grade 4 neutropenia lasting more than 7 days or neutropenic sepsis) in which case dose escalation may be resumed, starting at the lowest dose level where exclusively neutropenia-related DLTs have occurred, and will follow the same original schedule but with compulsory primary G-CSF prophylaxis.***

Section 8.1 Stratification and Covariate Analysis:

Original text:

No stratification by prognostic factors or tumor types is planned. If a disease is adequately represented, response rates might be analyzed descriptively, and time-related parameters might be analyzed according to the Kaplan-Meier method. Efficacy parameters could also be subjected to further analysis (if appropriate), considering correlation with factors of probable prognostic value such as subject PS at entry, disease burden, prior therapies, other disease-specific known prognostic factor, or population characteristics, etc. using the appropriate test (Fisher's exact test, Spearman test, etc.).

Change to:

No stratification by prognostic factors or tumor types is planned. If a disease is adequately represented, response rates might be analyzed descriptively, and time-related parameters might be analyzed according to the Kaplan-Meier method. Efficacy parameters could also be subjected to further analysis ***(if appropriate)***, considering correlation with factors of ***known*** prognostic value such as subject PS at entry, disease burden, prior therapies, other disease-specific known prognostic factor, ***or population characteristics***, etc. using the appropriate test (Fisher's exact test, Spearman test, etc.).

Section 8.3 Subgroups Analysis:

Original text:

If any cancer groups of patients are sufficiently represented, a separate analysis by tumor type and evaluation criteria (RECIST, GCIC) will be performed.

If there is a representative number of patients who receive a maximal total cumulative dose of 450 mg/m^2 of doxorubicine and continue treatment with PM01183 alone at the recommended dose as a single agent, a separate analysis will be performed and tables, listings and graphic representations for this population will be provided when applicable.

Exploratory safety and efficacy analyses considering the three groups (below RD, RD and over RD) will be performed if appropriate.

Change to:

If any cancer subtype ***or any other baseline characteristics of patients are adequately represented, a separate analysis by tumor type and efficacy as per RECIST v1.1, will be performed***.

If there is a representative number of patients who receive a maximal total cumulative dose of 450 mg/m^2 of doxorubicin and continue treatment with PM01183 alone, a separate analysis will be performed and tables, listings and graphic representations for this population will be provided when applicable.

Summary of changes in Section 9. Tables, Listings and Graphs:

The following new paragraphs have been added,

Original text:

Statistical outputs, whenever is applicable, will be displayed according to assignment to prophylactic G-CSF factors use or not as well as per Dose level. Totals numbers will be displayed independently, if applicable. Summary tables will have source data footnotes that will refer to the relevant listings. The tables' layout may change to adequately accommodate cohort size as appropriate.

Patients included and treated over 75 yrs old will be excluded from all tables, listings and graphs in this SAP. Detailed narratives of these patients will be shown in the CSR.

If the number of categories or items would not yield appropriate tabular or graphic representations, detailed listings will be shown instead.

Change to:

Statistical outputs, whenever is applicable, will be displayed according to assignment to prophylactic **CSF** factors use or not as well as per Dose level**/Dose group or by cancer type or primary site if adequate number of patients is represented.** Totals numbers will be displayed independently, if applicable. Summary tables will have source data footnotes that will refer to the relevant listings. The tables' layout may change to adequately accommodate cohort size as appropriate.

If the number of categories or items would not yield appropriate tabular or graphic representations, detailed listings will be shown instead.

Patients included and treated over 75 **years** old will be excluded from all tables, listings and graphs in this SAP. Detailed narratives of these patients will be shown in the clinical study report CSR.

Summary of changes in Section 10. Appendix I. Patients disposition:

New tables and variables have been included after clinical request and some minor changes and corrections have been done in the text and the mock shells to allow a clear and unambiguous communication of the science and statistics of the trial.

Section 10.1.1 Patients Treated, Elegible, and Evaluable:

In Table 10.1.1.4 Number of Patients Evaluable for the Analysis, a footnote has been added and categories have been reordered. Note:(*) Efficacy by RECIST v.1.1. A listing of patient non evaluable by RECIST v.1.1 will be provided.

Section 10.1.2 Treatment discontinuation:

Table 10.1.2.1 Treatment Discontinuation by Dose Level adds two more tables and the possibility of include other reasons for treatment discontinuation not included in the CRF categories and added, after clinical review. Notes:(*) Reasons for treatment discontinuation for patients who discontinued while the combination or PM alone will be provided, if required. (**) If applicable, a supporting listing 10.1.2.1.a will be provided and reasons for treatment discontinuation may suffer re-categorization after clinical review. A new table have been added Table 10.1.2.4 Listing of patients with Discontinuation after cycle 9. All tables have been renumbered.

Table 10.1.2.1 Treatment Discontinuation by Dose Level adds the following Note:(*) If applicable, a supporting listing 10.1.2.1.a will be provided and reasons for treatment discontinuation may suffer re-categorization after clinical review.

Table 10.1.2.4 Listing of patients with Discontinuation with PM01183 alone has been included.

Section 10.2.1 Patients Characteristics at Baseline:
Table 10.2.1.1 Age at Entry by Dose Level: categories of age are between 18 and 75 years (both inclusive).

Tables from Previous Section **10.2.9 Physical Examination, Vital Sings, Electrocardiogram and Other Tests** have been moved to **Section 10.2.1 Patient Characteristics at Baseline**.
Table 10.2.1.8 has been renamed to Demographic Parameters by Dose level and added the footnote Note: (*) Height (cm) and BSA (DuBois formula).

Section 10.2.2 Cancer History:

New tables have been added. Table 10.2.2.3 TTP Last Prior Therapy.

Table 10.2.2.4 Stage at Diagnosis by Dose Level and Table 10.2.2.5 Tumor Type by Dose level have been deleted by clinical indication and 10.2.2.4 Tumor type by dose level include the following footnote: Note: (*) CRF categories will be shown and a supportive table 10.2.2.6.a will be provided for subcategories (e.g. sarcomas).

New variables have been added to Table 10.2.2.7. See footnote as last TTP prior therapy and best response to prior therapy.

Section 10.2.3 Sites involved:

All tables included in this section will be shown by dose level and/or tumor type, if required.

Two new tables have been included: Table 10.2.3.5 Bulky Disease and Dose Level. Table 10.2.3.6 Median Sum of Diameter of Target Lesions (mm).

Section 10.2.4 Previous Treatment Summary.

Table 10.2.4.2 Previous systemic therapy type by dose level/tumor type has been added.

Section 10.2.7 Previous Anticancer Medical History.

All tables of this section have now the possibility of being displayed by Tumor type, if required. In addition, tables from Tables 10.2.7.1 Agents of Previous Anticancer Therapy (ATC level 1&4) by Dose Level/Tumor Type to Table 10.2.7.3 Summary Statistics. No of Lines of Prior Anticancer Therapy by Dose Level/Tumor Type will show only therapies with chemotherapy containing and excluding hormonal therapy.

