PM1183-B-005-14

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

STATISTICAL ANALYSIS PLAN

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TABLE OF CONTENTS

ABBREVIATIONS AND GLOSSARY

AAGP	Alpha-1 Acid Glycoprotein
AE(s)	Adverse Event(s)
AFP	Alpha-Fetoprotein
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BIMO	Bioresearch Monitoring
BL	Baseline
BRCA1/2	Breast Cancer 1 or Breast Cancer 2 Gene
BSA	Body Surface Area
C	Cycle
CI	Confidence Interval
CPK	Creatine Phosphokinase
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTFI	Chemotherapy Free Interval
DB	Database
DCR	Disease Control Rate
DR	Duration of Response
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EFTs	Ewing´s Family of Tumors
ER-/+	Estrogen Receptor -/+
FD	Flat Dose
G-CSF	Granulocyte-Colony Stimulating Factor
GCTs	Germ Cell Tumors
GGT	Gamma-glutamyltransferase
H0	Null Hypothesis
H1	Alternative Hypothesis
hCG	Human Chorionic Gonadotropin
HER-2	Human Epidermal Growth Factor receptor 2

H&N	Head and Neck Carcinoma
IA	Investigator's Assessment
ICH	International Conference on Harmonization
IB	Investigator's Brochure
IRC	Independent Review Committee
i.v.	Intravenous(ly)
K	Potassium
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MBC	Metastatic Breast Carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multiple-gated Acquisition Scan
NA	Sodium / Not applicable
NCI	National Cancer Institute
NCI-CTC	National Cancer Institute-Common Toxicity Criteria
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	Not Evaluable
NETs	Neuroendocrine Tumors
NOS	Not Otherwise Specified
ORR	Overall Response Rate
OS	Overall Survival
OSI	Office of Scientific Investigations
PD	Progressive Disease
PCI	Prophylactic Cranial Irradiation
PFS	Progression-free Survival
PGx	Pharmacogenomics
PK/PD	Pharmacokinetics/Pharmacodynamics
PR	Partial Response
PR-/+	Progesterone Receptor -/+
PS	Performance Status
PT	Prothrombin Time/Preferred Term
PTT	Partial Thromboplastin Time
q3wk	Every Three Weeks
R	Resistant
RBC	Red blood cell
RD	Recommended Dose
RR	Refractory

RECIST	Response Evaluation Criteria In Solid Tumors
S	Sensitive
SAE(s)	Serious Adverse Event(s)
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SOC	System Organ Class
Std.	Standard deviation
TEAE	Treatment Emergent Adverse Event
TTP	Time to Progression
ULN	Upper Limit of Normal
UK	Unknown
vs.	Versus
VS	Very Sensitive
WBC	White Blood Cells
WHO	World Health Organization
Wk(s)	Week(s)
y	Year

1 STUDY RATIONALE

- The management of advanced small cell lung cancer (SCLC), head and neck (H&N) cancer, neuroendocrine tumors (NETs), biliary tract carcinoma, endometrial carcinoma, BRCA1/2-associated metastatic breast cancer, carcinoma of unknown primary site, germ cell tumors (GCTs) and Ewing family of tumors (EFTs) represents an unmet medical need. Cytotoxic chemotherapy remains a crucial component of their therapeutic armamentarium but there is a need to develop new anticancer agents that broaden the clinical benefit.
- PM01183 is a new chemical entity that induces double-strand DNA breaks through binding to the DNA minor groove. Results of the COMPARE analysis revealed that it is unlikely that this drug shares a similar mechanism of action with any of the other 98 standard cytotoxic agents compared.
- PM01183 has shown antitumor activity in most of the tumor types selected in this clinical study. In the combination trial of PM01183 at 4.0 mg flat dose (FD) with 50 mg/m^2 of doxorubicin every three weeks (q3wk) (PM1183-A-003-10), five of 12 evaluable patients with SCLC achieved partial response (42.0%), with a median time-to-progression (TTP) of 2.0 months. In endometrial carcinoma, two of three patients treated with the combination PM01183 plus doxorubicin at the aforementioned dose and schedule had a complete response and a partial response, respectively. The third patient had disease stabilization longer than 4 months. The median TTP was 10.1 months. Also with this combination, a patient with NET had a partial response with a TTP of 4.5 months. In a phase II clinical trial of PM01183 as single agent in MBC, one of 54 patients with germline BRCA 1/2 mutation had a complete response (2%) and 21 patients had partial response (39%). Twenty-three additional patients had disease stabilization (43%). One patient with H&N carcinoma treated with PM01183 as single agent at 2.6 mg/m^2 q3wk achieved a disease stabilization of 4 months duration. Finally, one patient with a carcinoma of unknown primary site treated with PM01183 as single agent at 7 mg FD q3wk had disease stabilization for 2.6 months.
- The inclusion of patients with EFTs is mainly based on the similar mechanism of action of PM01183 and its related compound trabectedin. In sarcomas associated with translocations, such as myxoid liposarcoma, in which the translocation produces a fusion protein (FUS-CHOP) that acts as a deregulated transcription factor, trabectedin has been shown to interfere with the binding of this protein to specific DNA promoters, and hence with the synthesis of downstream proteins. Based on the structural and functional similarities of these fusion proteins, trabectedin could induce on other translocation-related sarcomas similar effects to those described in myxoid liposarcoma. In fact, trabectedin has shown efficacy in advanced pretreated patients with Ewing's sarcoma: three partial responses and seven disease stabilizations in 20 patients, with a 25% 6-month progression-free survival (PFS) rate. Since PM01183 has a favorable pharmacokinetic (PK) profile compared to trabectedin, as shown by a tolerated dose four times higher and an exposure 15.3 times higher than that of trabectedin at the RD, it has been postulated that its effect on rapidly growing tumors such as EFTs would be superior. In addition, an improved therapeutic index of PM01183 relative to trabectedin, as well as suppression of the EFTs fusion protein EWS/FLI1 activity by PM01183 at clinically achievable concentrations, have been reported.

- The finding of PM01183 activity in aggressive tumors with high proliferation index, such as BRCA germline mutation-positive breast carcinomas, neuroendocrine tumors and SCLC, led to the inclusion of GCTs and biliary tract carcinoma in this study.
- In conclusion, this clinical trial has been designed to establish or confirm the proof of concept of PM01183 anticancer activity in several difficult-to-treat tumors for potential further development.

2 STUDY DESIGN

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

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

- If no confirmed responses are observed in the first 15 evaluable patients of each cohort, the recruitment of the corresponding cohort will be stopped.
- If one confirmed response is observed in the first 15 evaluable patients of each cohort, the recruitment of this cohort will continue to up to 25 evaluable patients.
    - In the cohort of endometrial carcinoma, if ≥2 confirmed responses occur in the first 25 evaluable patients, the sample size will be doubled to 50 evaluable patients.
    - In the cohort of SCLC, if ≥2 confirmed responses occur in the first 25 evaluable patients, the sample size will be increased to 100 evaluable patients.
- If two confirmed responses are observed in the first 15 evaluable patients of each cohort, the recruitment of the corresponding cohort can be stopped.

Only in the SCLC cohort, an IRC will be performed on all images collected and will provide a radiographic response at each time point termed. These data and the clinical database information will be used to derive the independent review efficacy information following the RECIST v.1.1. Operational details for the IRC and the algorithm and its validation by an expert panel is described in detail in the IRC charter.

In addition, for safety reasons:

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

Finally,

- A determined cohort can be early closed by the Sponsor in case of a low recruitment rate.

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

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

All adverse events (AEs) will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4.

Treatment delays, dose reduction requirements and reason for treatment discontinuation will be monitored throughout the study. The safety profile of patients will be monitored throughout the treatment and up to 30 days (±7 days) after the last treatment infusion (end of treatment, EOT), until the patient starts a new antitumor therapy or until the date of death, whichever occurs first. Any treatment-related AEs will be followed until recovery to at least grade 1 or stabilization of symptoms or until the start of a new antitumor therapy, whichever occurs first.

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

3 OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

- To assess the antitumor activity of lurbinectedin (PM01183) in terms of overall response rate (ORR), according to the RECIST v.1.1, in the following advanced solid tumors: SCLC, H&N, NETs, biliary tract carcinoma, endometrial carcinoma, BRCA 1/2-associated MBC, carcinoma of unknown primary site, GCTs, and EFTs.

3.2 Secondary Objectives

- To further characterize the antitumor activity of PM01183 in terms of duration of response (DR), clinical benefit [ORR or stable disease (SD) lasting over four months (SD ≥ 4 months)], progression-free survival (PFS) by Investigator's assessment (IA), and overall survival (OS) in each cohort of advanced solid tumors.

- To further investigate the antitumor activity of PM01183 in terms of ORR, DR, clinical benefit [ORR or SD ≥ 4 months] and PFS by an Independent Review Committee (IRC) in the cohort of SCLC patients.

- To characterize the plasma pharmacokinetics (PK) of PM01183.
- To conduct an exploratory pharmacogenomic (PGx) and pharmacogenetic analysis.
- To evaluate the safety profile of PM01183 in this patient population.

3.3 Endpoints

The following are the endpoints defined in the protocol. See further detail in the efficacy section.

Primary Endpoint:

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

Secondary Endpoints:

Efficacy (all cohorts):

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

Efficacy (only in the SCLC cohort):

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

Plasma Pharmacokinetics (PK) of PM01183

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

Pharmacogenetics:

- This analysis will be performed in those patients who signed the written informed consent (IC) for the pharmacogenetic sub-study. The presence or absence of known polymorphisms from a

single sample collected at any time during the study, but preferably just before treatment start in Cycle 1, will be assessed to explain the individual variability in the main PK parameters.

Pharmacogenomics (PGx):

- This exploratory analysis will be performed on prior available paraffin-embedded tumor tissue samples from consenting patients of any arm. This sub-study will include factors involved in DNA repair mechanisms (such as nucleotide excision repair, homologous recombination repair and mismatch repair) and other factors related to the mechanism of action of PM01183 or to the pathogenesis of the disease, and their expression will be analyzed at the mRNA or protein level by quantitative polymerase chain reaction (PCR) and immunohistochemistry (IHC), respectively; their polymorphisms and mutations might be also analyzed, if relevant. Their correlation with clinical response and outcome after treatment will be assessed.

Safety Profile:

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

4 PATIENTS EVALUABILITY CRITERIA

The study population will include the following analysis sets definitions:

- "All Included Patients" analysis set is defined as all patients recorded in the database who have been included in the trial, regardless of whether they have received the study drug or not.
- "All Treated Patients" analysis set is defined as all included patients who have received any partial or complete infusion of PM01183.
- "All Evaluable Patients" analysis set is defined as all eligible patients, defined as patients accepted by the sponsor to take part in the trial, who have had at least one complete infusion of PM01183, and either have had at least one assessment (as per RECIST v1.1) or have been categorized as "treatment failures". Patients who discontinue treatment due to any treatment-related toxicity before an appropriate tumor assessment has been performed or those who experience early death due to malignant disease or those with treatment withdrawn due to clinical PD/symptomatic deterioration with no tumor assessments will be defined as "treatment failures". These patients will be included as non-evaluable for response in the analysis of objective response as per RECIST v1.1, although they will not be replaced as will be considered evaluable for efficacy. For the IRC assessment in SCLC patients same definition will be followed but based on its assessment.
- "All Responding Patients" analysis set is defined as all evaluable patients who have had a confirmed CR or PR as overall best response according to the RECIST v1.1. For the IRC assessment in SCLC patients same definition will be followed but based on its assessment.

4.1 Included Population

The "All Included Patients" dataset, defined as all patients accepted by the sponsor to take part in the trial, will be used for the descriptive analyses of disposition of patients in each cohort of advanced solid tumors.

4.2 Efficacy Populations

In all cohorts but SCLC, the "All Evaluable Patients" analysis set will be used for the primary endpoint analysis of ORR and for the secondary endpoints of DR, Clinical benefit (ORR or SD ≥ 4 months), PFS (including PFS4/PFS6 months), and OS6/OS12 months in each cohort of advanced solid tumors. The "All Treated Patients" analysis set will also be used for the sensitivity analyses.

In SCLC cohort, the "All Treated Patients" analysis set will be used for the primary endpoint analysis of ORR and for the secondary endpoints of DR, Clinical benefit (ORR or SD ≥ 4 months), PFS (including PFS4/PFS6 months), and OS6/OS12 months in each cohort of advanced solid tumors. The "All Evaluable Patients" analysis set will also be used for the sensitivity analyses.

The "All Responding Patients" set will be used for the secondary endpoint analysis of DR.

4.3 Safety Population

The safety analysis will be based on the "All Treated Patients" analysis set by cohort of tumor types and total population.

5 SAMPLE CONSIDERATIONS

5.1 Sample Size

Up to 25 evaluable patients in each tumor type will be recruited to test the null hypothesis that 1% or less patients get a response ($p \leq 0.01$) *versus* the alternative hypothesis that 10% or more patients get a response ($p \geq 0.10$). The variance of the standardized test is based on the null hypothesis. The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is 0.2 (normal approximation; ~0.3 if exact binomial distribution); hence, statistical power is 80% (normal approximation; ~70% if exact binomial distribution). With these assumptions, if the number of patients who achieve a confirmed response is ≥ 2, then this will allow the rejection of the null hypothesis.

- A phase III trial of PM01183 combined with doxorubicin in SCLC is ongoing. Hence, the sample size for the SCLC cohort of this study will be increased to 100 evaluable patients if the success boundary (≥2 confirmed responses) is reached in the first 25 evaluable patients. The type I/II error will be controlled with a Gamma family boundary (-1 to reject Ho, 0 to reject H1).

  Based on the newly available information, additional patients will be recruited to test the null hypothesis that 15% or less patients get a response ($p \leq 0.15$) versus the alternative hypothesis that 30% or more patients get a response ($p \geq 0.30$). The variance of the standardized test is based on the null hypothesis. The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is 0.051 (normal approximation; ~0.05 if exact binomial distribution); hence, statistical power is 95% (normal approximation; ~95% if exact binomial

distribution). With these assumptions, if the number of patients who achieve a confirmed response is ≥ 23, then this would allow the rejection of the null hypothesis. The judgement of patient's evaluability and replacement of non-evaluable patients were guided by the investigator assessment.

- A phase I trial of PM01183 combined with doxorubicin has shown encouraging antitumor activity in endometrial carcinoma. Hence, the sample size for the endometrial carcinoma cohort of this study will be doubled to 50 evaluable patients if the success boundary (≥2 confirmed responses) is reached in the first 25 evaluable patients. The type I/II error will be controlled with a Gamma family boundary (-1 to reject Ho, -3 to reject H1).

  Based on the newly available information, additional patients will be recruited to test the null hypothesis that 10% or less patients get a response ($p \leq 0.10$) versus the alternative hypothesis that 25% or more patients get a response ($p \geq 0.25$). The variance of the standardized test is based on the null hypothesis. The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is 0.144 (normal approximation; ~0.16 if exact binomial distribution); hence, statistical power is ~86% (normal approximation; ~84% if exact binomial distribution). With these assumptions, if the number of patients who achieve a confirmed response is ≥ 10, then this would allow the rejection of the null hypothesis.

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

6 STATISTICAL METHODOLOGY FOR EFFICACY

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

6.1 Planned Analyses and Definitions

Primary Endpoint

The primary study analysis except for SCLC cohort will be based on the ORR in the "All Evaluable Patients" population set. For SCLC cohort, the primary study analysis will be based on the ORR in the "All Treated Patients" population set.

Overall response rate (ORR) is calculated as the number of patients who have had a confirmed CR or PR as overall best response according to the RECIST v1.1, divided by the number of patients in the "All Evaluable Patients" ("All Treated Patients" in SCLC cohort) population set.

Secondary Endpoints

The following time-related parameters will be analyzed according to available follow-up data:

Duration of response (DR) is defined as the time from the first observation of response to the date of disease progression, recurrence or death. Other cases will be censored. Although the responses have to be confirmed according to RECIST v1.1, the first documentation (not the confirmation) will be taken into account to calculate DR. Patients who progress or die will be considered to have had an event,

except if this event occurs after the start of subsequent antitumor therapy, in which case the patient will be censored at the time of last disease assessment prior to or on the first day of the first subsequent antitumor therapy.

Clinical benefit rate is calculated as the number of patients who have had a confirmed CR, PR, or SD ≥ 4 months as overall best response according to the RECIST v1.1, divided by the number of patients in the "All Evaluable Patients" ("All Treated Patients" in SCLC cohort) analysis set.

Progression-free survival (PFS) is defined as the time from the date of start of treatment to the date of documented progressive disease (PD) by RECIST v1.1 or death (regardless of the cause of death), whichever comes first. Patients who progress or die will be considered to have had an event of progression, except if this event occurs after the start of subsequent antitumor therapy, in which case the patient will be censored at the time of last disease assessment prior to or on the first day of the first subsequent antitumor therapy. If the patient is lost for the assessment of progression during the follow-up period, or has more than one missing follow-up between the date of last tumor assessment and the date of progression, death or further antitumor therapy, the PFS/DR will be censored at the date of last valid disease assessment before the missing evaluations.

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

Overall survival (OS) is defined as the time from the date of start of treatment to the date of death or last contact. ***One year (1y-OS)/6 months overall survival*** is defined as the Kaplan-Meier estimate of the probability of patients being alive at 12/6 months after the date of start of treatment.

A sensitivity analysis for all cohorts but SCLC will be performed for ORR, Clinical Benefit Rate, PFS and OS in the "All Treated Patients population". For the SCLC cohort, the sensitivity analysis will be carried out the "All Evaluable Patients".

6.2 Efficacy Analysis Methods

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

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

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

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

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

The patient level response will be calculated by means of statistical programming. In the case of a Partial Response followed by a time point with a tumor size reduction lower than 30% compared to the baseline assessment but an increase in the size of the target lesions not qualifying for disease progression (e.g. increase of sum of target lesions compared with the nadir is lower than 20%) then the response will be considered maintained following RECIST advice(("The definition of SD: a clarification" http://recist.eortc.org/recist-1-1-2/).

Example: Baseline evaluation: 38 mm, first evaluation: 26 mm (Tumor Size Reduction from baseline = 31.6% PR), second evaluation: 28 mm (Reduction from baseline = 26.3%, but increase from nadir = 7.7%).

The best overall response will be considered as confirmed PR.

6.2.1 Primary Endpoint

Exact binomial estimates with 95% confidence intervals (CIs) in each cohort will be calculated for the analysis of the main endpoint (ORR according to RECIST v1.1 by Investigator assessment)

6.2.2 Secondary Endpoints

Exact binomial estimates with 95% confidence intervals (CIs) will be performed in the SCLC cohort for the analysis of the ORR according to RECIST v1.1 by IRC.

Time-to-event endpoints (DR, PFS and OS) and their set time estimates (i.e. PFS4, PFS6 and OS 6/12) will be analyzed according to the Kaplan-Meier method.

7 STATISTICAL METHODOLOGY FOR SAFETY

The safety analysis for the secondary endpoints will be based on the "All Treated Patients" population set in each cohort of advanced solid tumors or the total population (if applicable).

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

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

7.1 Toxicity and Adverse Events

All the adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The toxicity evaluation will be coded with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.

Treatment-emergent adverse events (TEAE) are defined as any adverse events aggravated in severity from baseline or having their onset between the first dose of the study drug and 30 days after the last treatment dose, death or date of further therapy (whichever comes first). Adverse Events Related to Study Drug or with Unknown relationship occurring more than 30 days after the last dose will also be taken into account as TEAEs.

Summary of overall AEs will be done by System Organ Class (SOC) and Preferred Term (PT), by severity (worst toxicity grade), by relationship to the study drug and by AE outcome. Tables will be

organized by category of events using SOC (i.e. alphabetical order) and PT in descending frequencies (i.e., from higher to lower).

A frequency table or listing will be made for the AEs leading to cycle delay, dose reduction or withdrawal of study medication. Adverse events with outcome of death will also be presented by relationship to the study drugs.

7.2 Clinical Laboratory Evaluation

Laboratory results will be classified according to the NCI-CTCAE v4.

The following hematological values (worst grade per patient and per cycle during treatment) will be displayed: white blood cells count (WBC), neutrophils count, lymphocytes count, platelets count and hemoglobin.

Overall cross tabulation will be presented for the worst grade during treatment *versus* the baseline severity grading of leukopenia, neutropenia, lymphopenia, thrombocytopenia and anemia.

If a grade ≥3 neutropenia or thrombocytopenia occurs during a cycle of treatment, the first day it reaches grade 3 or 4 (counting from the start of the cycle) and the duration of the abnormality (i.e., until recovery to grade ≤ 2) will be tabulated.

Similarly, the following biochemical values (worst grade per patient and per cycle during treatment) will be displayed: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (AP), creatine phosphokinase (CPK), creatinine, gamma-glutamyltransferase (GGT), calcium (corrected by albumin levels), potassium, sodium, magnesium, glucose and albumin.

If a grade ≥3 AST or ALT increase occurs during a cycle of treatment, both the day it peaked (counting from the start of the cycle) and the duration of the abnormality (i.e., until recovery to grade ≤ 2) will be tabulated.

Overall cross tabulation will be presented for the worst grade during treatment *versus* the baseline severity grading of biochemical abnormalities.

7.3 Vital Signs, Physical Examination, Left Ventricular Ejection Fraction and Electrocardiogram Findings

Tabulation will be made summarizing the performance status, body weight, left ventricular ejection fraction (LVEF) and electrocardiogram (ECG) abnormalities at baseline and during the treatment, if appropriate, for each cohort and patient.

7.4 Deaths and Other Serious Adverse Events

Deaths and other serious adverse events (SAEs) will be tabulated.

8 OTHER ANALYSES

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

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

8.1 Patient Disposition and Treatment/Study Discontinuation

The number of patients included in the study, the number of patients treated and the number of patients evaluable for the main endpoint will be shown. Also, accrual by center and country and the main dates of the study will be displayed. Reasons for treatment discontinuation and for study discontinuation will be tabulated.

8.2 Protocol Deviations

Analysis of inclusion/exclusion criteria deviations, retreatment restrictions, concomitant medication and clinically relevant discontinuations, among others, will be done as described in Appendix I.

8.3 Baseline and Demographic Data

Baseline data such as demographics, cancer history, prior therapy, prior relevant history, signs and symptoms, ECG, LVEF, physical examination, vital signs, laboratory values and concomitant medication, coded according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system, will be described following standard tables detailed in Appendix I.

Age, baseline weight, height, and body surface area (BSA) will be summarized descriptively.

Baseline weight and height will be recorded on the case report form (CRF).

Baseline BSA will be calculated using the Dubois & Dubois formula.

Age categories and race will be summarized with frequency counts.

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

For the cancer history: time from initial diagnosis, time from metastatic disease and time from last progression before the study entry will be recorded. These time calculations will be shown in months and summarized descriptively. Histology and characteristics of the disease at study entry will be tabulated.

Previous relevant medical history (other than cancer) will be listed.

A frequency tabulation of the number of patients with and the different types of previous surgery, radiotherapy, or therapy (number of lines) will be given.

Adverse events at baseline will be displayed by tabulation of frequencies according to NCI-CTCAE v4 toxicity grades. They will also be listed.

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

8.4 Treatment Administration

Total cumulative dose, dose intensity and relative dose intensity, time on treatment, cycle delays and dose reductions will be described following standard tables detailed in Appendix I.

Total cumulative dose, expressed in mg, will be the sum of all the study drug doses from the first cycle until the last cycle, including the dose received in the last cycle.

Patients will be considered to be on-treatment for the duration of their treatment and for 30 days after the last treatment dose. If the patient starts any new antitumor therapy outside this clinical trial or dies within 30 days of the last treatment dose, the date of administration of this new therapy or the date of death will be considered the date of treatment discontinuation.

However, as a convention, the duration of the last cycle will be considered to be 21 days (instead of 30 days) for dose intensity calculation purposes.

Intended dose intensity is the planned dose per cycle divided by the planned number of weeks per cycle.

Absolute dose intensity is the actual cumulative dose divided by the number of weeks of treatment. Relative dose intensity (%) is the ratio of absolute dose intensity divided by the intended dose intensity.

The CRF item «Infusion delayed: yes/no» will be used to calculate the delayed cycles. For those cycles considered as delayed by the Investigator, the delay will be calculated as follows:

Delay: Date of actual drug administration – Date of previous drug administration – 21.

The infusion of the first cycle will be excluded from all calculations regarding cycle delays and modifications.

8.5 Subsequent Therapy

A table summarizing the subsequent therapies received after treatment discontinuation will be shown.

8.6 Pharmacokinetic Analyses

This analysis will be detailed in a separate document.

8.7 Pharmacogenetics Analyses

This analysis will be detailed in a separate document.

8.8 Pharmacogenomic Analyses

This analysis will be detailed in a separate document.

8.9 Imputation of Incomplete Dates

The dates of certain historical or on-study clinical data are key components for statistical analysis. An incomplete date results from a missing day, month or year; in that case, the missing figure can be imputed, thus allowing the calculation of variables, such as duration and time of a specific event. However, when all dates (day, month and year) are missing, no imputation will be done unless otherwise specified. Whenever imputations are applicable, it will be clearly specified in the corresponding shell table, listing or figure in sections 10-16 of this SAP.

Before Registration

If the day of a month is unknown, then the imputed day will be the 1st. of the month; if the month is also unknown, then the imputed date will be the 1st of July. This assumption will only be valid if the imputed date occurs earlier than the first dose administration date; otherwise the imputed date will be the first day of the month of administration of the first dose (i.e. 01/ month of administration of the first dose/year).

Between treatment start and end of treatment

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

After End of Treatment

To ensure the most conservative approach for the time-to-event variables (i.e., DR, PFS and OS), which 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 the 1st; if the month is also unknown, then the imputed date will be the 1st of July. This assumption will be valid if the imputed date occurs later than the last drug administration date; otherwise the imputed date will be the date of the last drug administration plus the predefined cycle length (i.e., 21 days if PM01183), except if the patient dies before, in which case the date of death minus 1 will be used. For OS, if a patient dies the imputation event date should be the last date the patient is known to be alive minus one day.

For the determination of treatment emergent AEs with incomplete dates that do not allow to know if they occurred during the treatment period, the following imputation rules will apply:

- If the start day, month and year are missing, the event will be considered treatment emergent.
- If the start day and month are missing, no date imputation will be performed but the event will be considered TEAE, if the reported year is the same or occurs after the infusion year and also the reported year is the same or occurs before the EOT year.
- If the start day is missing, no imputation date will be performed but the event will be considered TEAE, if the reported month and year occur after the first infusion date (month/year) and before the EOT date (month/year).

-

8.10 Decimal Places

By default, all numeric results will be rounded to one decimal, except when variables are integers; in that case, they will be reported without decimals (for example, age in years, number of sites, etc.). Three decimal places will be used for Hazard Ratios or Odds Ratios. Four decimal places will be used for p-values.

8.11 Subgroup Analyses

Specific subgroup efficacy analyses will be done for patients with SCLC. These analyses will be performed by IA/IRC and in all evaluable/all treated patient populations, pre-specified analyses are by CTFI defined as the time from the last dose of the last platinum containing therapy to the occurrence of progressive disease,(< 90 days and ≥ 90 days and/or Refractory (RR) [<30 days], Resistant (R)[>=30 and <90 days], Sensitive (S) [>=90 and <180 days] and Very Sensitive (VS)[>=180 days]), excluding patients with CTFI<30 days and considering event to clinical progressions although they

were not documented by radiological images. Any other exploratory analyses requested by the physician at the time of the analysis will be clearly explained, specifying the selected patient population and following the same layout detailed for the other subgroup analyses.

If the number of patients recruited in any cohort differs at least 10% from the sample size assumptions, a sensitivity analysis for main efficacy endpoints using all evaluable patients will be performed.

Pre-specified safety subgroup analyses are: by sex (male *vs.* female), by age (<65 years-old *vs.* ≥65 years-old), by race (white *vs.* other), by number of prior lines (1 *vs.* >1 line), by BSA (<1.8 *vs.* ≥1.8) and by geographical area (USA *vs.* Europe *vs.* rest of the world).

No differentiation by center is planned.

8.12 Methods for Handling Missing Data

Missing values will be tabulated with their frequency but they will not be included in the calculation of percentages.

8.13 Interim and Group Sequential Analyses

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

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

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

8.14 Identification of Fixed or Random Effects Models

Not applicable.

8.15 Data Analysis Conventions

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

9 STATISTICAL SOFTWARE

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

EAST v5.4 has been used to calculate sample size. SAS v9.2 or higher will be used for all statistical analysis outputs.

APPENDIX I

Statistical output will be displayed by cohort of tumor types and/or total population, and it will be clearly identified with labels (also for subgroup analyses).

Each table, listing and figure will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

For this reason each SAP Table/Listing/Figure will have different granularity, i.e Table 11.1.1.1.x where "x" is a different sublevel of granularity. The following values apply:

Table/Listing/Figure granularity level	Contents
none	Totals all cohort
.b	BRCA 1/2-associated metastatic breast carcinoma
.i	Biliary tract carcinoma
.c	Carcinoma of unknown primary site
.e	Endometrial carcinoma
.w	Ewing's family of tumors (EFTs)
.g	Germ cell tumor (GCTs)
.h	Head and neck carcinoma (H&N)
.n	Neuroendocrine tumors (NETs)
.s	Small cell lung cancer (SCLC)
.s1	Resistant*
.s2	Sensitive*

(*)For tables to be produced for resistant (.s1) and sensitive (.s2) populations, please see indications in the respective table or figure footnote.

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 does not yield appropriate tabular or graphic representations, detailed listings will be shown instead.

10 Study Patients

10.1 Patient Disposition

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

Each table, listing and figure will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

Table 10.1.1 Number of patients included, treated and evaluable for the primary endpoint.

	N	%
Included patients		
Eligible patients*		
Treated patients		
Evaluable patients for efficacy**		
Evaluable patients for efficacy by IRC (SCLC cohort)***		

(*) Patients who were considered eligible according to the registration screening form and were accepted to take part in the trial with the sponsor's agreement in the screening reply form. (**) Includes patients treated with early death/or PD not documented by image (early PD). (***) For sensitivity analysis.

Listing 10.1.2 Patients who do not meet all the inclusion criteria.

Patient id.	Criterion number(s) and description

Listing 10.1.3 Patients who meet any exclusion criteria.

Patient id.	Criterion number(s) and description

Listing 10.1.4 Non-evaluable patients for efficacy analysis.

Patient id.	Reason

Listing 10.1.5 Non-evaluable patients for efficacy analysis by IRC (SCLC cohort).

Patient id.	Reason

Listing 10.1.6 Non-evaluable patients for safety (Non-treated patients).

Patient id.	Reason

Table 10.1.7 Patients accrual by institution.

			N	%
No. of patients included	Country 1	Institution 1		
		…		
		Total		
	…	Institution 1		
		…		

		Total		
	Total	Institution 1		
		…		
		Total		
No. of patients treated	Country 1	Institution 1		
		…		
		Total		
	…	Institution 1		
		…		
		Total		
	Total	Institution 1		
		…		
		Total		

Table 10.1.8 Study dates.

	Total
Date of first registration	
Date of first dose of the first patient	
Date of last registration	
Date of first dose of the last patient	
Date of last dose	
Date of last follow-up*	

(*) Last follow-up, examination or procedure before clinical cut-off or study closure.

10.2 Reasons for Treatment and Study Discontinuation

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable). The reasons for treatment discontinuation will be calculated in the treated patient's population. The rest of tables and listings in this section will be calculated in the included patient's population.

Table 10.2.1 Treatment discontinuation.

Reason	N	%
Progressive disease		
Treatment-related adverse event*		
Non treatment-related adverse event*		
Patient refusal to treatment*		
Death**		
Investigator's decision*		
Other*		
Ongoing at cutoff		
Total		

Note: Also for s1 and s2; (*) Specify (see Listing 10.2.2), (**) Cause of Death (See Table 12.3.2.1).

Listing 10.2.2 Reasons for treatment discontinuation other than progressive disease.

Patient id.	CTFI*	Reason	Last cycle	Comments

(*) Only for SCLC patients (RR, R, S, VS).

Table 10.2.3 Reasons for treatment discontinuation by cycles received.

