PM1183-B-003-11

A Multicenter Phase II Clinical Trial of PM01183 in BRCA 1/2-Associated or Unselected Metastatic Breast Cancer

STATISTICAL ANALYSIS PLAN

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ABBREVIATIONS AND GLOSSARY

AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BL	Baseline
BRCA1/2	Breast Cancer 1 or Breast Cancer 2 Susceptibility 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
DB	Database
DR	Duration of Response
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
FD	Flat Dose
G-CSF	Granulocyte-Colony Stimulating Factor
GGT	Gamma-glutamyltransferase
HER-2	Human Epidermal Growth Factor Receptor 2
IB	Investigator's Brochure
i.v.	Intravenous(ly)
K	Potassium
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MBC	Metastatic Breast Cancer
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
NOS	Not Otherwise Specified
ORR	Overall Response Rate
OS	Overall Survival
PARPi	Poly ADP Ribose Polymerase inhibitor
PD	Progressive Disease
PFS	Progression-free Survival
PGx	Pharmacogenomics
PK/PD	Pharmacokinetics/Pharmacodynamic
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time/Preferred Term
PTT	Partial Thromboplastin Time
q3wk	Every Three Weeks
RD	Recommended Dose
RECIST	Response Evaluation Criteria In Solid Tumors
SAE(s)	Serious Adverse Event(s)
SD	Stable Disease
SOC	System Organ Class
ULN	Upper Limit of Normal
UK	Unknown
vs.	Versus
WBC	White Blood Cells
WHO	World Health Organization
Wk(s)	Week(s)
y	Year

1 STUDY RATIONALE

Metastatic breast cancer (MBC) is a clinically heterogeneous and an aggressive disease from which most patients will ultimately die. Unfortunately a cure by the means of currently available treatment options still seems an elusive goal. Cytotoxic chemotherapy remains a crucial component of the therapeutic armamentarium and there is a need to develop more selective approaches to identify subgroups of patients with higher tumor sensitivity that may benefit the most.

PM01183 is a new chemical entity that induces double-strand DNA breaks through binding to the DNA minor groove. Results of the COMPARE analysis (see protocol reference 20) revealed that is unlikely that this drug shares a similar mechanism of action with any of the other 98 standard cytotoxic agents compared.

PM01183 has significant *in vitro* and *in vivo* wide antitumor activity, particularly in several breast cancer models.

PM01183 exposure primarily induces DNA damage, particularly to homologous recombinant deficient cells *in vitro* (see IB); thus, patients with BRCA deleterious mutation might be more sensitive to its antitumor effects than other patients. In order to test this hypothesis, two Cohorts of patients with advanced breast cancer will be prospectively evaluated in the trial according to their germline BRCA1/2 mutation status: known mutation (BRCA+, Cohort A) *vs.* unselected (BRCA– or -UK, Cohort B).

The goal of the trial is, on one hand, to find out whether the presence of a BRCA 1/2 mutation in Cohort A is associated with a higher response rate in MBC patients; and, on the other hand, to explore and benchmark the activity of PM01183 in MBC unselected patients. The study design has taken into account the higher sample heterogeneity of Cohort B by planning the recruitment of more patients in this group. Also, according to the BRCA status in the trial setting, a response rate of 40% or more in Cohort A (sample of patients with known deleterious BRCA 1/2 mutations) will be considered clinically worthy of further research, as well as a response rate of 25% or more in Cohort B.

The first-in-human phase I clinical trial found a RD of 7.0 mg FD of PM01183 when given as a one-hour i.v. infusion q3wk. This dose was safe, tolerable and manageable for a highly selected patient population. In particular, PM01183 induced predictable and short-lasting non-febrile neutropenia as the most relevant toxicity (up to 40% of patients treated at the RD). None of the patients treated at the RD were older than 75 years and/or had PS >1. Therefore, it is uncertain at this time if PM01183 RD is as tolerable and safe for a particularly vulnerable and frail population given the degree of myelosuppresion observed so far. Because toxicity, especially in aging patients, is usually an important consideration in order to select the more suitable treatment, it seems safer to exclude patients over 75 years old and/or with PS≥2 until more information regarding safety and pharmacokinetics of the drug becomes available.

2 STUDY DESIGN

This is a multicenter, open-label, exploratory, phase II clinical trial evaluating the efficacy and safety of PM01183 administration to patients with previously treated MBC, as follows.

Two Cohorts of MBC patients will be prospectively evaluated in the trial according to germline BRCA1/2 status (mutated [Cohort A] vs. unselected [Cohort B]). A third Cohort (Cohort A1) will include advanced breast cancer patients with deleterious BRCA1/2 mutation status who received prior treatment with poly (ADP-ribose) polymerase (PARP) inhibitors:

- Cohort A (BRCA+ Cohort): At least 53 evaluable patients with previously known deleterious BRCA1/2 mutation status at study entry.
- Cohort A1 (BRCA+/PARPi Cohort): 20 evaluable patients with known deleterious BRCA1/2 mutation status and prior treatment with PARP inhibitors (PARPi).
- Cohort B (unselected Cohort): At least 64 evaluable patients without known deleterious BRCA1/2 mutation status at study entry, i.e., either:
    - Patients known to have no deleterious BRCA1/2 mutations (BRCA−), or
    - Patients whose BRCA 1/2 mutation status is unknown (BRCA-UK); BRCA1/2 germline mutation status will be assessed in PM01183 responding patients in this subgroup.

In patients included in Cohort B who respond to PM01183 treatment and whose BRCA 1/2 mutation status is unknown at study entry, an analysis will be performed in order to confirm or exclude deleterious germline BRCA 1/2 mutation. To this end, a blood sample will be collected at the time of response. If a BRCA 1/2 mutation is found in her sample then the patient will be analyzed along with patients included in Cohort A.

The primary efficacy endpoint of the study is the overall response rate (ORR), defined as the percentage of patients with a response, either complete (CR) or partial (PR), according to RECIST v1.1 (protocol section 8.1).

An interim analysis based on the primary endpoint (ORR) is planned after 20 and 30 evaluable patients have been treated in Cohorts A and B, respectively (see protocol section 8.2 for details). No interim analysis is planned for Cohort A1. If less than four out of 20 patients in Cohort A, or less than three out of 30 patients in Cohort B achieve an objective confirmed response, recruitment to that Cohort will be terminated. Otherwise, recruitment will continue until at least 53 and 64 evaluable patients are included in Cohort A and Cohort B, respectively. Sample size and Cohort design will be re-evaluated at this point in order to estimate the 95% confidence interval (CI) with the desired precision. Recruitment to either Cohort (e.g., Cohort B) might be halted while interim analysis is being performed, if appropriate.

Patients will receive treatment in the absence of progressive disease (PD) or unacceptable toxicity for as long as it is considered to be in their own benefit (see protocol section 6.2.1.2 for details).

Patients will be evaluated using clinical and laboratory assessments before each treatment cycle (protocol sections 6.3 and 6.6). Appropriate radiological and/or clinical tumor

assessments will be done every six weeks until evidence of PD (protocol section 7.1). Patients no longer receiving study treatment will be followed up for survival (protocol section 6.8).

Any treatment-related AE will be followed until recovery to grade ≤ 1 or stabilization of symptoms, whenever possible (protocol section 7.2). Reasons for dose reduction, treatment delays and/or treatment discontinuation will be documented as appropriate.

3 OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

- To assess the antitumor activity of PM01183 in terms of ORR, according to RECIST v1.1, in each Cohort of MBC patients.

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 lasting over three months (SD > 3 months)], PFS, and one-year overall survival (1y-OS).
- To evaluate whether the presence of a known germline mutation in BRCA1/2 predicts response to PM01183 in MBC patients.
- To explore the activity of PM01183 in specific breast cancer subpopulations according to hormonal receptor status, HER-2 overexpression, number and/or type of prior therapies, or according to other available histological/molecular classifications.
- To evaluate the safety profile of this PM01183 administration schedule (Day 1, q3wk) in this patient population.
- To analyze the pharmacokinetics (PK) of PM01183 in this patient population.
- To explore PK/PD (pharmacokinetic / pharmacodynamic) correlations, if applicable.
- To evaluate the pharmacogenomic (PGx) expression profile of selected putative markers potentially predictive of response to PM01183, in tissues from archived tumor samples.

3.3 Endpoints

Primary endpoint:

- Overall response rate (ORR) in the population evaluable for efficacy, according to RECIST v1.1.

Secondary endpoints:

- Duration of response (DR).

- Clinical benefit, defined as the percentage of patients with ORR or SD > 3 months, according to RECIST v1.1.
- Progression-free survival (PFS).
- Overall survival rate at one year (1y-OS).
- Treatment safety: AEs, serious AEs (SAEs) and laboratory abnormalities will be graded according to the NCI-CTCAE (v4).
- PK analysis and PK/PD correlation, if applicable.
- PGx expression profile, in tissues from archived tumor samples.

4 PATIENTS EVALUABILITY CRITERIA

The study population will include patients with MBC histologically proven.

Analysis sets definitions:

- "All Included Patients" analysis set is defined as all patients recorded in the database who are included in the trial, independently of whether they have received the study drug or not.
- "All Treated Patients" analysis set is defined as all included patients who have received at least part of one infusion of PM01183.
- "All Evaluable Patients" analysis set is defined as all eligible patients who have at least one complete infusion of PM01183, and either have 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 withdrawn after more than two weeks on treatment without any formal evaluation will be defined as "treatment failures". These patients will be included as inevaluable for response in the analysis of objective response as per RECIST v1.1, although they will not need to be replaced as they will be considered evaluable for efficacy.
- "All Responder Patients" analysis set is defined as all evaluable patients who have had CR or PR as overall best response according to the RECIST v1.1 criteria.

4.1 Included Population

The "All Included Patients" data set will be used for the descriptive analysis of baseline characteristics.

4.2 Efficacy Populations

The "All Evaluable Patients" analysis set will be used for the primary endpoint analysis of ORR and for the secondary endpoints of PFS, 1y-OS and clinical benefit rate.

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

4.3 Safety Population

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

5 SAMPLE CONSIDERATIONS

5.1 Sample Size

The primary endpoint for this phase II study is to evaluate ORR.

- Cohort A (BRCA+):

  At least 53 evaluable patients will be recruited to test the null hypothesis that ORR is 20% or less ($p \leq 0.20$) *vs.* the alternative hypothesis that 40% or more patients have objective response ($p \geq 0.4$). With these assumptions, if the number of evaluable patients with objective response is ≥ 17, then this would allow the rejection of the null hypothesis.

- Cohort A1 (BRCA+/PARPi):

  At least 20 evaluable patients will be recruited for an exploratory analysis: if the number of patients responding is ≥ 4 (20%), the lower limit of the exact binomial 95% confidence interval will be higher than 5% and thus lack of activity in this subpopulation will be ruled out.

- Cohort B (unselected):

  At least 64 evaluable patients will be recruited to test the null hypothesis that ORR is 10% or less ($p \leq 0.10$) *vs.* the alternative hypothesis that 25% or more patients have objective response ($p \geq 0.25$). With these assumptions, if the number of evaluable patients with objective response is ≥ 12, then this would allow the rejection of the null hypothesis.

The variance of the standardized tests 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 <0.1; hence, statistical power is > 90%.

Futility analysis controlled by the Gamma family boundary will be performed when 20 and 30 patients have been evaluated in Cohorts A [Gm(-2)] and B [Gm(-1.5)], respectively. If less than four out of 20 patients in Cohort A, or less than three patients out of 30 in Cohort B achieve an objective response, recruitment to that Cohort will be stopped. About 110 evaluable patients are finally expected to be included in the three Cohorts: Cohort A (BRCA+), Cohort A1 (BRCA+/PARPi), and Cohort B (unselected).

6 STATISTICAL METHODOLOGY FOR EFFICACY

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

6.1 Planned Analysis and Definitions

Primary endpoint

The primary study analysis will be based on the ORR in the "All Evaluable Patients" analysis set.

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

Secondary endpoint

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

Duration of response (DR) is defined as time from first observation of response to the date of disease progression, recurrence of death. Other causes will be censored. Although the responses have to be confirmed according to RECIST v1.1 criteria, 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 CR or PR or SD $\geq$ 3 months as overall best response according to the RECIST v1.1 criteria, divided by the number of patients in the "All Evaluable Patients" analysis set.

Progression-free survival (PFS) is defined as the time from start of treatment to the date of documented progressive disease (PD) by RECIST v1.1 criteria or death (regardless of the cause of death), whichever comes first. 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. 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. ***1 year overall survival (1y-OS)*** is defined as the Kaplan-Meier estimate of the probability of patients alive after 12 months from the date of start of treatment.

6.2 Efficacy Analysis Methods

Continuous variables will be tabulated by Cohort and presented with summary statistics (i.e., median and range). Categorical variables will be summarized by Cohort in frequency tables by means of counts and percentages.

6.2.1 Primary Endpoint

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

6.2.2 Secondary Endpoints

Time-to-event endpoints (DR, PFS and OS) and their set time estimates (i.e. PFS3, PFS6 and 1y-OS) will be analyzed according to the Kaplan-Meier method.

A log-rank test or Cox regression for time-to-event endpoints could be performed as supportive analysis to compare both Cohorts.

If relevant, efficacy parameters versus baseline covariates will be analyzed and appropriate test will be used (i.e., the Fisher exact test and logistic regression for categorical variables, the log-rank test or Cox regression for time-to-event variables, etc.).

If appropriate, exploratory multivariate models (main effects or including interaction terms, if appropriate) will include all prognostic factors/covariates widely reported and recognized by oncologists: Cohort (BRCA (+) vs. BRCA (-) or unknown), BRCA (1 vs. 2 in cohorts A and A1), initial dose (7 mg FD vs 3.5 mg/m^2), age, age at diagnosis, race (Caucasian vs. other), baseline Eastern Cooperative Oncology Group performance status (ECOG PS) (0 vs. >0), histology type (Ductal vs. lobular carcinoma), histology grade (poorly vs. other), stage at diagnosis, primary tumor site (unilateral breast vs. bilateral), hormone receptor positive (estrogen or progesterone receptor +, or both +) vs. triple negative, HER-2 receptor (positive vs. negative), site of current disease such as liver metastases (yes vs. no), CNS metastases (yes vs. no), lung metastases (yes vs. no), non-visceral (including bone, skin, subcutaneous and lymph node vs. other), number of prior metastatic sites (1 vs. >1), body mass index (BMI), height, weight, body surface area (BSA), time from diagnosis to first infusion, prior surgery (yes vs. no), prior radiotherapy (yes vs. no), prior advanced treatment lines, prior advanced chemotherapy lines (0-1 vs. 2-3), prior anthracyclines (yes vs. no), prior taxane (yes vs. no), prior platinum (yes vs. no), prior PARPi (yes vs. no), last prior therapy PFS, first advanced chemotherapy PFS, last advanced chemotherapy PFS, PFS for anthracycline, taxane and platinum therapy, hormonotherapy (yes vs no), adjuvant/neoadjuvant therapy (yes vs no), platinum-free interval (in months), presence of any bulky (< 50 mm vs. ≥ 50 mm) lesion, albumin at baseline, CA-15.3 or 27.29 at baseline, any relevant concomitant medication at baseline (to be determinate by the oncologist) (yes vs. no) and the sum of all target lesion diameters.