A new table has been added: Table 10.2.7.5 No of Agents of Last Prior Anticancer Therapy before PM01183 treatment by Dose Level/Tumor type.

Section 10.2.8 to 10.2.11: All statistical outputs, whenever applicable, will be displayed according to assignment to prophylactic G-CSF factors use or not as well as per Dose level. Totals numbers will be displayed independently, if applicable.

Section 10.2.12 Signs and Symptoms at Baseline:
Table 10.2.12.2 has been renamed to Listing of Adverse events Grade > 1.

Section 10.2.13 Concomitant and Prophylactic Medication Starting Pre-Study:

New tables have been added: Table 10.2.13.4 No of Patients with Opioids Treatment at Baseline by Dose Level, Table 10.2.13.5 Median Number of No of Opioids at Baseline per patient by Dose Level. Table 10.2.13.6 No of patients with Steroids Treatment at Baseline by Dose Level. Table 10.2.13.7 Known CYP 3A4 Inducers/Inhibitors/Substrates Concomitant Therapies at BL and Listing 10.2.13.8 Known CYP 3A4 Inducers/ Inhibitors/Substrates) Concomitant Therapies at BL.

In addition, tables 10.2.13.4 and 10.3.5 have been renumbered to 10.2.13.7 and 10.2.13.8 and the following footnote has been added: Note: (*) Also the possibility of display one table for each category Inducers/Inhibitors or substrates. Some medication will be excluded by clinical request (e.g: Dexamethasone)

Summary of changes in Section 11. Appendix II Safety Evaluation:

All statistical outputs in this section, whenever applicable, will be displayed according to the discontinuation of the combination treatment. Treatment exposure, delays, omissions and reductions will be shown before and after discontinuation. Dose level may suffer categorization (e.g: RD≤ or RD), if required.

Each specific table and listing will have a comprehensive header identifying the group/cohort of treatment and/or the specific study drug, whenever necessary.

New tables and variables have been included after clinical request and some minor changes and corrections have been done in the text and the mock shells to allow a clear and unambiguous communication of the science and statistics of the trial.

Section 11.1.1 Cumulative Dose, Dose Intensity and Relative Dose Intensity:

Table 11.1.2.12 Reasons for Doxorubicin Dose reduction by Dose Level has been deleted because any dose reductions of doxorubicin will be a deviation and will be described in the Protocol Deviation section.

Tables 11.1.2.14 and 11.1.3.6 Listing of Cycles Delays/Reductions due to Nausea/Vomiting have been renamed to Listing of Cycles Delays due to Non-Hematological Adverse Events.

Section 11.2.1 Dose-Limiting Toxicities:

A new table has been added: Table 11.2.1.1 Summary of patients with DLT by Dose Level.

Section 11.3.1 Display of Adverse Events:

All statistical outputs, whenever applicable, will be displayed according to assignment to prophylactic CSF use or not as well as per Dose level. Total numbers will be displayed independently, if applicable.

Section 11.4.2 Serious Adverse Events:

The following text has been added. All serious adverse events will be listed only for the purpose of reconciliation with the database of pharmacovigilance. The listings provided by the Product Safety department will be used for the clinical study report.

Section 11.5.1 Hematological abnormalities:

New tables have been added: Table 11.5.1.6 Shift of Hematological Abnormalities. Baseline Grade vs. Worst Grade on First Cycle. and Table 11.5.1.8 Listing of patients with Biochemical Abnormalities >G2 and Experience Grade Increase (wpp) from Baseline and 11.5.1.9 Summary of Characteristics of Wpp Hematological Abnormalities G3-4.

Section 11.5.2 Biochemical Abnormalities:

New tables have been included: Table 11.5.2.7 Listing of patients with Biochemical Abnormalities >G2 and Experience Grade Increase (wpp) from Baseline and 11.5.2.8 Summary of Characteristics of Wpp Biochemical Abnormalities G3-4.

Section 11.5.3 MetabolicAbnormalities:

New tables have been added in this section: Table 11.5.3.5 Shift of Metabolic Abnormalities. Baseline Grade vs Worst Grade on First Cycle. Table 11.5.3.6 Shift of Metabolic Abnormalities. Baseline Grade vs Worst Grade on Treatment. Table 11.5.3.7 Listing of Patients with Metabolic Abnormalities >G2 and Experience Grade Increase (wpp) from Baseline. Table 11.5.3.8 Supportive Listing: Patients with Grade ≥ 3 Metabolic Abnormalities.

Section 11.5.4 Coagulation Abnormalities:

New tables have been added in this section: Table 11.5.4.4 Shift of Coagulation Abnormalities. Baseline Grade vs Worst Grade on First Cycle. Table 11.5.4.5 Shift of Coagulation Abnormalities. Baseline Grade vs Worst Grade on Treatment. Table 11.5.4.6 Listing of Patients with Metabolic Abnormalities >G2 and Experience Grade Increase (wpp) from Baseline.

Section 11.6.2 Electrocardiogram.

Tables of this section have been renumbered and new tables added. Table 11.6.2.5 Shift of QTc. Baseline Grade vs. Worst Grade on Treatment. Table 11.6.2.7 Listing of Patients with Grade ≥ 2 QTc Interval Prolonged.

Section 11.6.3 LVEF.

Tables of this section have been renumbered and new tables added. Table 11.6.3.3 Shift of LVEF. Baseline Grade vs. Worst Grade on Treatment. Table 11.6.3.4 Listing of Patients with Grade ≥ 2 LVEF Decrease.

Section 11.6.4 Pregnancy Test and Adequate Contraception.

Table 11.6.4.1 Patients with Positive Pregnancy Test and Not Adequate Contraception Method has been deleted. If any patients are positive for the pregnancy test or are not using an adequate contraception method, they will be reported in the Protocol Deviation section.

Section 11.7 Concomitant and Prophylactic Medication:

The titles of Tables 11.7.1.2 and 11.7.1.3 have been modified to EPO/RBC and Platelets transfusions/CSF. Also, the following footonote has been added: Note: (*) Non-prophylactic CSF use.

New tables have been added: Table 11.7.1.5 Known CYP 3A4 Inducers/Inhibitors/Substrates Concomitant Therapies During Study and Table 11.7.1.6. are renamed and depending on the number of observations will be shown separately and include the footnote Note: (*) Also the possibility of display one table for each category Inducers/Inhibitors or substrates. Some medication will be excluded by clinical request (e.g: Dexamethasone)

New tables have been included in this section, and therefore all tables have been renumbered. Table 11.1.7.5 No of Patients with Opioids Treatment During Treatment by Dose Level, Table 11.1.7.6 Median Number of No of Opioids During Treatment per Patient by Dose Level. Table 11.1.7.7 No of Patients with Steroids Treatment During Treatment by Dose Level.