Reason	Last cycle			
	1	2	…	Total

Progressive disease				
Treatment-related adverse event*				
Non treatment-related adverse event*				
Patient refusal to treatment*				
Death**				
Investigator's decision*				
Other*				
Ongoing at cutoff				
Total				

(*) Specify (see Listing 10.2.2); (**) Cause of Death (See Table 12.3.2.1);

When the reason for discontinuation is a study treatment-related adverse event or study treatment-related death, identify patients and describe them in detail here.

Listing 10.2.4 Treatment discontinuation due to adverse events.

Patient id.	CTFI*	Last cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Seriousness criteria

(*) Only for SCLC patients (RR, R, S, VS).

Table 10.2.5 Study discontinuation.

Reason	N	%
Never treated*		
Study termination (clinical cut-off)		
Patient's refusal		
Death**		
Lost to follow-up		
Other ***		
Total		

Note: Also for s1 and s2; (*) See Listing 10.2.6; (**) Cause of Death (See Table 12.3.2.1); (***) Specify (see listing 10.2.7).

Listing 10.2.6 Patients included but not treated.

Patient id.	Off-study reason

Listing 10.2.7 Study discontinuation due to other reason.

Patient id.	Specify

10.3 Protocol Deviations

Listing 10.3.1 Protocol deviations.

Patient id.	Deviation type	Description

11 Efficacy Evaluation

11.1 Demographic and Other Baseline Characteristics

Demographic and Other Baseline Characteristics will be carried out on the "All Treated Patients" population and narratives will be used to describe patients who are included but not treated.

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

11.1.1 Patient Characteristics at Baseline

Table 11.1.1.1 Baseline characteristics: Age at treatment registration.

Age	N	%
18-XX	X	XX.X
XX-YY		
≥65		
Total		
Mean, Std., Median, Range		

Note: Also for s1 and s2.

Table 11.1.1.2 Baseline characteristics: Gender.

	N	%
Male	X	XX.X
Female		
Total		

Note: Also for s1 and s2.

Table 11.1.1.3 Baseline characteristics: Race.

	N	%
American Indian or Alaskan Native	X	XX.X
Asian		
Black or African American		
Native Hawaiian or Other Pacific Islander		
White		
Other*		
Total		

Note: Also for s1 and s2; (*) See Listing 11.1.1.5

Listing 11.1.1.4 Other race, specify.

Patient id.	CTFI*	Specify

(*) Only for SCLC.

11.1.2 Disease at Diagnosis and Disease at Study Entry

Table 11.1.2.1 Time from first diagnosis to registration and Time from advanced disease to registration.

	N	Mean	Std.	Median	Min	Max
Time from diagnosis to registration (months)						
Time from advanced disease (months)						

Note: Also for s1 and s2.

Table 11.1.2.2 Histology type at diagnosis.

	N	%
Small cell lung cancer (SCLC)	X	XX.X
Head and neck carcinoma (H&N)		
Neuroendocrine tumors (NETs)		
Biliary tract carcinoma		
Endometrial carcinoma		
BRCA 1/2-associated metastatic breast carcinoma (MBC)		
Carcinoma of unknown primary site		
Germ cell tumor (GCTs)		
Ewing's family of tumors (EFTs)		
Total		

Table 11.1.2.3 Stage at diagnosis.

	N	%
Early	X	XX.X
Locally advanced		
Metastatic		
Total		

Note: Also for s1 and s2.

Table 11.1.2.4 TNM.

	N	%
T3N0M0	X	XX.X
….		
Total		

Table 11.1.2.5 Time from last progression before the study entry and TTP from last medical therapy.

	N	Mean	Std.	Median	Min	Max
Time from last PD (weeks)						
TTP to last medical therapy (months)						

Note: Also for s1 and s2.

Table 11.1.2.6 Sites of disease.

	N	%
Primary tumor	X	XX.X
Bone*		
Lung		
Liver		
Pleura		
Lymph node**		
Other***		

Note: Also for s1 and s2; (*) See Table 11.1.2.7; (**) See Table 11.1.2.8; (***) Other sites will be re-coded to specific sites by clinical review.

Listing 11.1.2.7 Bone location.

Patient id.	Specify

Table 11.1.2.8 Lymph node location.

	N	%
Neck	X	XX.X
Mediastinal		
…		

Table 11.1.2.9 Number of sites at baseline.

No. of sites	N	%
1	X	XX.X
2		
...		
Total		
Mean, Standard deviation, Median (Range)		

Note: Also for s1 and s2; (*) Sites of disease from cancer history.

Table 11.1.2.10 Sum of target lesions at baseline.

	N	%
>50 mm	X	XX.X
>100 mm		
Bulky disease*		

Note: Also for s1 and s2. (*) One lesion more than 50 mm.

11.1.3 Disease at Diagnosis and Disease at Study Entry: Small Cell Lung Cancer (SCLC)

Table 11.1.3.1 Stage at diagnosis.

	N	%
Limited	X	XX.X
Extended		
Total		

Note: Also for s1 and s2.

Table 11.1.3.2 History or current presence of CNS involvement.

	N	%
Yes	X	XX.X
No		
Total		

Note: Also for s1 and s2.

11.1.4 Disease at Diagnosis and Disease at Study Entry: Head and Neck Carcinoma (H&N)

Table 11.1.4.1 Anatomical subsite.

	N	%
Larynx	X	XX.X
……		
Total		

11.1.5 Disease at Diagnosis and Disease at Study Entry: Neuroendocrine Tumors (NETs)

Table 11.1.5.1 NET type.

	N	%
Gastroenteropancreatic neuroendocrine tumors (GEP NETs for short)	X	XX.X
……		
Other*		
Total		

(*) See Listing 11.1.5.2.

Listing 11.1.5.2 Other type.

Patient id.	Specify

Table 11.1.5.3 NET subtype.

	N	%
Functioning neuroendocrine tumors (F-NETs)	X	XX.X
Non-Functioning neuroendocrine tumors (NF-NET)		
Total		

Table 11.1.5.4 KI-67/MIB-1.

	N	%
<10%	X	XX.X
>10%		
Not done/Unknown		
Total		

11.1.6 Disease at Diagnosis and Disease at Study Entry: Biliary Tract Carcinoma

Table 11.1.6.1 Primary site.

	N	%
Intrahepatic cholangiocarcinoma	X	XX.X
Gallbladder		
Ampulla of Vater		
…		
Total		

Table 11.1.6.2 Histology type.

	N	%
Adenocarcinoma	X	XX.X
Papillary		
Intestinal type		
Other*		
Total		

(*) See Listing 11.1.6.3.

Listing 11.1.6.3 Other histology type.

Patient id.	Specify

11.1.7 Disease at Diagnosis and Disease at Study Entry: Endometrial Carcinoma

Table 11.1.7.1 Histology type.

	N	%
Endometrioid	X	XX.X
Serous/Papillary		
Clear cell		
…		
Other*		
Total		

(*) See Listing 11.1.7.2.

Listing 11.1.7.2 Other histology type.

Patient id.	Specify

11.1.8 Disease at Diagnosis and Disease at Study Entry: BRCA 1/2-associated Metastatic Breast Carcinoma (MBC)

Table 11.1.8.1 Primary site.

	N	%
Left	X	XX.X
Right		
Bilateral		
Total		

Table 11.1.8.2 Histology type.

	N	%
Ductal	X	XX.X
Lobular		
…		
Other*		
Total		

(*) See Listing 11.1.8.3.

Listing 11.1.8.3 Other histology type.

Patient id.	Specify

Table 11.1.8.4 Receptor status.

	Positive		Negative	
	N	%	N	%
Estrogen receptor	X	XX.X	X	XX.X
Progesterone receptor				
HER-2/neu receptor				

Table 11.1.8.5 Hormonal status.

	N	%
ER and/or PR positive and HER2 negative	X	XX.X
ER and/or PR positive and HER2 positive		
ER and/or PR negative and HER2 positive		
Triple negative		
Total		

Note: Triple negative: HER2 negative ER negative and PR negative.

Table 11.1.8.6 BRCA 1/2.

	N	%
BRCA 1	X	XX.X
BRCA 2		
Both		
Total		

Table 11.1.8.7 KI-67/MIB-1.

	N	%

<5%	X	XX.X
5-10%		
>10%		
Not done/Unknown		
Total		

11.1.9 Disease at Diagnosis and Disease at Study Entry: Carcinoma of Unknown Primary Site

Table 11.1.9.1 Histology type.

	N	%
Adenocarcinoma	X	XX.X
Carcinoma NOS		
Undifferentiated		
Total		

11.1.10 Disease at Diagnosis and Disease at Study Entry: Germ Cell Tumors (GCTs)

Table 11.1.10.1 Primary site.

		N	%
Gonadal	Testicular	X	XX.X
	Ovarian		
Retroperitoneal			
…			
Other*			
Total			

(*) See Listing 11.1.10.2.

Listing 11.1.10.2 Other primary sites.

Patient id.	Specify

Table 11.1.10.3 Histology type.

	N	%
Seminomatous	X	XX.X
Non-seminomatous*		
Total		

(*) If Non-Seminomatous see Table 11.1.10.4.

Listing 11.1.10.4 Non-seminomatous.

Patient id.	Specify

11.1.11 Disease at Diagnosis and Current Disease: Ewing's Family of Tumors (EFTs)

Table 11.1.11.1 Anatomical subtype.

	N	%
Osseous	X	XX.X
Extraosseous - Primitive neuroectodermal tumor		
Extraosseous - Askin tumor		
*		
Total		

(*) Other, in case of none of the others CRF categories apply.

11.1.12 Prior History

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

Table 11.1.12.1 Prior history.

SOC	Preferred term*	N	%
Gastrointestinal disorders	Constipation		
	Diarrhea NOS		
	…		
…	…		

(*) Only terms coded by the applicable dictionary.

Listing 11.1.12.2 Prior history (Ongoing events).

Patient id.	Description (Literal)	SOC	PT	Onset date

Table 11.1.12.3 Smoker status.

*	N	%
Former/current	X	XX.X
Never		
UK		
Total		

(*) Only for SCLC cohort and information obtained from CRF pages of Prior history.

Table 11.1.12.4 Paraneoplastic syndrome.

*	N	%
Yes	X	XX.X
No		
Total		

(*) Only for SCLC cohort and information obtained from CRF pages AEs at baseline and/or Prior history.

11.1.13 Prior Anticancer Therapy

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

Table 11.1.13.1 Patients with prior surgery.

	N	%
Yes	X	X.X
Palliative		
Curative		
No		
Total		

Table 11.1.13.2 Patients with prior radiotherapy

	N	%
Yes		
Brachytherapy	X	X.X
External (including IMRT)	X	X.X
IMRT		

No		
Total		

Table 11.1.13.3 Number of lines of prior therapy.

No. of systemic lines	N	%
1	X	XX.X
...		
Total		
Mean, Standard Deviation, Median (Range)		
Setting	N	%
Neoadjuvant	X	XX.X
Adjuvant		
Neoadjuvant + Adjuvant		
Advanced		
No. of advanced chemotherapy lines	N	%
1	X	XX.X
...		
Total		
Mean, Standard Deviation, Median (Range)		

Note: Also for s1 and s2.

Table 11.1.13.4 Prior anticancer agents.

Antineoplastic and immunomodulating agents (ATC-class.)	N	%
Antineoplastic agents (L01)	X	XX.X
Alkylating agents		
Nitrogen mustard analogues		
Alkyl sulphonates		
Prior anticancer agents*		
Hormones		
Prior Immunotherapy		
…		
Biological agents		
…		
….		

Note: Also for s1 and s2; (*) Therapies of interest for each tumor type e.g MBC, endometrial carcinoma, hormone, Biological agents etc…..

Table 11.1.13.5 PCI.

*	N	%
Yes	X	XX.X
No		
Total		

Note: Also for s1 and s2; (*) Only for SCLC patients.

Table 11.1.13.6 CTFI by subgroup.

*	N	%	Mean, Std., Median, Range**
CTFI< 90 days	X	XX.X	
RR			
R			
CTFI≥ 90 days			
S			
VS			
Total			

(*) Only for SCLC patients. (**) Units in months.

Table 11.1.13.7 Best response and TTP to last prior platinum.

*	N	%
CR	X	XX.X
PR		
SD		
PD		
UK/NA		
Total		
TTP to last previous platinum Mean, Std., Median, Range		

(*) Only for SCLC patients. Note: Also for s1 and s2.

11.1.14 Physical Examination and Performance Status at Baseline

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total (if applicable).

Table 11.1.14.1 Baseline physical examination.

	N	%
Normal	X	X.X
Abnormal		
Total		

Table 11.1.14.2 Baseline physical examination: BSA, Weight and Height.

	N	Mean	Std.	Median	Min	Max
BSA (m^2)						
Weight (Kg)						
Height (cm)						

Note: Also for s1 and s2.

Table 11.1.14.3 Baseline characteristics: ECOG Performance Status.

PS (ECOG)	N	%
0	X	XX.X
1		
2		
3		
4		
Total		

Note: Also for s1 and s2.

11.1.15 Vital Signs, Electrocardiogram, LVEF and other tests.

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total (if applicable).

For vital signs, electrocardiogram, LVEF and other tests, the last examination available before treatment will be described in the following tables.

Table 11.1.15.1 Baseline characteristics: vital signs.

Parameter	N	Mean	Std.	Median	Min	Max
Heart rate (beats/min)						
Systolic blood pressure (mmHg)						
Diastolic blood pressure (mmHg)						

Temperature (ºC)						

Table 11.1.15.2 Baseline characteristics: electrocardiogram result.

ECG	N	%
Normal	X	XX.X
Significant abnormalities*		
Non-significant abnormalities		

(*) See Listing 11.1.15.4.

Table 11.1.15.3 Baseline characteristics: electrocardiogram values.

Parameter	N	Mean	Std.	Median	Min	Max
PR interval (msec)						
Heart rate (bpm)						
QT interval (msec)						
QRS complex (msec)						
QTc Bazett's						
Fridericia corrected QT						

Listing 11.1.15.4 Patients with abnormal electrocardiogram.

Patient id.	Abnormality	Details*	Reason for clinically indicated repeat	PR interval (msec)	Heart rate (bpm)	QT interval (msec)	QRS complex (msec)	QTc Fridericia	QTc Bazett's**

(*)For non-significant abnormalities, for further details see prior medical history or Signs and symptoms; (**) QTc (Bazett's) = QT interval / √(60/Heart rate).

Table 11.1.15.5 Baseline characteristics: left ventricular ejection fraction (LVEF).

LVEF	N	%
Normal	X	XX.X
Abnormal*		
Total		

(*) See listing 11.1.15.7 for details.

Table 11.1.15.6 Baseline characteristics: LVEF values.

LVEF (%) by Method	N	Mean	Std.	Median	Min	Max
ECHO						
MUGA						
Both						

Listing 11.1.15.7 Patients with abnormal LVEF.

Patient id.	Abnormality	Details*	Reason for clinically indicated repeat	Method	LVEF (%)	Institution normal range

(*) For non-significant abnormalities, for further details see prior medical history or Signs and symptoms.

Table 11.1.15.8 Baseline characteristics: pregnancy test.

Pregnancy test	N	%
Positive	X	XX.X
Negative		
NA*		
Total		

Table 11.1.15.9 Baseline characteristics: adequate contraception.

Adequate birth control	N	%

Yes	X	XX.X
No		
NA*		
Total		

11.1.16 Hematological Values at Baseline

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

Table 11.1.16.1 Hematological abnormalities at baseline.

	Grade 1		…	Grade 4		All*	
	N	%	…	N	%	N	%
Anemia							
Leukopenia							
Neutropenia							
Lymphopenia							
Thrombocytopenia							

Note: Also for s1 and s2; (*) Any grade.

Table 11.1.16.2 Hematological values at baseline.

Parameter*	N	Mean	Std.	Median	Min	Max
Hemoglobin (g/dl)						
Platelets (x10*9/L)						
WBC (x10*9/L)						
Neutrophils (x10*9/L)						
Lymphocytes (x10*9/L)						
Monocytes (x10*9/L)						

Listing 11.1.16.3 Hematological tests not assessed at baseline.

Patient id.	Lab. test

Listing 11.1.16.4 Hematological abnormalities at baseline. Grade ≥ 2.

Patient id	Parameter	Value	Units	Grade

11.1.17 Biochemical Values at Baseline

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

Table 11.1.17.1 Biochemical abnormalities at baseline.

	Grade 1		…	Grade 4		All*	
	N	%	…	N	%	N	%
AST increased							
ALT increased							
Total bilirubin increased							
AP increased							

…							
Hyperglycemia							
Hypoglycemia							
…							

Note: Also for s1 and s2; (*) Any grade.

Table 11.1.17.2 Biochemical values at baseline.

	N	Mean	Std.	Median	Min	Max
AST (xULN)						
ALT (xULN)						
Direct bilirubin (xULN)						
Total bilirubin (xULN)						
AP (xULN)						
LDH (xULN)						
CPK (xULN)						
GGT (xULN)						
Creatinine (xULN)						
…						

Listing 11.1.17.3 Biochemical tests not assessed at baseline.

Patient id.	Lab. test
…	

Listing 11.1.17.4 Biochemical abnormalities at baseline. Grade ≥ 2.

Patient id	Parameter	Value	Units	Grade

Table 11.1.17.5 AAGP values at baseline.

	N	Mean	Std.	Median	Min	Max
AAGP (xULN)						

Table 11.1.17.6 Abnormal LDH at baseline.

*	N	%
Yes	X	XX.X
No		
Total		

(*) Only for SCLC cohort. Abnormal LDH: (>ULN).

11.1.18 Coagulation Values at Baseline

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

Table 11.1.18.1 Coagulation abnormalities at baseline.

	Grade 1		…	Grade 4		All*	
	N	%	…	N	%	N	%
INR increased							
PTT prolonged							

(*) Any grade.

Table 11.1.18.2 Coagulation values at baseline.

	N	Mean	Std.	Median	Min	Max
INR						
PT (sec)						
PT (ratio)						
PTT (sec)						
PTT (ratio)						

Listing 11.1.18.3 Coagulation tests not assessed at baseline.

Patient id.	Lab. test
…	

Listing 11.1.18.4 Coagulation abnormalities at baseline. Grade ≥ 2.

Patient id	Parameter	Value	Units	Grade

11.1.19 Adverse Events at Baseline

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

Table 11.1.19.1 Patients with adverse events at baseline.

No. of adverse events per patient	N	%
0	X	XX.X
1		
2		
≥ 3		
Mean, Standard Deviation, Median (Range)		

Table 11.1.19.2 Patients with disease-related adverse events at baseline.

No. of disease-related adverse events per patient	N	%
0	X	XX.X
1		
2		
≥ 3		
Mean, Standard Deviation, Median (Range)		

Table 11.1.19.3 Adverse events at baseline.

SOC	Preferred term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Gastrointestinal disorders	Constipation							
	Diarrhea NOS							
	…							
…	…							

Note: Also for s1 and s2; (*)Any grade.

11.1.20 Concomitant Therapy and Procedures at Baseline

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

Table 11.1.20.1 Concomitant medication at baseline (ATC1/ATC2/ATC3/ATC4/PN).

Concomitant medication at baseline	N	%
Alimentary tract and metabolism		
Antacids		
Magnesium compounds		
Magnesium adipate		
…		
Blood and blood forming organs		
Antithrombotic agents		
Vitamin K antagonists		
Acenocoumarol		
…		

Table 11.1.20.2 Summary of concomitant medication at baseline.

	N	%
No. of systems at BL (ATC1 level)		
0		
1		
2		
≥ 3		
Mean, Standard Deviation, Median (Range)		
No. of indications at BL (ATC2 level)		
0		
1		
2		
≥ 3		
Mean, Standard Deviation, Median (Range)		
No. of agent families at BL (ATC4 level)		
0		
1		
2		
≥ 3		
Mean, Standard Deviation, Median (Range)		
No. of agents at BL (PN level)		
0		
1		
2		
≥ 3		
Mean, Standard Deviation, Median (Range)		

If there are a relevant number of patients receiving the same concomitant medication, a table summarizing this information can be added.

11.2 Measurements of treatment compliance

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

11.3 Efficacy Analysis

Efficacy analysis will be carried out on the "All Evaluable Patients" population. For SCLC patients in "All Treated Patients" and in " All Evaluable Patients" by IA/IRC and in all pre-specified analyses, by CTFI (< 90 days and ≥ 90 days and/or Refractory (RR)[<30 days], Resistant (R) [>=30 and <90 days], Sensitive (S) [>=90 and <180 days] and Very Sensitive (VS) [>=180 days]), excluding patients with

CTFI<30 days and considering event in the clinical progressions although they were not documented by radiological images.

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort), the total population (if applicable) or SCLC patients by CTFI or sensitivity analysis if recruitment in any cohort differs at least 10% from the assumptions. Any other exploratory analyses will be clearly specified by selected patient population and will be performed following the same table layout detailed below.

11.3.1 Primary Analysis (excluding SCLC cohort)

Primary Analysis by IA:

Table 11.3.1.1 Response rate.

Response	N	%
Complete response (CR)		
Partial response (PR)		
Stable disease SD≥4 months		
Stable disease SD<4 months		
Progressive disease (PD)		
Inevaluable for response*		

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify)

Table 11.3.1.2 ORR.

	Percentage	Lower 95% limit	Upper 95% limit
Response rate*			

(*) Confirmed CR + PR. Binomial exact estimator and 95% CI.

11.3.2 Secondary Analyses (excluding SCLC cohort)

Secondary Analyses by IA:

Table 11.3.2.1 Descriptive Duration of response (DR).

	N	Mean	Std.Std.	Median	Min	Max

Table 11.3.2.2 DR.

	DR
N	
Events	
Censored	
Median DR	
DR at 4 months	
DR at 6 months	
DR at 12 months	

Kaplan-Meier plot will also be shown (Figure 11.3.2.2).

Table 11.3.2.3 Clinical benefit rate and Disease control rate.

	Percentage	Lower 95% limit	Upper 95% limit
Clinical benefit rate*			
Disease control rate**			

(*) CR + PR + SD ≥ 4 months. Binomial exact estimator and 95% CI.
(**) CR + PR + SD. Binomial exact estimator and 95% CI.

Table 11.3.2.4 PFS.

	PFS
N	
Events	
Censored	
Median PFS	
PFS at 4 months	
PFS at 6 months	
PFS at 12 months	

Kaplan-Meier plot will also be shown (Figure 11.3.2.4).

Table 11.3.2.5 OS.

	OS
N	
Events	
Censored	
Median OS	
OS at 6 months	
OS at 12 months	
OS at 24 months	

Kaplan-Meier plot will also be shown (Figure 11.3.2.5).

Listing 11.3.2.6 Characteristics of patients with clinical benefit*.

Baseline Characteristics**						Study treatment characteristics**				
Patient id.	PS / Age/Gender	Histology type / Histology grade	No. of prior regimens	Best response last therapy	TTP last therapy	Cycles received	Best response	PFS (mo)	OS (mo)	DR (mo)
…										

(*) CR + PR + SD ≥ 4 months.
(**) Any other clinically relevant variable will be added at the time of the analysis.

Table 11.3.2.7 Median follow-up.

Follow-up*	Median	95% CI/Range
PFS		
OS		

(*) Calculated using the Kaplan-Meier method reversing the censoring values and also by descriptive methods.

11.3.3 SCLC Cohort

Primary Analysis (ORR):

Table 11.3.3.1 Response rate by IA (All treated patients).

Response	N	%
Complete response (CR)		
Partial response (PR)		
Stable disease SD≥4 months		
Stable disease SD<4 months		
Progressive disease (PD)		
Inevaluable for response*		

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify)

Table 11.3.3.2 ORR by IA (All treated patients).

	Percentage	Lower 95% limit	Upper 95% limit
Response rate*			

(*) Confirmed CR + PR. Binomial exact estimator and 95% CI.

Secondary and Supportive Analysis for ORR:

Table 11.3.3.3 Response rate by IA (All evaluable patients).

Response	N	%
Complete response (CR)		
Partial response (PR)		
Stable disease SD≥4 months		
Stable disease SD<4 months		
Progressive disease (PD)		
Inevaluable for response*		

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify).

Table 11.3.3.4 ORR by IA (All evaluable patients).

	Percentage	Lower 95% limit	Upper 95% limit
Response rate*			

(*) Confirmed CR + PR. Binomial exact estimator and 95% CI.

Table 11.3.3.5 Response rate by IRC (All treated patients).

Response	N	%
Complete response (CR)		
Partial response (PR)		
Stable disease SD≥4 months		
Stable disease SD<4 months		
Progressive disease (PD)		
Inevaluable for response*		

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify).

Table 11.3.3.6 ORR by IRC (All treated patients).

	Percentage	Lower 95% limit	Upper 95% limit
Response rate*			

(*) Confirmed CR + PR. Binomial exact estimator and 95% CI.

Table 11.3.3.7 Response rate and reliability by IA and IRC (All treated patients).

Response		IA											
		Complete response (CR)		Partial response (PR)		Stable disease SD≥4 months		Stable disease SD<4 months		Progressive disease (PD)		Inevaluable for response*	
		N	%	N	%	N	%	N	%	N	%	N	%
IRC	Complete response (CR)												
	Partial response (PR)												
	Stable disease SD≥4 months												
	Stable disease SD<4 months												
	Progressive disease (PD)												
	Inevaluable for												

	response												
Test of Symmetry**													
Statistic (S)													
DF													
Pr > S													
Kappa statistics**													
		Value			ASE			95% Confidence Limits					
Simple kappa													
Weighted kappa													
Test of H0: Weighted Kappa = 0													
ASE under H0													
Z													
One-sided Pr > Z													
Two-sided Pr > |Z|													

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify).
For discrepancies see Listing 11.3.3.15. Percentage by columns. (**) Kappa Index for concordance of all response categories according to IA or IRC assessment.

Other Secondary Analyses:

Table 11.3.3.8 Descriptive* DR by IA and IRC.

	N	Mean	Std.	Median	Min	Max
IA						
IRC						

(*) Calculated with univariate procedures, not taking into account censoring, instead of Kaplan-Meier estimates.

Table 11.3.3.9 DR by IA and IRC.

	IA	IRC
N		
Events		
Censored		
Median DR		
DR at 4 months		
DR at 6 months		
DR at 12 months		

Kaplan-Meier plots will also be shown (Figure 11.3.3.9.1 DR by IA; Figure 11.3.3.9.2 DR by IRC and Figure 11.3.3.9.3 DR by IA and IRC)

Table 11.3.3.10 Clinical benefit rate and Disease control rate by IA and IRC (All treated patients).

		Percentage	Lower 95% limit	Upper 95% limit
IA	Clinical benefit rate*			
	Disease control rate**			
IRC	Clinical benefit rate*			
	Disease control rate**			

(*) CR + PR + SD ≥ 4 months. Binomial exact estimator and 95% CI.
(**) CR + PR + SD. Binomial exact estimator and 95% CI.

Table 11.3.3.11 PFS by IA and IRC (All treated patients).

	IA	IRC
N		
Events		
Censored		
Median PFS		
PFS at 4 months		
PFS at 6 months		
PFS at 12 months		

Kaplan-Meier plot will also be shown. (Figure 11.3.3.11.1 PFS by IA (All treated patients), Figure 11.3.3.11.2 PFS by IRC (All treated patients) and Figure 11.3.3.11.3 PFS by IA and IRC (All treated patients))

Table 11.3.3.12 OS (All treated patients).

	OS
N	
Events	
Censored	
Median OS	
OS at 6 months	
OS at 12 months	
OS at 24 months	

Kaplan-Meier plot will also be shown (Figure 11.3.3.12).

Listing 11.3.3.13 Characteristics of patients with clinical benefit* by CTFI by IA and IRC. (All treated patients).

Baseline characteristics							Study treatment characteristics				
Patient id.	CTFI**	PS / Age/ Gender	***	No. of prior regimens	Last prior therapy	Best response/TTP last therapy	Cycles received	Best response IA/IRC	PFS (mo) IA/IRC	DR (mo) IA/IRC	OS (mo)
…											

(*) CR + PR + SD ≥ 4 months.
(**) RR, R, S, VS.
(***) Any other clinical relevant variable (including sites of disease, limited/extended disease, LDH [normal/abnormal] and alpha-acid glycoprotein [xULN]) will be added at the analysis time.

Table 11.3.3.14 Median follow-up by IA and IRC. (All treated patients).

Follow-up*		Median	95% CI/Range
IA	PFS		
	OS		
IRC	PFS		

(*) Calculated using the Kaplan-Meier method reversing the censoring values and also by descriptive methods.

Listing 11.3.3.15 Concordance by IA and IRC. (All treated patients).

Patient id.	CTFI*	Study treatment characteristics by IA			Study treatment characteristics by IRC		
		Best response	PFS (mo)	DR (mo)	Best response	PFS (mo)	DR (mo)

(*) RR, R, S, VS.

Table 11.3.3.16 Progression type by IA and IRC. (All treated patients)

	IA		IRC	
	N	%	N	%
Target lesion				
Non-target lesion				
New lesions				
CNS				
CNS + Other				
No CNS				

Death due to malignant disease				
Other*				

(*)Please specify.

Table 11.3.3.17 Censoring reason by IA and IRC. (All treated patients)

	IA		IRC	
	N	%	N	%
Progression-free at last tumor assessment				
FU completed				
FU ongoing				
Subsequent therapy before documented progression				
Other*				

(*)Please specify.

Subgroup Analysis by CTFI (< 90 days and ≥ 90 days/or Refractory (RR) [<30 days], Resistant (R) [>=30 and <90 days], Sensitive (S) [>=90 and <180 days] and Very Sensitive (VS)[>=180 days]):

Table 11.3.3.18 Response rate IA and IRC by CTFI (All treated patients).

Response		CTFI< 90 days						CTFI≥ 90 days					
		RR		R		Total		S		VS		Total	
		N	%	N	%	N	%	N	%	N	%	N	%
IA	Complete response (CR)												
	Partial response (PR)												
	Stable disease SD≥4 months												
	Stable disease SD<4 months												
	Progressive disease (PD)												
	Inevaluable for response*												
IRC	Complete response (CR)												
	Partial response (PR)												
	Stable disease SD≥4 months												
	Stable disease SD<4 months												
	Progressive disease (PD)												
	Inevaluable for response*												

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify).

Table 11.3.3.19 ORR IA and IRC by CTFI (All treated patients).

Response rate*			Percentage	Lower 95% limit	Upper 95% limit
IA	CTFI< 90 days	RR			
		R			
		Total			
	CTFI≥ 90 days	S			
		VS			
		Total			
IRC	CTFI< 90 days	RR			
		R			
		Total			
	CTFI≥ 90 days	S			
		VS			
		Total			

(*) Confirmed CR + PR. Binomial exact estimator and 95% CI.

Table 11.3.3.20 Response rate IA and IRC by CTFI (All treated patients).

Response	IA

		Complete response (CR)		Partial response (PR)		Stable disease SD≥4 months		Stable disease SD<4 months		Progressive disease (PD)		Inevaluable for response*	
		N	%	N	%	N	%	N	%	N	%	N	%
CTFI< 90 days													
IRC	Complete response (CR)												
	Partial response (PR)												
	Stable disease SD≥4 months												
	Stable disease SD<4 months												
	Progressive disease (PD)												
	Inevaluable*												
CTFI≥ 90 days													
IRC	Complete response (CR)												
	Partial response (PR)												
	Stable disease SD≥4 months												
	Stable disease SD<4 months												
	Progressive disease (PD)												
	Inevaluable for response*												

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify).
For discrepancies see Listing 11.3.3.15; Percentage in columns

Table 11.3.3.21 Descriptive DR IA and IRC by CTFI.

			N	Mean	Std.	Median	Min	Max
IA	CTFI< 90 days	RR						
		R						
		Total						
	CTFI≥ 90 days	S						
		VS						
		Total						
IRC	CTFI< 90 days	RR						
		R						
		Total						
	CTFI≥ 90 days	S						
		VS						
		Total						

Table 11.3.3.22 DR IA by CTFI.

	CTFI< 90 days*			CTFI≥ 90 days*		
	RR**	R**	Total*	S**	VS**	Total*
N						
Events						
Censored						
Median DR						
DR at 4 months						
DR at 6 months						
DR at 12 months						

(*/**) Kaplan-Meier plot will also be shown. (*) Table/Figure 11.3.3.22.1 with the following categories (CTFI< 90 days and CTFI≥ 90

days), (**) Table /Figure 11.3.3.22.2 with the following categories RR, R, S and VS.

Table 11.3.3.23 DR IRC by CTFI.