All variables with a good percentage of valid cases (approximately ≥ 90%) and with a p-value lower than 0.10 in the univariate analysis will be included in the exploratory multivariate analysis. Within the multivariate stepwise Logistic/Cox regression analysis, the chosen significance level for entering an explanatory variable into the model will be 0.05 (for all variables not in the model, the one with the smallest p-value is entered if the p-value is less than or equal to the specified significance level). The significance level for removing an explanatory variable from the model is 0.05 (for all variables in the model, the one with the largest p-value will be removed if the p-value exceeds the specified significance level). The parameter estimates, hazard ratios and p-values for hazard ratios of the variables retained in the model will be presented.

If appropriate, multivariate analysis will be produced for a relevant subgroup of patients (e.g. by cohort).

7 STATISTICAL METHODOLOGY FOR SAFETY

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

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

7.1.1 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), version 4.

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

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 MedDRA.

A frequency table 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 version 4.

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

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

If a grade 3-4 neutropenia or thrombocytopenia increase occur during a cycle of treatment, the first day it reached the onset value (counting from the start of the cycle) and the duration of the abnormality (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 (K), sodium (NA), magnesium, glucose, phosphorus, triglycerides and albumin.

If a grade 3-4 AST or ALT increase occur during a cycle of treatment, both the day it peaked (counting from the start of the cycle) and the duration of the abnormality (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.

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 patient.

7.4 Deaths and Other Serious Adverse Events

Deaths and other SAEs will be tabulated.

8 OTHER ANALYSIS

Continuous variables will be tabulated and presented with summary statistics (i.e., 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, electrocardiogram, LVEF, physical examination, vital signs, laboratory values and concomitant medication, coded according to the Word 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.

Age will be calculated based on the date of birth and the date of informed consent.

Baseline weight and height are recorded on the CRF.

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

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

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 summarized. This time calculations will be shown in months and summarized descriptively. Histology and characteristics of the current disease 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.

Signs and symptoms at baseline will be displayed by tabulation of frequencies according to NCI-CTCAE version 4 toxicity grades. Signs and symptoms will be listed.

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

Baseline and demography characteristics in different subgroups of analysis (i.e. cohorts) will be compared by means of Fisher's exact test (categorical variables) and Mann-Whitney-Wilcoxon (continuous variables).

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, is the sum of all the study drug doses from the first cycle until last cycle, including the dose received in last cycle.

Patients will be considered to be on-treatment for the duration of their treatment and 30 days following the last treatment dose. If the patient starts any new antitumor therapy outside this clinical trial or dies within 30 days of 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 is considered to be 21 days (instead of 30 days) for dose intensity calculation purposes.

Intended dose intensity (mg/m^2) is the planned dose per cycle divided by the planned number of weeks per cycle.

Absolute dose intensity (mg) 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 item of the case report form (CRF) «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:

Delay: Date of current 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 Analysis

This analysis will be detailed in a separate document.

8.7 Pharmacogenomic Analysis

This analysis will be detailed in a separate document.

8.8 Imputation of Incomplete Dates

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

Before 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 first dose administration month date (i.e. 01/ first dose administration month date/year).

Between treatment start and end of treatment

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

8.9 Subgroup Analysis

The analysis will be done by Cohort and additionally, if clinically appropriate, the Cohorts might be pooled into one, whenever differences between Cohorts are considered not relevant. In such case, the point estimates and their 95% CIs will be also reassessed in order to obtain more accurate calculations.

Efficacy subgroup analysis will be performed in Cohort A according to prior treatment with platinum (Yes vs. No), BRCA status (BRCA1 vs. BRCA2), hormonal status (Triple negative vs. HR+), number of advanced chemotherapy lines , prior PARPi (Yes vs. No)and starting dose (7 mg FD vs. 3.5 mg/m^2).

Additional efficacy subgroup analysis will be performed in Cohorts A+A1 according to prior PARPi (Yes vs. No). Safety subgroup analysis will be performed according to starting dose (7 mg FD vs. 3.5 mg/m^2), these analysis include laboratory abnormalities and adverse events.

If clinically relevant, other subgroup analysis may be performed in order to explore the activity of PM01183 in specific breast cancer subpopulations.

No differentiation by center is planned.

8.10 Methods for Handling Missing Data

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

8.11 Interim and Group Sequential Analysis

An interim analysis based on the primary endpoint (ORR) is planned after 20 and 30 evaluable patients have been treated in Cohorts A and B, respectively. If less than four out of 20 patients in Cohort A, or less than three out of 30 patients in Cohort B achieve an objective confirmed response (CR or PR according to RECIST v1.1), recruitment to that Cohort will be terminated. Otherwise, recruitment will continue until at least 53 and 64 evaluable patients are included in Cohort A and Cohort B, respectively. Sample size and Cohort design will be re-evaluated at this point in order to estimate the 95% confidence interval (CI) with the desired precision. For further analysis details, see section 5.1 Sample size.

8.12 Identification of Fixed or Random Effects Models

Not applicable

9 STATISTICAL SOFTWARE

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

EAST v.5.4 has been used to calculate sample size. SAS version 9 will be used for all statistical analysis outputs.

APPENDIX I

Every output will be displayed by Cohort and/or total and they will be clearly identified with a label. To maintain simplicity, nested categories are not presented.

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.

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

	N	%
Included patients		
Eligible patients*		
Treated patients		
Evaluable patients for efficacy		

(*)Patients meeting all inclusion criteria and not meeting any exclusion criteria.

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

Patient id.	Criteria number(s) and description

Listing 10.1.3 Patients who meet any exclusion criteria.

Patient id.	Criteria 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 safety (Non-treated patients).

Patient id.	Reason

Table 10.1.6 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 10.1.7 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, exam or procedure before clinical cut-off or study closure

10.2 Reasons for Treatment Discontinuation

Table 10.2.1 Treatment discontinuation

Reason	N	%
Progressive disease		
Treatment related adverse event		
Non Treatment related adverse event		
Patient refusal to treatment		
Death (due to toxicity)*		
Death (non-treatment-related)**		
Investigator's decision***		
Other ***		
Total		

(*) Cause of death = Study drug related Adverse Event; (**) Cause of death = Malignant disease, Non-study drug related AE or Other; (***) See Listing 10.2.2

Listing 10.2.2 Reasons for treatment discontinuation other than progressive disease.

Patient id.	Reason	Last cycle	Comments

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 (due to toxicity)*				
Death (non-treatment-related)**				
Investigator's decision***				
Other ***				
Total				

(*) Cause of death = Study drug related Adverse Event; (**) Cause of death = Malignant disease, Non study drug related AE or Other; (***) See Listing 10.2.2

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

Listing 10.2.4 Treatment discontinuation due to AEs

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

Table 10.2.5 Study discontinuation

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

(*) See Listing 10.2.6; (**) Cause of death = Study drug related Adverse Event; (***) Cause of death = Malignant disease, Non study drug related AE or Other; (****) 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

11.1.1 Patient Characteristics at Baseline

Table 11.1.1.1 Baseline characteristics: Age at treatment registration

	N	Median	Min	Max
Age (years)				

Table 11.1.1.2 Baseline characteristics: Age grouped

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

Table 11.1.1.3 Baseline characteristics: Race

	N	%
Caucasian	X	XX.X
Asian		
Black		
Other*		
Total		

(*) See Listing 11.1.1.4;

Listing 11.1.1.4 Other race, specify

Patient id.	Specify

11.1.2 Disease at Diagnosis and Current Disease

Table 11.1.2.1 Time from first diagnosis to registration

	N	Median	Min	Max
Time from diagnosis to randomization (months)				

Table 11.1.2.2 Site of disease at diagnosis

	N	%
Right breast	X	XX.X
Left breast		
Bilateral		
Total		

Table 11.1.2.3 Histology type at diagnosis

	N	%
Ductal Carcinoma	X	XX.X
Lobular Carcinoma		
Total		

Table 11.1.2.4 Histology grade at diagnosis

	N	%
Well differentiated	X	XX.X
Moderately differentiated		
Poorly differentiated		
Unknown		
Total		

Table 11.1.2.5 Stage at diagnosis

	N	%
…	X	XX.X
…		
Total		

Table 11.1.2.6 BRCA in Arm A and Arm A1 (deletereous mutation).

	N	%
BRCA 1	X	XX.X
BRCA 2		
Both		

Table 11.1.2.7 BRCA in Arm B.

	N	%
Negative	X	XX.X
Unknown		

Table 11.1.2.8 Receptor status. Current disease.

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

Table 11.1.2.9 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 11.1.2.10 Time from Metastatic disease to registration

	N	Median	Min	Max
Time from metastatic disease (months)				

Table 11.1.2.11 Time from last progression before the study entry

	N	Median	Min	Max
Time from last PD (weeks)				

Table 11.1.2.12 Sites of metastatic disease. Current disease.

	N	%
Lymph node	X	XX.X
Bone		
Lung		
Liver		
Pleura		
…		

Table 11.1.2.13 Number of sites at baseline

No. of sites	N	%
1	X	XX.X
2		
...		
Total		
Median (Range)		

11.1.3 Prior History

Table 11.1.3.1 Prior history

SOC	Preferred Term	N	%
Gastrointestinal disorders	Constipation		
	Diarrhea NOS		
	…		
…	…		

Listing 11.1.3.2 Prior history (Ongoing events)

Patient id.	Description (Literal)	SOC	PT	Onset date

11.1.4 Prior Anticancer Therapy

Table 11.1.4.1 Patients with prior sugery

Prior surgery	N	%
Yes	X	X.X
No		
Total		

Table 11.1.4.2 Patients with prior radiotherapy

Prior radiotherapy	N	%
Yes	X	X.X
No		
Total		

Table 11.1.4.3 Number of lines of prior therapy

No. of systemic lines	N	%
1	X	XX.X
...		
Total		
Median (Range)		
Setting	N	%
Adjuvant	X	XX.X
Neoadjuvant		
Both		
Advanced		
No. of advanced chemotherapy lines	N	%
1	X	XX.X
...		
Total		
Median (Range)		
Prior chemotherapy regimens	N	%
Anthracycline and taxane	X	XX.X
Anthracycline, taxane and capecitabine		
Platinum		
No. of hormone* therapy lines	N	%
1	X	XX.X
...		
Total		
Median (Range)		

(*) Hormone therapy will be identified by the oncologist;

Table 11.1.4.4 Prior anticancer agents

Antineoplastic and immunomodulating agents (ATC-class.)	N	%
Antineoplastic agents (L01)	X	XX.X
Alkylating agents		
Nitrogen mustard analogues		
Alkyl sulphonates		
….		

11.1.5 Physical Examination and Performance Status at Baseline

Table 11.1.5.1 Baseline physical examination

	N	%
Normal	X	X.X
Abnormal		
Total		

Table 11.1.5.2 Baseline physical examination: BSA, Weight and Height

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

Table 11.1.5.3 Baseline characteristics: ECOG Performance Status

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

11.1.6 Vital Signs, Electrocardiogram, LVEF and other tests.

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

Table 11.1.6.1 Baseline characteristics: Vital signs

Parameter	N	Median	Min	Max
Heart rate (beats/min)				
Systolic blood pressure (mmHg)				
Diastolic blood pressure (mmHg)				
Temperature (ºC)				

Table 11.1.6.2 Baseline characteristics: Electrocardiogram result

ECG	N	%
Normal	X	XX.X
Abnormal*		
Total		

(*)See listing 11.1.6.4 for details

Table 11.1.6.3 Baseline characteristics: Electrocardiogram values

Parameter	N	Median	Min	Max
PR interval (msec)				
Heart rate (bpm)				
QT interval (msec)				
QRS complex (msec)				
QTc Fridericia				

Listing 11.1.6.4 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

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

Table 11.1.6.5 Baseline characteristics: Left Ventricular Ejection Fraction (LVEF)

LVEF	N	%
Normal	X	XX.X
Abnormal*		
Total		

(*)See listing 11.1.6.7 for details

Table 11.1.6.6 Baseline characteristics: LVEF values.

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

Listing 11.1.6.7 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 11.1.6.8 Baseline characteristics: Pregnancy test

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

(*) Specify reasons

Table 11.1.6.9 Baseline characteristics: Adequate contraception

Adequate birth control	N	%
Yes	X	XX.X
No		
NA*		
Total		

(*) Specify reasons

11.1.7 Hematological Values at Baseline

Table 11.1.7.1 Hematological abnormalities at baseline

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

(*)Any grade

Table 11.1.7.2 Hematology values at baseline

	N	Median	Min	Max
Hemoglobin (g/dL)				
Platelets (10^9/L)				
WBC (10^9/L)				
Neutrophils (10^9/L)				
Lymphocytes (10^9/L)				
Monocytes (10^9/L)				

Listing 11.1.7.3 Hematological tests not assessed at baseline

Patient id.	Lab. test

Listing 11.1.7.4 Hematological abnormalities at baseline. Grade ≥ 2

Patient id	Parameter	Value	Units	Grade

11.1.8 Biochemical Values at Baseline

Table 11.1.8.1 Biochemical abnormalities at baseline

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

(*)Any grade

Table 11.1.8.2 Biochemical values at baseline

	N	Median	Min	Max
AST (xULN)				
ALT (IU/L)				
Direct bilirubin (xULN)				
Total bilirubin (xULN)				
AP (xULN)				
LDH (xULN)				
CPK (xULN)				
GGT (xULN)				
Creatinine (xULN)				
Troponin T (ng/mL)				
…				

Listing 11.1.8.3 Biochemical tests not assessed at baseline

Patient id.	Lab. test
…	

Listing 11.1.8.4 Biochemical abnormalities at baseline. Grade ≥ 2

Patient id	Parameter	Value	Units	Grade

11.1.9 Coagulation Values at Baseline

Table 11.1.9.1 Coagulation abnormalities at baseline

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

(*)Any grade

Table 11.1.9.2 Coagulation values at baseline

	N	Median	Min	Max
INR				
PT (sec)				
PTT (sec)				

Listing 11.1.9.3 Coagulation tests not assessed at baseline

Patient id.	Lab. test
…	

Listing 11.1.9.4 Coagulation abnormalities at baseline. Grade ≥ 2

Patient id	Parameter	Value	Units	Grade

11.1.10 Signs and Symptoms at Baseline

Table 11.1.10.1 Patients with signs and symptoms at baseline

	N	%
No. signs and symptoms per patient		
0 1 2 ≥ 3		
Median (Range)		

Table 11.1.10.2 Patients with disease related signs and symptoms at baseline

	N	%
No. of disease related signs and symptoms per patient		
0 1 2 ≥ 3		
Median (Range)		

Table 11.1.10.3 Signs and symptoms at baseline

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

(*)Any grade

Listing 11.1.10.4 Signs and Symptoms at baseline

Patient id.	Sign/symptom	Grade*	Onset date	Relationship
…				

(*)Those events with grade ≥ 2 or with relationship='Prior study disease treatment' will be highlighted.