Section 11.7.1 Concomitant and Prophylactic Medication During Study.

This subsection includes new Table 11.7.1.5 Known CYP 3A4 Inducers/Inhibitors/Substrates Concomitant Therapies During Study and Table 11.7.1.6 Listing of CYP 3A4 Inducers or Inhibitors (or Substrates) Concomitant Therapies During Study.

Summary of changes in Section 12. Appendix III Efficacy Evaluation:

The Clinical Benefit criterion has been changed from when response is CR, PR or SD≥3 months to when response is CR, PR or SD≥4 months. In addition, the possibility of calculating time-to-event parameters PFS and DR at 12 and/or 24 months has been added.

Some other minor changes and corrections have been done in the text and the mock shells to allow a clear and unambiguous communication of the science and statistics of the trial.

Summary of changes in Section Figures 13.

A new Figure 13.6 Boxplot QTcF worst value by cycle has been included.

Section 15 SAP Version History has been included in order to be consistent with the Protocol amendment No. 1 of this study and due to the inclusion of new TLGs for the cancer subgroups that could be adequately represented in accordance with PharmaMar's SOPs.

15.2.SAP Version History v2.

Some other changes were implemented in a new version of the SAP (v.3) for adequate representation of cancer subgroups (highlighted in ***italic bold***) and a summary of changes are shown at the end of this section.

Summary of changes implemented in SAP (v.3).

- All TLGs detailed in Section 9 will be represented per Dose level or Dose group (RD<, etc..) and/or also per cancer type or primary site if an adequate number of patients is represented.
- The granulocyte colony-stimulating factor may be abbreviated indistinctively as CSF or as G-CSF in the tables and text detailed in Section 9.

- Some minor changes and corrections have been done in the text and the mock shells in order to provide a clear and unambiguous communication of the science and statistics of the trial.
- In addition to these changes, minor typographic corrections have been done throughout the document.

Summary of proposed changes by section:

Section 10.2.2 Cancer History

Table 10.2.2.5 has been renamed to 10.2.2.5 Summary of Cancer History per Patient ***and Tumor Type.*** A footnote has been added to this listing to include the possibility of displaying any specific characteristics of previous Patient History for each Tumor type. If required, tabulations for specific categories will be shown as Supportive tables.

Section 10.2.7 Previous Systemic Therapies

New tables have been included: ***Table 10.2.7.7 Agents of Prior Anticancer Therapy by Tumor Type/Dose Level*** and ***Table 10.2.7.9 Platinum-Free Survival by Tumor Type/Dose level***

Section 11.5 Clinical Laboratory Evaluation

New tables have been included: ***Table 11.5.1.10 Anemia wpp/wpc and Use of EPO per Dose Level, 11.5.1.11 Patients with Anemia Grade 3/4 in Cycle >1 and Use of EPO. , Table 11.5.1.14 Thrombocytopenia wpp/wpc and Use of Transfusions per Dose Level in Cycle>1., Table 11.5.1.15 Patients with Thrombocytopenia Grade 3/4 in Cycle >1 and Use of Transfusions; Table 11.5.18 Neuthropenia wpp/wpc and Use of Prophylactic CSF per Dose Level in Cycle>1, 11.5.13.19 Patients with Neutrophenia Grade 3/4 in Cycle >1 and Use of Prophylactic CSF.***

Section 11.7 Concomitant and Prophylactic Medication

A new table has been included: ***Table 11.7.1.5 Patients with Nausea and /or Vomiting G3/4 and Use of Antiemetics in Cycle >1***.

In Figure 13.1, the possibility of drawing pattern for Neutropenia for patients with prophylactic CSF vs. No CSF has been added.

New Figures 13.10 and 13.15 have been included for graphic representation of the subgroup populations and specific characteristics.

15.3.SAP Version History v3.

Two substantial protocol amendments “No. 2 and No. 3” and one “non-substancial protocol amendment “No.1” have been implemented after the approval of SAP v3; therefore, the SAP has been updated (highlighted in ***italic bold***) in accordance with the current version of the protocol (version 4.0) as follows:

- Dose escalation began at PM01183 3.0 mg FD and DOX 50.0 mg/m2 q3wk. Patients received DOX capped at 2.0 m² of BSA up to a maximum cumulative dose (MCD) of 450 mg/m². After DOX withdrawal, PM01183 administration could continue alone at its full single-agent RD (7.0 mg FD or 4.0 mg/m² on D1 q3wk). A first amendment to the protocol set a maximum age of 75 years for patients enrolled in the study and allowed primary G-CSF prophylaxis during dose escalation to explore the potential of this approach to reach a higher RD. However, DLTs occurred at the same dose level regardless of primary G-CSF prophylaxis, and they included grade 3/4 FN, grade 4 thrombocytopenia and grade 4 septic shock. Based on these results, the MTD was defined at PM01183 5.0 mg FD and DOX 50.0 mg/m² regardless of G-CSF support. The immediately lower DL (PM01183 4.0 mg and DOX 50.0 mg/m²) was then expanded, and DLTs were found in none of three patients with G-CSF and in one of ten (10%) patients without G-CSF (FN). Thus, PM01183 4.0 mg FD and DOX 50.0 mg/m² was defined as the RD for this combination, and was not further expanded with primary G-CSF prophylaxis.

  Objective antitumor activity was found in more than one third of patients across most tumor types at all DLs explored. It was particularly promising in small cell lung cancer (SCLC) patients treated as second-line after chemotherapy failure and in endometrial cancer patients. Hence, the RD was further expanded to confirm the preliminary antitumor activity observed in these settings. All DLTs found after RD expansion were myelosuppression-related. Three of 14 patients with endometrial cancer had DLTs. Less than one third of second-line SCLC patients had DLTs, but more than 20% of them had FN, thus suggesting further dose adjustment was also required in this subsetting.

  Following these findings, the initial RD underwent a 20% reduction in the DOX dose to 40 mg/m². In addition, the PM01183 dose was adapted to a BSA-based dose of 2.0 mg/m², after a logistic regression analysis of pooled data from phase II clinical trials with single-agent PM01183 in several solid tumors had suggested that patients with the lowest BSA values could have a greater risk of developing grade 3/4 thrombocytopenia.

- In the new cohort B, exploratory assessment for progression-free survival (PFS) and overall survival (OS) will be performed and patients will be followed for survival for up to 18 months after the first study dose.

- All TLGs described by DL will be also done by most adequate dose grouping/cohort/tumor type or other clinical relevant variable where appropriate. The tables' layout and headings may change to adequately accommodate cohort/group as appropriate.

- Some minor changes (e.g. clarify dose level grouping to dose level/cohort/Tumor type or other clinical relevant variable) and corrections in the text and in the mock shells have been done in order to achieve a clear, unambiguous communication of the science and statistics of the trial.