	CTFI< 90 days*			CTFI≥ 90 days*		
	RR**	R**	Total*	S**	VS**	Total*
N						
Events						
Censored						
Median DR						
DR at 4 months						
DR at 6 months						
DR at 12 months						

(*/**) Kaplan-Meier plot will also be shown. (*) Table/Figure 11.3.3.23.1 with the following categories (CTFI< 90 days and CTFI≥ 90 days), (**) Table /Figure 11.3.3.23.2 with the following categories RR, R, S and VS.

Table 11.3.3.24 Clinical benefit rate and Disease control rate IA and IRC by CTFI (All treated patients).

				Percentage	Lower 95% limit	Upper 95% limit
Clinical benefit rate*	IA	CTFI< 90 days	RR			
			R			
			Total			
		CTFI≥ 90 days	S			
			VS			
			Total			
	IRC	CTFI< 90 days	RR			
			R			
			Total			
		CTFI≥ 90 days	S			
			VS			
			Total			
Disease control rate**	IA	CTFI< 90 days	RR			
			R			
			Total			
		CTFI≥ 90 days	S			
			VS			
			Total			
	IRC	CTFI< 90 days	RR			
			R			
			Total			
		CTFI≥ 90 days	S			
			VS			
			Total			

(*) CR + PR + SD ≥ 4 months. Binomial exact estimator and 95% CI.
(**) CR + PR + SD. Binomial exact estimator and 95% CI.

Table 11.3.3.25 PFS IA by CTFI (All treated patients).

	CTFI< 90 days*			CTFI≥ 90 days*		
	RR**	R**	Total*	S**	VS**	Total*
N						
Events						
Censored						
Median PFS						
PFS at 4 months						
PFS at 6 months						
PFS at 12 months						

(*/**) Kaplan-Meier plots will also be shown. (*)Table/Figure 11.3.3.25.1 with the following categories (CTFI< 90 days and CTFI≥ 90 days), (**) Table/Figure 11.3.3.25.2 with the following categories RR, R, S and VS.

Table 11.3.3.26 PFS IRC by CTFI (All treated patients).

	CTFI< 90 days*			CTFI≥ 90 days*		
	RR**	R**	Total*	S**	VS**	Total*
N						
Events						
Censored						
Median PFS						
PFS at 4 months						
PFS at 6 months						
PFS at 12 months						

(*/**) Kaplan-Meier plots will also be shown. (*)Table/Figure 11.3.3.26.1 with the following categories (CTFI< 90 days and CTFI≥ 90 days), (**) Table/Figure 11.3.3.26.2 with the following categories RR, R, S and VS.

Table 11.3.3.27 OS by CTFI (All treated patients).

	CTFI< 90 days*			CTFI≥ 90 days*		
	R**	RR**	Total*	S**	VS**	Total*
N						
Events						
Censored						
Median OS						
OS at 6 months						
OS at 12 months						
OS at 24 months						

(*/**) Kaplan-Meier plots will also be shown. (*)Table/Figure 11.3.3.27.1 with the following categories (CTFI< 90 days and CTFI≥ 90 days), (**) Table/Figure 11.3.3.27.2 with the following categories RR, R, S and VS.

Subgroup Analysis excluding CTFI < 30 days:

Table 11.3.3.28 Response rate IA and IRC excluding CTFI<30 (All treated patients).

Response		N	%
IA	Complete response (CR)		
	Partial response (PR)		
	Stable disease SD≥4 months		
	Stable disease SD<4 months		
	Progressive disease (PD)		
	Inevaluable for response*		
IRC	Complete response (CR)		
	Partial response (PR)		
	Stable disease SD≥4 months		
	Stable disease SD<4 months		
	Progressive disease (PD)		
	Inevaluable for response*		

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify).

Table 11.3.3.29 ORR IA and IRC excluding CTFI<30 (All treated patients).

Response rate*	Percentage	Lower 95% limit	Upper 95% limit
IA			
IRC			

(*) Confirmed CR + PR. Binomial exact estimator and 95% CI.

Table 11.3.3.30 DR by IA and IRC excluding CTFI<30.

	IA	IRC
N		
Events		
Censored		

Median DR		
DR at 4 months		
DR at 6 months		
DR at 12 months		

Kaplan-Meier plot will also be shown (Figure 11.3.3.30.1 DR by IA excluding CTFI<30 (All treated patients), Figure 11.3.3.30.2 DR by IRC excluding CTFI<30 (All treated patients) and 11.3.3.30.3 DR by IA and IRC excluding CTFI<30 (All treated patients))

Table 11.3.3.31 Clinical benefit rate and Disease control rate by IA and IRC excluding CTFI<30 (All treated patients).

		Percentage	Lower 95% limit	Upper 95% limit
IA	Clinical benefit rate*			
	Disease control rate**			
IRC	Clinical benefit rate*			
	Disease control rate**			

(*) CR + PR + SD ≥ 4 months. Binomial exact estimator and 95% CI.
(**) CR + PR + SD. Binomial exact estimator and 95% CI.

Table 11.3.3.32 PFS IA and IRC excluding CTFI<30 (All treated patients).

	IA	IRC
N		
Events		
Censored		
Median PFS		
PFS at 4 months		
PFS at 6 months		
PFS at 12 months		

Kaplan-Meier plot will also be shown (Figure 11.3.3.32.1 PFS by IA excluding CTFI<30 (All treated patients), Figure 11.3.3.32.2 PFS by IRC excluding CTFI<30 (All treated patients) and Figure 11.3.3.32.3 PFS by IA and IRC excluding CTFI<30 (All treated patients))

Table 11.3.3.33 OS excluding CTFI<30 (All treated patients).

	OS
N	
Events	
Censored	
Median OS	
OS at 6 months	
OS at 12 months	
OS at 24 months	

Kaplan-Meier plot will also be shown (Figure 11.3.3.33).

DR and PFS considering event in the clinical progressions:

Table 11.3.3.34 DR IA giving event in clinical PD (All treated patients).

	DR
N	
Events	
Censored	
Median DR	
DR at 4 months	
DR at 6 months	
DR at 12 months	

Kaplan-Meier plot will also be shown (Figure 11.3.3.34).

Table 11.3.3.35 PFS IA giving event in clinical PD (All treated patients).

	PFS
N	
Events	
Censored	
Median PFS	
PFS at 4 months	
PFS at 6 months	
PFS at 12 months	

Kaplan-Meier plot will also be shown (Figure 11.3.3.35).

Survival in responders:

Table 11.3.3.36 OS in responders by IA and by CTFI (All treated patients).

	CTFI< 90 days*			CTFI≥ 90 days*			
	R**	RR**	Total*	S**	VS**	Total*	Total***
N							
Events							
Censored							
Median OS							
OS at 6 months							
OS at 12 months							
OS at 24 months							

(*/**/***) Kaplan-Meier plots will also be shown. (*)Table/Figure 11.3.3.36.1 with the following categories (CTFI< 90 days and CTFI≥ 90 days), (**) Table/Figure 11.3.3.36.2 with the following categories RR, R, S and VS. (***) Table/Figure 11.3.3.36.3 for totals.

Table 11.3.3.37 OS in responders by IRC and by CTFI (All treated patients).

	CTFI< 90 days*			CTFI≥ 90 days*			
	R**	RR**	Total*	S**	VS**	Total*	Total***
N							
Events							
Censored							
Median OS							
OS at 6 months							
OS at 12 months							
OS at 24 months							

(*/**/***) Kaplan-Meier plots will also be shown. (*)Table/Figure 11.3.3.37.1 with the following categories (CTFI< 90 days and CTFI≥ 90 days), (**) Table/Figure 11.3.3.37.2 with the following categories RR, R, S and VS. (***) Table/Figure 11.3.3.37.3 for totals.

Table 11.3.3.38 OS in responders by IA and IRC excluding CTFI<30 (All treated patients).

	IA	IRC
N		
Events		
Censored		
Median OS		
OS at 6 months		
OS at 12 months		
OS at 24 months		

Kaplan-Meier plot will also be shown (Figure 11.3.3.38.1 OS in responders by IA excluding CTFI<30 (All treated patients), Figure 11.3.3.38.2 OS in responders by IRC excluding CTFI<30 (All treated patients).

12 Safety Analysis

Safety analysis will be carried out on the "All Treated Patients" population by cohort of tumor types and total population.

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

12.1 Extent of Exposure

12.1.1 Treatment Administration

Table 12.1.1.1 Number of cycles administered and dose intensity.

No. of cycles administered per patient	N	%
1 2 3 …		
Mean, Standard Deviation, Median (Range)		
Time on treatment* (weeks) Median Range Mean Standard Deviation		
PM01183 cumulative dose (mg) Median Range Mean Standard Deviation		
PM01183 dose intensity (mg/m²/wk) Median Range Mean Standard Deviation		
PM01183 relative dose intensity (%) Median Range Mean Standard Deviation		

Note: Also for s1 and s2; (*) Time on treatment: defined as date of last infusion plus 30 days, or date of death or subsequent therapy (whichever comes first) minus date of first infusion.

12.1.2 Cycle Delays

The first cycle will be excluded from all calculations.

Listing 12.1.2.1 Delays.

Patient id.	CTFI*	Delayed cycle	Delayed cycle start date	Previous cycle	Previous cycle start date	Dose delay calculated. (days)	Reason for dose delay	Dose delay, spec.

(*) Only for SCLC (RR, R, S, VS).

Table 12.1.2.2 Number of patients and cycles with dosing delay, any relationship.

	N	%
No. of patients treated		
No. of patients susceptible of delay		
No. of patients with any dose delay		
No. of cycles administered		
No. of cycles susceptible to be delayed		
No. of cycles with dosing delay		
No. of patients with No cycles delayed 1 cycle delayed 2 cycles delayed ≥ 3 cycles delayed		

Note: Also for s1 and s2.

Table 12.1.2.3 Number of patients and cycles with dosing delay, treatment related.

	N	%
No. of patients treated		
No. of patients with drug related dose delay		
No. of cycles administered		
No. of cycles susceptible to be delayed		
No. of cycles with drug related dose delay		
No. of patients with No cycles delayed 1 cycle drug related delayed …..		

Note: Also for s1 and s2.

Table 12.1.2.4 Reasons for dosing delay according to the relationship.

Reasons for delays	N	%
No. of patients with any dose delay		
Treatment-related	X	XX.X
Hematological		
Non-hematological		
Both		
Non-treatment-related		
No. of cycles with any dose delay	N	%
Treatment-related	X	XX.X
Hematological		
Non-hematological		
Both		
Non-treatment-related		

Note: Also for s1 and s2;

Table 12.1.2.5 Length of dosing delay.

		Treatment-related**		Non-treatment-related		Total	
Length of delay	Median (range)						
Length of delay		N	%	N	%	N	%
<= 7 days							
>7 days and <=14 days							
> 14 days							

Note: Also for s1 and s2.

Listing 12.1.2.6 Cycle delays due to AEs.

Patient id.	CTFI*	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	No. of days with delay	Action taken	Significant consequences

AEs with action = 'Dose delayed' or 'Reduced and delayed'. (*) Only for SCLC (RR, R, S, VS).

12.1.3 Dose Reductions

The first cycle will be excluded from all calculations.

All dose reductions should be considered and described, specifying the reason for reduction (hematological toxicity, non-hematological toxicity or other causes).

Listing 12.1.3.1 Dose reductions.

Patient id.	CTFI*	Cycle	Day	Cycle start date	Previous dose	Reduced dose	Reason for dose reduction	Dose reduction Spec.

(*) Only for SCLC (RR, R, S, VS).

Table 12.1.3.2 Number of patients and cycles with dose reduction, any relationship.

	N	%
No. of patients treated	X	XX.X
No. of patients susceptible to have a dose reduction		
No. of patients with any dose reduced		
No. of patients with:		
No PM01183 reduction		
1 cycle with PM01183 dose reduced		
2 cycles with PM01183 dose reduced		
No. of cycles administered		
No. of cycles susceptible to have any dose reduced		
No. of cycles with PM01183 dose reduced		

Note: Also for s1 and s2.

Table 12.1.3.3 Number of patients and cycles with dose reduction, treatment related.

	N	%
No. of patients treated	X	XX.X
No. of patients with any dose reduced (Treatment-related)		
No. of patients with:		
No PM01183 reduction		
1 cycle with PM01183 dose reduced (Treatment-related)		
2 cycles with PM01183 dose reduced (Treatment-related)		
No. of cycles administered		
No. of cycles susceptible to have any dose reduced		
No. of cycles with PM01183 dose reduced (Treatment-related)		

Note: Also for s1 and s2.

Table 12.1.3.4 Number of patients and cycles with dose reduction according to the relationship.

Reasons for reductions	N	%
No. patients with reductions		
Treatment-related	X	XX.X
Hematological		
Non-hematological		
Both		
Non-treatment-related		
No. of cycles patients with reductions	N	%
Treatment-related	X	XX.X
Hematological		
Non-hematological		
Both		
Non-treatment-related		

Note: Also for s1 and s2.

Listing 12.1.3.5 Dose reductions due to AEs.

Patient id.	CTFI*	Total no. of cycles	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolution date	Action taken	Significant consequences

AEs with action = 'Dose reduced/adjusted' or 'Reduced and delayed'. (*) Only for SCLC (RR, R, S, VS).

12.1.4 Temporarily Interrupted Infusions

A listing of the patients who had temporarily interrupted infusions, with the corresponding reasons, will be provided.

Listing 12.1.4.1 Interrupted infusions.

Patient id.	Cycle	Reason

12.1.5 Prophylactic Medication Administration

A listing of the patients who have not received corticosterioids, 5-HT3 antagonists, prokinetics and other antiemetics or equivalents with the corresponding reasons will be reported.

Listing 12.1.5.1 Patients and cycles with prophylactic medication not taken per protocol.

Patient id.	Cycle	Prophylactic medication not taken*	Reason
…			

(*) Corticosterioids, 5-HT3 antagonists, prokinetics and other antiemetics.

12.2 Adverse Events

12.2.1 Treatment Emergent Adverse Events

Treatment emergent adverse events will be described in this section; treatment-related events (stated as related to the study drug or of unknown relationship) will be tabulated.

Type of toxicity and worst grade or severity by cycle and by patient will be summarized according to the Preferred Term coded with MedDRA. Tables will be organized per category of events using System Organ Class of MedDRA.

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) and the total population (if applicable).

12.2.2 Display of Treatment Emergent Adverse Events

Table 12.2.2.1 Summary of treatment emergent adverse events per patient.

Category**	N	%
Patients with at least one TEAE regardless of relationship		
Any treatment-related** AE		
Any grade ≥3 TEAE		
Any treatment-related grade ≥3 AE		
Any Treatment emergent SAE in DB		
Any treatment-related SAE		
Any grade ≥3 Treatment emergent SAE		
Any treatment-related grade ≥3 SAE		
TEAEs leading to death		
Treatment-related AE leading to death		
TEAEs leading to dose delay***		
TEAEs leading to dose reduction***		
TEAEs leading to treatment discontinuation		
Treatment-related AEs leading to treatment discontinuation		

Note: Also for s1 and s2; (*) Percentage based on number of treated patients; (**) Treatment related adverse event is every event whose relationship is 'Yes' or 'Unknown'. (***) TEAEs leading to dose delay and reduction according to the AE form, with no delay or reduction because the patient discontinues treatment and there is no additional cycle administered are not counted here.

Table 12.2.2.2 Treatment-related adverse events. Worst grade by patient.
Table 12.2.2.3 Treatment-related adverse events. Worst grade by cycle.
Table 12.2.2.4 Treatment emergent adverse events regardless of relationship. Worst grade by patient.
Table 12.2.2.5 Treatment emergent adverse events regardless of relationship. Worst grade by cycle.

Tables 12.2.2.2 to 12.2.2.5 will have the following pattern, but depending on the number and severity of the adverse events observed, the NCI-CTCAE v4 grades may be grouped as ≥1 and ≥3 categories.

SOC	Preferred term	Grade 1		…	Grade 4		Grade ≥1		Grade ≥3
		N	%	…	N	%	N	%	
Blood and lymphatic system disorders	Anemia NOS								
	...								
	…								
Cardiac disorders	Arrhythmia NOS								
	…								

Note: Tables 12.2.2.2 and 12.2.2.4 also for s1 and s2.

Listing 12.2.2.6 Treatment-related grade ≥3 adverse events. Worst grade per patient.
Listing 12.2.2.7 Treatment-related grade ≥3 adverse events. Worst grade by cycle.
Listing 12.2.2.8 Grade ≥3 treatment emergent adverse events regardless of relationship. Worst grade per patient.
Listing 12.2.2.9 Grade ≥3 treatment emergent adverse events regardless of relationship. Worst grade by cycle.

Listings 12.2.2.6 to 12.2.2.9 will have the following pattern:

Patient id.	CTFI**	Cycle*	SOC name	Preferred term	Grade

(*) NA in the per patient summaries; (**) CTFI only for SCLC patients (RR, R, S, VS).

At the time of the analysis, if appropriate, grouping of similar or clinically related AEs will be made.

12.3 Serious Adverse Events and Deaths.

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

12.3.1 Serious Adverse Events

Listing 12.3.1.1 SAEs.

Patient id.	Preferred term code	Onset cycle	Intended Dose of onset cycle (mg/m2)	Adverse event reported (verbatim)	Status	Grade	Relationship	Onset date	Resolution date	Action	Serious criteria

The Pharmacovigilance Department will provide the narratives of the SAEs from the Pharmacovigilance Database (DB).

Table 12.3.1.2 Treatment-related serious adverse events. Worst grade by patient.
Table 12.3.1.3 Treatment-related serious adverse events. Worst grade by cycle.
Table 12.3.1.4 Serious adverse events regardless of relationship. Worst grade by patient.
Table 12.3.1.5 Serious adverse events regardless of relationship. Worst grade by cycle.

Tables 12.3.1.2 to 12.3.1.5 will have the following pattern, but depending on the number and severity of the adverse events observed, the NCI-CTCAE v4 grades may be grouped as ≥1 and ≥3 categories.

SOC	Preferred term	Grade 1		…	Grade 4		Grade ≥1		Grade ≥3	
		N	%	…	N	%	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS									
	...									
	…									
Cardiac disorders	Arrhythmia NOS									
	…									

Note: Tables 12.3.1.2 and 12.3.1.4 also for s1 and s2;

Listing 12.3.1.6 Treatment-related grade ≥3 serious adverse events. Worst grade per patient.
Listing 12.3.1.7 Treatment-related grade ≥3 serious adverse events. Worst grade by cycle.
Listing 12.3.1.8 Grade ≥3 serious adverse events regardless of relationship. Worst grade per patient.
Listing 12.3.1.9 Grade ≥3 serious adverse events regardless of relationship. Worst grade by cycle.

Listings 12.3.1.6 to 12.3.1.9 will have the following pattern:

Patient id.	CTFI**	Cycle*	SOC name	Preferred term	Grade

(*)NA in the patient summaries; (**) CTFI only for SCLC patients (RR, R, S, VS).

12.3.2 Deaths

Table 12.3.2.1 Cause of death.

Reason*	N	%
Malignant disease		
Study drug-related TEAE		
Non-study drug-related TEAE		
Other		
Total		

Note: Also for s1 and s2; (*) Denominator=Number of patients who died.

Listing 12.3.2.2 Deaths.

Patient id.	CTFI***	Death date	Cause	No. of cycles administered	Last infusion date	Time on treatment*	Time from Last dose **	Comments	Autopsy

(*) Time on treatment: defined as date of last infusion plus 30 days, or date of death or subsequent therapy (whichever comes first) minus date of first infusion. (**) Time from last dose defined as date of death minus date of last infusion. (***) Only for SCLC cohort (RR, R, S, VS).

Listing 12.3.2.3 Adverse events with outcome of death.

Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Date of death	Action

12.4 Clinical Laboratory Evaluation

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

12.4.1 Hematological Abnormalities during Treatment

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

Table 12.4.1.1 Hematological abnormalities, worst grade per patient.
Table 12.4.1.2 Hematological abnormalities, worst grade per cycle.

Tables 12.4.1.1 and 12.4.1.2 will have the following pattern but depending on the number and severity of the adverse events observed, the NCI-CTCAE v4 grades may be grouped as ≥1 and ≥3 categories.

	Grade 1		…	Grade 4		Grade ≥1		Grade ≥3	
	N	%	…	N	%	N	%	N	%
Anemia									
Leukopenia									
Neutropenia									
Lymphopenia									
Thrombocytopenia									

Note: Tables 12.4.1.1 and 12.4.1.2 also for s1 and s2.

Listing 12.4.1.3 Grade ≥3 hematological abnormalities. Worst grade per patient.

Patient id.	Test	Grade

Listing 12.4.1.4 Grade ≥3 hematological abnormalities. Worst grade per cycle.

Patient id.	Cycle	Test	Grade

Listing 12.4.1.5 Hematological tests not assessed by patient and cycle.

Patient id.	Total number of cycles	Cycle with missing lab. test	Lab. test

12.4.2 Biochemical Abnormalities during Treatment

Table 12.4.2.1 Biochemical abnormalities, worst grade per patient.
Table 12.4.2.2 Biochemical abnormalities, worst grade per cycle.

Tables 12.4.2.1 and 12.4.2.2 will have the following pattern but depending on the number and severity of the adverse events observed, the NCI-CTCAE v4 grades may be grouped as ≥1 and ≥3 categories.

	Grade 1		…	Grade 4		Grade ≥1		Grade ≥3	
	N	%	…	N	%	N	%	N	%
AST increased									
ALT increased									
Total bilirubin increased									
AP increased									
Hyperglycemia									
Hypoglycemia									
…									

Note: Tables 12.4.2.1 and 12.4.2.2 also for s1 and s2.

Listing 12.4.2.3 Grade ≥3 biochemical abnormalities. Worst grade per patient.

Patient id.	Test	Grade

Listing 12.4.2.4 Grade ≥3 biochemical abnormalities. Worst grade per cycle.

Patient id.	Cycle	Test	Grade

Listing 12.4.2.5 Biochemical tests not assessed by patient and cycle.

Patient id.	Total number of cycles	Cycle with missing lab. test	Lab. test

12.4.3 Coagulation Abnormalities during Treatment

Table 12.4.3.1 Coagulation abnormalities, worst grade per patient.
Table 12.4.3.2 Coagulation abnormalities, worst grade per cycle.

Tables 12.4.3.1 and 12.4.3.2 will have the following pattern but depending on the number and severity of the adverse events observed, the NCI-CTCAE v4 grades may be grouped as 1-3 category.

	Grade 1		…	Grade 3		Grade ≥1		Grade ≥3	
	N	%	…	N	%	N	%	N	%
INR increased									
APTT prolonged									

Listing 12.4.3.3 Grade 3 coagulation abnormalities. Worst grade per patient.

Patient id.	Test	Grade

Listing 12.4.3.4 Grade 3 coagulation abnormalities. Worst grade per cycle.

Patient id.	Cycle	Test	Grade

Listing 12.4.3.5 Coagulation tests not assessed by patient and cycle.

Patient id.	Total number of cycles	Cycle with missing lab. test	Lab. test

12.4.4 Laboratory Values over Time

Table 12.4.4.1 Evolution of hematological abnormalities from baseline, worst case per patient.
Table 12.4.4.2 Evolution of hematological abnormalities from baseline, worst case in the first cycle per patient.
Table 12.4.4.3 Evolution of biochemical abnormalities from baseline, worst case per patient.
Table 12.4.4.4 Evolution of biochemical abnormalities from baseline, worst case in the first cycle per patient.

Tables 12.4.4.1 to 12.4.4.4 will have the following pattern:

		Baseline grade*	Worst grade per patient						Total	
			0		1		…			
			N	%	N	%	N	%	N	%
Baseline	Parameter 1	Grade 0								
		Grade 1								
		……								
	Parameter 2	Grade 0								
		Grade 1								
		……								
	….	Grade 0								
		Grade 1								
		……								

(*) Defined as the last value recorded before or on the date of first infusion.

Table 12.4.4.5 Platelet count time course pattern (summary).
Table 12.4.4.6 Neutrophil count time course pattern (summary).

Tables 12.4.4.5 and 12.4.4.6 will have the following pattern:

	All cycles	First cycle
	N, Mean, Std., Median, Range	N, Mean, Std., Median, Range
Grade ≥3* onset day		
Nadir (x10^9/L)		
Duration of grade ≥3 (days)		
Day of recovery to grade 1/2 or baseline values**		

(*) Grade 3 or 4; (**) grade 2 or less.

Table 12.4.4.7 AST time course pattern (summary).
Table 12.4.4.8 ALT time course pattern (summary).

Tables 12.4.4.7 and 12.4.4.8 will have the following pattern:

	All cycles	First cycle
	N, Mean, Std., Median, Range	N, Mean, Std., Median, Range
Grade ≥3* onset day		
Peak (xULN)		
Duration of grade ≥3 (days)		
Day of recovery to grade 1/2 or baseline values**		

(*) Grade 3 or 4; (**) grade 2 or less.

12.5 Physical Findings, PS, LVEF, ECG and Other Tests

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

12.5.1 Physical Findings and PS (ECOG)

Listing 12.5.1.1 ECOG performance status during the study.

	Cycle/ECOG PS*						
	0	1	2	3	4	…	EOT
Patient id.							
…							
…							

(*) Worst ECOG PS score of the cycle determinations.

Listing 12.5.1.2 Weight by patient per cycle.

	Cycle/Weight						
	0 (kg)	1* (%)	2* (%)	3* (%)	4* (%)	…* (%)	EOT* (%)
Patient id.							
…							

(*) % of changes compared to baseline.

12.5.2 LVEF, ECG and Other Related Tests

Listing 12.5.2.1 Patients with abnormal or clinical indicated LVEF during the study.

Patient id.	Assessment date	Abnormality	Specify	Reason for clinically indicated	Method	LVEF (%)	Institution normal range

Listing 12.5.2.2 Patients with abnormal or clinical indicated Electrocardiogram during the study.

Patient id.	Assessment date	Result	Specify	Reason for clinically indicated repeat	PR interval (msec)	Heart rate (bpm)	QT interval (msec)	QRS complex (msec)	QTc Fridericia	QTc* (Bazett's)

(*) QTc (Bazett's) = QT interval / √(60/Heart rate).

12.6 Concomitant Therapy / Procedures According to the ATC Classification.

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

Table 12.6.1 Concomitant medication during treatment (ATC1/ATC2/ATC3/ATC4/PN).

Concomitant medication	N	%
Alimentary tract and metabolism		
Antacids		
Magnesium compounds		
Magnesium adipate		
…		
Blood and blood forming organs		
Antithrombotic agents		
Vitamin K antagonists		
Acenocoumarol		
…		

Table 12.6.2 Summary of concomitant medication during treatment.

	N	%
No. of systems (ATC1 level) 0 1 2 ≥ 3 Mean, Standard Deviation, Median (Range)		
No. of indications (ATC2 level) 0 1 2 ≥ 3 Mean, Standard Deviation, Median (Range)		
No. of agent families (ATC4 level) 0 1 2 ≥ 3		

Mean, Standard Deviation, Median (Range)		
No. of agents (PN level) 0 1 2 ≥ 3 Mean, Standard Deviation, Median (Range)		

Table 12.6.3 Patients and cycles with any transfusions/GCSF during treatment.

	N	%
No. of patients with Platelet transfusions No. of cycles with Platelet transfusions		
No. of patients with RBC No. of cycles with RBC		
No. of patients with GCSF		

Note: Also for s1 and s2.

Listing 12.6.4 Patients with any transfusion during treatment.

Patient id.	Cycle	PM1183 dose in the previous cycle	Platelets / RB	Date of first transfusion	Date of last transfusion	No. of units required*

(*) No. of transfusions for platelets or No. of packed RBC transfusions.

Listing 12.6.5 Patients with GCSF during treatment.

Patient id.	Cycle	Date	Medication	Reason	Specify

12.7 Subsequent therapy.

Table 12.7.1 Any Subsequent medical therapy.

	N	%
Type		
Medical therapy		
Radiotherapy		
Surgery		
Number of subsequent medical therapies (Median and range)		
0		
1		
2		
…		
Subsequent agents of medical therapy (ATC)		
…		
…		

Note: Also for s1 and s2.

Table 12.7.2 First Subsequent medical therapy.

	N	%
Subsequent chemotherapy agents (ATC)		
…		
…		

Note: Also for s1 and s2.

Table 12.7.3 First Subsequent medical therapy. Best response (if available).

Best response	First Subsequent therapy

		CR	PR	SD	PD	NE
PM01183	CR					
	PR					
	SD					
	PD					
	NE					

Note: Also for s1 and s2; (*) If a low number of best responses to the subsequent therapy are available, a listing, instead of this table, will be provided. In case of sufficient number of subsequent Immunotherapy, a separate table/listing will be performed for patients having immunotherapy as first subsequent therapy.

Table 12.7.4 First Subsequent medical therapy. PFS (if available).

PFS (months)		First Subsequent therapy				
		<1 month	[1-3) months	[3-6) months	[6-12) months	≥12 months
PM01183	<1 month					
	[1-3) months					
	[3-6) months					
	[6-12) months					
	≥12 months					

Note: Also for s1 and s2;

Any other exploratory analyses will be performed at the analysis time if any relevant variable will be considered potentially relevant. Table's layout will follow the same prior patterns.

12.8 Subgroup Analyses Related to Safety.

Table 12.8.1 Worst grade ≥3 by patient in special subgroups (Sex).

Table 12.8.2 Worst grade ≥3 by cycle in special subgroups (Sex).

Table 12.8.3 Worst grade ≥3 by patient in special subgroups (Age*).

Table 12.8.4 Worst grade ≥3 by cycle in special subgroups (Age*).

Table 12.8.5 Worst grade ≥3 by patient in special subgroups (Race).

Table 12.8.6 Worst grade ≥3 by cycle in special subgroups (Race).

Table 12.8.7 Worst grade ≥3 by patient in special subgroups (Number of prior lines*).

Table 12.8.8 Worst grade ≥3 by cycle in special subgroups (Number of prior lines*).

Table 12.8.9 Worst grade ≥3 by patient in special subgroups (BSA*).

Table 12.8.10 Worst grade ≥3 by cycle in special subgroups (BSA*).

Table 12.8.11 Worst grade ≥3 by patient in special subgroups (ECOG).

Table 12.8.12 Worst grade ≥3 by cycle in special subgroups (ECOG).

Table 12.8.13 Worst grade ≥3 by patient in special subgroups (Geographical area*).

Table 12.8.14 Worst grade ≥3 by cycle in special subgroups (Geographical area*).

Table 12.8.15 Worst grade ≥3 by patient in special subgroups (AAGP*).

Table 12.8.16 Worst grade ≥3 by cycle in special subgroups (AAGP*).

Tables 12.8.1 to 12.8.16 will have the following pattern:

Laboratory abnormalities/ drug-related AEs	Subgroup 1			Subgroup 2			….		
	No. of patients/cycles evaluated	Grade ≥3	%	No. of patients/cycles evaluated	Grade ≥3	%	No. of patients/cycles evaluated	Grade ≥3	%
Thrombocytopenia									
Neutropenia									
AP									
Bilirubin									
AST									

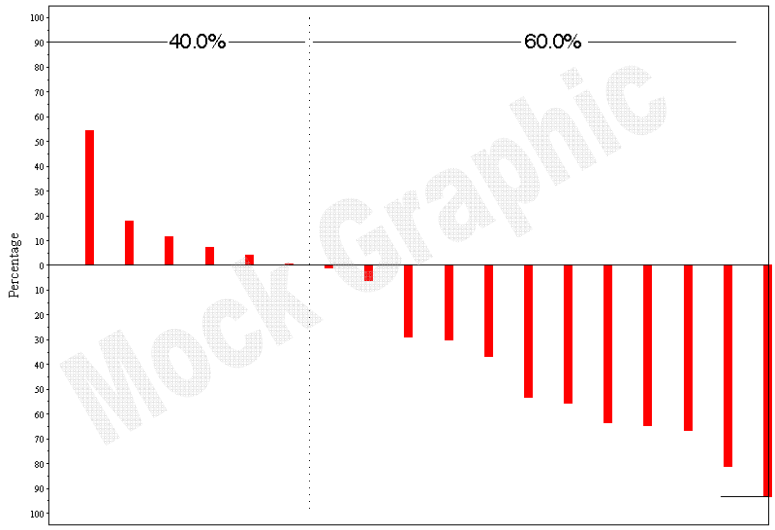
Laboratory abnormalities/ drug-related AEs	Subgroup 1			Subgroup 2			….		
	No. of patients/cycles evaluated	Grade ≥3	%	No. of patients/cycles evaluated	Grade ≥3	%	No. of patients/cycles evaluated	Grade ≥3	%
ALT									
CPK									
Nausea									
Vomiting									
Fatigue									
Other**									

(*) Categories Age (<65 yrs vs >=65 yrs); Number of prior lines (1 line vs >=2 lines); BSA (=< 1.8 m2 vs. > 1.8 m2) Geographical area (Europe vs US); Alpha-glycoprotein (ULN<= vs >ULN). (**)Any drug-related toxicity present in >=5% of patients in any group.