11.1.11 Concomitant Therapy and Procedures at Baseline

Concomitant medication at baseline according to the ATC classification.

Table 11.1.11.1 Concomitant medication at baseline (ATC1/ATC2/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 11.1.11.2 Summary of concomitant medication at baseline

	N	%
No. of systems at BL (ATC1 level)		
0		
1		
2		
≥ 3		
Median (range)		
No. of indications at BL (ATC2 level)		
0		
1		
2		
≥ 3		
Median (range)		
No. of agent families at BL (ATC4 level)		
0		
1		
2		
≥ 3		
Median (range)		

	N	%
No. of agents at BL (PN level)		
0		
1		
2		
≥ 3		
Median (range)		

Listing 11.1.11.3 Concomitant therapy

Patient	Type	Agent/Procedure	Route	Daily dose	Units	Start date	Reason	Indication	Details	Start date of study drug administration

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

11.1.12Baseline and demographic characteristic comparisons

Table 11.1.12.1 Baseline and demographic characteristic comparisons by cohorts

		N	**Cohort A**	**Cohort A1**	**Cohort B**	**p-value***
Age	Median (range)	X	X.X (XX-XX)	X.X (XX-XX)	X.X (XX-XX)	X.XXXX
PS (ECOG)	0	X	X (XX.X %)	X (XX.X %)	X (XX.X %)	X.XXXX
	1	.	X (XX.X %)	X (XX.X %)	X (XX.X %)	
BSA	Median (range)					
BRCA mutation	1					
	2					
Receptor status	Triple negative					
	HR+ / HER2 -					
	HER2 +					
Liver metastases	Yes					
	No					
CNS metastases	Yes					
	No					
Sites involvement	<3 sites					
	≥ 3 sites					
Advanced lines	Median (range)					
Advanced CT lines	Median (range)					
Prior Platinum	Yes					
	No					
Prior Anthracyclines	Yes					

		N	Cohort A	Cohort A1	Cohort B	p-value*
	No					
Prior Taxanes	Yes					
	No					
Prior Capecitabine	Yes					
	No					
Prior PARP Inhibitor	Yes					
	No					

*Fisher's exact test (categorical variables);Mann-Whitney-Wilcoxon (continuous variables)

Table 11.1.12.2 Baseline and demographic characteristic comparisons: Platinum Yes/No in Cohort A

		N	Prior platinum Yes	Prior platinum No	p-value*
Age	Median (range)	X	X.X (XX-XX)	X.X (XX-XX)	X.XXXX
PS (ECOG)	0	X	X (XX.X %)	X (XX.X %)	X.XXXX
	1	.	X (XX.X %)	X (XX.X %)	
…	…				

*Fisher's exact test (categorical variables);Mann-Whitney-Wilcoxon (continuous variables). For the complete list of covarites, see table 11.1.12.1

Table 11.1.12.3 Baseline and demographic characteristic comparisons: BRCA 1 vs 2 in Cohort A

		N	BRCA 1	BRCA 2	p-value*
Age	Median (range)	X	X.X (XX-XX)	X.X (XX-XX)	X.XXXX
PS (ECOG)	0	X	X (XX.X %)	X (XX.X %)	X.XXXX
	1	.	X (XX.X %)	X (XX.X %)	
…	…				

*Fisher's exact test (categorical variables);Mann-Whitney-Wilcoxon (continuous variables). For the complete list of covarites, see table 11.1.12.1

Table 11.1.12.4 Baseline and demographic characteristic comparisons: Prior PARPi Yes/No in Cohorts A+A1

		N	Prior PARPi Yes	Prior PARPi No	p-value*
Age	Median (range)	X	X.X (XX-XX)	X.X (XX-XX)	X.XXXX
PS (ECOG)	0	X	X (XX.X %)	X (XX.X %)	X.XXXX
	1	.	X (XX.X %)	X (XX.X %)	
…	…				

*Fisher's exact test (categorical variables);Mann-Whitney-Wilcoxon (continuous variables). For the complete list of covarites, see table 11.1.12.1

Table 11.1.12.5 Baseline and demographic characteristic comparisons: Initial dose 7 mg FD vs 3.5 mg/m^2 in Cohort A

		N	**7 mg FD**	**3.5 mg/m^2**	**p-value***
Age	Median (range)	X	X.X (XX-XX)	X.X (XX-XX)	X.XXXX
PS (ECOG)	0	X	X (XX.X %)	X (XX.X %)	X.XXXX
	1	.	X (XX.X %)	X (XX.X %)	
…	…				

*Fisher's exact test (categorical variables);Mann-Whitney-Wilcoxon (continuous variables). For the complete list of covarites, see table 11.1.12.1

Table 11.1.12.6 Baseline and demographic characteristic comparisons: Hormonal status triple negative vs Other

		N	**Triple negative Yes**	**Triple negative No**	**p-value***
Age	Median (range)	X	X.X (XX-XX)	X.X (XX-XX)	X.XXXX
PS (ECOG)	0	X	X (XX.X %)	X (XX.X %)	X.XXXX
	1	.	X (XX.X %)	X (XX.X %)	
…	…				

*Fisher's exact test (categorical variables);Mann-Whitney-Wilcoxon (continuous variables). For the complete list of covarites, see table 11.1.12.1

Table 11.1.12.7 Baseline and demographic characteristic comparisons: Advanced chemotherapy lines

		N	**0-1 lines**	**>1 lines**	**p-value***
Age	Median (range)	X	X.X (XX-XX)	X.X (XX-XX)	X.XXXX
PS (ECOG)	0	X	X (XX.X %)	X (XX.X %)	X.XXXX
	1	.	X (XX.X %)	X (XX.X %)	
…	…				

*Fisher's exact test (categorical variables);Mann-Whitney-Wilcoxon (continuous variables). For the complete list of covarites, see table 11.1.12.1

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.

Subgroup analysis will be performed in Cohort A according to prior treatment with platinum, BRCA status (BRCA1 vs. BRCA2), hormonal status (Triple negative vs. HR+), number of advanced chemotherapy lines , prior PARPi (Yes vs. No) and starting dose (7 mg FD vs. 3.5 mg/m^2).

Subgroup analysis will be performed in Cohorts A+A1 according to prior PARPi (Yes vs. No).

The tables included in each subgroup analysis are the following:

Table 11.3.1.1 Response rate

Table 11.3.1.2 Overall response rate

Table 11.3.2.1 Duration of response

Table 11.3.2.2 Progression-free survival (PFS)

Table 11.3.2.3 Overall survival (OS)

The tables will be annotated by adding a letter as suffix:

- BRCA status: a
- Prior platinum: b
- Hormonal status: c
- Advanced chemotherapy lines: d
- Starting dose: e
- Prior PARPi (Cohort A): f
- Prior PARPi (Cohorts A+A1): g

If any other disease characteristic is sufficiently represented and clinically relevant, subgroup analysis may be performed, and their corresponding tables will also be annotated by adding a letter to the table's name.

11.3.1 Primary Analysis

Table 11.3.1.1 Response rate

Response	N	%
Complete response (CR)		
Partial response (PR)		
Stable disease (SD)		
Progressive disease (PD)		
Inevaluable for efficacy*		

(*) Treatment failures

Table 11.3.1.2 Overall response rate

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

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

11.3.2 Secondary Analysis

Table 11.3.2.1 Duration of response (DR)

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

Kaplan-Meier plot will be also shown (Figure 11.3.2.1)

Table 11.3.2.2 Progression-free survival (PFS)

	PFS
N	
Events	
Censored	
Median PFS	
PFS at 3 months	
PFS at 6 months	
PFS at 12 months	

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

Table 11.3.2.3 Overall survival (OS)

	OS
N	
Events	
Censored	
Median OS	
OS at 12 months	
OS at 18 months	

Kaplan-Meier plot will be also shown (Figure 11.3.2.3)

Table 11.3.2.4 Clinical benefit rate

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

(*) CR + PR + SD > 3 months
Binomial exact estimator and 95% CI

Listing 11.3.2.5 Characteristics of patients with clinical benefit*.

Patient	PS / Age	BRCA status	Histology Type	Histology Grade	Hormonal Status	Sites	No. of prior lines	No. of advanced CT lines	Prior Platinum (Y/N)	Best response Prior platinum	Prior last therapy		
											Agents	Best response	PFS (months

(*) CR + PR + SD > 3 months

Patient	Initial dose	Cycles received	Best response	PFS (months)	OS (months)	DR (months)

(*) CR + PR + SD > 3 months

Table 11.3.2.6 Median follow-up*

Follow-up	Median	95% CI
PFS		
OS		

*Calculated using the Kaplan-Meier method reversing the censoring values.

Figure 11.3.2.7 “Waterfall plot” ΔSum of lesions from BL

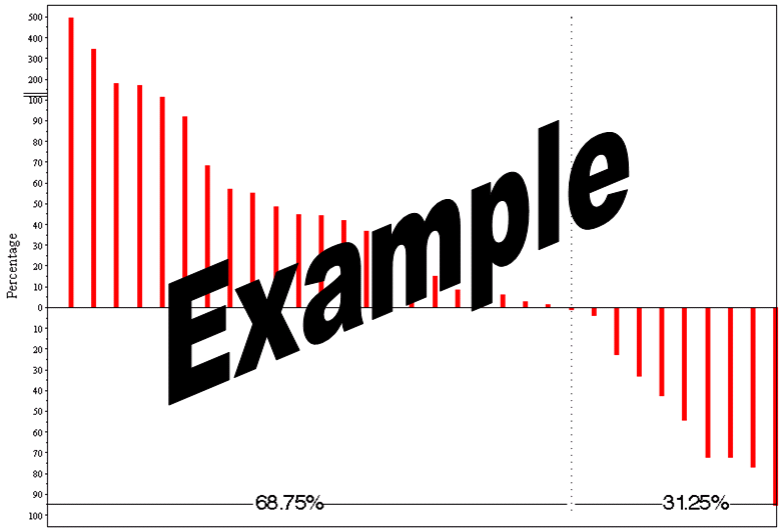


Figure 11.3.2.8 “Swimmer plot” PFS in Cohort A

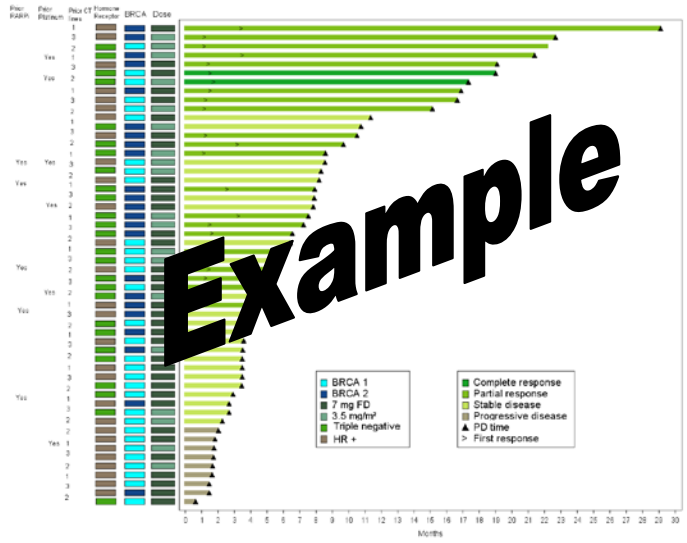


Figure 11.3.2.9 “Swimmer plot” PFS in Cohort A1

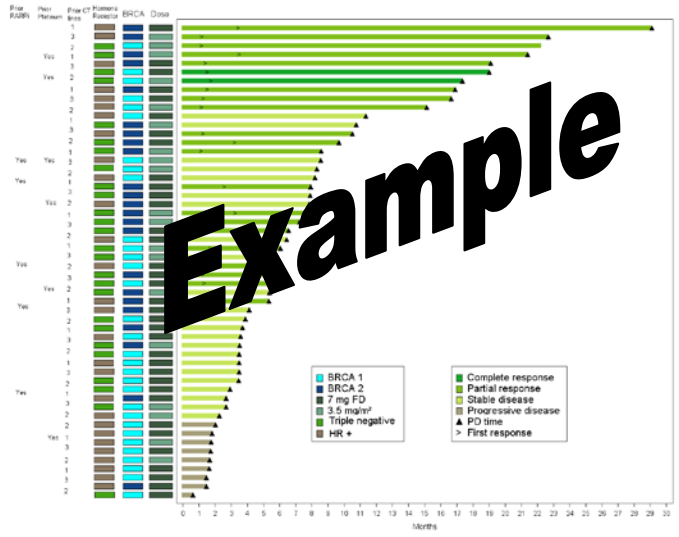
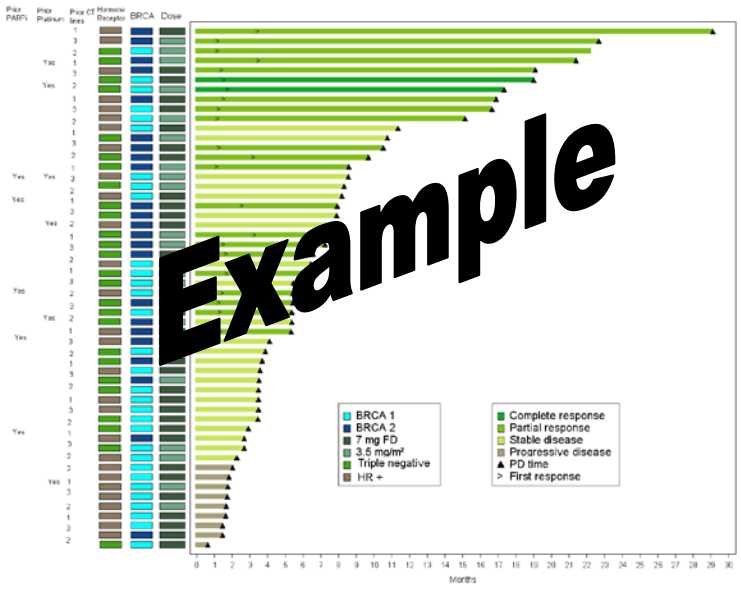


Figure 11.3.2.10 “Swimmer plot” PFS in Cohort B



11.3.3 Exploratory Univariate and Multivariate Analyses

Table 11.3.3.1 Univariate analysis of response rate

Variable label	Variable values	DF	Estimate	Standard error	Wald chi-square	Pr > ChiSq	Odds ratio estimate	95% Odds Ratio confidence limits

(See list of covariates in section 6.2.2).