Summary of changes implemented in SAP (v.4).

Section 2.1 Primary Objective:

Original text:

- To determine the maximum tolerated dose (MTD) and the recommended dose (RD) of PM01183 in combination with doxorubicin with primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) in patients with selected advanced solid tumors [if dose-limiting toxicities (DLTs) of the combination without G-CSF prophylaxis are exclusively related to neutropenia]**.**

Changes to:

- ***To determine the maximum tolerated dose (MTD) and the recommended dose (RD) of PM01183 in combination with doxorubicin in patients with selected advanced solid tumors.***

Section 2.1 Secondary Objectives:

Original text:

- To characterize the safety profile and feasibility of this combination in patients with selected advanced solid tumors.
- To characterize the pharmacokinetics (PK) of this combination and to detect major drug-drug PK interactions.
- To obtain preliminary information on the clinical antitumor activity of this combination in non-heavily pretreated selected solid tumor patients.
- To evaluate the pharmacogenomics (PGx) in tumor samples of patients exposed to PM01183 and doxorubicin at the RD in order to assess potential markers of response and/or resistance.

Changes to:

- ***To determine the MTD and the RD of PM01183 in combination with doxorubicin with primary prophylaxis with granulocyte-colony stimulating factor (G-CSF) in patients with selected advanced solid tumors [if dose-limiting toxicities (DLTs) of the combination without G-CSF prophylaxis are exclusively related to neutropenia].***
- To characterize the safety profile and feasibility of this combination in patients with selected advanced solid tumors.
- To characterize the pharmacokinetics (PK) of this combination and to detect major drug-drug PK interactions.
- To obtain preliminary information on the clinical antitumor activity of this combination in non-heavily pretreated selected solid tumor patients.
- ***Based on promising findings, to explore the feasibility, safety and efficacy of a potential improvable dose of this combination in selected tumor types [i.e. small cell lung cancer (SCLC) and endometrial cancer).***

- To evaluate the pharmacogenomics (PGx) in tumor samples of patients exposed to PM01183 and doxorubicin at the RD in order to assess potential markers of response and/or resistance.

Section 3 Study design:

Original text:

……

Cohorts of three to six patients will be included at each dose level (DL). If no DLT occurs in more than one patient within each cohort, escalation will proceed to the following dose level. If one of the first three evaluable patients experiences a DLT, the dose level should be expanded up to six patients. The MTD will be the lowest dose level explored during the dose escalation at which more than one evaluable patient experience a DLT in Cycle 1. All evaluable patients within a dose level will be followed for at least one cycle (i.e., three weeks) before dose escalation may proceed. Dose escalation will be terminated once the MTD or the last dose level (DL4) is reached, whichever occurs first, except if all DLTs occurring at a given dose level are related to neutropenia (e.g., febrile neutropenia, grade 4 neutropenia lasting more than 7 days or neutropenic sepsis) in which case dose escalation may be resumed, starting at the lowest dose level where exclusively neutropenia-related DLTs have occurred, and will follow the same original schedule but with compulsory primary G-CSF prophylaxis.

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

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

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

Patients will receive PM01183 and doxorubicin until progression, unacceptable toxicity, consent withdrawal or while it is considered to be in their best interest. More specifically, doxorubicin will be administered in the absence of disease progression or unacceptable toxicity until a maximal total cumulative dose of 450 mg/m² is reached; once this dose has been reached, the patients may continue treatment with PM01183 alone at the established single-agent RD, 7.0 mg FD q3wk.

Tumor assessments will be done every six weeks while on treatment. After treatment discontinuation, patients will be followed every four weeks until resolution or stabilization of all toxicities, if any. Patients discontinuing treatment without progression will be followed every two months until disease progression, other antitumor therapy, death or the date of study termination, whichever occurs first (see study protocol, section 5.9).

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

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

Changes to:

…..

Cohorts of three to six patients will be included at each dose level (DL). If no DLT occurs in more than one patient within each cohort, escalation will proceed to the following dose level.

The MTD will be the lowest dose level explored during the dose escalation at which more than one evaluable patient experience a DLT in Cycle 1. All evaluable patients within a dose level will be followed for at least one cycle (i.e., three weeks) before dose escalation may proceed. Dose escalation will be terminated once the MTD or the last dose level (DL4) is reached, whichever occurs first, except if all DLTs occurring at a given dose level are related to neutropenia (e.g., febrile neutropenia, grade 4 neutropenia lasting more than seven days or neutropenic sepsis) in which case dose escalation may be resumed, starting at the lowest dose level where exclusively neutropenia-related DLTs have occurred, and will follow the same original schedule but with compulsory primary G-CSF prophylaxis. ***An expansion cohort to complete a minimum of nine evaluable patients will be recruited at the immediate lower dose level, or at the last dose level (DL4) if the MTD is not defined yet. This level will be confirmed as the RD if less than one third of the first nine evaluable patients experience DLT during Cycle 1.***

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

In addition, a new cohort B of 20 evaluable patients with small cell lung cancer (SCLC) who failed treatment after first-line standard cytotoxic-containing therapy and at least nine evaluable patients with endometrial cancer will be included to further define the efficacy, safety and feasibility of a doxorubicin dose adaptation (doxorubicin 40 mg/m^2 and PM01183 2.0 mg/m^2). Patients in this cohort who have received ten cycles of the doxorubicin/PM01183 combination or have to discontinue doxorubicin due to a cardiac AE may continue receiving treatment with single-agent PM01183 at 4.0 mg/m^2 q3wk if patient benefit is perceived according to the Investigator. These patients will be followed every three months until death or the date of study termination, whichever occurs first.

Patients will be divided into two cohorts. Cohort A will consist of all patients included before the implementation of protocol amendment #3, and Cohort B will consist of all patients included after the implementation of protocol amendment #3.

……

Patients will receive PM01183 and doxorubicin until progression, unacceptable toxicity, consent withdrawal or while it is considered to be in their best interest. More specifically,

doxorubicin will be administered in the absence of disease progression or unacceptable toxicity ***before*** a maximal total cumulative dose of 450 mg/m^2 is reached. ***Thus, a maximum of ten cycles of the combination will be administered to patients with SCLC and endometrial cancer included in the new cohort B.*** Once this dose has been reached, the patients may continue treatment with PM01183 alone at the established single-agent RD, 7.0 mg FD q3wk ***and for patients included in the new cohort B they may continue treatment with PM01183 alone at 4.0 mg/m^2 q3wk.***

Tumor assessments will be done every six weeks while on treatment. After treatment discontinuation, patients will be followed every four weeks until resolution or stabilization of all toxicities, if any. Patients discontinuing treatment without progression will be followed every two months until disease progression, other antitumor therapy, death or the date of study termination, whichever occurs first (see study protocol, section 5.9).