13 Figures

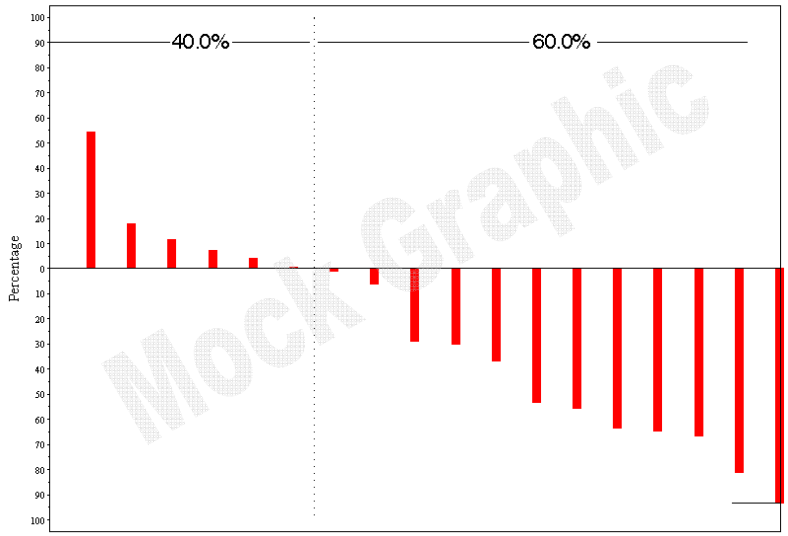
Figures displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable) and/or any other specific subgroups (e.g: CTFI categorized). See examples below, numbering will be updated accordingly.

Figure 13.1.1 Waterfall graph by subgroup.



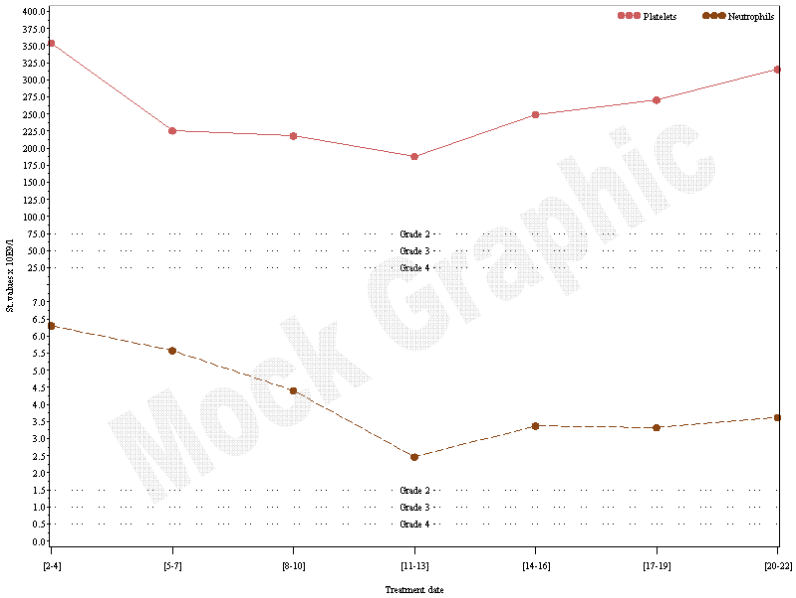
Waterfall for each tumor type will be also provided. Also SCLC by CTFI (RR, R, S VS).

Figure 13.1.2 Waterfall graph by IRC (SCLC cohort).



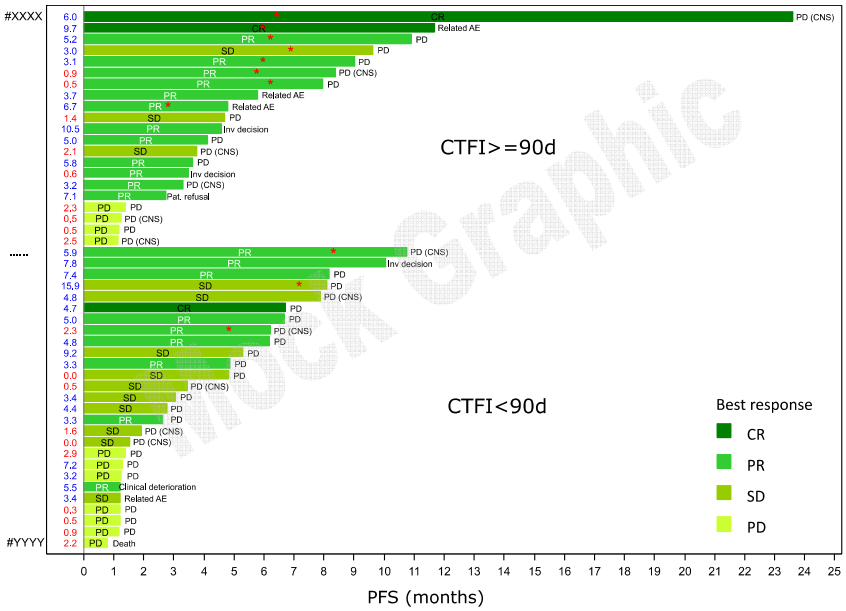
Waterfall for SCLC and by CTFI (RR, R, S VS).
NOTE: If the measurements of the first and the second radiologists are the same, the target lesions measurements of the first one will be selected. If the measurements of both radiologists are different and an adjudicator is involved, his/her endorsement will be selected.

Figure 13.1.3 Pattern of hematological/non-hematological abnormalities per tumor type.



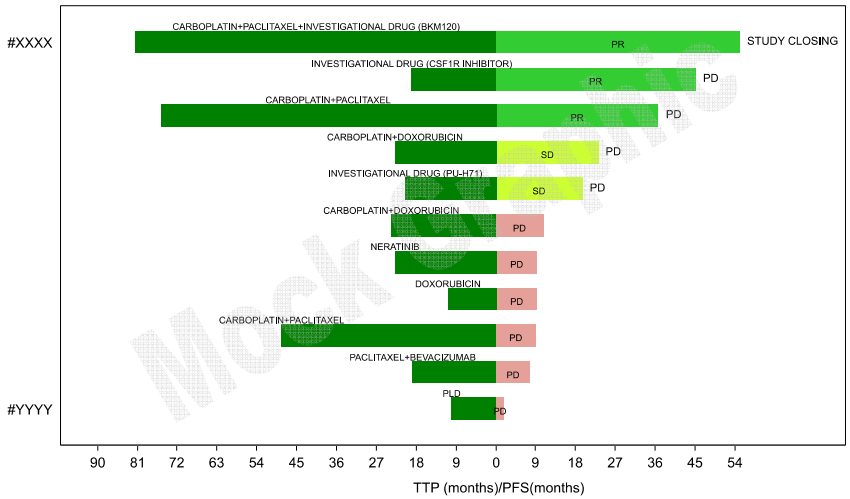
Hematological abnormalities include neutrophils and platelets; non-hematological abnormalities include AST and ALT.

Figure 13.1.4 Best response, PFS and Reasons for discontinuation (SCLC cohort).



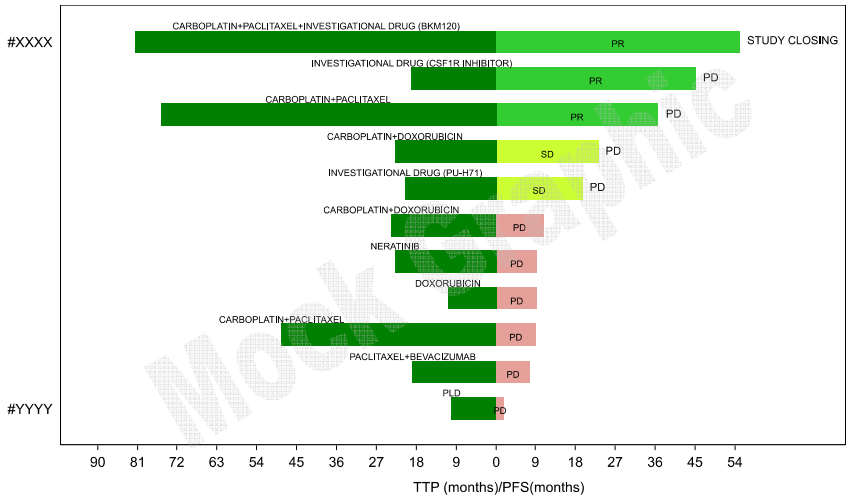
Also for s1 and s2.

Figure 13.1.5 Last previous TTP vs PFS PM01183 (SCLC cohort).

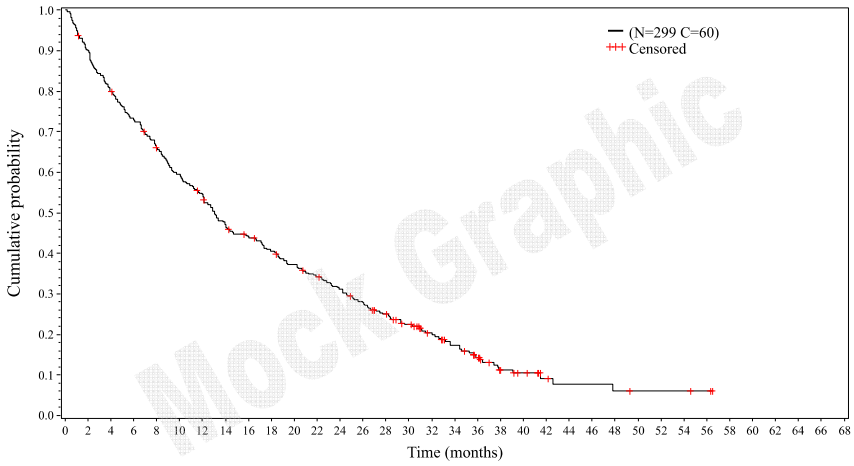


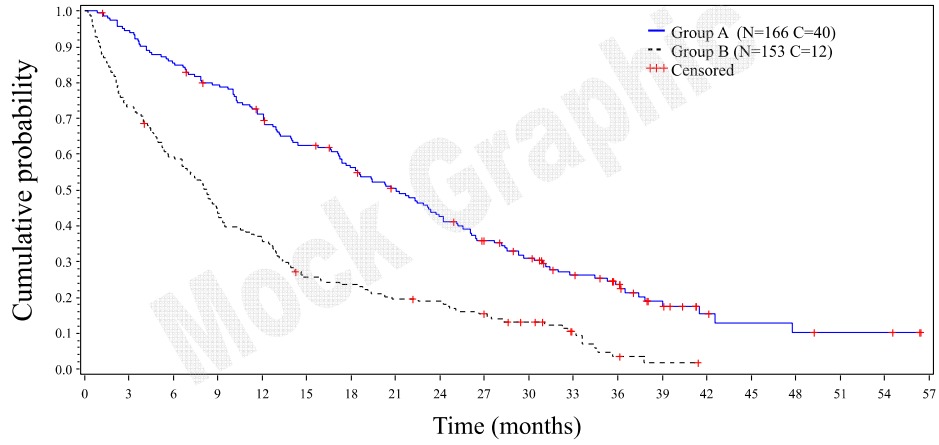
Note: For PM01183 responders and/or SD (if applicable)

Figure 13.1.6 Last previous Immunotherapy TTP vs PFS PM01183 (SCLC cohort).



Figures described in **Section 11.3 Efficacy Analysis** will have the following patterns depending on the number of groups represented:





Number of patients at risk

Group A	166	156	141	129	115	100	88	77	65	52	43	32	24	14	7	5	4	3	3
Group B	153	112	90	66	55	38	35	29	27	21	16	9	3	1					

APPENDIX II

14 DB Listings, BIMO and ICH listings

CRF Listings.

Listing 14.1.1: Cover.

Patient id.	Informed Consent Date	Part of QT substudy?	QT informed consent date	Patient QT inclusion accepted by Pharmamar?	PGN/PGx consent	PGN/PGx date

Listing 14.1.2: Study registration.

Patient id.	Patient inclusion accepted by Pharmamar?	Eligibility requirements?	Criterion identifier I/E	I/E details

Listing 14.1.3: Demography.

Patient id.	Age at inclusion	Gender	Race	Other Race, specify

Listing 14.1.4: Pregnancy test and adequate contraception.

		Pregnancy test						Adequate contraception	
Patient id.	Visit	Not applicable?	Reason	Not done?	Sample date	Result	Reason for clinically indicated repeat	Adequate contraception?	Specify

Listing 14.1.5: Prior medical history.

Patient id.	Event/Condition	System Organ Class	MedDRA Preferred Term	Onset date	End date	Ongoing?

Listing 14.1.6: Cancer history.

			Current stage				At diagnosis		
Patient id.	Tumor type	….*	Date of advanced/metastasic disease	Date of last PD	Sites:Primary tumor/local relapse (Not for UPS)	Sites**	Diagnosis date	Stage	TNM

(*) For each tumor type CRF has specific categories. e.g: Endometrial patients; (Carcinoma type, Histology type, Other)
(**)Tumor sites are nested for each patient obtained from Cancer History Form e.g: (Lung/Liver/LN:/Neck LN/Mediastinal LN);

Listing 14.1.7: Prior surgery.

Patient id.	None?	Site and Procedures	Date	Intention

Listing 14.1.8: Prior radiotherapy.

Patient id.	None?	Type	Intention	Site	Total dose	First dose	Last dose

Listing 14.1.9: Prior medical therapy.

Patient id.	None?	Regimen	Setting	Agent	Agent	Agent Class	Setting	Start Date	Stop Date	Best	Prog. Date	Non PD

					Coded					Resp.		

Listing 14.1.10: Hematological laboratory values.

Patient id.	Visit	Date	n	Clinically indicated repeat required?	Hemoglobin (g/dl)	Platelets (x10*9/L)	WBC (x10*9/L)	Neutrophils (x10*9/L)	Lymphocytes (x10*9/L)	Monocytes (x10*9/L)

Listing 14.1.11: Biochemical laboratory values.

Patient id.	Visit	Date	n	Clinically indicated repeat required?	Total Bilirubin (mg/dl)	Direct Bilirubin (mg/dl)	AST (IU/L)	ALT (IU/L)	AP (IU/L)	…..*

(*) GGT (IU/L), Glucose (mmol/L), Creatinine (mg/dl), CrCl (mL/min), NA (mmol/L), CL (mmol/L), K (mmol/L), LDH (IU/L), CPK (IU/L), Total Proteins (g/dl), Albumin (g/dl), CA (mmol/L), Mg (mg/dl), AFP (ng/m), hCG (IU/L).

Listing 14.1.12: Alpha Glycoprotein.

Patient id.	Visit	Date	n	Alpha-1-acid glycoprotein (MG/DL)	Comments 1	Comments 2

Listing 14.1.13: Coagulation laboratory values.

Patient id.	Visit	Date	n	Clinically indicated repeat required?	INR (ratio)	PT (sec/ratio)	PTT (sec/ratio)

Listing 14.1.14: Physical examination.

Patient id.	Visit	Not done	Date	Abnormalities	Weight (Kg)	Height (cm)	BSA (m2)	Body System	Findings	Clinical Significance

Listing 14.1.15: Performance status.

Patient id.	Not Done	Visit	ECOG

Listing 14.1.16: Vital signs.

Patient id.	Not done	Visit	Date	Heart Rate (BPM)	Systolic (mmHG)	Diastolic (mmHG)	Temperature (ºC)

Listing 14.1.17: Electrocardiogram.

Patient id.	Not done	Visit	ECG Date	Result	Abnormal, specify	PR Interval(msec)	Heart rate (bpm)	QT Interval(msec)	QRS Interval(msec)	Corrected QT Fridericia

Listing 14.1.18: LVEF.

Patient id.	Not done	Visit	LVEF Date	Type	Value	Range	Result	Abnormal, specify	Reason for clinically indicated

Listing 14.1.19: Prophylactic medication.

Patient	Visit	Medication	Drug	...*	Route	Daily	Units	Start	End	Time	Taken per	Specify

id.			Type			Dose		date	date		protocol	

(*) ATC1, ATC2, ATC3, ATC4.

Listing 14.1.20: Drug administration.

								Reductions		Delays		
Patient id.	Visit	Admin. date	Start time	End time	Intended dose	Total dose	Adm. Volume	Dose reduced?	Reason	Dose delayed?	Reason	Dose interrupted?

Listing 14.1.21: Adverse events (including adverse events at baseline).

Patient id.	Adverse Event Verbatim	NCI-CTC Grade	SAE	Onset cycle	Onset date	Ongoing	End cyc.	End date	Ongoing/ Continuing	Relationship Specify	Action taken	Seriousness Criteria

Listing 14.1.22: Concomitant therapy/procedures.

Patient id.	Medication type	Medication	Reason	…*	Route/Dose(Units)/Time interval	Start date	End date	Indication	AE	Other

(*) ATC1, ATC4

Listing 14.1.23: Tumor assessment.

	Target			Non target		New lesions		
Patient id.	…..*	Sum of Diameters	Var.(%)	….*	Response	…*	Longest diameter	Non-measurable

(*) Visit, Not done, lesion, organ site, date, method. Sort by Visit and then by Start date,

Listing 14.1.24: Evaluation of response by cycle.

Patient id.	Visit	Not done?	Date	Response Target lesions	Response Non Target Lesions	New lesions?	Overall cycle response

Listing 14.1.25: Best study overall response by IA and IRC and End of treatment.

Patient id.	CTFI*	Best Response by IA**	Best Response by IRC*	End of treatment Reason	End of treatment, Specify

(*) Only for SCLC cohort. (**) Data obtained from radiological assessment of response in the CRF

Listing 14.1.26: Follow up.

Patient id.	Follow-up date	Survival status	Previous PD or Therapy	TA Done	Reason	Type of therapy	Start date	End date	Treatment*	Best response**	Progression date**

(*) Procedure for surgery, localization for radiotherapy or agent for medical therapy.
(**) Only for Medical therapy. Sort by FU date first and then by Start date.

Listing 14.1.27: Off study and Death report form.

	Off study				Death report			
Patient id.	Off study Reason	If other Specify	Off study date	Best response	Death Date	Cause	Specify	Autopsy?

Listing 14.1.28: Investigator comments and Investigator comments before end of study.

Patient id.	Page name	Instance	Variable	Comment

To fulfil the Office of Scientific Investigations (OSI) request, the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications will be provided following the recommended standardized formats.

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

Listing 15.1 Site Level Summary.

Site	Patients Screened	Patients Treated	Patients End of Treatment	Patients Off Study

Listing 15.2 Consented Subjects by Site.

Site	Patient id.	Informed Consent date	Screening failure?	Date of Screening failure	Met Eligibility	Criterion Identifier	Details	Treated	Date of First treatment

Listing 15.3 Treatment Assignment by Site.

Site	Patient id.	DA Start date	First Intended dose

Listings 15.4 Discontinuations by Site.

Site	Patient id.	End of treatment Reason	End of treatment, Specify	Off study date	Off study Reason	If other Specify

Listings 15.5 Study Population by Site.

Site	Patient id.	Included population	Treated population	Reason	Evaluable population	Reason

Listings 15.6 Inclusion and Exclusion Criteria by Site.

Site	Patient id.	Eligibility requirements?	Criterion identifier I/E	I/E details

Listings 15.7 Adverse Events by Site.

Site	Patient id.	Adverse Event Verbatim	NCI-CTC Grade	SAE	Onset cycle	Onset date	End cyc.	End date	Relationship Specify	Action taken	Seriousness Criteria

Listings 15.8 Protocol Deviations by Site.

Site	Patient id.	Deviation type	Deviation

Listings 15.9 Efficacy Endpoints by Site.

Site	Patient id.	Best response by IA	Best response by IRC	PFS by IA (months)	PFS by IRC (months)	DOR by IA (months)	DOR by IA (months)	OS (months)	Death status

Listings 15.10 Concomitant Medications by Site.

Site	Patient id.	Medication type	Medication	Reason	…*	Route/Dose(Units)/Time interval	Start date	End date	Indication

(*) ATC1, ATC4

Listings 15.11.1 Laboratory measurements by Site.

Site	Patient id.	Visit	Date	Laboratory	Hemoglobin (g/dl)	Platelets (x10*9/L)	WBC (x10*9/L)	Neutrophils (x10*9/L)	Lymphocytes (x10*9/L)	Monocytes (x10*9/L)	…..*

(*) Total Bilirubin, Direct Bilirubin in (mg/dl), AST, ALT, AP, GGT in (IU/L), Glucose (mmol/L), Creatinine (mg/dl), CrCl (mL/min), NA (mmol/L), CL (mmol/L), K (mmol/L), LDH (IU/L), CPK (IU/L), Total Proteins (g/dl), Albumin (g/dl), CA (mmol/L), Mg (mg/dl), INR (ratio), PT (sec/ratio), PTT (sec/ratio) AFP (ng/m), hCG (IU/L), AAGP (mg/dl).

Listings 15.11.2 Electrocardiogram by Site.

Site	Patient id.	Not Done	Visit	Date	Results	Abnormal, Specify	PR interval (msec)	Heart rate (bpm)	QT Interval (msec)	QRS interval (msec)	Corrected QT Fridericia

Listings 15.11.3 LVEF by Site.

Site	Patient id.	Not Done	Visit	Date	Method	LVEF (%)	Range Lowe Limit	Abnormality	Specify	Reason for Clinically Indicated Repeat

In accordance with ICH E-3 guidelines, the patient listings specified as Section 16.2 will be prepared by tumor type and for the total of patients.

Listing 16.2.1 Discontinued Patients.

Patient id.	Institution	Treated	Cycles received	First infusion date	Last infusion date	Reason for end of treatment	Comments

Listing 16.2.2 Protocol Deviations.

Patient id.	Type	Description

Listing 16.2.3 Patients Not Included in the Efficacy Analysis.

Patient id.	Non evaluable reason

Listing 16.2.4 Demographic Data.

Patient id.	Tumor type	Histology type*	Stage*	Age/Gender	ECOG	Weight (kg)	Height (cm)	BSA (m2)	Prior Radiotherapy	Prior agents for the treatment

(*)At diagnosis.

Listing 16.2.5 Compliance and/or Drug Concentration Data.

Patient id.	Drug	First Intended dose (mg/m2)	Cycles received	Start date (First cycle)	Start date (Last cycle)	Total dose (mg/m2)	Dose intensity per week (mg/m2/wk)	Relative Dose intensity (%)	Delays*	Reductions*

(*) Delays/reductions will be nested for each patient (cycle and reasons of delay/reduction). e.g: C1 hematological toxicity/C3 non drug related.

Listing 16.2.6 Individual Efficacy Response Data.

Patient id.	Best Response by IA	Best Response by IRC*	PFS by IA (months)	PFS by IRC* (months)	DOR by IA (months)	DOR by IRC* (months)	OS (months)

(*) Only for SCLC

Listing 16.2.7 Adverse Event Listing.

Patient id.	Literal	Preferred Term	Grade Coded Value	SAE	Onset date	Resolved date	Relationship	Action taken	Serious criteria

Listing 16.2.8 Listing of Individual Laboratory Measurements by Patient.

				Hemoglobin (g/dL)	WBC (10*9/L)	Neutrophils (10*9/L)	Lymphocytes (10*9/L)	…*
Patient id.	Cycle	Examination date	Laboratory	Std.value	Std.value	Std.value	Std.value	Std.value

(*) Monocytes (x10*9/L), Direct Bilirubin (mg/dl),Total Bilirubin (mg/dl), AST IU/L), ALT (IU/L) AP (IU/L), GGT (IU/L), Glucose (mmol/L), Creatinine (mg/dl), CrCl (mL/min), NA (mmol/L), CL (mmol/L), K (mmol/L), LDH (IU/L), CPK (IU/L), Total Proteins (g/dl), Albumin (g/dl), CA (mmol/L), Mg (mg/dl), INR (ratio), PT (sec/ratio), PTT (sec/ratio), AFP (ng/m), hCG (IU/L), AAGP (mg/dl).

15 SAP VERSION HISTORY

15.1 SAP version history v1.0

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. 4 and No 5" were included; therefore the SAP has been updated (highlighted in ***italic bold***) in accordance with the new version (version 2) of the protocol as follows:

- Cohorts of SCLC and Endometrial carcinoma patients are expanded up to 100 and 50 patients, respectively.
- A QT evaluation study in a subset of sites of this clinical trial PM1183-B-005-14 was also performed. A specific CSR including its SAP was built to analyse it but some tables and listings excluded from the SAP of the QT substudy that are common to the main study were moved and will be displayed in the main study PM1183-B-005-14. With regards to the specific QT substudy data, if any relevant data differences occurred after the data cut-off date of the QT study and main study cut-off, these changes will be displayed in a new Appendix III using the original format and numbering specified in the QT substudy SAP.
- 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 by section:

Section 2: Study rationale

Original text:

- ……. In a phase II clinical trial of PM01183 as single agent in MBC, one of 17 patients with germline BRCA 1/2 mutation had a complete response (6%) and six had partial response (35%). Six additional patients had disease stabilization (35%). One patient with H&N carcinoma treated with PM01183 as single agent at 2.6 mg/m2 q3wk achieved disease stabilization for 4 months.

Changes to:

- …….. In a phase II clinical trial of PM01183 as single agent in MBC, two of ***54*** patients with germline BRCA 1/2 mutation had a complete response (***3.7***%) and ***20*** patients had partial response (***37%***). ***Twenty-three*** additional patients had disease stabilization (***43%***). One patient with H&N carcinoma treated with PM01183 as single agent at 2.6 mg/m2 q3wk achieved a disease stabilization of 4 months duration.

Section 2: Study design

Original text:

Patients with each of the aforementioned tumors will be enrolled in nine cohorts. Up to 25 evaluable patients are planned to be enrolled in each cohort. To consider that PM01183 has antitumor activity in

any of the tumor types analyzed, at least two confirmed responses [complete (CR) or partial response (PR)] per RECIST v.1.1 out of the 25 patients of each cohort are expected.

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

…..

Changes to:

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

- If no confirmed responses are observed in the first 15 evaluable patients of each cohort, the recruitment of the corresponding cohort will be stopped.
- If one confirmed response is observed in the first 15 evaluable patients of each cohort, the recruitment of this cohort will continue to up to 25 evaluable patients.
    - ***In the cohort of endometrial carcinoma, if ≥2 confirmed responses occur in the first 25 evaluable patients, the sample size will be doubled to 50 evaluable patients.***
    - ***In the cohort of SCLC, if ≥2 confirmed responses occur in the first 25 evaluable patients, the sample size will be increased to 100 evaluable patients.***

….

Section 3.2: Secondary objectives

Original text:

- To further characterize the antitumor activity of PM01183 in terms of duration of response (DR), clinical benefit [ORR or stable disease (SD) lasting over four months (SD ≥ 4 months)], PFS, and one-year overall survival (1y-OS) in each cohort of advanced solid tumors.

Changes to:

- To further characterize the antitumor activity of PM01183 in terms of duration of response (DR), clinical benefit [ORR or stable disease (SD) lasting over four months (SD ≥ 4 months)], PFS, and one-year overall survival (1y-OS) in each cohort of advanced solid tumors ***[overall survival (OS) in the cohort of SCLC patients]***.

Section 3.3: Endpoints (Secondary endpoints)

Original text:

- Clinical Benefit, defined as ORR or stable disease lasting over four months (SD ≥ 4 months).

- OS6/OS12, defined as the Kaplan-Meier estimates of the probability of being alive after the first infusion at these time points (6 and 12 months).

Changes to:

- OS6/OS12, defined as the Kaplan-Meier estimates of the probability of being alive after the first infusion at these time points (6 and 12 months) ***(overall survival in the cohort of SCLC patients)***.
- Clinical Benefit, defined as ~~ORR~~ response or stable disease lasting over four months (SD ≥ 4 months).

Section 5.1: Sample size

Original text:

Up to 25 evaluable patients in each tumor type will be recruited to test the null hypothesis that 1% or less patients get a response ($p \leq 0.01$) *versus* the alternative hypothesis that 10% or more patients get a response ($p \geq 0.10$). The variance of the standardized test is based on the null hypothesis. The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is 0.2; hence, statistical power is 80%. With these assumptions, if the number of patients who achieve a confirmed response is ≥ 2, then this will allow the rejection of the null hypothesis.

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

Changes to:

Up to 25 evaluable patients in each tumor type will be recruited to test the null hypothesis that 1% or less patients get a response ($p \leq 0.01$) *versus* the alternative hypothesis that 10% or more patients get a response ($p \geq 0.10$). The variance of the standardized test is based on the null hypothesis. The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is 0.2 ***(normal approximation; ~0.3 if exact binomial distribution)***; hence, statistical power is 80% ***(normal approximation; ~70% if exact binomial distribution)***. With these assumptions, if the number of patients who achieve a confirmed response is ≥ 2, then this will allow the rejection of the null hypothesis.

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

~~analysis, then H0 could be rejected and the study will have enough power to be stopped. On the contrary, if there is one confirmed response, the recruitment will be continued to up to 25 evaluable patients.~~

- ***A phase III trial of PM01183 combined with doxorubicin in SCLC is ongoing. Hence, the sample size for the SCLC cohort of this study will be increased to 100 evaluable patients if the success boundary (≥2 confirmed responses) is reached in the first 25 evaluable patients. The type I/II error will be controlled with a Gamma family boundary (-1 to reject Ho, 0 to reject H1).***

  Based on the newly available information, additional patients will be recruited to test the null hypothesis that 15% or less patients get a response ($p \leq 0.15$) versus the alternative hypothesis that 30% or more patients get a response ($p \geq 0.30$). The variance of the standardized test is based on the null hypothesis. The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is 0.051 (normal approximation; ~0.05 if exact binomial distribution); hence, statistical power is 95% (normal approximation; ~95% if exact binomial distribution). With these assumptions, if the number of patients who achieve a confirmed response is ≥ 23, then this would allow the rejection of the null hypothesis.
- ***A phase I trial of PM01183 combined with doxorubicin has shown encouraging antitumor activity in endometrial carcinoma. Hence, the sample size for the endometrial carcinoma cohort of this study will be doubled to 50 evaluable patients if the success boundary (≥2 confirmed responses) is reached in the first 25 evaluable patients. The type I/II error will be controlled with a Gamma family boundary (-1 to reject Ho, -3 to reject H1).***

  Based on the newly available information, additional patients will be recruited to test the null hypothesis that 10% or less patients get a response ($p \leq 0.10$) versus the alternative hypothesis that 25% or more patients get a response ($p \geq 0.25$). The variance of the standardized test is based on the null hypothesis. The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is 0.144 (normal approximation; ~0.16 if exact binomial distribution); hence, statistical power is ~86% (normal approximation; ~84% if exact binomial distribution). With these assumptions, if the number of patients who achieve a confirmed response is ≥ 10, then this would allow the rejection of the null hypothesis.

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

Section 8.11: Subgroup analysis

Original text adds:

Specific subgroup efficacy analysis will be done for all Evaluable patients with SCLC by CTFI (< 90 days and ≥ 90 days).

Section 8.13: Interim and Group Sequential Analyses

Original text adds:

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

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

Section 11.3: Efficacy Analysis

Original text:

Efficacy analysis will be carried out on the "All Evaluable Patients" population.

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

Changes to:

Efficacy analysis will be carried out on the "All Evaluable Patients" population ***and for all "Evaluable Patients" with SCLC by CTFI (< 90 days and ≥ 90 days)***.

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort), the total population (if applicable) ***or SCLC patients by CTFI***.

Section 11.3.2: Secondary Analysis. Add a new table

Table 11.3.2.1 Descriptive Duration of response (DR) by tumor type.

	N	Mean	Std. deviation	Median	Min	Max
SCLC*						
…..						
Total						

*Also by CTFI.