Table 11.3.3.2 Multivariate analysis of response rate

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

(See list of covariates in section 6.2.2. Only those covariates with a p-value < 0.10 in univariate analysis and with a 90% of valid observations will be included).

Table 11.3.3.3 Univariate analysis of PFS

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

(See list of covariates in section 6.2.2).

Table 11.3.3.4 Multivariate analysis of PFS

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

(See list of covariates in section 6.2.2. Only those covariates with a p-value < 0.10 in univariate analysis and with a 90% of valid observations will be included).

Table 11.3.3.5 Univariate analysis of OS

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

(See list of covariates in section 6.2.2).

Table 11.3.3.6 Multivariate analysis of OS

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

(See list of covariates in section 6.2.2. Only those covariates with a p-value < 0.10 in univariate analysis and with a 90% of valid observations will be included).

12 Safety Analysis

Safety analysis will be carried out on the "All Treated Patients" population.

12.1 Extent of Exposure

Subgroup analysis will be performed according to starting dose (7 mg FD vs. 3.5 mg/m^2).
The tables will be annotated by adding a letter as suffix.
The tables included in the subgroup analysis are the following:
Table 12.1.1.1 Number of cycles administered and dose intensity
Table 12.1.2.1.3 Number of patients and cycles with dosing delay according to relationship
Table 12.1.3.3 Number of patient and cycles with dose reduction according to relationship

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 …		
Median (range)		
Time on treatment* (weeks) Median Range		
PM01183 cumulative dose (mg) Median Range		
PM01183 dose intensity (mg/wk) Median Range		
PM01183 relative dose intensity (%) Median Range		

(*)Time on treatment: defined as last infusion date plus 30 days, or date of death or subsequent therapy (whichever comes first) minus first infusion date.

12.1.2 Cycle Delays

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

Listing 12.1.2.1.1 Delays

Patient id.	Delayed cycle	Delayed cycle start date	Previous cycle	Previous cycle start date	Dose Delay calculated. (days)	Reason for dose delay	Dose Delay Spec.

Table 12.1.2.1.2 Number of patients and cycles with dosing delay, any relationship

	N	%
No. of patients treated		
No. of patients susceptible to have any dose delayed		
No. of patients with any dose delayed		
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		

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

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

Reasons for delays		N	%
Cycles	No. of cycles with dosing delays*		
	Treatment-related	X	XX.X
	Hematological		
	Non-hematological		
	Both		
	Non-treatment-related		
Patients	No. of patients with dosing delays*		
	Treatment-related	X	XX.X
	Hematological		
	Non-hematological		
	Both		
	Non-treatment-related		

(*) Denominator= Number of patient/cycles susceptible to have a delay.

Table 12.1.2.1.5 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							

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

12.1.2.2 Number of Delays According to Cycle Number

Table 12.1.2.2.1 Number and reasons of delays according to cycle number

	No. of patients		No. of delays		Treatment-related*		Treatment-related						Non-treatment-related*	
							Hematological reason		Non-hematological reason		Both			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Cycle 2														
…														
Cycle 6														
…														

(*) Denominator= Number of cycles susceptible to be delayed.

Table 12.1.2.2.2 Dose reduction in cycles delayed

	Reduction			
	Yes		No	
	N	%	N	%
Cycle 2 … Cycle 6 …				
Total				

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

Listing 12.1.2.2.3 Cycle delays due to AEs

Patient id.	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'.

12.1.3 Dose Reductions

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.	Cycle	Day	Cycle start date	Previous dose	Reduced dose	Reason for dose reduction	Dose reduction Spec.

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 reduced		
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 according to the relationship

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

(*) Denominator= Number of patient/cycles susceptible to have a dose reduction.

Table 12.1.3.4 Number and reasons of reductions according to cycle number

	No. of patients		No. of cycles with reduction		Treatment-related*		Treatment-related						Non-treatment-related*	
							Hematological reason		Non-hematological reason		Both			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Cycle 1														
Cycle 2														
…														
Cycle 6														
…														

(*) Denominator= Number of cycles susceptible to be reduced.

Listing 12.1.3.5 Dose reductions due to AEs

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

AEs with action = ‘Dose reduced/adjusted’ or ‘Reduced and delayed’.

12.1.4 Infusions Temporarily Interrupted

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

Listing 12.1.4.1 Interrupted infusion listing.

Patient id.	Cycle	Reason

12.1.5 Prophylactic Medication Administration

A listing of the patients who have not received corticosterioids, 5-HT 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
…		No	

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

12.2 Adverse Events

12.2.1 Adverse Events

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

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.

Subgroup analysis will be performed according to starting dose (7 mg FD vs. 3.5 mg/m2) and Cohort.

The groups will include:

- Patient treated at 7 mg FD Cohort B
- Patient treated at 7 mg FD Cohort A
- Patient treated at 7 mg FD any Cohort
- Patient treated at 3.5 mg/m^2 Cohort A
- Patient treated at 3.5 mg/m^2 Cohort A1
- Patient treated at 3.5 mg/m^2 any Cohort

The tables will be annotated by adding a letter as suffix.

The tables included in the subgroup analysis are the following:
Table 12.2.2.2 Treatment related AEs. Worst grade by patient
Table 12.2.2.3 Treatment related AEs. Worst grade by cycle
Table 12.2.2.4 Adverse events regardless of relationship. Worst grade by patient
Table 12.2.2.5 Adverse events regardless of relationship. Worst grade by cycle

If clinically relevant the outputs could be split by initial dose or any other characteristic.

12.2.2 Display of Adverse Events

Table 12.2.2.1 Summary of AEs.

Category	N	%
Patients with at least one AE regardless relationship		
Any treatment-related AE		
Any grade 3/4 AE		
Any grade 3/4 treatment-related AE		
Any SAE in DB		
Any treatment-related SAE		
Any grade 3/4 SAE		
Any grade 3/4 treatment-related SAE		
AEs leading to death		
AEs treatment-related leading to death		
AEs leading to dose delay		
AEs leading to dose reduction		
AEs leading to treatment discontinuation		
AEs treatment-related leading to treatment discontinuation		

Table 12.2.2.2 Treatment-related AEs. Worst grade by patient

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS							
	...							
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

(*) Any grade

Table 12.2.2.3 Treatment-related AEs. Worst grade by cycle

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS							
	...							
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

* Any grade

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

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS							
	...							
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

(*) Any grade

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

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 12.2.2.6 Treatment-related grade 3-4 AEs. Worst grade per patient

Patient id.	SOC Name	Preferred term	Grade

Listing 12.2.2.7 Treatment-related grade 3-4 AEs. Worst grade by cycle

Patient id.	Cycle	SOC Name	Preferred term	Grade

Listing 12.2.2.8 Adverse Events grade 3-4 regardless of relationship. Worst grade per patient

Patient id.	SOC Name	Preferred term	Grade

Listing 12.2.2.9 Adverse Events grade 3-4 regardless of relationship. Worst grade by cycle

Patient id.	Cycle	SOC Name	Preferred term	Grade

Table 12.2.2.10 Treatment-related SAEs. Worst grade by patient

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS							
	...							
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

(*) Any grade

Table 12.2.2.11 Treatment-related SAEs. Worst grade by cycle

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS							
	...							

	…							
Cardiac disorders	Arrhythmia NOS							
	…							

* Any grade

Table 12.2.2.12 SAEs regardless of relationship. Worst grade by patient

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS							
	...							
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

(*) Any grade

Table 12.2.2.13 SAEs regardless of relationship. Worst grade by cycle

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS							
	...							
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

(*) Any grade

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

12.2.3 Evolution of signs and symptoms during the treatment

Worst grade signs and symptoms present during treatment and at baseline regardless of relationship will be shown.

Table 12.2.3.1 Shift of signs and symptoms during the treatment

MedDRA PT	Baseline grade	Worst grade per patient during treatment							
		Grade 1		Grade 2		Grade 3		Grade 4	
		N	%	N	%	N	%	N	%
Constipation	1								
	2								
	…								
Diarrhea	1								
	2								
	…								

12.3 Serious Adverse Events and Deaths.

12.3.1 Serious Adverse Events

Listing 12.3.1.1 SAEs

Patient id.	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Action	Serious criteria

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

12.3.2 Deaths

Table 12.3.2.1 Cause of death

Reason*	N	%
Malignant disease		
Study drug related adverse event		
Non-study drug related AE		
Other		
Total		

(*) Denominator=Number of patients who died

Listing 12.3.2.2 Deaths

Patient id.	Death date	Cause	Comments	Autopsy	Number of cycles administered	Last infusion date	Time on treatment*	Time from Last dose**

(*)Time on treatment: defined as last infusion date plus 30 days, or date of death or subsequent therapy (whichever comes first) minus first infusion date. (**)Time from last dose defined as death date minus last infusion date.

Listing 12.3.2.3 AEs with outcome death

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

12.4 Clinical Laboratory Evaluation

Subgroup analysis will be performed according to starting dose (7 mg FD vs. 3.5 mg/m^2) and Cohort.
The groups will include:

- Patient treated at 7 mg FD Cohort B
- Patient treated at 7 mg FD Cohort A
- Patient treated at 7 mg FD any Cohort
- Patient treated at 3.5 mg/m^2 Cohort A
- Patient treated at 3.5 mg/m^2 Cohort A1
- Patient treated at 3.5 mg/m^2 any Cohort

The tables will be annotated by adding a letter as suffix.
The tables included in the subgroup analysis are the following:
Table 12.4.1.1 Hematological abnormalities during treatment, worst grade per patient
Table 12.4.1.2 Hematological abnormalities during treatment, worst grade per cycle
Table 12.4.2.1 Biochemical abnormalities during treatment, worst grade per patient
Table 12.4.2.2 Biochemical abnormalities during treatment, worst grade per cycle
Table 12.4.3.1 Coagulation abnormalities during treatment, worst grade per patient
Table 12.4.3.2 Coagulation abnormalities during treatment, worst grade per cycle

12.4.1 Hematological Abnormalities

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

If serious toxicities happen, special follow-up, with descriptives and graphs (boxplots, line plots), will be made to find out the pattern of thrombocytopenia and neutropenia within and between the different cycles.

Table 12.4.1.1 Hematological abnormalities during treatment, worst grade per patient

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

(*) Any grade

Table 12.4.1.2 Hematological abnormalities during treatment, worst grade per cycle

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

(*) Any grade

Listing 12.4.1.3 Grade 3-4 hematological abnormalities during treatment. Worst grade per patient

Patient id.	Cycle	Test	Grade

Listing 12.4.1.4 Grade 3-4 hematological abnormalities during treatment. Worst grade per cycle

Patient id.	Cycle	Test	Grade

Listing 12.4.1.5 Hematological tests not assessed by patient and cycle

Patient id.	Cycle	Lab. test

12.4.2 Biochemical Abnormalities

Grades of liver toxicity and intercycle pattern of creatinine, CPK, bilirubin, transaminases increase and alkaline phosphatase increase during a cycle will be calculated, as it is explained in the section 7.2 for biochemical toxicities.

Table 12.4.2.1 Biochemical abnormalities during treatment, worst grade per patient

	N	Grade	…	Grade	All*

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

(*) Any grade

Table 12.4.2.2 Biochemical abnormalities during treatment, worst grade per cycle

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

(*) Any grade

Listing 12.4.2.3 Grade 3-4 biochemical abnormalities during treatment. Worst grade per patient

Patient id.	Cycle	Test	Grade

Listing 12.4.2.4 Grade 3-4 biochemical abnormalities during treatment. Worst grade per cycle

Patient id.	Cycle	Test	Grade

Listing 12.4.2.5 Biochemical tests not assessed by patient and cycle

Patient id.	Cycle	Lab. test

12.4.3 Coagulation Abnormalities

Table 12.4.3.1 Coagulation abnormalities during treatment, worst grade per patient

	N	Grade 1		…	Grade 3		All*	
		N	%	…	N	%	N	%
INR increased								
APTT prolonged								

(*) Any grade

Table 12.4.3.2 Coagulation abnormalities during treatment, worst grade per cycle

	N	Grade 1		…	Grade 3		All*	
		N	%	…	N	%	N	%
INR increased								
APTT prolonged								

(*) Any grade

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

Patient id.	Cycle	Test	Grade

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

Patient id.	Cycle	Test	Grade

Listing 12.4.3.5 Coagulation tests not assessed by patient and cycle

Patient id.	Cycle	Lab. test

12.4.4 Laboratory Values Over Time

In this section, grades 3-4 hematological and liver enzyme abnormalities will be displayed according to the cycle in which they occurred.

Table 12.4.4.1 Evolution of hematological abnormalities from baseline, worst case per patient.

		Baseline grade*	Worst grade per patient						Total	
			0		1		…			
			N	%	N	%	N	%	N	%
Baseline	Neutropenia	Grade 0								
		Grade 1								
		……								
	Thrombocytopenia	Grade 0								
		Grade 1								
		……								
	….	Grade 0								
		Grade 1								
		……								

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

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

		Baseline grade*	Worst grade in the first cycle per patient						Total	
			0		1		…			
			N	%	N	%	N	%	N	%
Baseline	Neutropenia	Grade 0								
		Grade 1								
		……								
	Thrombocytopenia	Grade 0								
		Grade 1								
		……								
	….	Grade 0								
		Grade 1								
		……								

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

Table 12.4.4.3 Evolution of hematological abnormalities from baseline, worst case in the last cycle per patient.

		Baseline grade*	Worst grade in the last cycle per patient						Total	
			0		1		…			
			N	%	N	%	N	%	N	%
Baseline	Neutropenia	Grade 0								
		Grade 1								
		……								
	Thrombocytopenia	Grade 0								
		Grade 1								
		……								
	….	Grade 0								
		Grade 1								
		……								

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

Table 12.4.4.4 Evolution of biochemical abnormalities from baseline, worst case per patient.

		Baseline grade*	Worst grade per patient						Total	
			0		1		…			
			N	%	N	%	N	%	N	%
Baseline	AST increase	Grade 0								
		Grade 1								
		……								
	ALT increase	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 Evolution of biochemical abnormalities from baseline, worst case in the first cycle per patient.