In the new cohort B, patients with SCLC and endometrial cancer will be followed every three months until death or the date of study termination, whichever occurs first. Antitumor response will be assessed using the RECIST v.1.1 and/or serum tumor markers as appropriate (e.g., ovarian cancer markers).

No serum markers will be evaluated in patients with SCLC and endometrial cancer included in the new cohort B. Patients will be evaluated at scheduled visits on three study periods: Pre-treatment, Treatment and Follow-up (see study protocol, section 5.2).

In addition, a new cohort B of 20 evaluable patients with small cell lung cancer (SCLC) who failed treatment after first-line standard cytotoxic-containing therapy and at least nine evaluable patients with endometrial cancer will be included to further define the efficacy, safety and feasibility of a doxorubicin dose adaptation. These patients will be treated with doxorubicin at 40 mg/m^2 administered as an i.v. bolus/short infusion followed by PM01183 at 2.0 mg/m^2 as a 1-hour i.v. infusion on Day 1 q3wk. The administered doses of both PM01183 and doxorubicin will be capped at 2.0 m^2 of body surface area (BSA) for any patients exceeding this BSA value. Patients in this cohort who have received ten cycles of the doxorubicin/PM01183 combination or have to discontinue doxorubicin due to a cardiac AE may continue receiving treatment with single-agent PM01183 at 4.0 mg/m^2 q3wk if patient benefit is perceived according to the Investigator. These patients will be followed every three months until death or the date of study termination, whichever occurs first.

Section 4.1 Sample size:

Original text:

The number of patients may vary depending both on the tolerability to PM01183 combined with doxorubicin and the number of dose levels required to identify the MTD. Approximately between four and 27 evaluable patients will participate in this study.

Changes to:

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

Section 4.2 Dose escalation:

Original text:

The dose escalation schedule is summarized in the following table:

Dose escalation schedule

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

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

….

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

Changes to:

The dose escalation schedule is summarized in the following table:

Dose escalation schedule ***(cohort A).***

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

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

….

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

New cohort after implementation of protocol amendment #3 (Cohort B):

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

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

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

PM01183 doses will be rounded to the first decimal, if necessary. Doxorubicin doses will be rounded according to institutional guidelines/standard practices.

Section 5.1 Patient evaluability criteria:

Original text:

….

The "All Evaluable for Efficacy Patients" analysis set is defined as all evaluable patients measured according to the RECIST v.1.1 at least six weeks after treatment initiation in all patients with measurable disease, and/or by CA-125 levels if applicable, i.e. ovarian cancer with at least 2 x upper limit of normal (ULN) at baseline [according to the Gynecologic Cancer Intergroup (GCIG/Rustin) specific criteria].

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

All analyses will be performed as per protocol rather than on an intention-to-treat-basis. Any departure from the planned treatment according to the study schedule will be listed and documented in the clinical study report.

Changes to:

….

The "All Evaluable for Efficacy Patients" analysis set is defined as all evaluable patients measured according to the RECIST v.1.1 at least six weeks after treatment initiation in all patients with measurable disease, and/or by CA-125 levels if applicable, i.e. ovarian cancer with at least 2 x upper limit of normal (ULN) at baseline [according to the Gynecologic Cancer Intergroup (GCIG/Rustin) specific criteria]. ***No serum markers will be evaluated in patients with SCLC and endometrial cancer included in the new cohort B.***

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

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

All analyses will be performed as per protocol rather than on an intention-to-treat-basis. Any departure from the planned treatment according to the study schedule will be listed and documented in the clinical study report.

Section 5.2.1.1 Determination of MTD and RD:

Original text:

A minimum of three patients will be included at each dose level. If no patients experience a DLT during the first cycle, the dose will be escalated. If one of three patients experiences a DLT, three additional patients will be included at that level. If >1 evaluable patient during dose escalation at a given dose level experience a DLT during the first cycle, that level will be considered the MTD and dose escalation will be terminated except if all DLTs occurring at a given dose level are related to neutropenia (e.g., febrile neutropenia, grade 4 neutropenia lasting more than 7 days or neutropenic sepsis) in which case dose escalation may be resumed, starting at the lowest dose level where exclusively neutropenia-related DLTs have occurred, and will follow the same original schedule but with compulsory primary G-CSF prophylaxis

Determination of the maximum tolerated dose.

No. of patients evaluable* for DLT	**No. of patients with DLTs in Cycle 1**	**Action**
3	0	Escalate DL until DL4 is reached
	1	Add 3 patients
	>1	MTD
6	1	Escalate DL until DL4 is reached
	>1	MTD
DL, dose level; DLT, dose-limiting toxicities; MTD, maximum tolerated dose. * Patients not evaluable for DLT during dose optimization must be replaced.		

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

Changes to:

A minimum of three patients will be included at each dose level. If no patients experience a DLT during the first cycle, the dose will be escalated. If one of three patients experiences a DLT, three additional patients will be included at that level. If >1 evaluable patient during dose escalation at a given dose level experience a DLT during the first cycle, that level will be considered the MTD and dose escalation will be terminated except if all DLTs occurring at a given dose level are related to neutropenia (e.g., febrile neutropenia, grade 4 neutropenia lasting more than 7 days or neutropenic sepsis) in which case dose escalation may be resumed, starting at the lowest dose level where exclusively neutropenia-related DLTs have occurred, and will follow the same original schedule but with compulsory primary G-CSF prophylaxis ***The DL immediately below the MTD, or DL4 if the MTD is not reached during dose escalation and the last dose level (DL4) is reached, was to be initially expanded up to a minimum of nine evaluable patients. If less than three among the first nine evaluable patients treated within the expansion cohort experience a DLT during Cycle 1 this DL will be the RD.***

Further to the finding of encouraging antitumor activity in the first 43 evaluable patients (13 responses, including four complete responses, with five partial responses in eight patients with SCLC, and one complete and one partial response in three patients with

endometrial cancer), expansion of the cohort treated at the RD has been increased to include approximately 30 additional patients, for a total of around 39 patients.

Determination of the maximum tolerated dose.

No. of patients evaluable* for DLT	**No. of patients with DLTs in Cycle 1**	**Action**
3	0	Escalate DL until DL4 is reached
	1	Add 3 patients
	>1	MTD
6	1	Escalate DL until DL4 is reached
	>1	MTD
DL, dose level; DLT, dose-limiting toxicities; MTD, maximum tolerated dose. * Patients not evaluable for DLT during dose optimization must be replaced. ***** For replacement of patients and replacement of patients after implementation of Amendment #3 (see Protocol section 5.3).***		

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

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

Section 5.2.2.2 Efficacy:

Original text:

Although it is not the main objective of this study, antitumor activity will be measured according to the RECIST v.1.1 at least six weeks after treatment initiation in all patients with measurable disease, or by evaluation of tumor markers if applicable (e.g., ovarian cancer). Patients included at the RD in the expansion cohort must be evaluable per RECIST v.1.1 or by evaluation of tumor markers (see Section 7.4 for efficacy evaluation).