Tables 11.3.2.2 Duration of response (DR), Table 11.3.2.4 Progression-free survival (PFS) and table 11.3.2.4 Overall survival (OS) add the following footnote: Kaplan-Meier plot will also be shown (Figure 13.1.1). ***All cohorts and SCLC by CTFI***.

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

Table 12.1.2.3 is changed.

Table 12.1.2.1.3 Number of patients and cycles with dosing delay according to the relationship.

	~~Treatment related~~**		~~Non-treatment related~~	
	~~N~~	~~%~~	~~N~~	~~%~~
~~No. of patients with~~ ~~1 cycle delayed~~ ~~2 cycles delayed~~ ~~≥ 3 cycles delayed~~				
~~No. of cycles with dosing delay*~~				

~~(*) Denominator= Number of cycles susceptible to be delayed. (**) Hematological reason, non-hematological reason or both.~~

Table 12.1.2.1.3 Number of patients and cycles with dosing delay, treatment related.

	N	%
No. of patients treated		
No. of patients with drug related dose delay		
No. of cycles administered		
No. of cycles susceptible to be delayed*		
No. of cycles with drug related dosing delay**		
No. of patients with No cycles delayed 1 cycle drug related delayed …..		

(*) All cycles excluding first cycle. (**) Denominator= Number of cycles susceptible to be delayed.

Section 12.1.3: Dose reductions

Table 12.1.3.2 Number of patients and cycles with dose reduction, any relationship.

	N	%
No. of patients treated	X	XX.X
No. of patients with any dose reduced		
No. of patients with:		
No PM01183 reduction		
1 cycle with PM01183 dose reduced		
2 cycles with PM01183 dose reduced		
No. of cycles administered		
No. of cycles susceptible to have any dose reduced*		
No. of cycles with PM01183 dose reduced **		
~~No. of cycles with PM01183 dose reduced (Treatment related)**~~		

(*) All cycles excluding first cycle. (**) Denominator= Number of cycles susceptible to have a dose reduction.

Table 12.1.3.3 Number of patients and cycles with dose reduction, treatment related.

	N	%

No. of patients treated	X	XX.X
No. of patients with any dose reduced (Treatment related)		
No. of patients with:		
No PM01183 reduction		
1 cycle with PM01183 dose reduced (Treatment-related)		
2 cycles with PM01183 dose reduced (Treatment-related)		
No. of cycles administered		
No. of cycles susceptible to have any dose reduced*		
No. of cycles with PM01183 dose reduced (Treatment-related)**		

(*) All cycles excluding first cycle. (**) Denominator= Number of cycles susceptible to have a dose reduction.

Section 12.6: Concomitant therapy/ Procedures According to the ATC Classification. Add a new table

Listing 12.6.4 Patients with GCSF during treatment.

Patient	Cycle	Date	Medication	Reason	Specify

Section 13: Figures

Figures 13.1.1 to 13.1.3 add the following footnote:

Kaplan-Meier curve of overall survival. ***All cohorts and SCLC by CTFI***.

15.2 SAP version history v2.0

After the second version of the SAP was approved, a new protocol "substantial amendment No. 6" and "Non-Substantial Amendment No.2" were included; therefore the SAP has been updated to version 3 in accordance with the new version of the protocol as follows:

- Study objectives. Assessment of antitumor activity by an Independent Review Committee (IRC) is included as a secondary objective in the small cell lung carcinoma (SCLC) cohort.
- Patient population. The maximum number of evaluable patients in this clinical trial is increased to 350 mainly because of the elevated recruitment in the endometrial carcinoma cohort, which exceeded in 20 patients the planned number, together with the increase in the SCLC cohort to 100 evaluable patients, and the re-opening of the metastatic breast carcinoma BRCA-positive cohort, which will recruit up to 25 patients. Consequently, clarification of the statistical analysis to be performed in case the number of evaluable patients included in any cohort of the study was higher than planned is incorporated.
- In order to have a deeper insight into the survival, the overall survival (OS), OS rate at 6 months and 12 months will be determined in each cohort.
- Other not relevant minor comments/clarifications.

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

Any changes in the automatic numbering of tables, sections and references in the SAP are not listed but will be implemented in the new version.

Section 1: Rationale

Original text:

- PM01183 has shown antitumor activity in most of the tumor types selected in this clinical study. In the combination trial of PM01183 at 4.0 mg flat dose (FD) with 50 mg/m^2 of doxorubicin every three weeks (q3wk) (PM1183-A-003-10), five of 12 evaluable patients with SCLC achieved partial response (42.0%), with a median time-to-progression (TTP) of 2.0 months. In endometrial carcinoma, two of three patients treated with the combination PM01183 plus doxorubicin at the aforementioned dose and schedule had a complete response and a partial response, respectively. The third patient had disease stabilization longer than 4 months. The median TTP was 10.1 months. Also with this combination, a patient with NET had a partial response with a TTP of 4.5 months. In a phase II clinical trial of PM01183 as single agent in MBC, two of 54 patients with germline BRCA 1/2 mutation had a complete response (3.7%) and 20 patients had partial response (37%). Twenty-three additional patients had disease stabilization (43%). One patient with H&N carcinoma treated with PM01183 as single agent at 2.6 mg/m^2 q3wk achieved a disease stabilization of 4 months duration. Finally, one patient with a carcinoma of unknown primary site treated with PM01183 as single agent at 7 mg FD q3wk had disease stabilization for 2.6 months.

Changes to:

- PM01183 has shown antitumor activity in most of the tumor types selected in this clinical study. In the combination trial of PM01183 at 4.0 mg flat dose (FD) with 50 mg/m^2 of doxorubicin every three weeks (q3wk) (PM1183-A-003-10), five of 12 evaluable patients with SCLC achieved partial response (42.0%), with a median time-to-progression (TTP) of 2.0 months. In endometrial carcinoma, two of three patients treated with the combination PM01183 plus doxorubicin at the aforementioned dose and schedule had a complete response and a partial response, respectively. The third patient had disease stabilization longer than 4 months. The median TTP was 10.1 months. Also with this combination, a patient with NET had a partial response with a TTP of 4.5 months. In a phase II clinical trial of PM01183 as single agent in MBC, ***one*** of 54 patients with germline BRCA 1/2 mutation had a complete response (**2%**) and ***21*** patients had partial response (***39%***). Twenty-three additional patients had disease stabilization (43%). One patient with H&N carcinoma treated with PM01183 as single agent at 2.6 mg/m^2 q3wk achieved a disease stabilization of 4 months duration. Finally, one patient with a carcinoma of unknown primary site treated with PM01183 as single agent at 7 mg FD q3wk had disease stabilization for 2.6 months.

Section 2.: Study Design

Original text:

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

(….)

Finally,

- A determined cohort can be early closed by the Sponsor in case of a low recruitment rate.

(….)

Patients will be evaluated at scheduled visits on three study periods: Pre-treatment, Treatment and Follow-up. This clinical trial will finish (clinical cut-off) when all evaluable patients have at least 12 months of follow-up.

Changes to:

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

Only in the ***SCLC cohort, an IRC will be performed on all images collected and will provide a radiographic response at each time point termed. These data and the clinical database information will be used to derive the independent review efficacy information following the RECIST v.1.1. Operational details for the IRC and the algorithm and its validation by an expert panel is described in detail in the IRC charter.***

(….)

Finally,

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

(….)

Patients will be evaluated at scheduled visits on three study periods: Pre-treatment, Treatment and Follow-up. This clinical trial will finish (clinical cut-off ***for each cohort except SCLC cohort***) when all evaluable patients ***within each cohort*** have at least 12 months of follow-up ***from the first PM01183 infusion. Patients with SCLC will be followed-up until death.***

Section 3.2: Secondary objectives

Original text:

- To further characterize the antitumor activity of PM01183 in terms of duration of response (DR), clinical benefit [ORR or stable disease (SD) lasting over four months (SD ≥ 4 months)], PFS, and one-year overall survival (1y-OS) in each cohort of advanced solid tumors [overall survival (OS) in the cohort of SCLC patients].

Changes to:

- To further characterize the antitumor activity of PM01183 in terms of duration of response (DR), clinical benefit [ORR or stable disease (SD) lasting over four months (SD ≥ 4 months)], ***progression-free survival (PFS) by Investigator's assessment (IA), and overall survival (OS) in each cohort of advanced solid tumors***

- ***To further investigate the antitumor activity of PM01183 in terms of ORR, DR, clinical benefit [ORR or SD ≥ 4 months] and PFS by an Independent Review Committee (IRC) in the cohort of SCLC patients.***

Section 3.3: Endpoints

Original text:

Secondary Endpoints:

Efficacy:

- Duration of Response (DR), defined as the time between the date when the response criteria (PR or CR, whichever one is first reached) are fulfilled to the first date when PD, recurrence or death is documented.
- Clinical Benefit, defined as response or stable disease lasting over four months (SD ≥ 4 months).
- Progression-free Survival (PFS), defined as the period of time from the date of first infusion to the date of PD, death (of any cause), or last tumor evaluation.
- PFS4/PFS6, defined as the Kaplan-Meier estimates of the probability of being free from progression and death after the first infusion at these time points (4 and 6 months).
- OS6/OS12, defined as the Kaplan-Meier estimates of the probability of being alive after the first infusion at these time points (6 and 12 months) (overall survival in the cohort of SCLC patients).

Changes to:

Secondary Endpoints:

Efficacy (all cohorts):

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

Efficacy (only in the SCLC cohort):

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

(…..)

Safety Profile:

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

- ***Reasons for dose reduction and treatment delays.***

Section 4: Patients evaluability criteria

Original text:

(….)

- "All Evaluable Patients" analysis set is defined as all eligible patients who have had at least one complete infusion of PM01183, and either have had at least one assessment (as per RECIST v1.1) or have been categorized as "treatment failures". Patients who discontinue treatment due to any treatment-related toxicity before an appropriate tumor assessment has been performed or those who experience early death due to malignant disease will be defined as "treatment failures". These patients will be included as non-evaluable for response in the analysis of objective response as per RECIST v1.1, although they will not be replaced as will be considered evaluable for efficacy.
- "All Responding Patients" analysis set is defined as all evaluable patients who have had a confirmed CR or PR as overall best response according to the RECIST v1.1.

Changes to:

(…)

- "All Evaluable Patients" analysis set is defined as all eligible patients, ***defined as patients accepted by the sponsor to take part in the trial***, who have had at least one complete infusion of PM01183, and either have had at least one assessment (as per RECIST v1.1) or have been categorized as "treatment failures". Patients who discontinue treatment due to any treatment-related toxicity before an appropriate tumor assessment has been performed or those who experience early death due to malignant disease ***or those with treatment withdrawn due to clinical PD/symptomatic deterioration with no tumor assessments*** will be defined as "treatment failures". These patients will be included as non-evaluable for response in the analysis of objective response as per RECIST v1.1, although they will not be replaced as will be considered evaluable for efficacy. ***For the IRC assessment in SCLC patients same definition will be followed but based on its assessment.***
- "All Responding Patients" analysis set is defined as all evaluable patients who have had a confirmed CR or PR as overall best response according to the RECIST v1.1. ***For the IRC assessment in SCLC patients same definition will be followed but based on its assessment.***

Section 4.1 Included Population:

Original text:

The "All Included Patients" dataset will be used for the descriptive analyses of disposition of patients and baseline characteristics.

Changes to:

The "All Included Patients" dataset***, defined as all patients accepted by the sponsor to take part in the trial,*** will be used for the descriptive analyses of disposition of patients and baseline characteristics ***in each cohort of advanced solid tumors***.

Section 4.2 Efficacy Populations:

Original text:

The "All Evaluable Patients" analysis set will be used for the primary endpoint analysis of ORR and for the secondary endpoints of DR, Clinical benefit (ORR or SD ≥ 4 months), PFS (including PFS4/PFS6 months), and OS6/OS12 months in each cohort of advanced solid tumors.

Changes to:

In all cohorts but SCLC, the "All Evaluable Patients" analysis set will be used for the primary endpoint analysis of ORR and for the secondary endpoints of DR, Clinical benefit (ORR or SD ≥ 4 months), PFS (including PFS4/PFS6 months), and OS6/OS12 months ***in each cohort of advanced solid tumors. The "All Treated Patients" analysis set will also be used for the sensitivity analyses.***

In SCLC cohort, the "All Treated Patients" analysis set will be used for the primary endpoint analysis of ORR and for the secondary endpoints of DR, Clinical benefit (ORR or SD ≥ 4 months), PFS (including PFS4/PFS6 months), and OS6/OS12 months in each cohort of advanced solid tumors. The "All Evaluable Patients" analysis set will also be used for the sensitivity analyses.

Section 4.3 Safety Population:

Original text:

The safety analysis will be based on the "All Treated Patients" analysis set.

Changes to:

The safety analysis will be based on the "All Treated Patients" analysis set ***by cohort of tumor types and total population***.

Section 5.1: Sample size

Original text:

(….)

The variance of the standardized test is based on the null hypothesis. The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is 0.051 (normal approximation; ~0.05 if exact binomial distribution); hence, statistical power is 95% (normal approximation; ~95% if exact binomial distribution). With these assumptions, if the number of patients who achieve a confirmed response is ≥ 23, then this would allow the rejection of the null hypothesis.

Changes to:

(…)

The variance of the standardized test is based on the null hypothesis. The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is 0.051 (normal approximation; ~0.05 if exact binomial distribution); hence, statistical power is 95% (normal approximation; ~95% if exact binomial distribution). With these assumptions, if the number of patients who achieve a confirmed response is ≥ 23, then this would allow the rejection of the null hypothesis. ***The judgement of patient's evaluability and replacement of non-evaluable patients were guided by the investigator assessment.***

Section 6.1 Planned Analyses and Definitions

Primary endpoint

Original text:

The primary study analysis except for SCLC cohort will be based on the ORR in the "All Evaluable Patients" population set.

Overall response rate (ORR) is calculated as the number of patients who have had a confirmed CR or PR as overall best response according to the RECIST v1.1, divided by the number of patients in the "All Evaluable Patients" population set.

Changes to:

The primary study analysis ***except for SCLC cohort*** will be based on the ORR in the "All Evaluable Patients" population set. ***For SCLC cohort, the primary study analysis will be based on the ORR in the "All Treated Patients" population set.***

Overall response rate (ORR) is calculated as the number of patients who have had a confirmed CR or PR as overall best response according to the RECIST v1.1, divided by the number of patients in the "All Evaluable Patients" ***("All Treated Patients" in SCLC cohort)*** population set.

Secondary endpoints

Original text:

(…)

Duration of response (DR) is defined as the time from the first observation of response to the date of disease progression, recurrence or death. Other causes will be censored. Although the responses have to be confirmed according to RECIST v1.1, the first documentation (not the confirmation) will be taken into account to calculate DR. Patients who progress or die will be considered to have had an event, except if this event occurs after the start of subsequent antitumor therapy, in which case the patient will be censored at the time of last disease assessment prior to or on the first day of the first subsequent antitumor therapy.

Clinical benefit rate is calculated as the number of patients who have had a confirmed CR, PR, or SD ≥ 4 months as overall best response according to the RECIST v1.1, divided by the number of patients in the "All Evaluable Patients" analysis set.

Progression-free survival (PFS) is defined as the time from the date of start of treatment to the date of documented progressive disease (PD) by RECIST v1.1 or death (regardless of the cause of death), whichever comes first. Patients who progress or die will be considered to have had an event of progression, except if this event occurs after the start of subsequent antitumor therapy, in which case

the patient will be censored at the time of last disease assessment prior to or on the first day of the first subsequent antitumor therapy. If the patient is lost for the assessment of progression during the follow-up period, or has more than one missing follow-up between the date of last tumor assessment and the date of progression, death or further antitumor therapy, the PFS will be censored at the date of last valid disease assessment before the missing evaluations.

Overall survival (OS) is defined as the time from the date of start of treatment to the date of death or last contact. ***One year (1y-OS)/6 months overall survival*** is defined as the Kaplan-Meier estimate of the probability of patients being alive at 12/6 months after the date of start of treatment.

Changes to:

(…)

Duration of response (DR) is defined as the time from the first observation of response to the date of disease progression, recurrence or death. Other ***cases*** will be censored. Although the responses have to be confirmed according to RECIST v1.1, the first documentation (not the confirmation) will be taken into account to calculate DR. Patients who progress or die will be considered to have had an event, except if this event occurs after the start of subsequent antitumor therapy, in which case the patient will be censored at the time of last disease assessment prior to or on the first day of the first subsequent antitumor therapy.

Clinical benefit rate is calculated as the number of patients who have had a confirmed CR, PR, or SD ≥ 4 months as overall best response according to the RECIST v1.1, divided by the number of patients in the "All Evaluable Patients" ***("All Treated Patients" in SCLC cohort)*** analysis set.

Progression-free survival (PFS) is defined as the time from the date of start of treatment to the date of documented progressive disease (PD) by RECIST v1.1 or death (regardless of the cause of death), whichever comes first. Patients who progress or die will be considered to have had an event of progression, except if this event occurs after the start of subsequent antitumor therapy, in which case the patient will be censored at the time of last disease assessment prior to or on the first day of the first subsequent antitumor therapy. If the patient is lost for the assessment of progression during the follow-up period, or has more than one missing follow-up between the date of last tumor assessment and the date of progression, death or further antitumor therapy, the PFS***/DR*** will be censored at the date of last valid disease assessment before the missing evaluations.

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

(…)

Overall survival (OS) is defined as the time from the date of start of treatment to the date of death or last contact. ***One year (1y-OS)/6 months overall survival*** is defined as the Kaplan-Meier estimate of the probability of patients being alive at 12/6 months after the date of start of treatment.

A sensitivity analysis for all cohorts but SCLC will be performed for ORR, Clinical Benefit Rate, PFS and OS in the "All Treated Patients population". For the SCLC cohort, the sensitivity analysis will be carried out the "All Evaluable Patients".

Section 6.2: Efficacy Analysis Methods

Original text:

Counts and percentages, with their corresponding exact 95% confidence intervals, will be calculated for the binomial endpoints (e.g., ORR, clinical benefit).

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

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

Changes to:

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

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

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

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

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

The patient level response will be calculated by means of statistical programming. In the case of a Partial Response followed by a time point with a tumor size reduction lower than 30% compared to the baseline assessment but an increase in the size of the target lesions not qualifying for disease progression (e.g. increase of sum of target lesions compared with the nadir is lower than 20%) then the response will be considered maintained following RECIST advice(("The definition of SD: a clarification" http://recist.eortc.org/recist-1-1-2/).

Example: Baseline evaluation: 38 mm, first evaluation: 26 mm (Tumor Size Reduction from baseline = 31.6% PR), second evaluation: 28 mm (Reduction from baseline = 26.3%, but increase from nadir = 7.7%).

The best overall response will be considered as confirmed PR.

Section 6.2.1: Primary Endpoint

Original text:

Exact binomial estimates with 95% confidence intervals (CIs) in each cohort will be calculated for the analysis of the main endpoint (ORR according to RECIST v1.1)

Changes to:

Exact binomial estimates with 95% confidence intervals (CIs) in each cohort will be calculated for the analysis of the main endpoint (ORR according to RECIST v1.***1by Investigator assessment)***

Section 6.2.2: Secondary Endpoint

Original text:

Time-to-event endpoints (DR, PFS and OS) and their set time estimates (i.e. PFS4, PFS6 and OS 6/12) will be analyzed according to the Kaplan-Meier method.

Changes to:

Exact binomial estimates with 95% confidence intervals (CIs) will be performed in the SCLC cohort for the analysis of the ORR according to RECIST v1.1 by IRC.

Time-to-event endpoints (DR, PFS and OS) and their set time estimates (i.e. PFS4, PFS6 and OS 6/12) will be analyzed according to the Kaplan-Meier method.

Section 7: Statistical Methodology for Safety

Original text:

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

Changes to:

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

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

Section 7.1.1 changes to 7.1: Toxicity and Adverse Events

Original text:

(…)

The toxicity evaluation will be coded with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.

Summary of overall AEs will be done by System Organ Class (SOC) and Preferred Term (PT), by severity (worst toxicity grade), by relationship to the study drug and by AE outcome. Tables will be sorted by SOC/PT coded with MedRA.

(…)

Changes to:

(…)

The toxicity evaluation will be coded with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.

Treatment-emergent adverse events (TEAE) are defined as any adverse events aggravated in severity from baseline or having their onset between the first dose of the study drug and 30 days after the last treatment dose, death or date of further therapy (whichever comes first). Adverse

Events Related to Study Drug or with Unknown relationship occurring more than 30 days after the last dose will also be taken into account as TEAEs.

Summary of overall AEs will be done by System Organ Class (SOC) and Preferred Term (PT), by severity (worst toxicity grade), by relationship to the study drug and by AE outcome. ***Tables will be organized by category of events using SOC (i.e. alphabetical order) and PT in descending frequencies (i.e., from higher to lower).***

(…)

Section 7.2 Clinical Laboratory Evaluation

Original text:

Overall cross tabulation will be presented for the worst grade during treatment *versus* the baseline toxicity grading of leukopenia, neutropenia, lymphopenia, thrombocytopenia and anemia.

If a grade 3/4 neutropenia or thrombocytopenia occurs during a cycle of treatment, the first day it reaches grade 3 or 4 (counting from the start of the cycle) and the duration of the abnormality (i.e., until recovery to grade ≤ 2) will be tabulated.

(…)

If a grade 3/4 AST or ALT increase occurs during a cycle of treatment, both the day it peaked (counting from the start of the cycle) and the duration of the abnormality (i.e., until recovery to grade ≤ 2) will be tabulated.

Overall cross tabulation will be presented for the worst grade during treatment *versus* the baseline toxicity grading of biochemical abnormalities.

Changes to:

Overall cross tabulation will be presented for the worst grade during treatment *versus* the baseline ***severity*** grading of leukopenia, neutropenia, lymphopenia, thrombocytopenia and anemia.

If a grade ***≥3*** neutropenia or thrombocytopenia occurs during a cycle of treatment, the first day it reaches grade 3 or 4 (counting from the start of the cycle) and the duration of the abnormality (i.e., until recovery to grade ≤ 2) will be tabulated.

(…)

If a grade ***≥3*** AST or ALT increase occurs during a cycle of treatment, both the day it peaked (counting from the start of the cycle) and the duration of the abnormality (i.e., until recovery to grade ≤ 2) will be tabulated.

Overall cross tabulation will be presented for the worst grade during treatment *versus* the baseline ***severity*** grading of biochemical abnormalities.

Section 8.9 Imputation of Incomplete Dates:

Original text:

The dates of certain historical or on-study clinical data are key components for statistical analysis. An incomplete date results from a missing day, month or year; in that case, the missing figure can be imputed, thus allowing the calculation of variables, such as duration and time of a specific event. However, when all dates (day, month and year) are missing, no imputation will be done.

Before Registration

If the day of a month is unknown, then the imputed day will be the 15th of the month; if the month is also unknown, then the imputed date will be the 1st of July. This assumption will only be valid if the imputed date occurs earlier than the first dose administration date; otherwise the imputed date will be the first day of the month of administration of the first dose (i.e. 01/ month of administration of the first dose/year).

(…)

After End of Treatment

To ensure the most conservative approach for the time-to-event variables (i.e., DR, PFS and OS), which 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 the 1st; if the month is also unknown, then the imputed date will be the 1st of July. This assumption will be valid if the imputed date occurs later than the last drug administration date; otherwise the imputed date will be the date of the last drug administration plus the predefined cycle length (i.e., 21 days if PM01183), except if the patient dies before, in which case the date of death minus 1 will be used.

Changes to:

The dates of certain historical or on-study clinical data are key components for statistical analysis. An incomplete date results from a missing day, month or year; in that case, the missing figure can be imputed, thus allowing the calculation of variables, such as duration and time of a specific event. However, when all dates (day, month and year) are missing, no imputation will be ***done unless otherwise specified. Whenever imputations are applicable, it will be clearly specified in the corresponding shell table, listing or figure in sections 10-16 of this SAP.***

Before Registration

If the day of a month is unknown, then the imputed day will be the ***1st.*** of the month; if the month is also unknown, then the imputed date will be the 1st of July. This assumption will only be valid if the imputed date occurs earlier than the first dose administration date; otherwise the imputed date will be the first day of the month of administration of the first dose (i.e. 01/ month of administration of the first dose/year).

Between treatment start and end of treatment

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

After End of Treatment

To ensure the most conservative approach for the time-to-event variables (i.e., DR, PFS and OS), which 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 the 1st; if the month is also unknown, then the imputed date will be the 1st of July. This assumption will be valid if the imputed date occurs later than the last drug administration date; otherwise the imputed date will be the date of the last drug administration plus the predefined cycle length (i.e., 21 days if PM01183), except if the patient dies before, in which case the date of death minus 1 will be used. For OS, if a patient dies, the imputation event date should be the last date the patient is known to be alive plus one day.

Section 8.10: Decimal Places

Original text:

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

Changes to:

By default, all numeric results will be rounded to one decimal, except when variables are integers; in that case, they will be reported without decimals (for example, age in years, number of sites, etc.). ***Three decimal places will be used for Hazard Ratios or Odds Ratios. Four decimal places will be used for p-values.***

Section 8.11: Subgroup Analyses

Original text:

Specific subgroup efficacy analysis will be done for all Evaluable patients with SCLC by CTFI (< 90 days and ≥ 90 days).

No other specific subgroup analysis is being planned for the analysis.

Changes to:

Specific subgroup efficacy analyses will be done for patients with SCLC. These analyses will be performed by IA/IRC and in all evaluable/all treated patient populations. Pre-specified analyses are planned by CTFI (< 90 days and ≥ 90 days and/or Refractory (RR)[<30 days], Resistant (R) [>=30 and <90 days], Sensitive (S)[>=90 and <180 days] and Very Sensitive (VS)[>=180 days]), excluding patients with CTFI<30 days and considering event to clinical progressions although they were not documented by radiological images. Any other exploratory analysis requested by physician at the analysis time will be clearly explained, specifying the selected patient population and following the same layout detailed for the other subgroup analyses.

If the number of patients recruited in any cohort differs at least 10% from the sample size assumptions, a sensitivity analysis for main efficacy endpoints using all evaluable patients will be performed.

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

Section 8.15 Data Analysis Conventions
Original text:
All data analysis conventions, data calculations and grouping needed to perform the statistical analysis will be described in separate documents not included in this SAP.

Changes to:
All data analysis conventions, data calculations and grouping needed to perform the statistical analysis ***not included in this SAP*** will be described in separate document.

APPENDIX I

Original text:

Each table, listing and figure will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

…..

Changes to:

Each table, listing and figure will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

For this reason each SAP Table/Listing/Figure will have different granularity, i.e Table 11.1.1.1.x where "x" is a different sublevel of granularity. The following values apply:

Table/Listing/Figure granularity level	*Contents*
none	*Totals all cohort*
.b	*BRCA 1/2-associated metastatic breast carcinoma*
.i	*Biliary tract carcinoma*
.c	*Carcinoma of unknown primary site*
.e	*Endometrial carcinoma*
.w	*Ewing's family of tumors (EFTs)*
.g	*Germ cell tumor (GCTs)*
.h	*Head and neck carcinoma (H&N)*
.n	*Neuroendocrine tumors (NETs)*
.s	*Small cell lung cancer (SCLC)*
.s1	*Resistant**
.s2	*Sensitive**

(*)For tables to be produced for resistant (.s1) and sensitive (.s2) populations, please see indications in the respective table or figure footnote.

Section 10.1: Patient Disposition.

Add new columns and tables:

Table 10.1.1 Number of patients included, treated and evaluable for the primary endpoint.

	N	%
Included patients		
Eligible patients*		
Treated patients		
Evaluable patients for efficacy		
Evaluable patients for efficacy by IRC (SCLC cohort)		

(*) Patients who were considered eligible according to the registration screening form and were accepted to take part in the trial with the sponsor's agreement in the screening reply form. (**) For sensitivity analysis.

Listing 10.2.2 Reasons for treatment discontinuation other than progressive disease and Listing 12.2.4 Treatment discontinuation due to adverse events add one new column ***CTFI**** and the footnote ***(*) Only for SCLC patients (RR, R, S, VS).***

Table 10.1.5 Non-evaluable patients for efficacy analysis by IRC (SCLC cohort).

Patient id.	Reason

Section 10.2: Reasons for Treatment Discontinuation.

Table 10.2.1 Treatment discontinuation and Table 10.2.3 Reasons for treatment discontinuation by cycles received. Add new columns for the cutoff:

Table 10.2.1 Treatment discontinuation

Reason	N	%
Progressive disease		
Treatment-related adverse event*		
Non treatment-related adverse event*		
Patient refusal to treatment*		
Death**		
Investigator's decision*		
Other*		
Ongoing at cutoff		
Total		

Note: Also for s1 and s2; (*) Specify (see Listing 10.2.2), (**) Cause of Death (See Table 12.3.2.1).

Listing 12.2.2 Reasons for treatment discontinuation other than progressive disease and Listing 12.2.4 Treatment discontinuation due to adverse events add one new column ***CTFI**** and the footnote ***(*) Only for SCLC patients (RR, R, S, VS).***

Table 10.2.3 Reasons for treatment discontinuation by cycles received.

Reason	Last cycle			
	1	2	…	Total

Progressive disease				
Treatment-related adverse event*				
Non treatment-related adverse event*				
Patient refusal to treatment*				
Death**				
Investigator's decision*				
Other*				
Ongoing at cutoff				
Total				

(*) Specify (see Listing 10.2.2); (**) Cause of Death (See Table 12.3.2.1);

Table 10.2.5 Study discontinuation. Add the following footnote ***Note: Also for s1 and s2;***

Section 11.1.1 Patients Characteristics at Baseline.

Original text:

Table 11.1.1.1 Baseline characteristics: Age at treatment registration.

	N	Mean	Std. Deviation	Median	Min	Max
Age (years)						

Table 11.1.1.2 Baseline characteristics: Age group.

Age	N	%
18-XX	X	XX.X
XX-YY		
≥65		
Total		

Table 11.1.1.3 Baseline characteristics: Race.

	N	%
American Indian or Alaskan Native	X	XX.X
Asian		
Black or African American		
Native Hawaiian or Other Pacific Islander		
White		
Other*		
Total		

(*) See Listing 11.1.1.4.

Table 11.1.1.4 Other race, specify.

Patient id.	Specify

Changes to:

Table 11.1.1.1 Baseline characteristics: Age at treatment registration.

Age	N	%
18-XX	X	XX.X
XX-YY		
≥65		
Total		
Mean, Std., Median, Range		

Note: Also for s1 and s2.

Table 11.1.1.2 Baseline characteristics: Gender.

	N	%
Male	X	XX.X
Female		
Total		

Note: Also for s1 and s2.

Table 11.1.1.***3*** Baseline characteristics: Race.

	N	%
American Indian or Alaskan Native	X	XX.X
Asian		
Black or African American		
Native Hawaiian or Other Pacific Islander		
White		
Other*		
Total		

Note: ***Also for s1 and s2***; (*) See Listing 11.1.1.***5***.

Table 11.1.1.***4*** Other race, specify.

Patient id.	***CTFI****	Specify

(*) Only for SCLC.

Section 11.1.2 Disease at Diagnosis and Disease at Study Entry.

Table 11.1.2.1 Time from first diagnosis to registration and Table 11.1.2.5 Time from advanced disease to registration are merged into one table.

Tables 11.1.2.3 Stage at diagnosis, previous Table 11.2.2.7 changes to Table 11.1.2.6 Sites of disease and previous Table 11.1.2.10 changes to 11.1.2.9 Number of sites at baseline add the following footnote ***Note: Also for s1 and s2.***

Previous Listing 11.1.2.8 changes to listing 11.1.2.7 Bone location add last column is removed.

Patient id.	Specify

Previous Table 11.2.2.6 changes to Table 11.2.2.5 Time from last progression before the study entry, add a new variable and footnote.

Table 11.1.2.1 Time from first diagnosis to registration ***and Time from advanced disease to registration.***

	N	Mean	Std.	Median	Min	Max
Time from diagnosis to registration (months)						
Time from advanced disease (months)						

Note: Also for s1 and s2.

Table 11.1.2.5 Time from last progression before study entry ***and TTP from last medical therapy.***

	N	Mean	Std.	Median	Min	Max
Time from last PD (weeks)						
TTP to last medical therapy (months)						

Note: Also for s1 and s2.

A new table is included.

Table 11.1.2.10 Sum of target lesions at baseline.