		Baseline grade*	Worst grade in first cycle per patient						Total	
			0		1		…			
			N	%	N	%	N	%	N	%
Baseline	AST increase	Grade 0								
		Grade 1								
		……								
	ALT increase	Grade 0								
		Grade 1								
		……								
	…	Grade 0								
		Grade 1								
		……								

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

Table 12.4.4.6 Evolution of biochemical abnormalities from baseline, worst case in last cycle per patient.

		Baseline grade*	Worst grade in last cycle per patient						Total	
			0		1		…			
			N	%	N	%	N	%	N	%
Baseline	AST increase	Grade 0								
		Grade 1								
		……								
	ALT increase	Grade 0								
		Grade 1								
		……								
	…	Grade 0								
		Grade 1								
		……								

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

Table 12.4.4.7 Grade 3-4 laboratory abnormalities in the first cycle and in all other cycles

Laboratory abnormalities	Cycle 1			Cycle>1		
	No. of cycles evaluated	No. of cycles grade 3-4	%	No. of cycles evaluated	No. of cycles grade 3-4	%
Thrombocytopenia						
AP						
Total bilirubin						
AST						
ALT						
CPK						
…						

Listing 12.4.4.8 Summary of grade 4 neutropenia and G-CSF administration

Patient	Total number of cycles received	Cycle numbers with grade 4 neutropenia	Cycle numbers with G-CSF administration	Cycle numbers with dose reduction

Listing 12.4.4.9 Summary of grade 4 thrombocytopenia and platelets transfusions

Patient	Total number of cycles received	Cycle numbers with grade 4 thrombocytopenia	Cycle numbers with platelets transfusions	Cycle numbers with dose reduction

Listing 12.4.4.10 Summary of grade 4 anemia and EPO/transfusions

Patient	Total number of cycles received	Cycle numbers with grade 4 anemia	Cycle numbers with EPO administration	Cycle numbers with RBC transfusions	Cycle numbers with dose reduction

Table 12.4.4.11 Platelet count time course pattern (summary)

	Dose received						Total	
	7 mg FD / 3.5 mg/m^2		6 mg FD / 2.6 mg/m^2		5 mg FD/ 2.0 mg/m^2			
	N	Median (range)	N	Median (range)	N	Median (range)	N	Median (range)
Platelet transfusion=Yes								
Baseline grade 0								
1st cycle								
Onset day grade 4								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 4								
...								
Total								
Onset day grade 4								
...								
Baseline grade 1, 2								
...								

	Dose received						Total	
	7 mg FD / 3.5 mg/m^2		6 mg FD / 2.6 mg/m^2		5 mg FD/ 2.0 mg/m^2			
	N	Median (range)	N	Median (range)	N	Median (range)	N	Median (range)
Platelet transfusion=No								
…								
Total								
Total								
1st cycle								
Onset day grade 4								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 4								
...								
Total								
Onset day grade 4								
Nadir day grade 4								
Nadir value grade 4								
Recovery day to grade ≤ 3								
Duration in days to grade 3								
Recovery day to grade ≤ 2								
Duration in days to grade 2								
Recovery day to grade ≤ 1								
Duration in days to grade 1								

Table 12.4.4.12 Platelet count time course pattern (freqs)

	Dose received						Total	
	7 mg FD / 3.5 mg/m^2		6 mg FD / 2.6 mg/m^2		5 mg FD/ 2.0 mg/m^2			
	N	%	N	%	N	%	N	%
Platelet transfusion=Yes								
Baseline grade 0								
1st cycle								
Onset day grade 4 ≤ 7 8-14 ≥ 15								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 4 ≤ 7 8-14 ≥ 15								
...								
Total								
Onset day grade 4 ≤ 7 8-14 ≥ 15								
...								
Baseline grade 1, 2 ….								
...								
Platelet transfusion=No								
…								
Total								
Total								
1st cycle								

	Dose received						Total	
	7 mg FD / 3.5 mg/m^2		6 mg FD / 2.6 mg/m^2		5 mg FD/ 2.0 mg/m^2			
	N	%	N	%	N	%	N	%
Onset day grade 4 ≤ 7 8-14 ≥ 15								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 4 ≤ 7 8-14 ≥ 15								
...								
Total								
Onset day grade 4 ≤ 7 8-14 ≥ 15								
Nadir day grade 4 ≤ 7 8-14 ≥ 15								
Recovery day to grade ≤ 3 ≤ 22 23-28 ≥ 29								
Duration in days to grade 3 ≤ 5 6-10 ≥ 11								
Recovery day to grade ≤ 2 ≤ 22 23-28 ≥ 29								
Duration in days to grade 2 ≤ 5 6-10 ≥ 11								
Recovery day to grade ≤ 1 ≤ 22 23-28 ≥ 29								
Duration in days to grade 1 ≤ 5 6-10 ≥ 11								

Table 12.4.4.13 Neutrophil count time course pattern (summary)

	Dose received						Total	
	7 mg FD / 3.5 mg/m^2		6 mg FD / 2.6 mg/m^2		5 mg FD/ 2.0 mg/m^2			
	N	Median (range)	N	Median (range)	N	Median (range)	N	Median (range)
G-CSF=Yes								
Baseline grade 0								
1st cycle								
Onset day grade 4								
...								

	Dose received						Total	
	7 mg FD / 3.5 mg/m^2		6 mg FD / 2.6 mg/m^2		5 mg FD/ 2.0 mg/m^2			
	N	Median (range)	N	Median (range)	N	Median (range)	N	Median (range)
2nd cycle, 3rd cycle ….								
Onset day grade 4								
...								
Total								
Onset day grade 4								
...								
Baseline grade 1, 2								
...								
G-CSF=No								
…								
Total								
Total								
1st cycle								
Onset day grade 4								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 4								
...								
Total								
Onset day grade 4								
Nadir day grade 4								
Nadir value grade 4								
Recovery day to grade ≤ 3								
Duration in days to grade 3								
Recovery day to grade ≤ 2								
Duration in days to grade 2								
Recovery day to grade ≤ 1								
Duration in days to grade 1								

Table 12.4.4.14 Neutrophil count time course pattern (freqs)

	Dose received						Total	
	7 mg FD / 3.5 mg/m^2		6 mg FD / 2.6 mg/m^2		5 mg FD/ 2.0 mg/m^2			
	N	%	N	%	N	%	N	%
G-CSF=Yes								
Baseline grade 0								
1st cycle								
Onset day grade 4 ≤ 7 8-14 ≥ 15								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 4 ≤ 7 8-14 ≥ 15								
...								
Total								
Onset day grade 4 ≤ 7 8-14 ≥ 15								

	Dose received						Total	
	7 mg FD / 3.5 mg/m^2		6 mg FD / 2.6 mg/m^2		5 mg FD/ 2.0 mg/m^2			
	N	%	N	%	N	%	N	%
...								
Baseline grade 1, 2								
...								
G-CSF=No								
…								
Total								
Total								
1st cycle								
Onset day grade 4 ≤ 7 8-14 ≥ 15								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 4 ≤ 7 8-14 ≥ 15								
...								
Total								
Onset day grade 4 ≤ 7 8-14 ≥ 15								
Nadir day grade 4 ≤ 7 8-14 ≥ 15								
Recovery day to grade ≤ 3 ≤ 22 23-28 ≥ 29								
Duration in days to grade 3 ≤ 5 6-10 ≥ 11								
Recovery day to grade ≤ 2 ≤ 22 23-28 ≥ 29								
Duration in days to grade 2 ≤ 5 6-10 ≥ 11								
Recovery day to grade ≤ 1 ≤ 22 23-28 ≥ 29								
Duration in days to grade 1 ≤ 5 6-10 ≥ 11								

Table 12.4.4.15 AST time course pattern (summary)

	Dose received	Total

	7 mg FD / 3.5 mg/m^2		6 mg FD / 2.6 mg/m^2		5 mg FD/ 2.0 mg/m^2			
	N	Median (range)	N	Median (range)	N	Median (range)	N	Median (range)
Baseline grade 0								
1st cycle								
Onset day grade 3/4								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 3/4								
...								
Total								
Onset day grade 3/4								
...								
Baseline grade 1, 2								
...								
Total								
1st cycle								
Onset day grade 3/4								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 3/4								
...								
Total								
Onset day grade 3/4								
Peak day grade 3/4								
Peak value grade 3/4								
Recovery day to grade ≤ 2								
Duration in days to grade 2								
Recovery day to grade ≤ 1								
Duration in days to grade 1								

Table 12.4.4.16 AST time course pattern (freqs)

	Dose received						Total	
	7 mg FD / 3.5 mg/m^2		6 mg FD / 2.6 mg/m^2		5 mg FD/ 2.0 mg/m^2			
	N	%	N	%	N	%	N	%
Baseline grade 0								
1st cycle								
Onset day grade 3/4 ≤ 7 8-14 ≥ 15								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 3/4 ≤ 7 8-14 ≥ 15								
...								
Total								
Onset day grade 3/4 ≤ 7 8-14 ≥ 15								
...								
Baseline grade 1, 2								

	Dose received						Total	
	7 mg FD / 3.5 mg/m^2		6 mg FD / 2.6 mg/m^2		5 mg FD/ 2.0 mg/m^2			
	N	%	N	%	N	%	N	%
...								
Total								
1st cycle								
Onset day grade 3/4 ≤ 7 8-14 ≥ 15								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 3/4 ≤ 7 8-14 ≥ 15								
...								
Total								
Onset day grade 3/4 ≤ 7 8-14 ≥ 15								
Peak day grade 3/4 ≤ 7 8-14 ≥ 15								
Recovery day to grade ≤ 2 ≤ 22 23-28 ≥ 29								
Duration in days to grade 2 ≤ 5 6-10 ≥ 11								
Recovery day to grade ≤ 1 ≤ 22 23-28 ≥ 29								
Duration in days to grade 1 ≤ 5 6-10 ≥ 11								

Table 12.4.4.17 ALT time course pattern (summary)

	Dose received						Total	
	7 mg FD / 3.5 mg/m^2		6 mg FD / 2.6 mg/m^2		5 mg FD/ 2.0 mg/m^2			
	N	Median (range)	N	Median (range)	N	Median (range)	N	Median (range)
Baseline grade 0								
1st cycle								
Onset day grade 3/4								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 3/4								
...								
Total								
Onset day grade 3/4								
...								

	Dose received						Total	
	7 mg FD / 3.5 mg/m^2		6 mg FD / 2.6 mg/m^2		5 mg FD/ 2.0 mg/m^2			
	N	Median (range)	N	Median (range)	N	Median (range)	N	Median (range)
Baseline grade 1, 2								
...								
Total								
1st cycle								
Onset day grade 3/4								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 3/4								
...								
Total								
Onset day grade 3/4								
Peak day grade 3/4								
Peak value grade 3/4								
Recovery day to grade ≤ 2								
Duration in days to grade 2								
Recovery day to grade ≤ 1								
Duration in days to grade 1								

Table 12.4.4.18 ALT time course pattern (freqs)

	Dose received						Total	
	7 mg FD / 3.5 mg/m^2		6 mg FD / 2.6 mg/m^2		5 mg FD/ 2.0 mg/m^2			
	N	%	N	%	N	%	N	%
Baseline grade 0								
1st cycle								
Onset day grade 3/4 ≤ 7 8-14 ≥ 15								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 3/4 ≤ 7 8-14 ≥ 15								
...								
Total								
Onset day grade 3/4 ≤ 7 8-14 ≥ 15								
...								
Baseline grade 1, 2								
...								
Total								
1st cycle								
Onset day grade 3/4 ≤ 7 8-14 ≥ 15								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 3/4 ≤ 7 8-14								

	Dose received						Total	
	7 mg FD / 3.5 mg/m^2		6 mg FD / 2.6 mg/m^2		5 mg FD/ 2.0 mg/m^2			
	N	%	N	%	N	%	N	%
≥ 15								
...								
Total								
Onset day grade 3/4 ≤ 7 8-14 ≥ 15								
Peak day grade 3/4 ≤ 7 8-14 ≥ 15								
Recovery day to grade ≤ 2 ≤ 22 23-28 ≥ 29								
Duration in days to grade 2 ≤ 5 6-10 ≥ 11								
Recovery day to grade ≤ 1 ≤ 22 23-28 ≥ 29								
Duration in days to grade 1 ≤ 5 6-10 ≥ 11								

12.5 Physical Findings, PS, LVEF, ECG and Other Tests Related to Safety

12.5.1 Physical Findings and PS (ECOG)

Table 12.5.1.1 ECOG performance status during the study

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

(*) Worst ECOG PS of the cycle determinations.

Table 12.5.1.2 Physical examination during the study

	Cycle/Physical examination result*						
	0	1	2	3	4	…	EOT
Patient id.							
…							

(*) Worst result per cycle.

Table 12.5.1.3 Weight by patient per cycle

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

(*) % of changes respect to baseline

12.5.2 LVEF, ECG and Other Related Tests

Listing 12.5.2.1 LVEF evolution during the study.

Patient id.	LVEF(%)		
	Baseline*	Minimun*	End of treatment*
Median(Range)			

(*) 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.

Listing 12.5.2.3 Troponin I and Troponin T values. Evolution during the study.

Patient id.	Cycle	Test	Value	ULN

12.6 Concomitant Therapy / Procedures According to the ATC Classification.

Table 12.6.1 Concomitant medication during treatment (ATC1, ATC2 and ATC4 levels)

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

Table 12.6.2 Summary of concomitant medication during treatment

	N	%
No. of systems (ATC1 level) 0 1 2 ≥ 3 Median (range)		
No. of indications (ATC2 level) 0 1 2 ≥ 3 Median (range)		
No. of agent families (ATC4 level) 0 1 2 ≥ 3 Median (range)		
No. of agents (PN level) 0 1 2 ≥ 3 Median (range)		

Listing 12.6.3 Patients with any transfusion during treatment

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

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

Listing 12.6.4 Patients with G-CSF during treatment

Patient	Cycle	Agent	PT	Dose	Start date	End date

Table 12.6.5 Transfusions and G-CSF by dose

	7 mg FD		3.5 mg/m^2		Total	
	N	%	N	%	N	%
Transfusions						
RBC						
Platelets						
G-CSF						

Table 12.6.6 Subsequent therapy

	N	%
Type		
Chemotherapy		
…		
Subsequent chemotherapy agents (ATC)		
…		
…		

Table 12.6.7 Subsequent therapy. Best response (if available).

Best response		Subsequent therapy				
		CR	PR	SD	PD	NE
PM01183	CR					
	PR					
	SD					
	PD					
	NE					

(*) If a low number of best response to the subsequent therapy is available, a listing, instead of this table, will be provided.