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

…..

Changes to:

Although it is not the main objective of this study, antitumor activity will be measured according to the RECIST v.1.1 at least six weeks after treatment initiation in all patients with measurable disease, or by evaluation of tumor markers if applicable (e.g., ovarian cancer). Patients included at the RD in the expansion cohort must be evaluable per RECIST v.1.1 or by evaluation of tumor markers (see Section 7.4 for efficacy evaluation).

No serum markers will be evaluated in patients with SCLC and endometrial cancer included in the new cohort B.

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

In the new cohort B, exploratory assessment for progression-free survival (PFS) and overall survival (OS) will be performed.

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

.....

Section 7.3.1 Treatment Administration and Exposure

Original text:

Exposure to each treatment will be described by dose level (or most adequate dose grouping) for all patients who have received at least one of the study treatments.

…..

The number of cases, median, standard deviations, 95% confidence interval (CI), minimum and maximum values for the parameters defined above will be tabulated by dose level (or most adequate dose grouping) and drug (PM01183 and doxorubicin).

Changes to:

….

Exposure to each treatment will be described by dose level ***(or most adequate dose grouping/cohort/tumor type or other clinical relevant variable)*** for all patients who have received at least one of the study treatments.

…

The number of cases, median, standard deviations, 95% confidence interval (CI), minimum and maximum values for the parameters defined above will be tabulated by dose level ***(or most adequate dose grouping/cohort/tumor type or other clinical relevant variable)*** and drug (PM01183 and doxorubicin).

Section 7.4.1. Exploratory Analysis of Antitumor Activity:

Original text:

….

Response rates will be characterized using descriptive statistics (95% confidence interval). If applicable, overall response rate (percentage of patients with PR or CR), percentages for PR or CR separately and percentage of patients with SD ≥3 and/or 4 months will be analyzed.

…

The characteristics of the patients achieving an objective response or SD ≥ 3 and/or 4 months by RECIST v.1.1, or a clinically significant improvement measured by tumor markers, will be displayed.

Changes to:

….

Response rates will be characterized using descriptive statistics (95% confidence interval). If applicable, overall response rate (percentage of patients with PR or CR), percentages for PR or CR separately and percentage of patients with SD ≥ ***4 months*** will be analyzed.

….

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

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

Section 9. Tables, Listings and Figures:

Original text:

Statistical outputs, whenever is applicable, will be displayed according to assignment to prophylactic CSF use or not as well as per Dose level/Dose group or by cancer type or primary site if adequate number of patients is represented. Totals numbers will be displayed independently, if applicable. Summary tables will have source data footnotes that will refer to the relevant listings. The tables' layout may change to adequately accommodate cohort size as appropriate.

If the number of categories or items would not yield appropriate tabular or graphic representations, detailed listings will be shown instead.

Patients included and treated over 75 years old will be excluded from all tables, listings and graphs in this SAP. Detailed narratives of these patients will be shown in the clinical study report CSR.

….

Changes to:

After the implementation of Amendment #3, a new cohort B of patients with SCLC and endometrial cancer has been included. All statistical outputs will be displayed according to dose level (grouped)/cohort/tumor type or primary site/CSF use or not/other relevant clinical variable, whenever applicable and if an adequate number of patients is represented. Summary tables will have source data footnotes that will refer to the relevant listings. The tables' layout may change to adequately accommodate cohort/group size as appropriate.

If the number of categories or items would not yield appropriate tabular or graphic representations, detailed listings will be shown instead.

~~Patients included and treated over 75 years old will be excluded from all tables, listings and graphs in this SAP. Detailed narratives of these patients will be shown in the clinical study report (CSR).~~

The abbreviation DL shown in the mock tables might refer to dose level (grouped <RD, RD, etc…)/cohort (i.e. Cohort A and B)/tumor type or primary site (i.e. Ovarian, SCLC (2nd line), etc…)/CSF use or not/ other clinical relevant variable …..

Sections 10.2.8 Hematological Evaluation at Baseline to 10.2.11 Other Metabolic Evaluations at Baseline ; 11.3.1 Display of Adverse Events; 11.5 Clinical Laboratory Evaluations; 11.6 Vital Signs, Physical findings and Pregnancy tests, ECG,LVEF; Appendix III 12.1 Efficacy Analysis

The following paragraph has been removed from the aforementioned sections:

"All statistical outputs in this section, whenever applicable, will be displayed according to assignment to prophylactic CSF use or not as well as per Dose level/Dose group or by cancer type or primary site if adequate number of patients is represented. Total numbers will be displayed independently, if applicable."

And the following text replaces the removed paragraph in the following sections: **10. Appendix I. Patients Characteristics; 11. Appendix II. Safety Evaluation; 12. Appendix III. Efficacy Evaluation.**

"All statistical outputs will be displayed according to dose level (grouped)/cohort/tumor type or primary site/ CSF use or not/other relevant clinical variable, whenever applicable and if an adequate number of patients is represented. Summary tables will have source data footnotes that will refer to the relevant listings. The tables' layout may change to adequately accommodate cohort/group size as appropriate."

Section 10.2.1 Patients Characteristics at Baseline

A footnote has been added.

Table 10.2.1.1. Age at Entry by Dose Level.

Age at entry	DL I		DL II		⋯		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
18-45 years										
46-55 years										
⋯										
< 76* years										
Total										

Note: Percentages based on number of patients by dose level. (*) *Example categories.*

Section 10.2.7 Previous Anticancer Medical Therapy

New tables have been included:

Table 10.2.7.9 CTFI by Dose Level/Cohort/Tumor type

CTFI/TFI*	DL I		DL II		⋯		DL n		Total	
	N	%	N	%	N	%	N	%	N	%
Resistant										
Sensitive										
…										
Total										

Note: (*) CTFI (chemotheraphy free interval)/for SCLC patients and TFI (Systemic chemotherapy free interval) for Endometrial patients. Calculated from the last therapy previous therapy with ATC coded "L01XA" and calculated as the difference from the end of therapy to the PD, e.g: for SCLC patients Categories R (resistant) and S (sensitive).

Table 10.2.7.10 Summary Statistics: CTFI by Dose Level/Cohort/Tumor type.

Tumor type*/Median and range	DL I	DL II	⋯	DL n	Total
N					
Mean					
Median					
Min					
Max					
STD					

Note: (*) Tumor type, if apply

Section 11. Safety Evaluation.

Original:

All statistical outputs in this section, whenever applicable, will be displayed according to the discontinuation of the combination treatment. Treatment exposure, delays, omissions and reductions will be shown before and after discontinuation.