	N	%
>50 mm	***X***	***XX.X***
>100 mm		
Bulky disease*		

Note: Also for s1 and s2. (*) One lesion more than 50 mm.

Section 11.1.3 Disease at Diagnosis and Disease at Study Entry: Small Cell Lung Cancer (SCLC). New table and all tables add the following footnote Note: Also for s1 and s2.

Table 11.1.3.2 History or current presence of CNS involvement.

*	N	%
Yes	X	XX.X
No		
Total		

Note: Also for s1 and s2.

Section 11.1.7 Disease at Diagnosis and Disease at Study Entry: Endometrial carcinoma.

Table 11.1.7.1 Endometrial carcinoma type (I/II is removed. This information will be available in data base listings.

Section 11.1.8 Disease at Diagnosis and Disease at Study Entry: BRCA 1/2-associated Metastatic Breast Carcinoma (MBC).

Original text:

Table 11.1.8.4 Hormonal status.

	N	%
Triple negative	X	XX.X
ER and/or PR positive + HER2 negative		
ER and/or PR positive + HER2 positive		
ER and PR negative + HER2 positive		
Total		

Table 11.1.8.4 Hormonal status.

	N	%
Triple negative	X	XX.X
ER and/or PR positive + HER2 negative		
Hormone receptor positive*		
Total		

(*) ER and/or PR positive + HER2 positive and ER and PR negative + HER2 positive

Section 11.1.11 Disease at Diagnosis and Disease at Study Entry: Ewing's Family of Tumors (EFTs). Table 11.1.11.1 Anatomical subtype adds a new category.

Table 11.1.11.1 Anatomical subtype.

	N	%
Osseous	X	XX.X
Extraosseous - Primitive neuroectodermal tumor		

Extraosseous - Askin tumor		
*		
Total		

(*) Other, in case of none of the others CRF categories apply.

Section 11.1.13 Prior anticancer therapy. Some tables add new categories and add two new tables.

Table 11.1.13.1 Patients with prior surgery.

	N	%
Yes	X	X.X
Palliative		
Curative		
No		
Total		

Previous Table 11.1.3.2 and 11.1.13.3 changes to Table 11.1.3.2 Patient with prior radiotherapy.

	N	%
Yes	X	X.X
Brachytherapy		
External (including IMRT)		
IMRT		
No		
Total		

Table 11.1.13.4 Prior anticancer agents.

Antineoplastic and immunomodulating agents (ATC-class.)	N	%
Antineoplastic agents (L01)	X	XX.X
Alkylating agents		
Nitrogen mustard analogues		
Alkyl sulphonates		
Prior anticancer agents*		
Hormones		
Prior Immunotherapy		
…		
Biological agents		
…		
….		

(*) Therapies of interest for each tumor type e.g MBC, endometrial carcinoma, hormone, Biological agents etc…..

Table 11.1.13.5 PCI.

*	***N***	***%***
Yes	***X***	***XX.X***
No		
Total		

(*) Only for SCLC patients.

Table 11.1.13.6 CTFI by subgroup.

*	***N***	***%***	***Mean, Std., Median, Range*****
CTFI< 90 days	***X***	***XX.X***	
RR			
R			
CTFI≥ 90 days			
S			
VS			

Total			

(*) Only for SCLC patients.

Table 11.1.13.7 Best response and TTP to last prior platinum.

*	*N*	*%*
CR	***X***	***XX.X***
PR		
SD		
PD		
UK/NA		
Total		
TTP to last previous platinum Mean, Std., Median, Range		

(*) Only for SCLC patients. Note: Also for s1 and s2;

Sections 11.1.14 Physical examination and Performance Status at Baseline, section 11.1.15 Vital Signs, Electrocardiogram, LVEF and other tests, section 11.1.16 Hematological Values at Baseline and section 11.1.17 Biochemical Values at Baseline.

Footnote is removed from the following tables: Table 11.1.14.1 Baseline physical examination, Table 11.1.15.8 Baseline characteristics: pregnancy test and Table 11.1.15.9 Baseline characteristics: adequate contraception.

Table 11.1.14.2 Baseline physical examination: BSA, Weight and Height/Table 11.1.14.3 Baseline characteristics: ECOG Performance Status/table 11.1.16.1 Hematological abnormalities at baseline/Table 11.1.17.1 Biochemical abnormalities at baseline add the following footnote: ***Note: Also for s1 and s2***.

Original text:

Table 11.1.16.2 Hematological values at baseline.

Parameter*	N	Mean	Std.	Median	Min	Max
Hemoglobin						
Platelets						
WBC						
Neutrophils						
Lymphocytes						
Monocytes						

(*) Parameter standard units in CRF.

Changes to:

Table 11.1.16.2 Hematological values at baseline.

Parameter*	N	Mean	Std.	Median	Min	Max
Hemoglobin ***(g/dl)***						
Platelets ***(x10*9/L)***						
WBC ***(x10*9/L)***						
Neutrophils ***(x10*9/L)***						
Lymphocytes ***(x10*9/L)***						
Monocytes ***(x10*9/L)***						

Section 11.1.15 Vital Signs, Electrocardiogram, LVEF and other tests

Listing 11.1.1.15 Patients with abnormal electrocardiogram.

Patient id.	Abnormality	Details*	Reason for clinically indicated repeat	PR interval (msec)	Heart rate (bpm)	QT interval (msec)	QRS complex (msec)	***QTc Fridericia***	QTc Bazett's**

(*)For non-significant abnormalities, for further details see prior medical history or Signs and symptoms; (**) QTc (Bazett's) = QT interval / √(60/Heart rate).

Section 11.1.18 Coagulation Values at Baseline

Original text:

Table 11.1.18.2 Coagulation values at baseline.

	N	Mean	Std. deviation	Median	Min	Max
INR						
PT (sec)						
PTT (sec)						

Changes to:

Table 11.1.18.2 Coagulation values at baseline.

	N	Mean	Std.	Median	Min	Max
INR						
PT (sec)						
PT (ratio)						
PTT (sec)						
PTT (ratio)						

Sections 11.1.19 Adverse Events at Baseline

Table 11.1.19.3 Adverse events at baseline adds the following footnote: ***Note: Also for s1 and s2***. and Listing 11.1.19.4 Adverse events at baseline is removed.

Section 11.1.20 Concomitant Therapy and Procedures at Baseline

Table 11.2.20.1 Concomitant medication at baseline (ATC1/ATC2/***ATC3***/ATC4/PN). Add a new variable. And Table 11.1.20.3 Concomitant therapy is removed.

Section 11.3: Efficacy Analysis

Original text:

Efficacy analysis will be carried out on the "All Evaluable Patients" population and for all "Evaluable Patients" with SCLC by CTFI (< 90 days and ≥ 90 days).

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort), the total population (if applicable) or SCLC patients by CTFI.

Changes to:

Efficacy analysis will be carried out on the "All Evaluable Patients" population. ***For SCLC patients in "All Treated Patients" and in "All Evaluable Patients" by IA/IRC and in all pre-specified analyses, by CTFI (< 90 days and ≥ 90 days and/or Refractory (RR)[<30 days], Resistant (R) [>=30 and <90 days], Sensitive (S)[>=90 and <180 days] and Very Sensitive (VS)[>=180 days]), excluding patients with CTFI<30 days and considering event in the clinical progressions although they were not documented by radiological images.***

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort), the total population (if applicable) or SCLC patients by CTFI ***or sensitivity analysis if recruitment in any cohort differs at least 10% from the assumptions. Any other exploratory analyses will be clearly specified by selected patient population and will be performed following the same table layout detailed below***.

Section 11.3.1: Primary analysis. ***(Excluding SCLC cohort)***

Add a new section by IRC,

Primary Analysis by IA:

Table 11.3.1.1 Response rate.

Response	N	%
Complete response (CR)		
Partial response (PR)		
Stable disease SD≥4 months		
Stable disease SD<4 months		
Progressive disease (PD)		
Inevaluable for response*		

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify).

Table 11.3.3.2 ORR.

	Percentage	Lower 95% limit	Upper 95% limit
Response rate*			

(*) Confirmed CR + PR. Binomial exact estimator and 95% CI.

Section 11.3.2 Secondary Analyses adds **(excluding SCLC cohort).**

Original tables:

Table 11.3.2.1 Descriptive Duration of response (DR) by tumor type.

	N	Mean	Std. deviation	Median	Min	Max
SCLC*						
…..						
Total						

*Also by CTFI.

Table 11.3.2.2 Duration of response (DR).

	DR
N	
Events	
Censored	
Median DR	
DR at 6 months	

DR at 12 months	

Kaplan-Meier plot will also be shown (Figure 13.1.1). All cohorts and SCLC by CTFI.

Table 11.3.2.3 Clinical benefit rate.

	Percentage	Lower 95% limit	Upper 95% limit
Clinical benefit rate*			

(*) CR + PR + SD ≥ 4 months. Binomial exact estimator and 95% CI.

Table 11.3.2.4 Progression-free survival (PFS).

	PFS
N	
Events	
Censored	
Median PFS	
PFS at 4 months	
PFS at 6 months	

Kaplan-Meier plot will also be shown (Figure 13.1.2). All cohorts and SCLC by CTFI.

Table 11.3.2.5 Overall survival (OS).

	OS
N	
Events	
Censored	
Median OS	
OS at 6 months	
OS at 12 months	

Kaplan-Meier plot will also be shown (Figure 13.1.3). All cohorts and SCLC by CTFI.

Table 11.3.2.6 Characteristics of patients with clinical benefit*.

Baseline characteristics							Study treatment characteristics				
Cohort	Pat.	PS / Age/Gender	Histology type / Histology grade	No. of prior regimens	Best response last therapy	TTP last therapy	Cycles received	Best response	PFS (mth)	OS (mth)	DR (mth)
	…										

(*) CR + PR + SD SD ≥ 4 months.

Table 11.3.2.7 Median follow-up.

Follow-up*	Median	95% CI
PFS		
OS		

*Calculated using the Kaplan-Meier method reversing the censoring values. By descriptive methods also available under clinical request.

Changes to:

<u>Secondary Analyses by IA:</u>

Table 11.3.2.1 Descriptive Duration of response (DR).

	N	Mean	Std.Std.	Median	Min	Max

Table 11.3.2.2 DR.

	DR
N	
Events	
Censored	
Median DR	
DR at 4 months	
DR at 6 months	
DR at 12 months	

Kaplan-Meier plot will also be shown (Figure 11.3.2.2).

Table 11.3.2.3 Clinical benefit rate ***and Disease control rate***.

	Percentage	Lower 95% limit	Upper 95% limit
Clinical benefit rate*			
Disease control rate*			

(*) CR + PR + SD ≥ 4 months. Binomial exact estimator and 95% CI.

(**) CR + PR + SD. Binomial exact estimator and 95% CI.

Table 11.3.2.4 PFS.

	PFS
N	
Events	
Censored	
Median PFS	
PFS at 4 months	
PFS at 6 months	

Kaplan-Meier plot will also be shown (Figure 11.3.2.4).

Table 11.3.2.5 OS.

	OS
N	
Events	
Censored	
Median OS	
OS at 6 months	
OS at 12 months	

Kaplan-Meier plot will also be shown (Figure 11.3.2.5).

Listing 11.3.2.6 Characteristics of patients with clinical benefit*.

Baseline Characteristics**						Study treatment characteristics**				
Patient id.	PS / Age/Gender	Histology type / Histology grade	No. of prior regimens	Best response last therapy	TTP last therapy	Cycles received	Best response	PFS (mo)	OS (mo)	DR (mo)
…										

(*) CR + PR + SD ≥ 4 months.

(**) Any other clinically relevant variable will be added at the time of the analysis.

Table 11.3.2.7 Median follow-up.

Follow-up*	Median	95% CI/Range
PFS		
OS		

(*) Calculated using the Kaplan-Meier method reversing the censoring values and also by descriptive methods.

New Section ***11.3.3 SCLC cohort***.

Primary Analysis (ORR):

Table 11.3.3.1 Response rate by IA (All treated patients).

Response	*N*	*%*
Complete response (CR)		
Partial response (PR)		
Stable disease SD≥4 months		
Stable disease SD<4 months		
Progressive disease (PD)		
*Inevaluable for response**		

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify).

Table 11.3.3.2 ORR by IA (All treated patients).

	Percentage	*Lower 95% limit*	*Upper 95% limit*
*Response rate**			

(*) Confirmed CR + PR. Binomial exact estimator and 95% CI.

Secondary and Supportive Analysis for ORR:

Table 11.3.3.3 Response rate by IA (All evaluable patients).

Response	*N*	*%*
Complete response (CR)		
Partial response (PR)		
Stable disease SD≥4 months		
Stable disease SD<4 months		
Progressive disease (PD)		
*Inevaluable for response**		

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify).

Table 11.3.3.4 ORR by IA (All evaluable patients).

	Percentage	*Lower 95% limit*	*Upper 95% limit*
*Response rate**			

(*) Confirmed CR + PR. Binomial exact estimator and 95% CI.

Table 11.3.3.5 Response rate by IRC (All treated patients).

Response	*N*	*%*
Complete response (CR)		
Partial response (PR)		
Stable disease SD≥4 months		
Stable disease SD<4 months		
Progressive disease (PD)		
*Inevaluable for response**		

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify).

Table 11.3.3.6 ORR IRC (All treated patients).

	Percentage	*Lower 95% limit*	*Upper 95% limit*
*Response rate**			

(*) Confirmed CR + PR. Binomial exact estimator and 95% CI.

Table 11.3.3.7 Response rate by IA and IRC (All treated patients).

Response	*IA*

		Complete response (CR)		Partial response (PR)		Stable disease SD≥4 months		Stable disease SD<4 months		Progressive disease (PD)		Inevaluable for response*	
		N	%	N	%	N	%	N	%	N	%	N	%
IRC	Complete response (CR)												
	Partial response (PR)												
	Stable disease SD≥4 months												
	Stable disease SD<4 months												
	Progressive disease (PD)												
	Inevaluable for response*												

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify).
. For discrepancies see Listing 11.3.3.15. Percentage by columns.

Other Secondary Analyses:

Table 11.3.3.8 Descriptive DR by IA and IRC.*

	N	Mean	Std.Std.	Median	Min	Max
IA						
IRC						

(*) Calculated with univariate procedures, not taking into account censoring, instead of Kaplan-Meier estimates.

Table 11.3.3.9 DR by IA and IRC.

	IA	IRC
N		
Events		
Censored		
Median DR		
DR at 4 months		
DR at 6 months		
DR at 12 months		

Kaplan-Meier plots will also be shown (Figure 11.3.3.9.1 DR by IA; Figure 11.3.3.9.2 DR by IRC and Figure 11.3.3.9.3 DR by IA and IRC)

Table 11.3.3.10 Clinical benefit rate and Disease control rate by IA and IRC (All treated patients).

		Percentage	Lower 95% limit	Upper 95% limit
IA	Clinical benefit rate*			
	Disease control rate**			
IRC	Clinical benefit rate*			
	Disease control rate**			

(*) CR + PR + SD ≥ 4 months. Binomial exact estimator and 95% CI.
(**) CR + PR + SD. Binomial exact estimator and 95% CI.

Table 11.3.3.11 PFS by IA and IRC (All treated patients).

	IA	IRC
N		
Events		
Censored		
Median PFS		

PFS at 4 months		
PFS at 6 months		

Kaplan-Meier plot will also be shown. (Figure 11.3.3.11.1 PFS by IA (All treated patients), Figure 11.3.3.11.2 PFS by IRC (All treated patients) and Figure 11.3.3.11.3 PFS by IA and IRC (All treated patients))

Table 11.3.3.12 OS (All treated patients).

	OS
N	
Events	
Censored	
Median OS	
OS at 6 months	
OS at 12 months	

Kaplan-Meier plot will also be shown (Figure 11.3.3.12).

Listing 11.3.3.13 Characteristics of patients with clinical benefit by CTFI by IA and IRC. (All treated patients).

Baseline characteristics***						Study treatment characteristics***				
Patient id.	CTFI**	PS / Age/ Gender	No. of prior regimens	Last prior therapy	Best response/TTP last therapy	Cycles received	Best response IA/IRC	PFS (mo) IA/IRC	DR (mo) IA/IRC	OS (mo)
…										

(*) CR + PR + SD ≥ 4 months.
(**) RR, R, S, VS.
(***) Any other clinical relevant variable will be added at the analysis time.

Table 11.3.3.14 Median follow-up by IA and IRC. (All treated patients).

Follow-up*		***Median***	***95% CI/Range***
IA	***PFS***		
	OS		
IRC	***PFS***		

(*) Calculated using the Kaplan-Meier method reversing the censoring values and also by descriptive methods.

Listing 11.3.3.15 Concordance by IA and IRC. (All treated patients).

Patient id.	***CTFI****	***Study treatment characteristics by IA***			***Study treatment characteristics by IRC***		
		Best response	***PFS (mo)***	***DR (mo)***	***Best response***	***PFS (mo)***	***DR (mo)***

(*) RR, R, S, VS.

Table 11.3.3.16 Progression type by IA and IRC. (All treated patients)

	IA		***IRC***	
	N	***%***	***N***	***%***
Target lesion				
Non-target lesion				
New lesions				
CNS				
CNS + Other				
No CNS				

Death due to malignant disease				
Other*				

(*)Please specify;

Table 11.3.3.17 Censoring reason by IA and IRC. (All treated patients)

	IA		***IRC***	
	N	***%***	***N***	***%***
Progression-free at last tumor assessment				
FU completed				
FU ongoing				
Subsequent therapy before documented progression				
Other*				

(*)Please specify;

Subgroup Analysis by CTFI (< 90 days and ≥ 90 days/or Refractory (RR) [<30 days], Resistant (R) [>=30 and <90 days], Sensitive (S) [>=90 and <180 days] and Very Sensitive (VS)[>=180 days]):

Table 11.3.3.18 Response rate IA and IRC by CTFI (All treated patients).

Response		***CTFI< 90 days***						***CTFI≥ 90 days***					
		RR		***R***		***Total***		***S***		***VS***		***Total***	
		N	***%***	***N***	***%***	***N***	***%***	***N***	***%***	***N***	***%***	***N***	***%***
IA	***Complete response (CR)***												
	Partial response (PR)												
	Stable disease SD≥4 months												
	Stable disease SD<4 months												
	Progressive disease (PD)												
	Inevaluable for response*												
IRC	***Complete response (CR)***												
	Partial response (PR)												
	Stable disease SD≥4 months												
	Stable disease SD<4 months												
	Progressive disease (PD)												
	Inevaluable for response*												

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify).

Table 11.3.3.19 ORR IA and IRC by CTFI (All treated patients).

Response rate*			***Percentage***	***Lower 95% limit***	***Upper 95% limit***
IA	***CTFI< 90 days***	***RR***			
		R			
		Total			
	CTFI≥ 90 days	***S***			
		VS			
		Total			
IRC	***CTFI< 90 days***	***RR***			
		R			
		Total			
	CTFI≥ 90 days	***S***			
		VS			
		Total			

(*) Confirmed CR + PR. Binomial exact estimator and 95% CI.

Table 11.3.3.20 Response rate IA and IRC by CTFI (All treated patients).

Response	***IA***

		Complete response (CR)		Partial response (PR)		Stable disease SD≥4 months		Stable disease SD<4 months		Progressive disease (PD)		Inevaluable for response*	
		N	%	N	%	N	%	N	%	N	%	N	%
CTFI< 90 days													
IRC	Complete response (CR)												
	Partial response (PR)												
	Stable disease SD≥4 months												
	Stable disease SD<4 months												
	Progressive disease (PD)												
	Inevaluable*												
CTFI≥ 90 days													
IRC	Complete response (CR)												
	Partial response (PR)												
	Stable disease SD≥4 months												
	Stable disease SD<4 months												
	Progressive disease (PD)												
	Inevaluable for response*												

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify).
For discrepancies see Listing 11.3.3.15; Percentage in columns

Table 11.3.3.21 Descriptive DR IA and IRC by CTFI.

			N	Mean	Std.	Median	Min	Max
IA	CTFI< 90 days	RR						
		R						
		Total						
	CTFI≥ 90 days	S						
		VS						
		Total						
IRC	CTFI< 90 days	RR						
		R						
		Total						
	CTFI≥ 90 days	S						
		VS						
		Total						

Table 11.3.3.22 DR IA by CTFI.

	CTFI< 90 days*			CTFI≥ 90 days*		
	RR**	R**	Total*	S**	VS**	Total*
N						
Events						
Censored						
Median DR						
DR at 4 months						
DR at 6 months						
DR at 12 months						

(/**) Kaplan-Meier plot will also be shown. (*) Table/Figure 11.3.3.22.1 with the following categories (CTFI< 90 days and CTFI≥*

90 days), (**) Table /Figure 11.3.3.22.2 with the following categories RR, R, S and VS.

Table 11.3.3.23 DR IRC by CTFI.

	*CTFI< 90 days**			*CTFI≥ 90 days**		
	*RR***	*R***	*Total**	*S***	*VS***	*Total**
N						
Events						
Censored						
Median DR						
DR at 4 months						
DR at 6 months						
DR at 12 months						

(/**) Kaplan-Meier plot will also be shown. (*) Table/Figure 11.3.3.23.1 with the following categories (CTFI< 90 days and CTFI≥ 90 days), (**) Table /Figure 11.3.3.23.2 with the following categories RR, R, S and VS.*

Table 11.3.3.24 Clinical benefit rate and Disease control rate IA and IRC by CTFI (All treated patients).

				Percentage	*Lower 95% limit*	*Upper 95% limit*
*Clinical benefit rate**	*IA*	*CTFI< 90 days*	*RR*			
			R			
			Total			
		CTFI≥ 90 days	*S*			
			VS			
			Total			
	IRC	*CTFI< 90 days*	*RR*			
			R			
			Total			
		CTFI≥ 90 days	*S*			
			VS			
			Total			
*Disease control rate***	*IA*	*CTFI< 90 days*	*RR*			
			R			
			Total			
		CTFI≥ 90 days	*S*			
			VS			
			Total			
	IRC	*CTFI< 90 days*	*RR*			
			R			
			Total			
		CTFI≥ 90 days	*S*			
			VS			
			Total			

(*) CR + PR + SD ≥ 4 months. Binomial exact estimator and 95% CI.
(**) CR + PR + SD. Binomial exact estimator and 95% CI.

Table 11.3.3.25 PFS IA by CTFI (All treated patients).

	*CTFI< 90 days**			*CTFI≥ 90 days**		
	*RR***	*R***	*Total**	*S***	*VS***	*Total**
N						
Events						
Censored						
Median PFS						
PFS at 4 months						
PFS at 6 months						

(/**) Kaplan-Meier plots will also be shown. (*)Table/Figure 11.3.3.25.1 with the following categories (CTFI< 90 days and CTFI≥ 90 days), (**) Table/Figure 11.3.3.25.2 with the following categories RR, R, S and VS.*

Table 11.3.3.26 PFS IRC by CTFI (All treated patients).

	*CTFI< 90 days**			*CTFI≥ 90 days**		
	RR*	***R****	***Total****	***S****	***VS****	***Total****
N						
Events						
Censored						
Median PFS						
PFS at 4 months						
PFS at 6 months						

(*/**) Kaplan-Meier plots will also be shown. (*)Table/Figure 11.3.3.26.1 with the following categories (CTFI< 90 days and CTFI≥ 90 days), (**) Table/Figure 11.3.3.26.2 with the following categories RR, R, S and VS.

Table 11.3.3.27 OS by CTFI (All treated patients).

	*CTFI< 90 days**			*CTFI≥ 90 days**		
	R*	***RR****	***Total****	***S****	***VS****	***Total****
N						
Events						
Censored						
Median OS						
OS at 6 months						
OS at 12 months						

(*/**) Kaplan-Meier plots will also be shown. (*)Table/Figure 11.3.3.27.1 with the following categories (CTFI< 90 days and CTFI≥ 90 days), (**) Table/Figure 11.3.3.27.2 with the following categories RR, R, S and VS.

Subgroup Analysis excluding CTFI < 30 days:

Table 11.3.3.28 Response rate IA and IRC excluding CTFI<30 (All treated patients).

Response		***N***	***%***
IA	***Complete response (CR)***		
	Partial response (PR)		
	Stable disease SD≥4 months		
	Stable disease SD<4 months		
	Progressive disease (PD)		
	Inevaluable for response*		
IRC	***Complete response (CR)***		
	Partial response (PR)		
	Stable disease SD≥4 months		
	Stable disease SD<4 months		
	Progressive disease (PD)		
	Inevaluable for response*		

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify).

Table 11.3.3.29 ORR IA and IRC excluding CTFI<30 (All treated patients).

Response rate*	***Percentage***	***Lower 95% limit***	***Upper 95% limit***
IA			
IRC			

(*) Confirmed CR + PR. Binomial exact estimator and 95% CI.

Table 11.3.3.30 DR by IA and IRC excluding CTFI<30.

	IA	***IRC***
N		
Events		
Censored		
Median DR		
DR at 4 months		
DR at 6 months		
DR at 12 months		

Kaplan-Meier plot will also be shown (Figure 11.3.3.30.1 DR by IA excluding CTFI<30 (All treated patients), Figure 11.3.3.30.2 DR by IRC excluding CTFI<30 (All treated patients) and 11.3.3.30.3 DR by IA and IRC excluding CTFI<30 (All treated patients))

Table 11.3.3.31 Clinical benefit rate and Disease Control Rate by IA and IRC excluding CTFI<30 (All treated patients).

		Percentage	*Lower 95% limit*	*Upper 95% limit*
IA	*Clinical benefit rate**			
	*Disease control rate***			
IRC	*Clinical benefit rate**			
	*Disease control rate***			

(*) CR + PR + SD ≥ 4 months. Binomial exact estimator and 95% CI.
(**) CR + PR + SD. Binomial exact estimator and 95% CI.

Table 11.3.3.32 PFS IA and IRC excluding CTFI<30 (All treated patients).

	IA	*IRC*
N		
Events		
Censored		
Median PFS		
PFS at 4 months		
PFS at 6 months		

Kaplan-Meier plot will also be shown (Figure 11.3.3.32.1 PFS by IA excluding CTFI<30 (All treated patients), Figure 11.3.3.32.2 PFS by IRC excluding CTFI<30 (All treated patients) and Figure 11.3.3.32.3 PFS by IA and IRC excluding CTFI<30 (All treated patients))

Table 11.3.3.33 OS excluding CTFI<30 (All treated patients).

	OS
N	
Events	
Censored	
Median OS	
OS at 6 months	
OS at 12 months	

Kaplan-Meier plot will also be shown (Figure 11.3.3.33).

DR and PFS considering event in the clinical progressions:

Table 11.3.3.34 DR IA giving event in clinical PD (All treated patients).

	DR
N	
Events	
Censored	
Median DR	
DR at 4 months	
DR at 6 months	
DR at 12 months	

Kaplan-Meier plot will also be shown (Figure 11.3.3.34).

Table 11.3.3.35 PFS IA giving event in clinical PD (All treated patients).

	PFS
N	
Events	
Censored	
Median PFS	
PFS at 4 months	
PFS at 6 months	

Kaplan-Meier plot will also be shown (Figure 11.3.3.35).

12. Safety Analysis

Original text:

Safety analysis will be carried out on the "All Treated Patients" population.

Changes to:

Safety analysis will be carried out on the "All Treated Patients" population by cohort ***of tumor types and total population***.

Section 12.1.1 Treatment Administration.

Table 12.1.1 Number of cycles administered and dose intensity adds the following footnote: ***Note: Also for s1 and s2***.

Sections 12.1.2 Cycles Delays and 12.1.3 Dose Reductions: The following clarification has been added to both sections.

The first cycle will be excluded from all calculations.

Section 12.1.2 Cycle delays.

Listing 12.1.2.1 Delays and Listing 12.1.2.6 Cycle delays due to AEs add one new column ***CTFI**** and the footnote ***(*) Only for SCLC patients (RR, R, S, VS).***

Table 12.1.2.2 Number of patients and cycles with dosing delay, any relationship.

	N	%
No. of patients treated		
No. of patients susceptible of delay		
No. of patients with any dose delay		
No. of cycles administered		
No. of cycles susceptible to be delayed		
No. of cycles with dosing delay		
No. of patients with No cycles delayed 1 cycle delayed 2 cycles delayed ≥ 3 cycles delayed		

Note: Also for s1 and s2;

Table 12.1.2.3 Number of patients and cycles with dosing delay, treatment related adds the following footnote: ***Note: Also for s1 and s2***.

Table 12.1.2.4 Reasons for dosing delay according to the relationship is split into two by patients and cycles.

Reasons for delays	N	%
No. of patients with any dose delay		
Treatment-related	X	XX.X
Hematological		
Non-hematological		
Both		
Non-treatment-related		
No. of cycles with any dose delay	N	%
Treatment-related	X	XX.X
Hematological		
Non-hematological		
Both		
Non-treatment-related		

Note: Also for s1 and s2;

Table 12.1.2.5 Length of dosing delay adds the following footnote: ***Note: Also for s1 and s2***.

Section 12.1.3 Dose Reductions.

Listing 12.1.3.1 Dose Reductions and Listing 12.1.3.5 Dose reductions due to AEs add one new column ***CTFI**** and the footnote ***(*) Only for SCLC patients (RR, R, S, VS).***

Table 12.1.3.2 Number of patients and cycles with dose reduction, any relationship.

	N	%
No. of patients treated	X	XX.X
No. of patients susceptible to have a dose reduction		
No. of patients with any dose reduced		
No. of patients with:		
No PM01183 reduction		
1 cycle with PM01183 dose reduced		
2 cycles with PM01183 dose reduced		
No. of cycles administered		
No. of cycles susceptible to have any dose reduced		
No. of cycles with PM01183 dose reduced		

Note: Also for s1 and s2;

Table 12.1.3.3 Number of patients and cycles with dose reduction, treatment related adds the following footnote: ***Note: Also for s1 and s2***.

Table 12.1.3.4 Number of patients and cycles with dose reduction according to the relationship is split into two by patients and cycles.

Reasons for reductions	N	%
No. patients with reductions		
Treatment-related	X	XX.X
Hematological		
Non-hematological		
Both		
Non-treatment-related		
No. of cycles patients with reductions	***N***	***%***
Treatment-related	***X***	***XX.X***
Hematological		
Non-hematological		
Both		
Non-treatment-related		

Note: Also for s1 and s2;

Section 12.2.1 Adverse Events changes to **Treatment Emergent Adverse Events**

Original text:

Adverse events will be described in this section; treatment-related events (stated as related to the study drug or of unknown relationship) will be tabulated.

(…)

Changes to:

Treatment emergent adverse events will be described in this section; treatment-related events (stated as related to the study drug or of unknown relationship) will be tabulated.

Section 12.2.2 Display of Adverse Events changes to **12.2.2 Treatment Emergent Adverse Events.**

Original text:

Table 12.2.2.1 Summary of adverse events per patient

Category*	N	%
Patients with at least one AE regardless of relationship		
Any treatment-related** AE		
Any grade ***≥3*** AE		
Any treatment-related grade ≥3 AE		
Any SAE in DB		
Any treatment-related SAE		
Any grade ***≥3*** SAE		
Any treatment-related grade ≥3 SAE		
AEs leading to death		
Treatment-related AEs leading to death		
AEs leading to dose delay		
AEs leading to dose reduction		
AEs leading to treatment discontinuation		
Treatment-related AEs leading to treatment discontinuation		

(…)

Table 12.2.2.2 Adverse events regardless of relationship. Worst grade by patient.
Table 12.2.2.3 Adverse events regardless of relationship. Worst grade by cycle.

Tables 12.2.2.2 to 12.2.2.5 will have the following pattern, but depending on the number and severity

of the adverse events observed, the NCI-CTCAE v4 grades may be grouped as 1-4 and 3/4 categories.

SOC	Preferred term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS							
	...							
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

(*)Any grade

Listing 12.2.2.7 Treatment-related grade 3/4 adverse events. Worst grade by cycle.

Listing 12.2.2.8 Grade 3/4 adverse events regardless of relationship. Worst grade per patient.
Listing 12.2.2.9 Grade 3/4 adverse events regardless of relationship. Worst grade by cycle.

Listings 12.2.2.6 to 12.2.2.9 will have the following pattern:

(….)