APPENDIX II

13 DB Listings

CRF Listings.

-Listing 13.1.1: Investigator comments
-Listing 13.1.2: Study registration
-Listing 13.1.3: Demography
-Listing 13.1.4: Pregnancy test and adequate contraception
-Listing 13.1.5: Prior medical history
-Listing 13.1.6: Cancer history
-Listing 13.1.7: Prior surgery
-Listing 13.1.8: Prior radiotherapy
-Listing 13.1.9: Prior medical therapy
-Listing 13.1.10: Hematological laboratory values
-Listing 13.1.11: Biochemical laboratory values
-Listing 13.1.12: Coagulation laboratory values
-Listing 13.1.13: Physical examination
-Listing 13.1.14: Performance status
-Listing 13.1.15: Vital signs
-Listing 13.1.16: Electrocardiogram
-Listing 13.1.17: LVEF
-Listing 13.1.18: Prophylactic medication
-Listing 13.1.19: Drug administration
-Listing 13.1.20: Adverse events (including signs and symptoms)
-Listing 13.1.21: Concomitant therapy/procedures
-Listing 13.1.22: Tumor assessment
-Listing 13.1.23: Evaluation of response by cycle
-Listing 13.1.24: Best study overall response
-Listing 13.1.25: End of treatment
-Listing 13.1.26: Follow up
-Listing 13.1.27: Death report form
-Listing 13.1.28: Off study
-Listing 13.1.29: BRCA 1/2 germline mutation

ICH Listings.

-Listing 16.2.1 Discontinued patients
-Listing 16.2.2 Protocol deviations
-Listing 16.2.3 Patients excluded from the efficacy analysis
-Listing 16.2.4 Demographic data
-Listing 16.2.5 Compliance and-or Drug Concentration Data
-Listing 16.2.6 Individual Efficacy Response data
-Listing 16.2.7 Adverse event listings
-Listing 16.2.8 Individual laboratory measurements

14 SAP Version History

14.1 From version 1.0 to version 2.0

After the first version of the statistical plan was approved, some new protocol "substantial amendments No. 1 (Nov2013), No. 2 (Oct2014) and No. 3 (Feb2016)" were implemented. The Statistical Analysis Plan has been updated (changes are highlighted in ***italic bold***) in accordance with the currently available version of the protocol (i.e., version 4) as follows:

Section 2 Study Design

Original text:

This is a multicenter, open-label, exploratory, phase II clinical trial evaluating the efficacy and safety of PM01183 administration to patients with previously treated MBC, as follows.

Two Cohorts of MBC patients will be prospectively evaluated in the trial, initially according to germline BRCA1/2 status (mutated *vs.* unselected):

- Cohort A (BRCA+ Cohort): At least 53 evaluable patients with previously known deleterious BRCA1/2 mutation status at study entry.
- Cohort B (unselected Cohort): At least 64 evaluable patients without known deleterious BRCA1/2 mutation status at study entry, i.e., either:
    - Patients known to have no deleterious BRCA1/2 mutations (BRCA−), or
    - Patients whose BRCA 1/2 mutation status is unknown (BRCA-UK); BRCA1/2 germline mutation status will be assessed in PM01183 responding patients in this subgroup.

[…]

An interim analysis based on the primary endpoint (ORR) is planned after 20 and 30 evaluable patients have been treated in Cohorts A and B, respectively (see Section **¡Error! No se encuentra el origen de la referencia.** for details). If less than four out of 20 patients in Cohort A, or less than three out of 30 patients in Cohort B achieve an objective confirmed response, recruitment to that Cohort will be terminated.

Changed to:

This is a multicenter, open-label, exploratory, phase II clinical trial evaluating the efficacy and safety of PM01183 administration to patients with previously treated MBC, as follows.

Two Cohorts of MBC patients will be prospectively evaluated in the trial according to germline BRCA1/2 status (mutated [Cohort A] vs. unselected [Cohort B]). A third Cohort (Cohort A1) will include advanced breast cancer patients with deleterious BRCA1/2 mutation status who received prior treatment with poly (ADP-ribose) polymerase (PARP) inhibitors:

- Cohort A (BRCA+ Cohort): At least 53 evaluable patients with previously known deleterious BRCA1/2 mutation status at study entry.
- ***Cohort A1 (BRCA+/PARPi Cohort): 20 evaluable patients with known deleterious BRCA1/2 mutation status and prior treatment with PARP inhibitors (PARPi).***
- Cohort B (unselected Cohort): At least 64 evaluable patients without known deleterious BRCA1/2 mutation status at study entry, i.e., either:
    - Patients known to have no deleterious BRCA1/2 mutations (BRCA−), or
    - Patients whose BRCA 1/2 mutation status is unknown (BRCA-UK); BRCA1/2 germline mutation status will be assessed in PM01183 responding patients in this subgroup.

[….]
An interim analysis based on the primary endpoint (ORR) is planned after 20 and 30 evaluable patients have been treated in Cohorts A and B, respectively (see Section **¡Error! No se encuentra el origen de la referencia.** for details). ***No interim analysis is planned for Cohort A1.*** If less than four out of 20 patients in Cohort A, or less than three out of 30 patients in Cohort B achieve an objective confirmed response, recruitment to that Cohort will be terminated.

Section 5.1 Sample Size

Original text

The primary endpoint for this phase II study is to evaluate ORR.

- Cohort A (BRCA+): At least 53 evaluable patients will be recruited to test the null hypothesis that ORR is 20% or less ($p \leq 0.20$) vs. the alternative hypothesis that 40% or more patients have objective response ($p \geq 0.4$). With these assumptions, if the number of evaluable patients with objective response is ≥ 17, then this would allow the rejection of the null hypothesis.
- Cohort B (unselected): At least 64 evaluable patients will be recruited to test the null hypothesis that ORR is 10% or less ($p \leq 0.10$) vs. the alternative hypothesis that 25% or more patients have objective response ($p \geq 0.25$). With these assumptions, if the number of evaluable patients with objective response is ≥ 12, then this would allow the rejection of the null hypothesis.

The variance of the standardized tests 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 <0.1; hence, statistical power is > 90%. Futility analysis controlled by the Gamma family boundary will be performed when 20 and 30 patients have been evaluated in Cohorts A [Gm(-2)] and B [Gm(-1.5)], respectively. If less than four out of 20 patients in Cohort A, or less than three patients out of 30 in Cohort B achieve an objective response, recruitment to that Cohort will be stopped. Therefore, between 50 and at least 117 evaluable patients will be included in this study.

Changed to:

The primary endpoint for this phase II study is to evaluate ORR.

- Cohort A (BRCA+):

  At least 53 evaluable patients will be recruited to test the null hypothesis that ORR is 20% or less ($p \leq 0.20$) *vs.* the alternative hypothesis that 40% or more patients have objective response ($p \geq 0.4$). With these assumptions, if the number of evaluable patients with objective response is ≥ 17, then this would allow the rejection of the null hypothesis.

- ***Cohort A1 (BRCA+/PARPi):***

  At least 20 evaluable patients will be included for an exploratory analysis: if the number of patients responding is ≥ 4 (20%), the lower limit of the exact binomial 95% confidence interval will be higher than 5% and thus lack of activity in this subpopulation will be ruled out.

- Cohort B (unselected):

  At least 64 evaluable patients will be recruited to test the null hypothesis that ORR is 10% or less ($p \leq 0.10$) *vs.* the alternative hypothesis that 25% or more patients have objective response ($p \geq 0.25$). With these assumptions, if the number of evaluable patients with objective response is ≥ 12, then this would allow the rejection of the null hypothesis.

The variance of the standardized tests 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 <0.1; hence, statistical power is > 90%.
Futility analysis controlled by the Gamma family boundary will be performed when 20 and 30 patients have been evaluated in Cohorts A [Gm(-2)] and B [Gm(-1.5)], respectively. If less than four out of 20 patients in Cohort A, or less than three patients out of 30 in Cohort B achieve an objective response, recruitment to that Cohort will be stopped. ~~Therefore, between 50 and at least 117 evaluable patients will be included in this study~~. ***About 110 evaluable patients are finally expected to be included in the three Cohorts: Cohort A (BRCA+), Cohort A1 (BRCA+/PARPi), and Cohort B (unselected).***

Section 6.2.2 Secondary Endpoints

Original text:
[…]

A log-rank test or Cox regression for time-to-event endpoints could be performed as supportive analysis to compare both Cohorts.

[…]

If appropriate, exploratory multivariate models (main effects or including interaction terms, if appropriate) will include all prognostic factors/covariates widely reported and recognized by oncologists: Cohort (BRCA (+) *vs.* BRCA (-) or unknown), BRCA (1 *vs.* 2 *vs.* both *vs.* negative/unkown), age, age at diagnosis, race (Caucasian *vs.* other), baseline Eastern Cooperative Oncology Group performance status (ECOG PS) (0 *vs.* >0), histology type (Ductal *vs.* lobular carcinoma), histology grade (poorly *vs.* other), stage at diagnosis,

primary tumor site (unilateral breast *vs.* bilateral), estrogen receptor (positive *vs.* negative), progesterone receptor (positive *vs.* negative), HER-2 receptor (positive *vs.* negative), site of current disease (CNS *vs.* liver *vs.* lung *vs.* non-visceral (including bone, skin, subcutaneous and lymph node) *vs.* other), liver metastases (yes *vs.* no), CNS metastases (yes *vs.* no), number of prior metastatic sites (1 *vs.* >1), body mass index (BMI), height, weight, body surface area (BSA), time from diagnosis to first infusion, prior surgery (yes *vs.* no), prior radiotherapy (yes *vs.* no), prior advanced treatment lines, prior advanced chemotherapy lines (1 *vs.* >1), prior anthracyclines (yes *vs.* no), prior taxane (yes *vs.* no), prior platinum (yes *vs.* no), anthracycline cumulative dose, last prior therapy PFS, first advanced chemotherapy PFS, last advanced chemotherapy PFS; PFS for anthracycline, taxane and platinum therapy, hormonotherapy (yes vs no), adjuvant/neoadjuvant therapy (yes vs no), presence of any bulky (< 50 mm *vs.* ≥ 50 mm) lesion, albumin at baseline, CA-15.3 or 27.29 at baseline, any relevant concomitant medication at baseline (to be determinate by the oncologist) (yes *vs.* no) and the sum of all target lesion diameters.

[…]

Changed to:

[…]

A log-rank test or Cox regression for time-to-event endpoints could be performed as supportive analysis to compare ~~both Cohorts~~ ***between different cohorts and /or defined groups***.

[…]

If appropriate, exploratory multivariate models (main effects or including interaction terms, if appropriate) will include all prognostic factors/covariates widely reported and recognized by oncologists: Cohort (BRCA (+) *vs.* BRCA (-) or unknown), BRCA (1 *vs.* 2 *vs.* both *vs.* negative/unkown), ***initial dose (7 mg FD vs 3.5 mg/m^2),*** age, age at diagnosis, race (Caucasian *vs.* other), baseline Eastern Cooperative Oncology Group performance status (ECOG PS) (0 *vs.* >0), histology type (Ductal *vs.* lobular carcinoma), histology grade (poorly *vs.* other), stage at diagnosis, primary tumor site (unilateral breast *vs.* bilateral), ***hormone receptor positive (estrogen or progesterone receptor +, or both +) vs. triple negative,*** HER-2 receptor (positive *vs.* negative), site of current disease (CNS *vs.* liver *vs.* lung *vs.* non-visceral (including bone, skin, subcutaneous and lymph node) *vs.* other), liver metastases (yes *vs.* no), CNS metastases (yes *vs.* no), number of prior metastatic sites (1 *vs.* >1), body mass index (BMI), height, weight, body surface area (BSA), time from diagnosis to first infusion, prior surgery (yes *vs.* no), prior radiotherapy (yes *vs.* no), prior advanced treatment lines, prior advanced chemotherapy lines ***(0-1 vs. 2-3),*** prior anthracyclines (yes *vs.* no), prior taxane (yes *vs.* no), prior platinum (yes *vs.* no), ***prior PARPi (yes vs. no),*** anthracycline cumulative dose, last prior therapy PFS, first advanced chemotherapy PFS, last advanced chemotherapy PFS; PFS for anthracycline, taxane and platinum therapy, hormonotherapy (yes vs no), adjuvant/neoadjuvant therapy (yes vs no), presence of any bulky (< 50 mm *vs.* ≥ 50 mm) lesion, albumin at baseline, CA-15.3 or 27.29 at baseline, any relevant concomitant medication at baseline (to be determinate by the oncologist) (yes *vs.* no) and the sum of all target lesion diameters.

[…]

Section 8.9 Subgroup Analysis

Original Text:

The analysis will be done by Cohort and additionally, if clinically appropriate, the two Cohorts might be pooled into one, whenever differences between Cohorts are considered not relevant. In such case, the point estimates and their 95% CIs will be also reassessed in order to obtain more accurate calculations.

No other specific subgroup analysis is being planned for the analysis. However, if any of the disease characteristics is sufficiently represented and clinically relevant, subgroup analysis may be performed in order to explore the activity of PM01183 in specific breast cancer subpopulations according to hormonal receptor status, HER-2 overexpression, number and/or type of prior therapies, or according to other available histological/molecular classifications.

Changed to:

The analysis will be done by Cohort and additionally, if clinically appropriate, the ~~two~~ Cohorts might be pooled into one, whenever differences between Cohorts are considered not relevant. In such case, the point estimates and their 95% CIs will be also reassessed in order to obtain more accurate calculations.

Efficacy subgroup analysis will be performed in Cohort A according to prior treatment with platinum, BRCA status (BRCA1 vs. BRCA2), hormonal status (Triple negative vs HR+), number of advanced chemotherapy lines (0-1 vs. 2-3) and starting dose (7 mg FD vs. 3.5 mg/m^2).

Safety subgroup analysis will be performed according to starting dose (7 mg FD vs. 3.5 mg/m^2), these analysis include laboratory abnormalities and adverse events.

~~No other specific subgroup analysis is being planned for the analysis. However, if any of the disease characteristics is sufficiently represented and clinically relevant,~~ If clinically relevant, other subgroup analysis may be performed in order to explore the activity of PM01183 in specific breast cancer subpopulations~~. according to hormonal receptor status, HER-2 overexpression, number and/or type of prior therapies, or according to other available histological/molecular classifications.~~

Section 11.3 Efficacy Analysis

Original text:

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

If any of the disease characteristics is sufficiently represented and clinically relevant, subgroup analysis may be performed in order to explore the activity of PM01183 in specific breast cancer subpopulations according to hormonal receptor status, HER-2 overexpression, number and/or type of prior therapies, or according to other available histological/molecular classifications.