Changes to:

All statistical outputs in this section, whenever applicable, will be displayed according to the discontinuation of the combination treatment. Treatment exposure, delays, omissions and reductions will be shown ***considering the whole study treatment and/or before and after discontinuation, if appropriate.***

Table 11.1.1.4. Dose Intensity by Dose Level:

Original table:

Drug	Dose intensity	DL I	DL II	⋯	DL n	Total
PM01183 (mg/week)	N Mean Median Min Max					
Doxorubicin (mg/m²/week)	N Mean Median Min Max					

Changes to:

Drug	Dose intensity	DL I	DL II	⋯	DL n	Total
PM01183* (mg/week)	N Mean Median Min Max STD					
PM01183* (mg/m²/week)	***N*** ***Mean*** ***Median*** ***Min*** ***Max***					

Drug	Dose intensity	DL I	DL II	···	DL n	Total
	STD					
	N					
	Mean					
Doxorubicin	Median					
(mg/m²/week)	Min					
	Max					
	STD					

(*) Results of dose intensity maybe grouped and presented in mg/m²/week for patients treated in the Cohort A, if appropriate.

Section 11.3.1 Display of Adverse Events.

The following paragraph is added:

All adverse events tables will be listed by cohort and dose level (or most adequate dose grouping/tumor type/other clinical relevant variable or according to the discontinuation of the combination treatment, if required).

Section 12. Efficacy Evaluation.

Original:

All statistical outputs will be displayed according to Dose level (grouped)/Cohort/Cancer type or primary site/CSF use or not/other clinical relevant variable, whenever applicable and if an adequate number of patients is represented. Summary tables will have source data footnotes that will refer to the relevant listings. The tables' layout may change to adequately accommodate cohort/group size as appropriate.

Changes to:

All statistical outputs will be displayed according to Dose level (grouped)/Cohort/Cancer type or primary site/CSF use or not/other clinical relevant variable ***(e.g. 2nd line SCLC by CTFI),*** whenever applicable and if an adequate number of patients is represented. Summary tables will have source data footnotes that will refer to the relevant listings. The tables' layout may change to adequately accommodate cohort/group size as appropriate.

Section 12.1.1 Response.

Table 12.1.1.9 add the following footnote:

Note: (*) If any particular tumor type ***or any other clinically relevant variable*** is adequately represented and PFS at 12, and 24 months also if available data.

The following category has been added to Table 12.1.1.10.

Table12.1.1.10 Duration of Response.

Summary*
N=XX
Events X (XX.X%)
Censored X (XX.X%)
Median X.X 95% CI (X.X-X.X)
Duration of Response at 3 months XX.X% 95% CI XX.X%-XX.X%)
Duration of Response at 6 months XX.X% 95% CI XX.X%-XX.X%)

(*) If any particular tumor type or any other clinically relevant variable is adequately represented and DR at 12 and 24 months also if available data.

The following new Table 12.1.1.11 has been added.

Table 12.1.1.11 Overall survival.

Summary*
N=XX
Events X (XX.X%)
Censored X (XX.X%)
Median X.X 95% CI (X.X-X.X)
OS at 6 months XX.X% 95% CI XX.X%-XX.X%)
OS at 12 months XX.X% 95% CI XX.X%-XX.X%)
OS at 18 months XX.X% 95% CI XX.X%-XX.X%)

(*) Only for Cohort B but if requested also for cohort A.

Section 13. Figures.

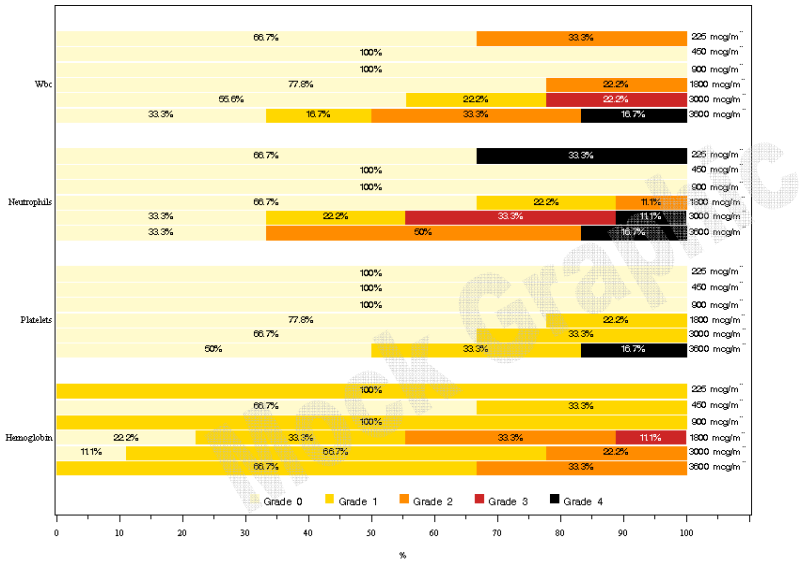
The following paragraph is added:

All statistical outputs will be displayed according to Dose level (grouped)/Cohort/Cancer type or primary site/CSF use or not/other clinical relevant variable (e.g. 2nd line SCLC by CTFI), whenever applicable and if an adequate number of patients is represented. The figures' layout may change to adequately accommodate cohort/group size as appropriate.

Figures from this section have changed table numbering due to the inclusion of new graphs and the modification of others.

Original graph:

Figure 13.1.3 Barcharts of Hematological/Biochemical Abnormalities by Dose level



Changes to:

Figure 13.1.3 Barcharts of Adverse Events or Laboratory Abnormalities

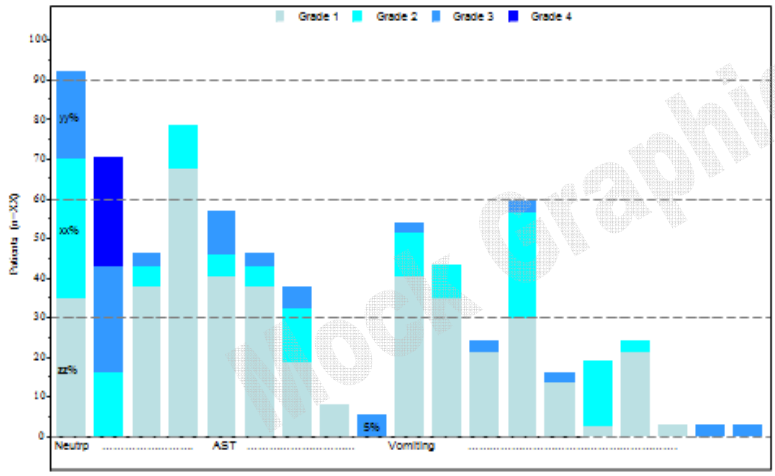
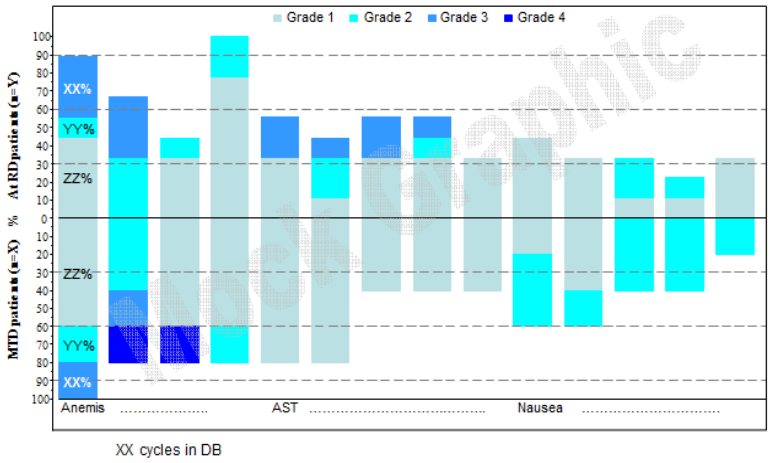