Patient id.	Cycle*	SOC name	Preferred term	Grade

(*)NA in the patient summaries;

Changes to:

Table 12.2.2.1 Summary of ***Treatment emergent*** adverse events per patient.

Category**	N	%
Patients with at least one ***TEAE*** regardless of relationship		
Any treatment-related** AE		
Any grade ≥3 ***TEAE***		
Any treatment-related grade ≥3 AE		
Any Treatment emergent SAE in DB		
Any treatment-related SAE		
Any grade ≥3 Treatment emergent SAE		
Any treatment-related grade ≥3 SAE		
TEAEs leading to death		
Treatment-related AE leading to death		
TEAEs leading to dose delay***		
TEAEs leading to dose reduction***		
TEAEs leading to treatment discontinuation		
Treatment-related AEs leading to treatment discontinuation		

Note: Also for s1 and s2; (*) Percentage based on number of treated patients; (**) Treatment related adverse event is every event whose relationship is 'Yes' or 'Unknown'. ***(***) TEAEs leading to dose delay and reduction according to the AE form, with no delay or reduction because the patient discontinues treatment and there is no additional cycle administered are not counted here.***

Table 12.2.2.2 ***Treatment emergent*** adverse events regardless of relationship. Worst grade by patient.
Table 12.2.2.3 ***Treatment emergent*** adverse events regardless of relationship. Worst grade by cycle.

(…)

Tables 12.2.2.2 to 12.2.2.5 will have the following pattern, but depending on the number and severity of the adverse events observed, the NCI-CTCAE v4 grades may be grouped as ***≥1*** and ***≥3*** categories.

SOC	Preferred term	Grade 1		…	Grade 4		***Grade ≥1***		***Grade ≥3***	
		N	%	…	N	%	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS									
	...									
	…									
Cardiac disorders	Arrhythmia NOS									

Note: Tables 12.2.2.2 and 12.2.2.4 also for s1 and s2;

(….)

Listings 12.2.2.6 to 12.2.2.9 will have the following pattern:

Patient id.	***CTFI****	Cycle*	SOC name	Preferred term	Grade

(*) NA in the per patient summaries;(**) CTFI only for SCLC patients (RR, R, S, VS)

Listing 12.2.2.7 Treatment-related grade ***≥3*** adverse events. Worst grade by cycle.
Listing 12.2.2.8 Grade ***≥3 treatment emergent*** adverse events regardless of relationship. Worst grade per patient.
Listing 12.2.2.9 Grade ***≥3 treatment emergent*** adverse events regardless of relationship. Worst grade by cycle.

Section 12.3.1 Serious Adverse Events.

Original text:

Table 12.3.1.1 SAEs

Patient id.	Preferred term code	Adverse event reported (verbatim)	Status	Grade	Relationship	Onset date	Resolution date	Action	Serious criteria

Changes to:

Table 12.3.1.1 SAEs

Patient id.	Preferred term code	***Onset Cycle***	***Intended Dose of onset cycle (mg/m2)***	Adverse event reported (verbatim)	Status	Grade	Relationship	Onset date	Resolution date	Action	Serious criteria

Also the following tables are included:

Table 12.3.1.2 Treatment-related serious adverse events. Worst grade by patient.

Table 12.3.1.3 Treatment-related serious adverse events. Worst grade by cycle.

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

Table 12.3.1.5 Serious adverse events regardless of relationship. Worst grade by cycle.

Tables 12.3.1.2 to 12.3.1.5 will have the following pattern, but depending on the number and

severity of the adverse events observed, the NCI-CTCAE v4 grades may be grouped as ≥1 and ≥3 categories.

SOC	*Preferred term*	*Grade 1*		*…*	*Grade 4*		*All**	
		N	*%*	*…*	*N*	*%*	*N*	*%*
Blood and lymphatic system disorders	***Anemia NOS***							
	…							
	…							
Cardiac disorders	***Arrhythmia NOS***							
	…							

Note: Tables 12.312.2 and 12.3.1.4 also for s1 and s2;

Table 12.3.1.6 Treatment-related grade ≥3 serious adverse events. Worst grade per patient.

Table 12.3.1.7 Treatment-related grade ≥3 adverse events. Worst grade by cycle.

Table 12.3.1.8 Grade ≥3 adverse events regardless of relationship. Worst grade per patient.

Table 12.3.1.9 Grade ≥3 adverse events regardless of relationship. Worst grade by cycle.

Listings 12.3.1.6 to 12.3.1.9 will have the following pattern:

Patient id.	*CTFI***	*Cycle**	*SOC name*	*Preferred term*	*Grade*

(*)NA in the patient summaries ;(**) CTFI only for SCLC patients (RR, R, S, VS)

Section 12.3.2 Deaths

Original text:

Table 12.3.2.1 Cause of death.

Reason*	N	%
Malignant disease		
Study drug-related AE		
Non-study drug-related AE		
Other		
Total		

(*) Denominator=Number of patients who died.

Listing 12.3.2.2 Deaths.

Patient id.	Death date	Cause	No. of cycles administered	Last infusion date	Time on treatment*	Time from Last dose **	Comments	Autopsy

(*) Time on treatment: defined as date of last infusion plus 30 days, or date of death or subsequent therapy (whichever comes first) minus date of first infusion. (**) Time from last dose defined as date of death minus date of last infusion.

Listing 12.3.2.3 Adverse events with outcome death.

Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Date of death	Action

Changes to:

Table 12.3.2.1 Cause of death.

Reason*	N	%
Malignant disease		
Study drug-related ***TEAE***		
Non-study drug-related ***TEAE***		
Other		
Total		

Note: Also for s1 and s2; (*) Denominator=Number of patients who died.

Listing 12.3.2.2 Deaths.

Patient id.	***CTFI******	Death date	Cause	No. of cycles administered	Last infusion date	Time on treatment*	Time from Last dose **	Comments	Autopsy

(*) Time on treatment: defined as date of last infusion plus 30 days, or date of death or subsequent therapy (whichever comes first) minus date of first infusion. (**) Time from last dose defined as date of death minus date of last infusion. ***(***) Only for SCLC cohort (RR, R, S, VS).***

Listing 12.3.2.3 Adverse events with outcome ***of*** death.

Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Date of death	Action

Section 12.4.1 Hematological Abnormalities during Treatment and section 12.4.2 Biochemical Abnormalities during Treatment.

Tables 12.4.1.1 to 12.4.1.2 and Tables 12.4.2/3.1 to 12.4.2/3.2 will have the following pattern, but depending on the number and severity of the adverse events observed the NCI-CTCAE v4 grades may be grouped as ***≥1*** and ***≥3*** categories.

	Grade 1		…	Grade 4*		***Grade ≥1***		***Grade ≥3***	
	N	%	…	N	%	N	%	N	%
….									
….									

Note: Tables 12.4.1/2.1 and 12.4.1/2.2 also for s1 and s2;

Section 12.5.2 LVEF, ECG and Other Related Tests

Original text:

Listing 12.5.2.1 LVEF evolution during the study.

	LVEF(%)		
	Baseline*	Minimun*	End of treatment*
Patient id.			
Median (Range) Mean, Standard Deviation			

(*) LVEF (%) value and method.

Listing 12.5.2.2 Electrocardiogram results. Evolution during the study.

	Cycle/ECG result*						
	0	1	2	3	4	…	EOT
Patient id.							
…							

(*) Worst result of the cycle determinations.

Changes to:

Listing 12.5.2.1Patients with abnormal or clinical indicated LVEF during the study.

Patient id.	Assessment date	Abnormality	Specify	Reason for clinically indicated repeat	Method	LVEF (%)	Institution normal range

Listing 12.5.2.2 Patients with abnormal or clinical indicated Electrocardiogram during the study.

Patient id.	Assessment date	Result	Specify	Reason for clinically indicated repeat	PR interval (msec)	Heart rate (bpm)	QT interval (msec)	QRS complex (msec)	QTc Fridericia	QTc* (Bazett's)

(*) QTc (Bazett's) = QT interval / √(60/Heart rate).

Section 12.6 Concomitant Therapy / Procedures According to the ATC Classification. Add new tables and new variables in existing tables. New numbering of tables is needed

Table 12.6.1 Concomitant medication during treatment (ATC1, ATC2, ***ATC3*** and ATC4 levels).

Table 12.6.3 Patients and cycles with any transfusions during treatment.

	N	%
No. of patients with Platelet transfusions ***No. of cycles with Platelet transfusions***		
No. of patients with RBC ***No. of cycles with RBC***		
No. of patients with GCSF		

Section 12.4.4 Laboratory Values over Time.

Original text:

Tables 12.4.4.5 and 12.4.4.6 will have the following pattern:

	All cycles		First cycle	
	N	%	N	%
Grade 3/4* onset day				
Nadir ($x10^9$/L)				
Duration of grade 3/4 decrease				
Day of recovery to grade 1/2 or baseline values**				

(*) Grade 3 or 4; (**) grade 2 or less.

Tables 12.4.4.7 and 12.4.4.8 will have the following pattern:

	All cycles		First cycle	
	N	%	N	%

Grade 3/4* onset day				
Peak (x10^9/L)				
Duration of grade 3/4 decrease				
Day of recovery to grade 1/2 or baseline values**				

(*) Grade 3 or 4; (**) grade 2 or less.

Changes to:

Tables 12.4.4.5 and 12.4.4.6 will have the following pattern:

	All cycles	First cycle
	N, mean, Std., median, Range	***N, mean, Std., median, Range***
Grade ***≥3**** onset day		
Nadir (x10^9/L)		
Duration of grade ***≥3 (days)***		
Day of recovery to grade 1/2 or baseline values**		

(*) Grade 3 or 4; (**) grade 2 or less.

Tables 12.4.4.7 and 12.4.4.8 will have the following pattern:

	All cycles	First cycle
	N, mean, Std., median, Range	***N, mean, Std,. median, Range***
Grade ***≥3**** onset day		
Peak (x10^9/L)		
Duration of grade ***≥3 (days)***		
Day of recovery to grade 1/2 or baseline values**		

(*) Grade 3 or 4; (**) grade 2 or less.

New Section 12.7 Subsequent therapy. This section contains some tables from previous **section 12.6 Concomitant Therapy / Procedures According to the ATC Classification**. Tables 12.6.5 First Subsequent therapy and Table 12.6.6 First Subsequent therapy. Best Response (if available).

Original text:

Table 12.6.5 First Subsequent therapy.

	N	%
Type		
Medical therapy		
…		
Subsequent chemotherapy agents (ATC)		
…		
…		

Table 12.6.6 First Subsequent therapy. Best response (if available).

Best response		First Subsequent therapy				
		CR	PR	SD	PD	NE
PM01183	CR					
	PR					
	SD					
	PD					
	NE					

(*) If a low number of best responses to the subsequent therapy are available, a listing, instead of this table, will be provided.

Changes to:

Table 12.7.1 Any Subsequent medical therapy.

	N	%
Type		
Medical therapy		
Radiotherapy		
Surgery		
Number of subsequent medical therapies (Median and range)		
0		
1		
2		
…		
Subsequent agents of medical therrapy (ATC)		
…		
…		

Note: Also for s1 and s2;

Table 12.7.2 First Subsequent medical therapy.

	N	%
Subsequent chemotherapy agents (ATC)		
…		
…		

Note: Also for s1 and s2;

Table 12.7.3 First Subsequent medical therapy. Best response (if available).

Best response		First Subsequent therapy				
		CR	PR	SD	PD	NE
PM01183	CR					
	PR					
	SD					
	PD					
	NE					

Note: Also for s1 and s2; ***(*) If a low number of best responses to the subsequent therapy are available, a listing, instead of this table, will be provided***. In case of sufficient number of subsequent Immunotherapy, a separate table/listing will be performed for patients having immunotherapy as first subsequent therapy.

Table 12.7.4 First Subsequent medical therapy. PFS (if available).

PFS (months)		First Subsequent therapy				
		<1 month	[1-3) months	[3-6) months	[6-12) months	≥12 months
PM01183	<1 month					
	[1-3) months					
	[3-6) months					
	[6-12) months					
	≥12 months					

Note: Also for s1 and s2;

Any other exploratory analyses will be performed at the analysis time if any relevant variable will be considered potentially relevant. Table's layout will follow the same prior patterns.

Any other exploratory analyses will be performed at the analysis time if any relevant variable will be considered potentially relevant. Table's layout will follow the same prior patterns.

New Section 12.8 Subgroup Analyses Related to Safety

Table 12.8.1 Worst grade ≥3by patient in special subgroups (Sex).

Table 12.8.2 Worst grade ≥3 by cycle in special subgroups (Sex).

Table 12.8.3 Worst grade ≥3 by patient in special subgroups (Age).

Table 12.8.4 Worst grade ≥3 by cycle in special subgroups (Age).

Table 12.8.5 Worst grade ≥3 by patient in special subgroups (Race).

Table 12.8.6 Worst grade ≥3 by cycle in special subgroups (Race).

Table 12.8.7 Worst grade ≥3 by patient in special subgroups (Number of prior lines).

Table 12.8.8 Worst grade ≥3 by cycle in special subgroups (Number of prior lines).

Table 12.8.9 Worst grade ≥3 by patient in special subgroups (BSA).

Table 12.8.10 Worst grade ≥3 by cycle in special subgroups (BSA).

Table 12.8.11 Worst grade ≥3 by patient in special subgroups (ECOG).

Table 12.8.12 Worst grade ≥3 by cycle in special subgroups (ECOG).

Table 12.8.13 Worst grade ≥3 by patient in special subgroups (Geographical area).

Table 12.8.14 Worst grade ≥3 by cycle in special subgroups (Geographical area).

Tables 12.8.1 to 12.8.12 will have the following pattern:

Laboratory abnormalities/ drug-related AEs	*Subgroup 1*			*Subgroup 2*			*….*		
	No. of patients evaluated	*Grade ≥3*	*%*	*No. of patients evaluated*	*Grade ≥3*	*%*	*No. of patients evaluated*	*Grade ≥3*	*%*
Thrombocytopenia									
Neutropenia									
AP									
Bilirubin									
AST									
ALT									
CPK									
Nausea									
Vomiting									

Laboratory abnormalities/ drug-related AEs	*Subgroup 1*			*Subgroup 2*			….		
	No. of patients evaluated	*Grade ≥3*	*%*	*No. of patients evaluated*	*Grade ≥3*	*%*	*No. of patients evaluated*	*Grade ≥3*	*%*
Fatigue									
Other*									

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

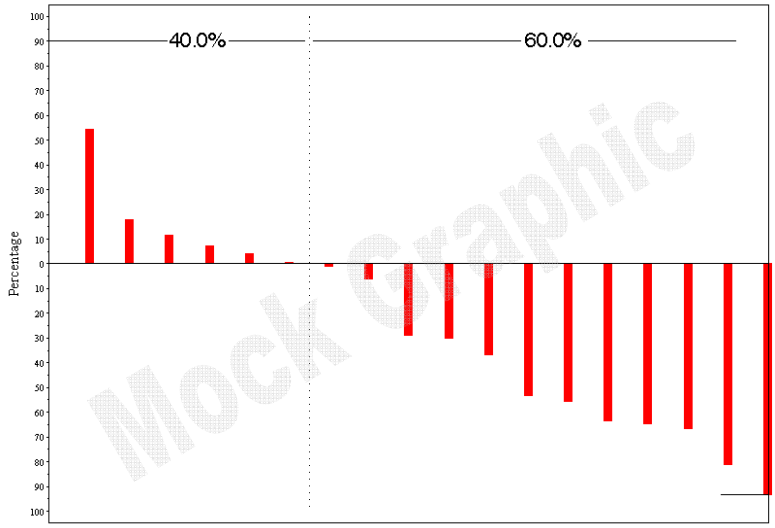
Section 13: Figures. This section has been updated according to the planned number of analysis described in section 11.3 Efficacy Analysis and due to the elevated number of figures displayed in this section the numbering of the figures is changed accordingly.

The following paragraph is added:

Figures displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable) ***and/or any other specific subgroups (e.g: CTFI categorized). See examples below, numbering will be updated accordingly.***

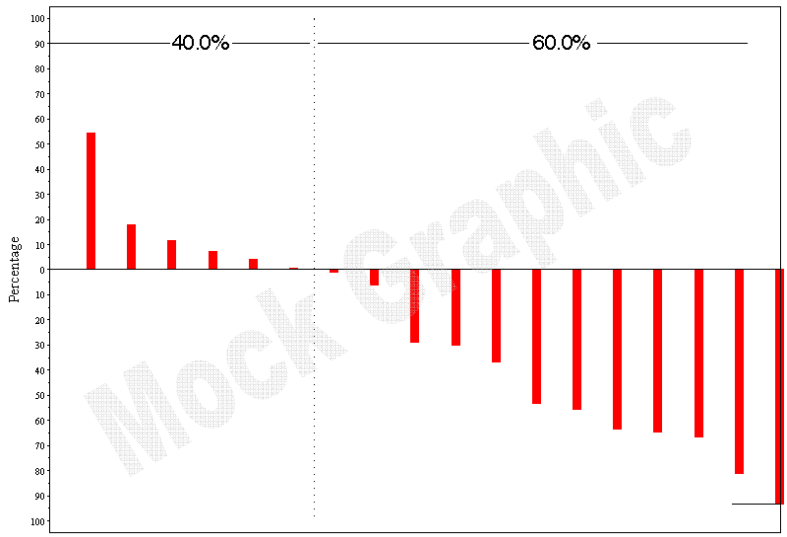
Previous Figures from 13.1.4 Best RECIST Efficacy assessment in evaluable pts per tumor type to 13.1.7 Barcharts of hematological/biochemical laboratory abnormalities per tumor type and 13.19 Box-plots of change in LVEF/QTcF from baseline to lowest/highest value during study per tumor type/cycle are deleted.

Figure 13.1.2 Waterfall graph.



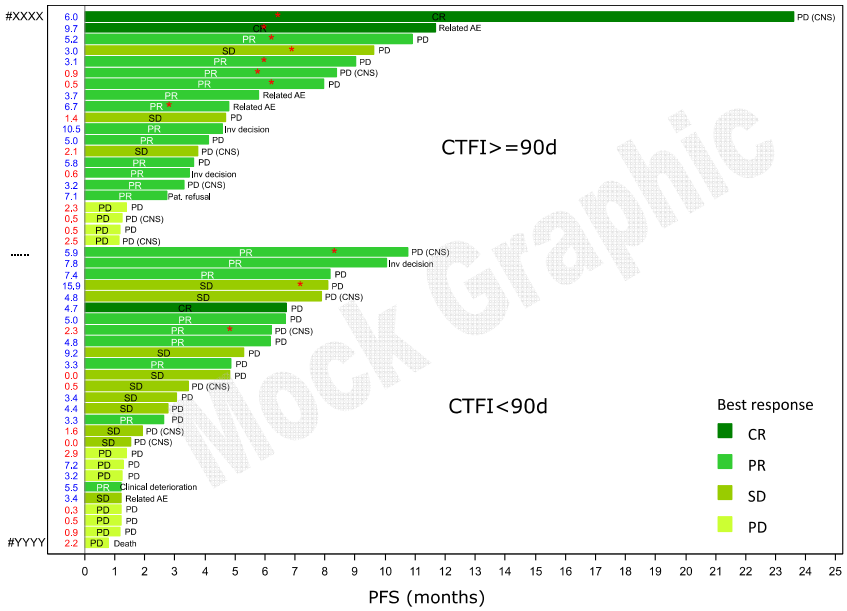
Waterfall for each tumor type will be also provided. Also SCLC by CTFI ***(RR, R, S VS).***

Figure 13.1.2 Waterfall graph per tumor type by IRC (SCLC cohort)



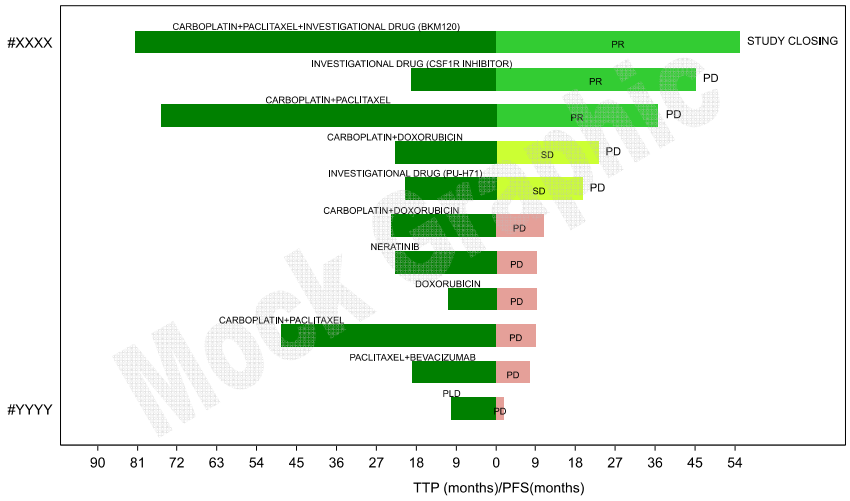
Waterfall for SCLC and by CTFI (RR, R, S, VS).
NOTE: If the measurements of the first and the second radiologists are the same, the target lesions measurements of the first one will be selected. If the measurements of both radiologists are different and an adjudicator is involved, his/her endorsement will be selected.

Figure 13.1.4 Best response, PFS and Reasons for discontinuation (SCLC cohort)



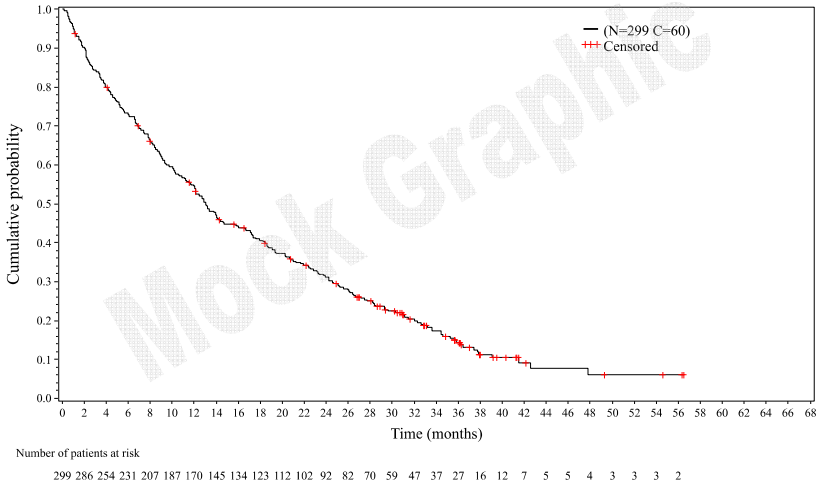
Also for s1 and s2.

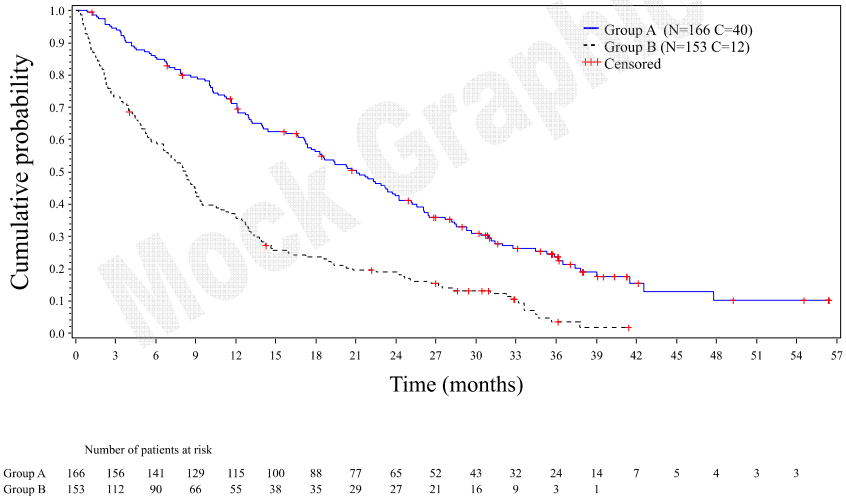
Figure 13.1.5 Last previous TTP vs PFS PM01183 (SCLC cohort).



Note: For PM01183 responders and/or SD (if applicable)

Figures described in **Section 11.3 Efficacy Analysis** will have the following pattern depending on the number of groups represented.





Section 14: DB Listings.

DB listings, ICH and BIMO listings are included in a new section renamed to Section **14. DB Listings, BIMO and ICH Listings**.

All listings in this section add a mock table and include the name of variables to be listed.

CRF Listings.

Original text:

- Listing 14.1.1: Cover
- Listing 14.1.2: Study registration
- Listing 14.1.3: Demography
- Listing 14.1.4: Pregnancy test and adequate contraception
- Listing 14.1.5: Prior medical history
- Listing 14.1.6: Cancer history
- Listing 14.1.7: Prior surgery
- Listing 14.1.8: Prior radiotherapy
- Listing 14.1.9: Prior medical therapy
- Listing 14.1.10: Hematological laboratory values
- Listing 14.1.11: Biochemical laboratory values
- Listing 14.1.12: Coagulation laboratory values
- Listing 14.1.13: Physical examination
- Listing 14.1.14: Performance status
- Listing 14.1.15: Vital signs
- Listing 14.1.16: Electrocardiogram
- Listing 14.1.17: LVEF
- Listing 14.1.18: Prophylactic medication
- Listing 14.1.19: Drug administration
- Listing 14.1.20: Adverse events (including adverse events at baseline)
- Listing 14.1.21: Concomitant therapy/procedures
- Listing 14.1.22: Tumor assessment

- Listing 14.1.23: Evaluation of response by cycle
- Listing 14.1.24: Best study overall response
- Listing 14.1.25: End of treatment
- Listing 14.1.26: Follow up
- Listing 14.1.27: Death report form
- Listing 14.1.28: Off study

Changes to:

Listing 14.1.1: Cover.

Patient id.	*Informed Consent Date*	*Part of QT substudy?*	*QT informed consent date*	*Patient QT inclusion accepted by Pharmamar?*	*PGN/PGx consent*	*PGN/PGx date*

Listing 14.1.2: Study registration.

Patient id.	*Patient inclusion accepted by Pharmamar?*	*Eligibility requirements?*	*Criterion identifier I/E*	*I/E details*

Listing 14.1.3: Demography.

Patient id.	*Age at inclusion*	*Gender*	*Race*	*Other Race, specify*

Listing 14.1.4: Pregnancy test and adequate contraception.

		Pregnancy test						*Adequate contraception*	
Patient id.	*Visit*	*Not applicable?*	*Reason*	*Not done?*	*Sample date*	*Result*	*Reason for clinically indicated repeat*	*Adequate contraception?*	*Specify*

Listing 14.1.5: Prior medical history.

Patient id.	*Event/Condition*	*System Organ Class*	*MedDRA Preferred Term*	*Onset date*	*End date*	*Ongoing?*

Listing 14.1.6: Cancer history.

			Current stage				*At diagnosis*		
Patient id.	*Tumor type*	*….**	*Date of advanced/metastasic disease*	*Date of last PD*	*Sites:Primary tumor/local relapse (Not for UPS)*	*Sites***	*Diagnosis date*	*Stage*	*TNM*

(*) For each tumor type CRF has specific categories. e.g: Endometrial patients; (Carcinoma type, Histology type, Other)
(**)Tumor sites are nested for each patient obtained from Cancer History Form e.g: (Lung/Liver/LN:/Neck LN/Mediastinal LN);

Listing 14.1.7: Prior surgery.

Patient id.	*None?*	*Site and Procedures*	*Date*	*Intention*

Listing 14.1.8: Prior radiotherapy.

Patient id.	*None?*	*Type*	*Intention*	*Site*	*Total dose*	*First dose*	*Last dose*

Listing 14.1.9: Prior medical therapy.

Patient id.	*None?*	*Regimen*	*Setting*	*Agent*	*Agent Coded*	*Agent Class*	*Setting*	*Start Date*	*Stop Date*	*Best Resp.*	*Prog. Date*	*Non PD*

Listing 14.1.10: Hematological laboratory values.

Patient id.	*Visit*	*Date*	*n*	*Clinically indicated repeat required?*	*Hemoglobin (g/dl)*	*Platelets (x10*9/L)*	*WBC (x10*9/L)*	*Neutrophils (x10*9/L)*	*Lymphocytes (x10*9/L)*	*Monocytes (x10*9/L)*

Listing 14.1.11: Biochemical laboratory values.

Patient id.	*Visit*	*Date*	*n*	*Clinically indicated repeat required?*	*Total Bilirubin (mg/dl)*	*Direct Bilirubin (mg/dl)*	*AST (IU/L)*	*ALT (IU/L)*	*AP (IU/L)*	*…..**

(*)GGT (IU/L), Glucose (mg/dL), Creatinine (mg/dl), CrCl (mL/min), NA (mmol/L), CL (mmol/L), K (mmol/L), LDH (xULN), CPK (IU/L), Total Proteins (g/dl), Albumin (g/dl), CA (mg/dl), Mg (mg/dl), INR (ratio), PT (sec/ratio), PTT (sec/ratio), AFP (ng/m), hCG (IU/L)

A new listing is included:

Listing 14.1.12: Alpha Glycoprotein.

Patient id.	*Visit*	*Date*	*n*	*Alpha-1-acid glycoprotein (MG/DL)*	*Comments 1*	*Comments 2*

Listing 14.1.***13***: Coagulation laboratory values.

Patient id.	*Visit*	*Date*	*n*	*Clinically indicated repeat required?*	*INR (ratio)*	*PT (sec)*	*PTT (sec)*

Listing 14.1.***14***: Physical examination.

Patient id.	*Visit*	*Not done*	*Date*	*Abnormalities*	*Weight (Kg)*	*Height (cm)*	*BSA (m2)*	*Body System*	*Findings*	*Clinical Significance*

Listing 14.1.***15***: Performance status.

Patient id.	*Not Done*	*Visit*	*ECOG*

Listing 14.1.***16***: Vital signs.

Patient id.	*Not done*	*Visit*	*Date*	*Heart Rate (BPM)*	*Systolic (mmHG)*	*Diastolic (mmHG)*	*Temperature (ºC)*

Listing 14.1.***17***: Electrocardiogram.

Patient id.	*Not done*	*Visit*	*ECG Date*	*Result*	*Abnormal, specify*	*PR Interval(msec)*	*Heart rate*	*QT Interval(msec)*	*QRS Interval(msec)*	*Corrected QT*

							(bpm)			*Fridericia*

Listing 14.1.***18***: LVEF.

Patient id.	*Not done*	*Visit*	*LVEF Date*	*Type*	*Value*	*Range*	*Result*	*Abnormal, specify*	*Reason for clinically indicated*

Listing 14.1.***19***: Prophylactic medication.

Patient id.	*Visit*	*Medication*	*Drug Type*	*...**	*Route*	*Daily Dose*	*Units*	*Start date*	*End date*	*Time*	*Taken per protocol*	*Specify*

(*) ATC1, ATC2, ATC3, ATC4.

Listing 14.1.***20***: Drug administration.

								Reductions		*Delays*		
Patient id.	*Visit*	*Admin. date*	*Start time*	*End time*	*Intended dose*	*Total dose*	*Adm. Volume*	*Dose reduced?*	*Reason*	*Dose delayed?*	*Reason*	*Dose interrupted?*

Listing 14.1.***21***: Adverse events (including adverse events at baseline).

Patient id.	*Adverse Event Verbatim*	*NCI-CTC Grade*	*SAE*	*Onset cycle*	*Onset date*	*Ongoing*	*End cyc.*	*End date*	*Ongoing/ Continuing*	*Relationship Specify*	*Action taken*	*Seriousness Criteria*

Listing 14.1.***22***: Concomitant therapy/procedures.

Patient id.	*Medication type*	*Medication*	*Reason*	*…**	*Route/Dose(Units)/Time interval*	*Start date*	*End date*	*Indication*	*AE*	*Other*

(*) ATC1, ATC4

Listing 14.1.***23***: Tumor assessment.

	Target			*Non target*		*New lesions*		
Patient id.	*…..**	*Sum of Diameters*	*Var.(%)*	*….**	*Response*	*…**	*Longest diameter*	*Non-measurable*

(*) Visit, Not done, lesion, organ site, date, method. Sort by Visit and then by Start date,

Listing 14.1.***24***: Evaluation of response by cycle.

Patient id.	*Visit*	*Not done?*	*Date*	*Response Target lesions*	*Response Non Target Lesions*	*New lesions?*	*Overall cycle response*

Listing 14.1.25: Best study overall response by IA and IRC and End of treatment.