Changed to:

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

Subgroup analysis will be performed in Cohort A according to prior treatment with platinum, BRCA status (BRCA1 vs. BRCA2), hormonal status (Triple negative vs. HR+), number of advanced chemotherapy lines (0-1 vs. 2-3) and starting dose (7 mg FD vs. 3.5 mg/m^2).

The tables included in each subgroup analysis are the following:

Table 11.3.1.1 Response rate

Table 11.3.1.2 Overall response rate

Table 11.3.2.1 Duration of response

Table 11.3.2.2 Progression-free survival (PFS)

Table 11.3.2.3 Overall survival (OS)

The tables will be annotated by adding a letter as suffix:

- ***BRCA status: a***
- ***Prior platinum: b***
- ***Hormonal status: c***
- ***Advanced chemotherapy lines: d***
- ***Starting dose: e***

If any ~~of the~~ other disease characteristic~~s~~ is sufficiently represented and clinically relevant, subgroup analysis may be performed, and their corresponding tables will also be annotated by adding a letter to the table's name. ~~according to hormonal receptor status, HER-2 overexpression, number and/or type of prior therapies, or according to other available histological/molecular classifications.~~

Section 12.1 Extent of Exposure

Added text:

Subgroup analysis will be performed according to starting dose (7 mg FD vs. 3.5 mg/m^2).
The tables will be annotated by adding a letter as suffix.
The tables included in the subgroup analysis are the following:
Table 12.1.1.1 Number of cycles administered and dose intensity
Table 12.1.2.1.3 Number of patients and cycles with dosing delay according to relationship
Table 12.1.3.3 Number of patient and cycles with dose reduction according to relationship

Section 12.2.1 Adverse Events

Added text:
Subgroup analysis will be performed according to starting dose (7 mg FD vs. 3.5 mg/m^2) and Cohort.
The groups will include:

- ***Patient treated at 7 mg FD Cohort B***
- ***Patient treated at 7 mg FD Cohort A***
- ***Patient treated at 7 mg FD any Cohort***
- ***Patient treated at 3.5 mg/m^2 Cohort A***
- ***Patient treated at 3.5 mg/m^2 Cohort A1***
- ***Patient treated at 3.5 mg/m^2 any Cohort***

The tables will be annotated by adding a letter as suffix.
The tables included in the subgroup analysis are the following:
Table 12.2.2.2 Treatment related AEs. Worst grade by patient
Table 12.2.2.3 Treatment related AEs. Worst grade by cycle
Table 12.2.2.4 Adverse events regardless of relationship. Worst grade by patient
Table 12.2.2.5 Adverse events regardless of relationship. Worst grade by cycle

Section 12.4 Clinical Laboratory Evaluation

Added text:
Subgroup analysis will be performed according to starting dose (7 mg FD vs. 3.5 mg/m^2) and Cohort.
The groups will include:

- ***Patient treated at 7 mg FD Cohort B***
- ***Patient treated at 7 mg FD Cohort A***
- ***Patient treated at 7 mg FD any Cohort***
- ***Patient treated at 3.5 mg/m^2 Cohort A***
- ***Patient treated at 3.5 mg/m^2 Cohort A1***
- ***Patient treated at 3.5 mg/m^2 any Cohort***

The tables will be annotated by adding a letter as suffix.
The tables included in the subgroup analysis are the following:
Table 12.4.1.1 Hematological abnormalities during treatment, worst grade per patient
Table 12.4.1.2 Hematological abnormalities during treatment, worst grade per cycle
Table 12.4.2.1 Biochemical abnormalities during treatment, worst grade per patient
Table 12.4.2.2 Biochemical abnormalities during treatment, worst grade per cycle
Table 12.4.3.1 Coagulation abnormalities during treatment, worst grade per patient
Table 12.4.3.2 Coagulation abnormalities during treatment, worst grade per cycle

14.2 From version 2.0 to version 3.0

The Statistical Analysis Plan has been updated (changes are highlighted in ***italic bold***) in order to include some relevant analysis according to the medical responsible, to clarify some of the analyses and to correct several typos found in the previous SAP version.

Section 5.1 Sample size

Original text:

[…]

- Cohort A1 (BRCA+/PARPi):

  At least 20 evaluable patients will be for an exploratory analysis: if the number of patients responding is ≥ 4 (20%), the lower limit of the exact binomial 95% confidence interval will be higher than 5% and thus lack of activity in this subpopulation will be ruled out.

Changed to:

[…]

- Cohort A1 (BRCA+/PARPi):

  At least 20 evaluable patients will be ***recruited*** for an exploratory analysis: if the number of patients responding is ≥ 4 (20%), the lower limit of the exact binomial 95% confidence interval will be higher than 5% and thus lack of activity in this

subpopulation will be ruled out.

Section 6.2.2 Secondary Endpoints

Original text:

[…]

If relevant, efficacy parameters versus baseline covariates will be analyzed and appropriate test will be used (i.e., the Fisher exact test and logistic regression for categorical variables, the log-rank test or Cox regression for time-to-event variables, etc.).

If appropriate, exploratory multivariate models (main effects or including interaction terms, if appropriate) will include all prognostic factors/covariates widely reported and recognized by oncologists: Cohort (BRCA (+) vs. BRCA (-) or unknown), BRCA (1 vs. 2 vs. both vs. negative/unkown), initial dose (7 mg FD vs 3.5 mg/m^2), age, age at diagnosis, race (Caucasian vs. other), baseline Eastern Cooperative Oncology Group performance status (ECOG PS) (0 vs. >0), histology type (Ductal vs. lobular carcinoma), histology grade (poorly vs. other), stage at diagnosis, primary tumor site (unilateral breast vs. bilateral), hormone receptor positive (estrogen or progesterone receptor +, or both +) vs. triple negative, HER-2 receptor (positive vs. negative), site of current disease (CNS vs. liver vs. lung vs. non-visceral (including bone, skin, subcutaneous and lymph node) vs. other), liver metastases (yes vs. no), CNS metastases (yes vs. no), number of prior metastatic sites (1 vs. >1), body mass index (BMI), height, weight, body surface area (BSA), time from diagnosis to first infusion, prior surgery (yes vs. no), prior radiotherapy (yes vs. no), prior advanced treatment lines, prior advanced chemotherapy lines (0-1 vs. 2-3), prior anthracyclines (yes vs. no), prior taxane (yes vs. no), prior platinum (yes vs. no), prior PARPi (yes vs. no), anthracycline cumulative dose, last prior therapy PFS, first advanced chemotherapy PFS, last advanced chemotherapy PFS; PFS for anthracycline, taxane and platinum therapy, hormonotherapy (yes vs no), adjuvant/neoadjuvant therapy (yes vs no), presence of any bulky (< 50 mm vs. ≥ 50 mm) lesion, albumin at baseline, CA-15.3 or 27.29 at baseline, any relevant concomitant medication at baseline (to be determinate by the oncologist) (yes vs. no) and the sum of all target lesion diameters.

All variables with a good percentage of valid cases (approximately ≥ 90%) will be included in the exploratory multivariate analysis. […]

Changed to:

[…]

If appropriate, exploratory multivariate models (main effects or including interaction terms, if appropriate) will include all prognostic factors/covariates widely reported and recognized by oncologists: Cohort (BRCA (+) vs. BRCA (-) or unknown), BRCA (1 vs. 2 ~~***vs. both vs. negative/unknown***~~ ***in cohorts A and A1***), initial dose (7 mg FD vs 3.5 mg/m^2), age, age at diagnosis, race (Caucasian vs. other), baseline Eastern Cooperative Oncology Group performance status (ECOG PS) (0 vs. >0), histology type (Ductal vs. lobular carcinoma), histology grade (poorly vs. other), stage at diagnosis, primary tumor site (unilateral breast vs. bilateral), hormone receptor positive (estrogen or progesterone receptor +, or both +)

vs. triple negative, HER-2 receptor (positive vs. negative), site of current disease ***such as liver metastases (yes vs. no), CNS metastases (yes vs. no), lung metastases (yes vs. no),*** ~~***(CNS vs. liver vs.***~~ non-visceral (including bone, skin, subcutaneous and lymph node~~***)***~~ vs. other), ~~***liver metastases (yes vs. no), CNS metastases (yes vs. no),***~~ number of prior metastatic sites (1 vs. >1), body mass index (BMI), height, weight, body surface area (BSA), time from diagnosis to first infusion, prior surgery (yes vs. no), prior radiotherapy (yes vs. no), prior advanced treatment lines, prior advanced chemotherapy lines (0-1 vs. 2-3), prior anthracyclines (yes vs. no), prior taxane (yes vs. no), prior platinum (yes vs. no), prior PARPi (yes vs. no), ~~***anthracycline cumulative dose,***~~ last prior therapy PFS, first advanced chemotherapy PFS, last advanced chemotherapy PFS, PFS for anthracycline, taxane and platinum therapy, hormonotherapy (yes vs no), adjuvant/neoadjuvant therapy (yes vs no), ***platinum-free interval (in months),*** presence of any bulky (< 50 mm vs. ≥ 50 mm) lesion, albumin at baseline, CA-15.3 or 27.29 at baseline, any relevant concomitant medication at baseline (to be determinate by the oncologist) (yes vs. no) and the sum of all target lesion diameters.

All variables with a good percentage of valid cases (approximately ≥ 90***%) and with a p-value lower than 0.10 in the univariate analysis*** will be included in the exploratory multivariate analysis. […]

If appropriate, multivariate analysis will be produced for a relevant subgroup of patients (e.g. by cohort).

Section 8.3 Baseline and Demographic Data

Original text

[…]

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

Changed to:

[…]

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

Baseline and demography characteristics in different subgroups of analysis (i.e. cohorts) will be compared by means of Fisher's exact test (categorical variables) and Mann-Whitney-Wilcoxon (continuous variables).

Section 8.8 Imputation of incomplete dates

Added:

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 not earlier than the treatment start date; otherwise, the imputed date will be the treatment start date).

Section 8.9 Subgroup Analysis

Original text:
[…]
Efficacy subgroup analysis will be performed in Cohort A according to prior treatment with platinum (Yes Vs No), BRCA status (BRCA1 vs. BRCA2), hormonal status (Triple negative vs. HR+), number of advanced chemotherapy lines (0-1 vs. 2-3) and starting dose (7 mg FD vs. 3.5 mg/m^2).

Changed to:
[…]

Efficacy subgroup analysis will be performed in Cohort A according to prior treatment with platinum (Yes ***vs.*** ~~***Vs***~~ No), BRCA status (BRCA1 vs. BRCA2), hormonal status (Triple negative vs. HR+), number of advanced chemotherapy lines ~~***(0-1 vs. 2-3)***~~***, prior PARPi (Yes vs. No)*** and starting dose (7 mg FD vs. 3.5 mg/m^2).

Additional efficacy subgroup analysis will be performed in Cohorts A+A1 according to prior PARPi (Yes vs. No).

Table 11.1.4.3 Number of lines of prior therapy

Typo correction: *Antracycline* has been corrected to ***Anthracycline.***

Table 11.1.6.3 Baseline characteristics: Electrocardiogram values

Original table:

Parameter	N	Median	Min	Max
PR interval (msec)				
Heart rate (bpm)				
QT interval (msec)				
QRS complex (msec)				
QTc Bazett's*				

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

Changed to:

Parameter	N	Median	Min	Max
PR interval (msec)				
Heart rate (bpm)				
QT interval (msec)				
QRS complex (msec)				
QTc ***Fridericia*** ~~***Bazett's***~~*				

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

Listing 11.1.6.4 Patients with abnormal electrocardiogram

Original listing:

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

Changed to:

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

Listing 11.1.10.4 Signs and Symptoms at baseline

Original listing:

Patient id.	Sign/symptom	Grade*	Onset date	Relationship	Treated*
…					

Changed to:

Patient id.	Sign/symptom	Grade*	Onset date	Relationship	~~*Treated**~~
…					

Section 11.1.12 Baseline and demographic characteristic comparisons

Section added:

Table 11.1.12.1 Baseline and demographic characteristic comparisons by cohorts

		N	*Cohort A*	*Cohort A1*	*Cohort B*	*p-value**
Age	***Median (range)***	***X***	***X.X (XX-XX)***	***X.X (XX-XX)***	***X.X (XX-XX)***	***X.XXXX***
PS (ECOG)	***0***	***X***	***X (XX.X %)***	***X (XX.X %)***	***X (XX.X %)***	***X.XXXX***
	1	***.***	***X (XX.X %)***	***X (XX.X %)***	***X (XX.X %)***	
BSA	***Median (range)***					
BRCA mutation	***1***					
	2					
Receptor status	***Triple negative***					
	HR+ / HER2 -					

		N	Cohort A	Cohort A1	Cohort B	p-value*
	HER2 +					
Liver metastases	Yes					
	No					
CNS metastases	Yes					
	No					
Sites involvement	<3 sites					
	≥ 3 sites					
Advanced lines	Median (range)					
Advanced CT lines	Median (range)					
Prior Platinum	Yes					
	No					
Prior Anthracyclines	Yes					
	No					
Prior Taxanes	Yes					
	No					
Prior Capecitabine	Yes					
	No					
Prior PARP Inhibitor	Yes					
	No					

**Fisher's exact test (categorical variables);Mann-Whitney-Wilcoxon (continuous variables)*

Table 11.1.12.2 Baseline and demographic characteristic comparisons: Platinum Yes/No in Cohort A

		N	Prior platinum Yes	Prior platinum No	p-value*
Age	Median (range)	X	X.X (XX-XX)	X.X (XX-XX)	X.XXXX
PS (ECOG)	0	X	X (XX.X %)	X (XX.X %)	X.XXXX
	1	.	X (XX.X %)	X (XX.X %)	
…	…				

**Fisher's exact test (categorical variables);Mann-Whitney-Wilcoxon (continuous variables). For the complete list of covarites, see table 11.1.12.1*

Table 11.1.12.3 Baseline and demographic characteristic comparisons: BRCA 1 vs 2 in Cohort A

		N	BRCA 1	BRCA 2	p-value*
Age	Median (range)	X	X.X (XX-XX)	X.X (XX-XX)	X.XXXX
PS (ECOG)	0	X	X (XX.X %)	X (XX.X %)	X.XXXX

		N	*BRCA 1*	*BRCA 2*	*p-value**
	1	*.*	*X (XX.X %)*	*X (XX.X %)*	
…	*…*				

Fisher's exact test (categorical variables);Mann-Whitney-Wilcoxon (continuous variables). For the complete list of covarites, see table 11.1.12.1