Figure 13.1.3 Barcharts of Adverse Events or Laboratory Abnormalities by Dose Level/Cohort/Tumor type/or Other Clinical Relevant Variable.



The following graphics representations have been included:

Figure 13.1.9 Waterfall Graphs change to 13.1.11 and change layout to allow grouping graphical representations.

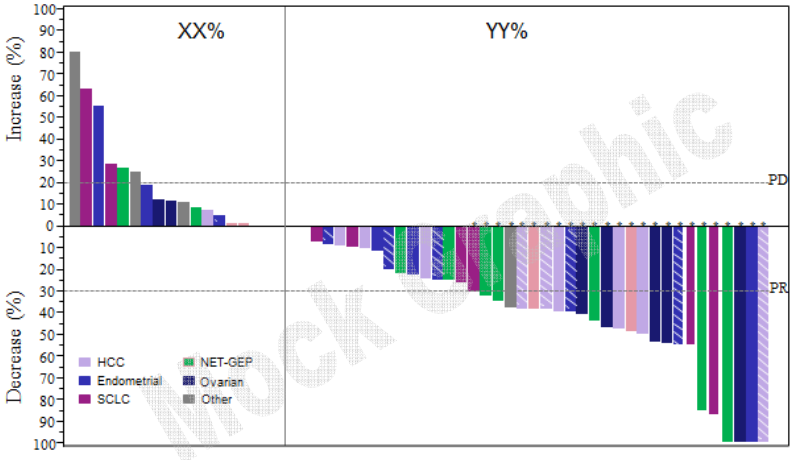


Figure 13.1.10 Overall Survival

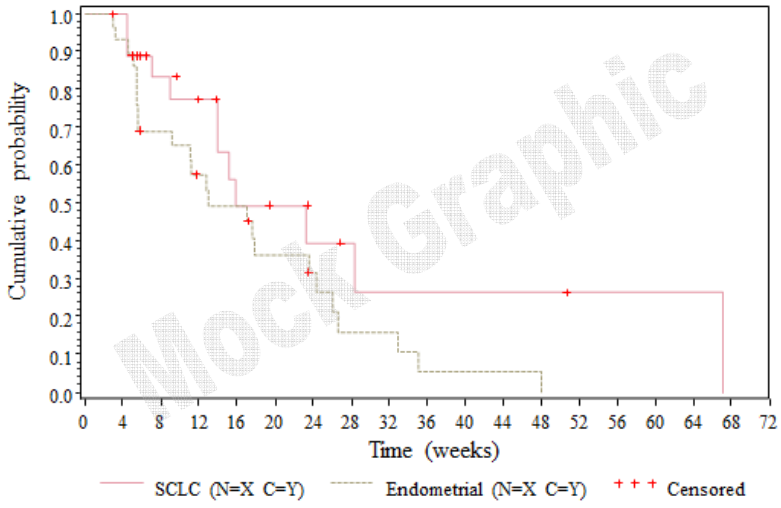


Figure 13.1.12 Spider plot: Evolution of RECIST v1.1 Assessments.

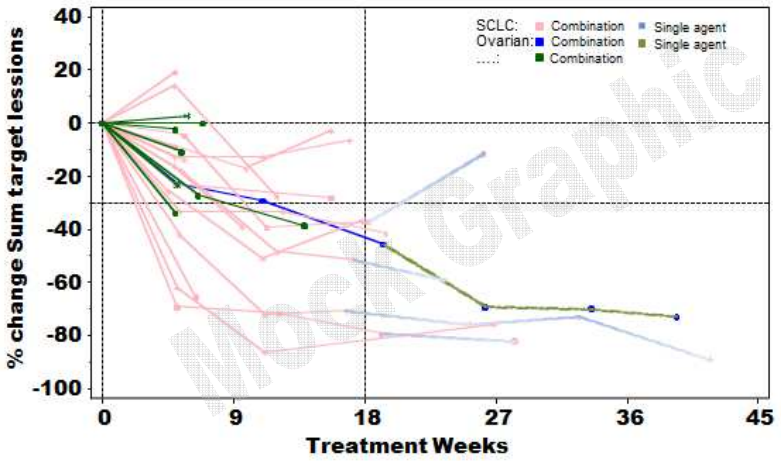


Figure 13.1.18 Efficacy and individual TTP in Selected Patients by BSA/CTFI and Treatment Discontinuation.

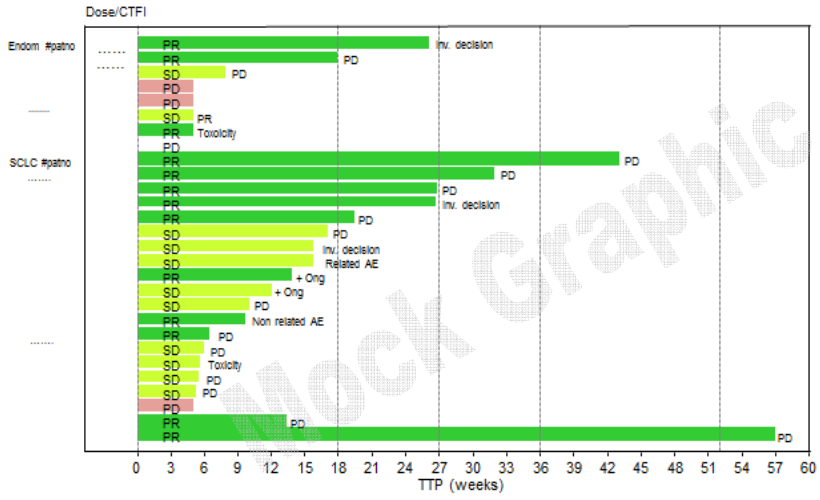


Figure 13.1.19 Number of Cycles, Reason for Treatment Discontinuation and Response in Patients who Received PM001183 alone.