Patient id.	*CTFI**	*Best Response by IA***	*Best Response by IRC**	*End of treatment Reason*	*End of treatment, Specify*

(*) Only for SCLC cohort. (**) Data obtained from radiological assessment of response in the CRF

Listing 14.1.***26***: Follow up.

Patient id.	*Follow-up date*	*Survival status*	*Previous PD or Therapy*	*TA Done*	*Reason*	*Type of therapy*	*Start date*	*End date*	*Treatment**	*Best response***	*Progression date***

(*) Procedure for surgery, localization for radiotherapy or agent for medical therapy.
(**) Only for Medical therapy. Sort by FU date first and then by Start date.

Listing 14.1.27: Off study and Death report form.

	Off study				*Death report*			
Patient id.	*Off study Reason*	*If other Specify*	*Off study date*	*Best response*	*Death Date*	*Cause*	*Specify*	*Autopsy?*

Listing 14.1.28: Investigator comments and Investigator comments before end of study.

Patient id.	*Page name*	*Instance*	*Variable*	*Comment*

In the SCLC cohort and to fulfil the Office of Scientific Investigations (OSI) request that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications will be provided following the recommended standardized formats.

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

Table 15.1 Site Level Summary SCLC PM1183B00514

Site	*Patients Screened*	*Patients Treated*	*Patients End of Treatment*	*Patients Off Study*

Listings:

Listing 15.2 Consented Subjects by Site.

Site	*Patient id.*	*Informed Consent date*	*Screening failure?*	*Date of Screening failure*	*Met Eligibility*	*Criterion Identifier*	*Details*	*Treated*	*Date of First treatment*

Listing 15.3 Treatment Assignment by Site.

Site	*Patient id.*	*DA Start date*	*First Intended dose*

Listings 15.4 Discontinuations by Site.

Site	*Patient id.*	*End of treatment Reason*	*End of treatment, Specify*	*Off study date*	*Off study Reason*	*If other Specify*

Listings 15.5 Study Population by Site.

Site	*Patient id.*	*Included population*	*Treated population*	*Reason*	*Evaluable population*	*Reason*

Listings 15.5 Inclusion and Exclusion Criteria by Site.

Site	*Patient id.*	*Eligibility requirements?*	*Criterion identifier I/E*	*I/E details*

Listings 15.6 Adverse Events by Site.

Site	*Patient id.*	*Adverse Event Verbatim*	*NCI-CTC Grade*	*SAE*	*Onset cycle*	*Onset date*	*End cyc.*	*End date*	*Relationship Specify*	*Action taken*	*Seriousness Criteria*

Listings 15.7 Protocol Deviations by Site.

Site	*Patient id.*	*Deviation type*	*Deviation*

Listings 15.8 Efficacy Endpoints by Site.

Site	*Patient id.*	*Best response by IA*	*Best response by IRC*	*PFS by IA (months)*	*PFS by IRC (months)*	*DOR by IA (months)*	*DOR by IA (months)*	*OS (months)*	*Death status*

Listings 15.9 Concomitant Medications by Site.

Site	*Patient id.*	*Medication type*	*Medication*	*Reason*	*…**	*Route/Dose(Units)/Time interval*	*Start date*	*End date*	*Indication*

(*) ATC1, ATC4

In accordance with ICH E-3 guidelines, the patient listings specified as Section 16.2 will be prepared by tumor type and for the total of patients.

Listing 16.2.1 Discontinued Patients.

Patient id.	*Institution*	*Treated*	*Cycles received*	*First infusion date*	*Last infusion date*	*Reason for end of treatment*	*Comments*

Listing 16.2.2 Protocol Deviations.

Patient id.	*Type*	*Description*

Listing 16.2.3 Patients Not Included in the Efficacy Analysis.

Patient id.	*Non evaluable reason*

Listing 16.2.4 Demographic Data.

Patient id.	*Tumor type*	*Histology type**	*Stage**	*Age/Years*	*ECOG*	*Weight (kg)*	*Height (cm)*	*BSA (m2)*	*Prior Radiotherapy*	*Prior agents for the treatment*

(*)At diagnosis.

Listing 16.2.5 Compliance and/or Drug Concentration Data.

Patient id.	*Drug*	*First Intended dose (mg/m2)*	*Cycles received*	*Start date (First cycle)*	*Start date (Last cycle)*	*Total dose (mg/m2)*	*Dose intensity per week (mg/m2/wk)*	*Relative Dose intensity (%)*	*Delays**	*Reductions**

(*) Delays/reductions will be nested for each patient (cycle and reasons of delay/reduction). e.g: C1 hematological toxicity/C3 non drug related.

Listing 16.2.6 Individual Efficacy Response Data.

Patient id.	*Best Response by IA*	*Best Response by IRC**	*PFS by IA (months)*	*PFS by IRC* (months)*	*DOR by IA (months)*	*DOR by IRC* (months)*	*OS (months)*

(*) Only for SCLC

Listing 16.2.7 Adverse Event Listing.

Patient id.	*Literal*	*Preferred Term*	*Grade Coded Value*	*SAE*	*Onset date*	*Resolved date*	*Relationship*	*Action taken*	*Serious criteria*

Listing 16.2.8 Listing of Individual Laboratory Measurements by Patient.

				Hemoglobin (g/dL)	*WBC (10*9/L)*	*Neutrophils (10*9/L)*	*Lymphocytes (10*9/L)*	*…**
Patient id.	*Cycle*	*Examination date*	*Laboratory*	*Std.value*	*Std.value*	*Std.value*	*Std.value*	*Std.value*

(*) Monocytes (x10*9/L), Direct Bilirubin (mg/dl),Total Bilirubin (mg/dl), AST IU/L), ALT (IU/L) AP (IU/L), GGT (IU/L), Glucose (mg/dL), Creatinine (mg/dl), CrCl (mL/min), NA (mmol/L), CL (mmol/L), K (mmol/L), LDH (xULN), CPK (IU/L), Total Proteins (g/dl), Albumin (g/dl), CA (mg/dl), Mg (mg/dl), INR (ratio), PT (sec/ratio), PTT (sec/ratio), AFP (ng/m), hCG(IU/L).

15.3 SAP version history v3.0

After the third version of the SAP was approved, in order to maintain the consistency in the SCLC cohort the "All Treated Patients" population set will be used for the descriptive analyses of baseline characteristics. The "All Included Patients" dataset will be used for the descriptive analyses of disposition of patients in each cohort of advanced solid tumors. In order to maintain the consistency in the presented cohorts all treated population will be used also for baseline characteristics in the other cohorts.

- The "All treated patients" dataset will be used to describe baseline characteristics, and narratives will be used to describe patients who are included but not treated.
- Other descriptive tables of interest for the SCLC cohort are included.
- Other not relevant minor comments/clarifications.

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

Any changes in the automatic numbering of tables, sections and references in the SAP are not listed but will be implemented in the new version.

Section 4.1: Included population

Original text:

The "All Included Patients" dataset, defined as all patients accepted by the sponsor to take part in the trial, will be used for the descriptive analyses of disposition of patients and baseline characteristics in each cohort of advanced solid tumors.

Changes to:

The "All Included Patients" dataset, defined as all patients accepted by the sponsor to take part in the trial, will be used for the descriptive analyses of disposition of patients ~~***and baseline characteristics***~~ in each cohort of advanced solid tumors.

Section 10.1: Patient Disposition.

Adds ** and clarifies evaluable patients.

Table 10.1.1 Number of patients included, treated and evaluable for the primary endpoint.

	N	%
Included patients		
Eligible patients*		
Treated patients		
Evaluable patients for efficacy**		
Evaluable patients for efficacy by IRC (SCLC cohort)***		

(*) Patients who were considered eligible according to the registration screening form and were accepted to take part in the trial with the sponsor's agreement in the screening reply form. ***(**) Includes patients treated with early death/or PD not documented by image (early PD).*** (***) For sensitivity analysis.

Section 10.2 Reasons for Treatment Discontinuation.

Original text:

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

Changes to:

Section 10.2 Reasons for Treatment *and Study* Discontinuation.

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable). ***The reasons for treatment discontinuation will be calculated in the treated patient's population. The rest of tables and listings in this section will be calculated in the included patient's population.***

Section 11.1: Demographic and Other Baseline Characteristics.

Original text:

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

Changes to:

Demographic and Other Baseline Characteristics will be carried out on the "All Treated Patients" population and narratives will be used to describe patients who are included but not treated.

Each table, listing and figure displayed in this section will have a comprehensive header identifying the tumor type (cohort) or the total population (if applicable).

Section 10.1.8: Disease at Diagnosis and Disease at Study Entry: BRCA 1/2-associated Metastatic Breast Carcinoma (MBC).

Original text:

Table 11.1.8.5 Receptor status.

	Positive		Negative	
	N	%	N	%
Estrogen receptor	X	XX.X	X	XX.X
Progesterone receptor				
HER-2/neu receptor				
Total				

Table 11.1.8.6 Hormonal status.

	N	%
Triple negative	X	XX.X
ER and/or PR positive + HER2 negative		
Hormone receptor positive*		
Total		

(*) ER and/or PR positive + HER2 positive and ER and PR negative + HER2 positive

Changes to:

Table 11.1.8.5 Receptor status.

	Positive		Negative	
	N	%	N	%
Estrogen receptor	X	XX.X	X	XX.X
Progesterone receptor				
HER-2/neu receptor				
~~Total~~				

Table 11.1.8.6 Hormonal status.

	N	%
ER and/or PR positive and HER2 negative	***X***	***XX.X***
ER and/or PR positive and HER2 positive		
ER and/or PR negative and HER2 positive		
Triple negative		
Total		

Note: Triple negative: HER2 negative ER negative and PR negative

Section 11.1.12: Prior History. Adds new tables of interest for SCLC cohort

Table 11.1.12.3 Smoker status.

*	N	%
Former/current	X	XX.X
Never		
UK		
Total		

(*) Only for SCLC cohort and information obtained from CRF pages of Prior history.

Table 11.1.12.4 Paraneoplastic syndrome.

*	N	%
Yes	X	XX.X
No		
Total		

(*) Only for SCLC cohort and information obtained from CRF pages AEs at baseline and/or Prior history.

Section 11.1.17: Biochemical values at baseline. Add new tables of interest for SCLC cohort

Table 11.1.17.5 AAGP values at baseline.

	N	Mean	Std.	Median	Min	Max
AAGP (xULN)						

Table 11.1.17.6 Abnormal LDH at baseline.

*	N	%

Yes	X	XX.X
No		
Total		

(*) Only for SCLC cohort. Abnormal LDH: (>ULN)

Section 11.3 Efficacy Analysis.

Original text:

Listing 11.3.3.13 Characteristics of patients with clinical benefit by CTFI by IA and IRC. (All treated patients).

Baseline characteristics							Study treatment characteristics				
Patient id.	CTFI**	PS / Age/ Gender	***	No. of prior regimens	Last prior therapy	Best response/TTP last therapy	Cycles received	Best response IA/IRC	PFS (mo) IA/IRC	DR (mo) IA/IRC	OS (mo)
…											

(*) CR + PR + SD ≥ 4 months.
(**) RR, R, S, VS.
(***) Any other clinical relevant variable will be added at the analysis time.

Changes to:

Listing 11.3.3.13 Characteristics of patients with clinical benefit***** by CTFI by IA and IRC. (All treated patients).

Baseline characteristics							Study treatment characteristics				
Patient id.	CTFI**	PS / Age/ Gender	***	No. of prior regimens	Last prior therapy	Best response/TTP last therapy	Cycles received	Best response IA/IRC	PFS (mo) IA/IRC	DR (mo) IA/IRC	OS (mo)
…											

(*) CR + PR + SD ≥ 4 months.
(**) RR, R, S, VS.
(***) Any other clinical relevant variable ***(including sites of disease, limited/extended disease, LDH [normal/abnormal] and alpha-acid glycoprotein [xULN])*** will be added at the analysis time.

Section 12.6 Concomitant Therapy / Procedures According to the ATC Classification. Add new variables in existing tables.

Original text:

Table 12.6.1 Concomitant medication during treatment (ATC1, ATC2, ATC3 and ATC4 levels).

Changes to:

Table 12.6.1 Concomitant medication during treatment ***(ATC1/ATC2/ATC3/ATC4/PN)***.

Section 12.8 Subgroup Analyses Related to Safety. Includes two new more listings and (*) specifies categorization.

Original text:

Tables 12.8.1 to 12.8.12 will have the following pattern:

Laboratory abnormalities/ drug-related AEs	Subgroup 1			Subgroup 2			….		
	No. of patients evaluated	Grade ≥3	%	No. of patients evaluated	Grade ≥3	%	No. of patients evaluated	Grade ≥3	%
Thrombocytopenia									
Neutropenia									
AP									
Bilirubin									
AST									
ALT									
CPK									
Nausea									
Vomiting									
Fatigue									
Other*									

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

Changes to:

Table 12.8.15 Worst grade ≥3 by patient in special subgroups (AAGP*).

Table 12.8.16 Worst grade ≥3 by cycle in special subgroups (AAGP*).

Tables 12.8.1 to 12.8.16 will have the following pattern:

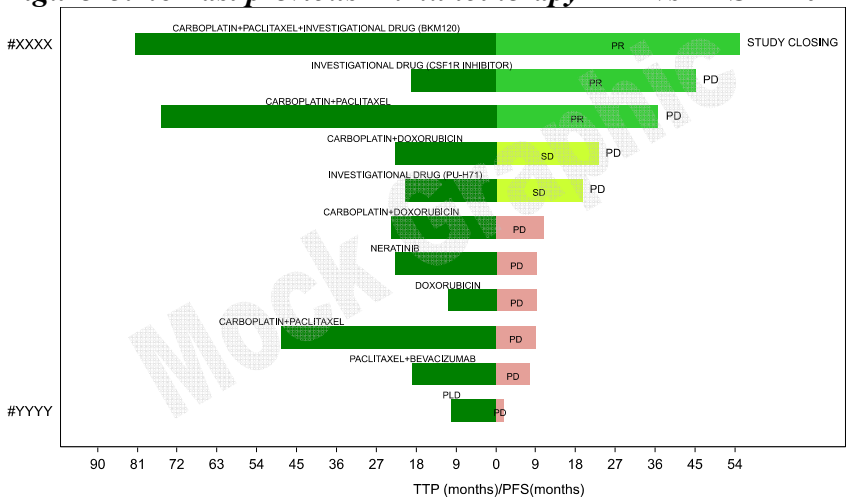
Laboratory abnormalities/ drug-related AEs	Subgroup 1			Subgroup 2			….		
	No. of patients***/cycles*** evaluated	Grade ≥3	%	No. of patients***/cycles*** evaluated	Grade ≥3	%	No. of patients***/cycles*** evaluated	Grade ≥3	%
Thrombocytopenia									
Neutropenia									
AP									
Bilirubin									
AST									
ALT									
CPK									
Nausea									
Vomiting									
Fatigue									

Laboratory abnormalities/ drug-related AEs	Subgroup 1			Subgroup 2			….		
	No. of patients/***cycles*** evaluated	Grade ≥3	%	No. of patients/***cycles*** evaluated	Grade ≥3	%	No. of patients/***cycles*** evaluated	Grade ≥3	%
Other**									

(*) Categories Age (<65 yrs vs >=65 yrs); Number of prior lines (1 line vs >=2 lines); BSA (=< 1.8 m2 vs. > 1.8 m2) Geographical area (Europe vs US.); Alpha-glycoprotein (ULN<= vs >ULN). (**)Any drug-related toxicity present in >=5% of patients in any group.

Section 13: Figures. Adds a new graph.

Figure13.1.6 Last previous Immunotherapy TTP vs PFS PM01183 (SCLC cohort).



Section 14 DB Listings, BIMO and ICH listing.

Original text:

Listing 14.1.11 Biochemical laboratory values

Patient id.	Visit	Date	n	Clinically indicated repeat required?	Total Bilirubin (mg/dl)	Direct Bilirubin (mg/dl)	AST (IU/L)	ALT (IU/L)	AP (IU/L)	…..*

(*)GGT (IU/L), Glucose (mg/dL), Creatinine (mg/dl), CrCl (mL/min), NA (mmol/L), CL (mmol/L), K (mmol/L), LDH (xULN), CPK (IU/L), Total Proteins (g/dl), Albumin (g/dl), CA (mg/dl), Mg (mg/dl), INR (ratio), PT (sec/ratio), PTT (sec/ratio), AFP (ng/m), hCG (IU/L)

Changes to:

Listing 14.1.11 Biochemical laboratory values

Patient id.	Visit	Date	n	Clinically indicated repeat required?	Total Bilirubin (mg/dl)	Direct Bilirubin (mg/dl)	AST (IU/L)	ALT (IU/L)	AP (IU/L)	…..*

(*)GGT (IU/L), Glucose (mg/dL), Creatinine (mg/dl), CrCl (mL/min), NA (mmol/L), CL (mmol/L), K (mmol/L), LDH (xULN), CPK (IU/L), Total Proteins (g/dl), Albumin (g/dl), CA (mg/dl), Mg (mg/dl), ~~***INR (ratio), PT (sec/ratio), PTT (sec/ratio),***~~ AFP (ng/m), hCG (IU/L)

Original text:

Listing 14 1.13 Coagulation laboratory values.

Patient id.	Visit	Date	n	Clinically indicated repeat required?	INR (ratio)	PT (sec)	PTT (sec)

Changes to:

Listing 14 1.13 Coagulation laboratory values.

Patient id.	Visit	Date	n	Clinically indicated repeat required?	INR (ratio)	PT (sec***/ratio***)	PTT (sec***/ratio***)

Original text:

Listing 16.2.4 Demographic Data.

Patient id.	Tumor type	Histology type*	Stage*	Age/Years	ECOG	Weight (kg)	Height (cm)	BSA (m2)	Prior Radiotherapy	Prior agents for the treatment

(*)At diagnosis.

Changes to:

Listing 16.2.4 Demographic Data.

Patient id.	Tumor type	Histology type*	Stage*	Age/***Gender***	ECOG	Weight (kg)	Height (cm)	BSA (m2)	Prior Radiotherapy	Prior agents for the treatment

(*)At diagnosis.

15.4 SAP version history v4.0

After the fourth version of the SAP was approved, a new protocol "substantial amendment No. 7" was included; therefore the SAP has been updated (highlighted in ***italic bold***) in accordance with the new version (version 4) of the protocol as follows:

- The duration of follow-up of patients in the SCLC cohort has been changed to at least 18 months from the first lurbinectedin infusion.
- Other not relevant minor comments/clarifications/corrections.

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

Any changes in the automatic numbering of tables, sections and references in the SAP are not listed but will be implemented in the new version.

Section 2 Study Design

Original text:

(….)

Patients will be evaluated at scheduled visits on three study periods: Pre-treatment, Treatment and Follow-up. This clinical trial will finish (clinical cut-off for each cohort except SCLC cohort) when all evaluable patients within each cohort have at least 12 months of follow-up from the first PM01183 infusion. Patients with SCLC will be followed-up until death.

Changes to:

(….)

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

Section 8.9 Imputation of Incomplete dates

Original text:

(….)

After End of Treatment

To ensure the most conservative approach for the time-to-event variables (i.e., DR, PFS and OS), which 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 the 1st; if the month is also unknown, then the imputed date will be the 1st of July. This assumption will be valid if the imputed date occurs later than the last drug administration date; otherwise the imputed date will be the date of the last drug administration plus the predefined cycle length (i.e., 21 days if PM01183), except if the patient dies before, in which case the date of death minus 1 will be used. For OS, if a patient dies the imputation event date should be the last date the patient is known to be alive plus one day.

Changes to:

(….)

After End of Treatment

To ensure the most conservative approach for the time-to-event variables (i.e., DR, PFS and OS), which 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 the 1st; if the month is also unknown, then the imputed date will be the 1st of July. This assumption will be valid if the imputed date occurs later than the last drug administration date; otherwise the imputed date will be the date of the last drug administration plus the predefined cycle length (i.e., 21 days if PM01183), except if the patient dies before, in which case the date of death minus 1 will be used. For OS, if a patient dies the imputation event date should be the last date the patient is known to be alive ~~minus~~ ***plus*** one day.

For the determination of treatment emergent AEs with incomplete dates that do not allow to know if they occurred during the treatment period, the following imputation rules will apply:

- ***If the start day, month and year are missing, the event will be considered treatment emergent.***
- ***If the start day and month are missing, no date imputation will be performed but the event will be considered TEAE, if the reported year is the same or occurs after the infusion year and also the reported year is the same or occurs before the EOT year.***
- ***If the start day is missing, no imputation date will be performed but the event will be considered TEAE, if the reported month and year occur after the first infusion date (month/year) and before the EOT date (month/year).***

Section 8.11 Subgroup Analysis

Original text:

Specific subgroup efficacy analyses will be done for patients with SCLC. These analyses will be performed by IA/IRC and in all evaluable/all treated patient populations, pre-specified analyses are by CTFI (< 90 days and ≥ 90 days and/or Refractory (RR) [<30 days], Resistant (R)[>=30 and <90 days], Sensitive (S) [>=90 and <180 days] and Very Sensitive (VS)[>=180 days]), excluding patients with CTFI<30 days and considering event to clinical progressions although they were not documented by radiological images. Any other exploratory analyses requested by the physician at the time of the analysis will be clearly explained, specifying the selected patient population and following the same layout detailed for the other subgroup analyses.

If the number of patients recruited in any cohort differs at least 10% from the sample size assumptions, a sensitivity analysis for main efficacy endpoints using all evaluable patients will be performed.

Changes to:

Specific subgroup efficacy analyses will be done for patients with SCLC. These analyses will be performed by IA/IRC and in all evaluable/all treated patient populations, pre-specified analyses are by CTFI ***defined as the time from the last dose of the last platinum containing therapy to the occurrence of progressive disease***, (< 90 days and ≥ 90 days and/or Refractory (RR) [<30 days], Resistant (R)[>=30 and <90 days], Sensitive (S) [>=90 and <180 days] and Very Sensitive (VS)[>=180 days]), excluding patients with CTFI<30 days and considering event to clinical progressions although they were not documented by radiological images. Any other exploratory analyses requested by the physician at the time of the analysis will be clearly explained, specifying the selected patient population and following the same layout detailed for the other subgroup analyses.

If the number of patients recruited in any cohort differs at least 10% from the sample size assumptions, a sensitivity analysis for main efficacy endpoints using all evaluable patients will be performed.

Section 11 Efficacy Evaluation

In all survival tables and graphs PFS at 12 months and OS at 24 months will be also calculated.

Table 11.3.3.7 add new information.

Table 11.3.3.7 Response rate and ***reliability*** by IA and IRC (All treated patients).

Response		IA											
		Complete response (CR)		Partial response (PR)		Stable disease SD≥4 months		Stable disease SD<4 months		Progressive disease (PD)		Inevaluable for response*	
		N	%	N	%	N	%	N	%	N	%	N	%
IRC	Complete response (CR)												
	Partial response (PR)												
	Stable disease SD≥4 months												
	Stable disease												

	SD<4 months												
	Progressive disease (PD)												
	Inevaluable for response												

Test of Symmetry*	
Statistic (S)	
DF	
Pr > S	

Kappa statistics*			
	Value	***ASE***	***95% Confidence Limits***
Simple kappa			
Weighted kappa			

Test of H0: Weighted Kappa = 0	
ASE under H0	
Z	
One-sided Pr > Z	
Two-sided Pr > |Z*	

(*) for example: early death, malignant disease; toxicity; tumor assessments not repeated/incomplete; other (specify).
For discrepancies see Listing 11.3.3.15. Percentage by columns. ***(**) Kappa Index for concordance of all response categories according to IA or IRC assessment.***

New tables and graphs are included:

Survival in responders

Table 11.3.3.36 OS in responders by IA and by CTFI (All treated patients).

	CTFI< 90 days*			***CTFI≥ 90 days****			***Total****
	R*	***RR****	***Total****	***S****	***VS****	***Total****	
N							
Events							
Censored							
Median OS							
OS at 6 months							
OS at 12 months							
OS at 24 months							

(*/**/) Kaplan-Meier plots will also be shown. (*)Table/Figure 11.3.3.36.1 with the following categories (CTFI< 90 days and CTFI≥ 90 days), (**) Table/Figure 11.3.3.36.2 with the following categories RR, R, S and VS. (***) Table/Figure 11.3.3.36.3 for totals.***

Table 11.3.3.37 OS in responders by IRC and by CTFI (All treated patients).

	CTFI< 90 days*			***CTFI≥ 90 days****			***Total****
	R*	***RR****	***Total****	***S****	***VS****	***Total****	
N							
Events							
Censored							
Median OS							
OS at 6 months							
OS at 12 months							
OS at 24 months							

(*/**/) Kaplan-Meier plots will also be shown. (*)Table/Figure 11.3.3.37.1 with the following categories (CTFI< 90 days and CTFI≥ 90 days), (**) Table/Figure 11.3.3.37.2 with the following categories RR, R, S and VS. (***) Table/Figure 11.3.3.37.3 for totals.***

…

Table 11.3.3.38 OS in responders by IA and IRC excluding CTFI<30 (All treated patients).

	IA	***IRC***
N		
Events		
Censored		
Median OS		
OS at 6 months		
OS at 12 months		
OS at 24 months		

Kaplan-Meier plot will also be shown (Figure 11.3.3.38.1 OS in responders by IA excluding CTFI<30 (All treated patients), Figure 11.3.3.38.2 OS in responders by IRC excluding CTFI<30 (All treated patients).

Section 12.3.1 Serious Adverse Events

Original text:

Tables 12.3.1.2 to 12.3.1.5 will have the following pattern, but depending on the number and severity of the adverse events observed, the NCI-CTCAE v4 grades may be grouped as ≥1 and ≥3 categories.

SOC	Preferred term	Grade 1		…	Grade 4		Grade ≥1		Grade ≥3
		N	%	…	N	%	N	%	
Blood and lymphatic system disorders	Anemia NOS								
	...								
	…								
Cardiac disorders	Arrhythmia NOS								
	…								

Note: Tables 12.3.2.2 and 12.2.3.4 also for s1 and s2;

Changes to:

SOC	Preferred term	Grade 1		…	Grade 4		Grade ≥1		Grade ≥3	
		N	%	…	N	%	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS									
	...									
	…									
Cardiac disorders	Arrhythmia NOS									
	…									

Note: Tables 12.3.***1.***2 and 12.2.***1.***4 also for s1 and s2;

Section 12.4.4 Laboratory Values over Time

Original table:

Tables 12.4.4.7 and 12.4.4.8 will have the following pattern:

	All cycles	First cycle
	N, Mean, Std., Median, Range	N, Mean, Std., Median, Range
Grade ≥3* onset day		
Peak ($x10^9$/L)		
Duration of grade ≥3 (days)		
Day of recovery to grade 1/2 or baseline values**		

(*) Grade 3 or 4; (**) grade 2 or less

Changes to:

Tables 12.4.4.7 and 12.4.4.8 will have the following pattern:

	All cycles	First cycle
	N, Mean, Std., Median, Range	N, Mean, Std., Median, Range
Grade ≥3* onset day		
Peak (x~~10^9/L~~ **ULN**)		
Duration of grade ≥3 (days)		
Day of recovery to grade 1/2 or baseline values**		

(*) Grade 3 or 4; (**) grade 2 or less

Section 14 DB Listings, BIMO and ICH Listings

Original table:

Listing 14.1.4 Pregnancy test and adequate contraception

		Pregnancy test						Adequate contraception	
Patient id.	Visit	Not applicable?	Reason	Not done?	Sample date	Result	Reason for clinically indicated repeat	Adequate contraception?	Specify

Changes to:

Listing 14.1.4 Pregnancy test and adequate contraception

		Pregnancy test						Adequate contraception	
Patient id.	Visit	Not applicable?	Reason	~~Not done?~~	Sample date	Result	Reason for clinically indicated repeat	Adequate contraception?	Specify

Original table:

Footnote from Listing 14.1.11 Biochemical laboratory values.

(*)GGT (IU/L), Glucose (mg/dL), Creatinine (mg/dl), CrCl (mL/min), NA (mmol/L), CL (mmol/L), K (mmol/L), LDH (xULN), CPK (IU/L), Total Proteins (g/dl), Albumin (g/dl), CA (mg/dl), Mg (mg/dl), AFP (ng/m), hCG (IU/L)

Changes to:

(*)GGT (IU/L), Glucose (~~mg/dL~~ ***mmol/L***), Creatinine (mg/dl), CrCl (mL/min), NA (mmol/L), CL (mmol/L), K (mmol/L), LDH (~~xULN~~ ***IU/L***), CPK (IU/L), Total Proteins (g/dl), Albumin (g/dl), CA (~~mg/dl~~ ***mmol/L***), Mg (mg/dl), AFP (ng/m)~~,~~ hCG (IU/L)

Original text:

In the SCLC cohort and to fulfil the Office of Scientific Investigations (OSI) request that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications will be provided following the recommended standardized formats.

…

Table 15.1 Site Level Summary SCLC PM1183B00514

Site	Patients Screened	Patients Treated	Patients End of Treatment	Patients Off Study

Changes to:

~~In the SCLC cohort and~~ To fulfil the Office of Scientific Investigations (OSI) request***, ~~that~~*** the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications will be provided following the recommended standardized formats.

…

Listing 15.1 Site Level Summary ***~~SCLC PM1183B00514~~.***

Site	Patients Screened	Patients Treated	Patients End of Treatment	Patients Off Study

New BIMO listings are added:

Listings 15.11.1 Laboratory measurements by Site.

Site	***Patient id.***	***Visit***	***Date***	***Laboratory***	***Hemoglobin (g/dl)***	***Platelets (x10*9/L)***	***WBC (x10*9/L)***	***Neutrophils (x10*9/L)***	***Lymphocytes (x10*9/L)***	***Monocytes (x10*9/L)***	***…..****

(*) Total Bilirubin, Direct Bilirubin in (mg/dl), AST, ALT, AP, GGT in (IU/L), Glucose (mmol/L), Creatinine (mg/dl), CrCl (mL/min), NA (mmol/L), CL (mmol/L), K (mmol/L), LDH (IU/L), CPK (IU/L), Total Proteins (g/dl), Albumin (g/dl), CA (mmol/L), Mg (mg/dl), INR (ratio), PT (sec/ratio), PTT (sec/ratio) AFP (ng/m), hCG (IU/L), AAGP (mg/dl).

Listings 15.11.2 Electrocardiogram by Site.

Site	*Patient id.*	*Not Done*	*Visit*	*Date*	*Results*	*Abnormal, Specify*	*PR interval (msec)*	*Heart rate (bpm)*	*QT Interval (msec)*	*QRS interval (msec)*	*Corrected QT Fridericia*

Listings 15.11.3 LVEF by Site.

Site	*Patient id.*	*Not Done*	*Visit*	*Date*	*Method*	*LVEF (%)*	*Range Lowe Limit*	*Abnormality*	*Specify*	*Reason for Clinically Indicated Repeat*

Original table:

Footnote from Listing 16.2.8 Listing of Individual Laboratory Measurements by Patient.

(*) Monocytes (x10*9/L), Direct Bilirubin (mg/dl),Total Bilirubin (mg/dl), AST IU/L), ALT (IU/L) AP (IU/L), GGT (IU/L), Glucose (mg/dL), Creatinine (mg/dl), CrCl (mL/min), NA (mmol/L), CL (mmol/L), K (mmol/L), LDH (xULN), CPK (IU/L), Total Proteins (g/dl), Albumin (g/dl), CA (mg/dl), Mg (mg/dl), INR (ratio), PT (sec/ratio), PTT (sec/ratio), AFP (ng/m), hCG(IU/L).

Changes to:

(*)Monocytes (x10*9/L), Direct Bilirubin (mg/dl),Total Bilirubin (mg/dl), AST IU/L), ALT (IU/L) AP (IU/L), GGT (IU/L), Glucose (~~mg/dL~~ ***mmol/L***), Creatinine (mg/dl), CrCl (mL/min), NA (mmol/L), CL (mmol/L), K (mmol/L), LDH (~~xULN~~ ***IU/L***), CPK (IU/L), Total Proteins (g/dl), Albumin (g/dl), CA (~~mg/dl~~ ***mmol/L***), Mg (mg/dl), INR (ratio), PT (sec/ratio), PTT (sec/ratio), AFP (ng/m), hCG (IU/L), ***AAGP (mg/dl).***