Table 11.1.12.4 Baseline and demographic characteristic comparisons: Prior PARPi Yes/No in Cohorts A+A1

		N	*Prior PARPi Yes*	*Prior PARPi No*	*p-value**
Age	*Median (range)*	*X*	*X.X (XX-XX)*	*X.X (XX-XX)*	*X.XXXX*
PS (ECOG)	*0*	*X*	*X (XX.X %)*	*X (XX.X %)*	*X.XXXX*
	1	*.*	*X (XX.X %)*	*X (XX.X %)*	
…	*…*				

Fisher's exact test (categorical variables);Mann-Whitney-Wilcoxon (continuous variables). For the complete list of covarites, see table 11.1.12.1

Table 11.1.12.5 Baseline and demographic characteristic comparisons: Initial dose 7 mg FD vs 3.5 mg/m^2 in Cohort A

		N	*7 mg FD*	*3.5 mg/m^2*	*p-value**
Age	*Median (range)*	*X*	*X.X (XX-XX)*	*X.X (XX-XX)*	*X.XXXX*
PS (ECOG)	*0*	*X*	*X (XX.X %)*	*X (XX.X %)*	*X.XXXX*
	1	*.*	*X (XX.X %)*	*X (XX.X %)*	
…	*…*				

Fisher's exact test (categorical variables);Mann-Whitney-Wilcoxon (continuous variables). For the complete list of covarites, see table 11.1.12.1

Table 11.1.12.6 Baseline and demographic characteristic comparisons: Hormonal status triple negative vs Other

		N	**Triple negative Yes**	**Triple negative No**	**p-value***
Age	Median (range)	X	X.X (XX-XX)	X.X (XX-XX)	X.XXXX
PS (ECOG)	0	X	X (XX.X %)	X (XX.X %)	X.XXXX
	1	.	X (XX.X %)	X (XX.X %)	
…	…				

*Fisher's exact test (categorical variables);Mann-Whitney-Wilcoxon (continuous variables). For the complete list of covarites, see table 11.1.12.1

Table 11.1.12.7 Baseline and demographic characteristic comparisons: Advanced chemotherapy lines

		N	0-1 lines	>1 lines	p-value*
Age	Median (range)	X	X.X (XX-XX)	X.X (XX-XX)	X.XXXX
PS (ECOG)	0	X	X (XX.X %)	X (XX.X %)	X.XXXX
	1	.	X (XX.X %)	X (XX.X %)	
…	…				

*Fisher's exact test (categorical variables);Mann-Whitney-Wilcoxon (continuous variables). For the complete list of covarites, see table 11.1.12.1

Section 11.3 Efficacy Analysis

Original text:

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

Subgroup analysis will be performed in Cohort A according to prior treatment with platinum, BRCA status (BRCA1 vs. BRCA2), hormonal status (Triple negative vs. HR+), number of advanced chemotherapy lines (0-1 vs. 2-3) and starting dose (7 mg FD vs. 3.5 mg/m^2).

The tables included in each subgroup analysis are the following:

[…]

- Prior PARPi: f

Changed to:

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

Subgroup analysis will be performed in Cohort A according to prior treatment with platinum, BRCA status (BRCA1 vs. BRCA2), hormonal status (Triple negative vs. HR+), number of advanced chemotherapy lines ~~***(0-1 vs. 2-3)***~~, ***prior PARPi (Yes vs. No)*** and starting dose (7 mg FD vs. 3.5 mg/m^2).

Subgroup analysis will be performed in Cohorts A+A1 according to prior PARPi (Yes vs. No).

The tables included in each subgroup analysis are the following:

[…]

- Prior PARPi ***(Cohort A)***: f
- **Prior PARPi (Cohorts A+A1): g**

Listing 11.3.2.5 Characteristics of patients with clinical benefit*

Original listing:

Patient	PS / Age	Histology Type	Histology Grade	Hormonal Status (ER +/-; PR +/-; HER2 +/-)	No. of prior lines	No. of advanced prior lines	Prior last therapy		
							Agents	Best response	PFS (months)

Patient	Cycles received	Best response	PFS (months)	OS (months)	DR (months)

Changed to:

Patient	PS / Age	***BRCA status***	Histology Type	Histology Grade	Hormonal Status ~~***(ER +/-; PR +/-; HER2 +/-)***~~	***Sites***	No. of prior lines	No. of advanced ***CT*** ~~***prior***~~ lines	***Prior Platinum (Y/N)***	***Best response Prior platinum***	Prior last therapy		
											Agents	Best response	PFS (month

Patient	***Initial dose***	Cycles received	Best response	PFS (months)	OS (months)	DR (months)

Section 11.3.2 Secondary analyses

Added:

Figure 11.3.2.8 “Swimmer plot” PFS in Cohort A

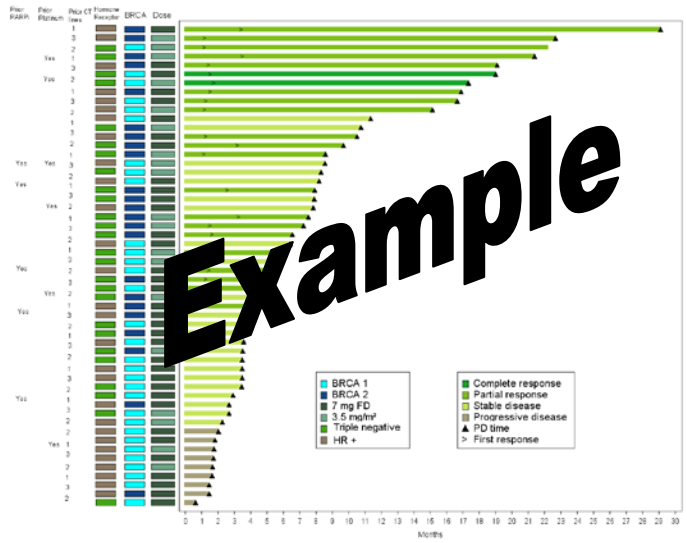


Figure 11.3.2.9 “Swimmer plot” PFS in Cohort A1

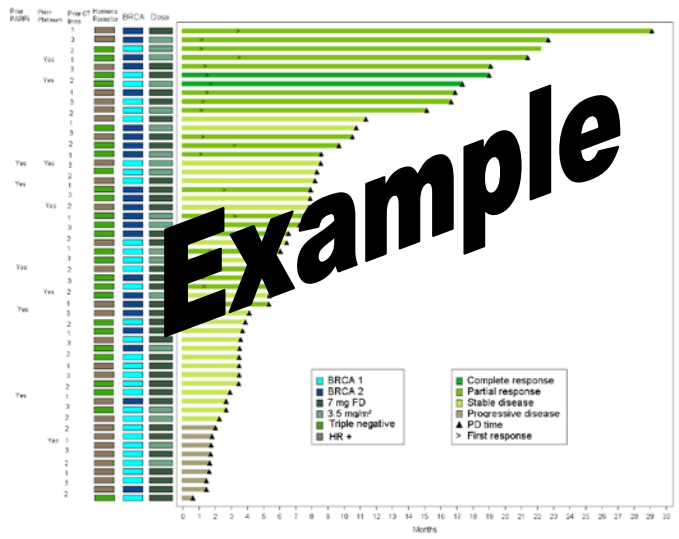
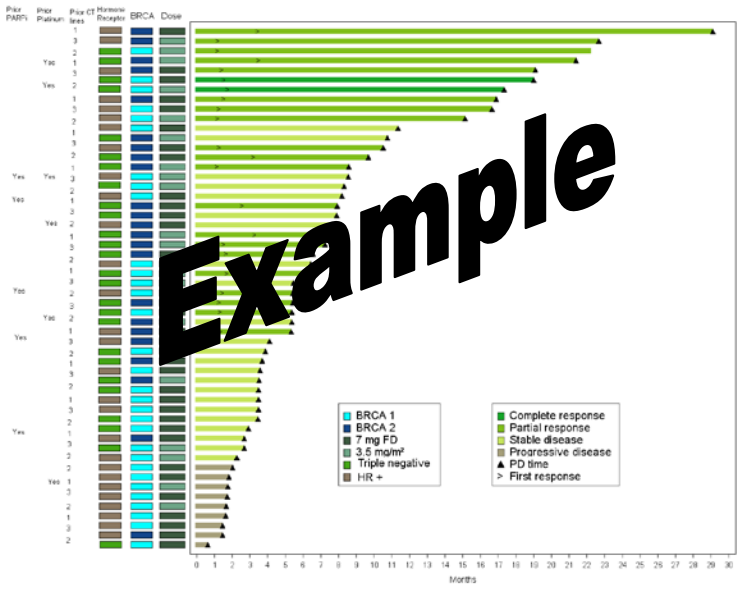


Figure 11.3.2.10 “Swimmer plot” PFS in Cohort B



Section 11.3.3 Exploratory Multivariate Analysis

Section title has been modified.

Original title:

11.3.3 Exploratory Multivariate Analysis

Changed to:

11.3.3 Exploratory ***Univariate and*** Multivariate Analys***e***s

Original section:

Table 11.3.3.1 Multivariate analysis of response rate

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

(See list of covariates in section 6.2.2).

Table 11.3.3.2 Multivariate analysis of PFS

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

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

(See list of covariates in section 6.2.2).

Table 11.3.3.3 Multivariate analysis of OS

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

(See list of covariates in section 6.2.2).

Changed to:

Table 11.3.3.1 Univariate analysis of response rate

Variable label	***Variable values***	***DF***	***Estimate***	***Standard error***	***Wald chi-square***	***Pr > ChiSq***	***Odds ratio estimate***	***95% Odds Ratio confidence limits***

(See list of covariates in section 6.2.2).

Table ~~***11.3.3.1***~~ ***11.3.3.2*** Multivariate analysis of response rate

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

(See list of covariates in section 6.2.2. ***Only those covariates with a p-value < 0.10 in univariate analysis and with a 90% of valid observations will be included***).

Table 11.3.3.3 Univariate analysis of PFS

Variable label	***Variable values***	***DF***	***Parameter estimate***	***Standard error***	***Chi-square***	***Pr > ChiSq***	***Hazard ratio***	***95% Hazard ratio confidence limits***

(See list of covariates in section 6.2.2).

Table ~~***11.3.3.2***~~ ***11.3.3.4*** Multivariate analysis of PFS

Analysis of Maximum Likelihood Estimates

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

(See list of covariates in section 6.2.2. ***Only those covariates with a p-value < 0.10 in univariate analysis and with a 90% of valid observations will be included***).

Table 11.3.3.5 Univariate analysis of OS

Variable label	***Variable values***	***DF***	***Parameter estimate***	***Standard error***	***Chi-square***	***Pr > ChiSq***	***Hazard ratio***	***95% Hazard ratio confidence limits***

(See list of covariates in section 6.2.2).

Table ~~***11.3.3.3***~~ ***11.3.3.6*** Multivariate analysis of OS

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

(See list of covariates in section 6.2.2. ***Only those covariates with a p-value < 0.10 in univariate analysis and with a 90% of valid observations will be included***).

Table 12.1.2.1.2 Number of patients and cycles with dosing delay, any relationship

Original table:

	N	%
No. of patients treated		
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		

Changed to:

	N	%
No. of patients treated		
No. of patients susceptible to have any dose delayed		
No. of patients with any dose delay***ed***		
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		

Table 12.1.2.1.4 Number of patients and cycles with dosing delay according to the relationship

Original table:

Reasons for delays	N	%
No. of cycles with dosing delays*		
Treatment-related	X	XX.X
Hematological		
Non-hematological		
Both		
Non-treatment-related		

(*) Denominator= Number of cycles susceptible to have a delay.

Changed to:

Reasons for delays		N	%
Cycles	No. of cycles with dosing delays*		
	Treatment-related	X	XX.X
	Hematological		
	Non-hematological		
	Both		
	Non-treatment-related		
Patients	***No. of patients with dosing delays****		
	Treatment-related	***X***	***XX.X***
	Hematological		
	Non-hematological		
	Both		
	Non-treatment-related		

(*) Denominator= Number of ***patient/***cycles susceptible to have a delay.

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

Original table:

	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)**		

Changed to:

	N	%
No. of patients treated	X	XX.X
No. of patients susceptible to have a dose reduced		
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)**		

Table 12.1.3.3 Number of patients and cycles with dose reduction according to the relationship

Original table:

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

(*) Denominator= Number of cycles susceptible to have a dose reduction.

Changed to:

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

(*) Denominator= Number of ***patient***/cycles susceptible to have a dose reduction.

Section 12.2.2 Display of Adverse Events

Added:

Table 12.2.2.10 Treatment-related SAEs. Worst grade by patient

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS							
	...							
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

(*) Any grade

Table 12.2.2.11 Treatment-related SAEs. Worst grade by cycle

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS							
	...							
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

* Any grade

Table 12.2.2.12 SAEs regardless of relationship. Worst grade by patient

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS							
	...							
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

(*) Any grade

Table 12.2.2.13 SAEs regardless of relationship. Worst grade by cycle

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 12.2.2.6 Treatment-related grade 3-4 AEs. Worst grade per patient

Original Listing:

Patient id.	Cycle	SOC Name	Preferred term	Grade

Changed to:

Patient id.	~~***Cycle***~~	SOC Name	Preferred term	Grade

Listing 12.2.2.8 Adverse Events grade 3-4 regardless of relationship. Worst grade per patient

Original Listing:

Patient id.	Cycle	SOC Name	Preferred term	Grade

Changed to:

Patient id.	~~***Cycle***~~	SOC Name	Preferred term	Grade

Listing 12.3.1.1 SAEs

Original Listing:

Patient id.	Preferred term code	Adverse event reported (verbatim)	Status	Grade	Relationship	Onset date	Resolved date	Action	Serious criteria

Changed to:

Patient id.	Preferred term code	Adverse event reported (verbatim)	~~***Status***~~	Grade	Relationship	Onset date	Resolved date	Action	Serious criteria

Section 12.4.4 Laboratory Values Over Time

Tables:

12.4.4.11 Platelet count time course pattern (summary)
12.4.4.12 Platelet count time course pattern (freqs)
12.4.4.13 Neutrophil count time course pattern (summary)
12.4.4.14 Neutrophil count time course pattern (freqs)
12.4.4.15 AST time course pattern (summary)
12.4.4.16 AST time course pattern (freqs)
12.4.4.17 ALT time course pattern (summary)

Original table headers:

	Dose received			Total
	7 mg FD	6 mg FD	5 mg FD	

Changed to:

	Dose received			Total
	7 mg FD ***/ 3.5 mg/m^2***	6 mg FD ***/ 2.6 mg/m^2***	5 mg FD***/ 2.0 mg/m^2***	

Table added:

Table 11.4.4.18 ALT time course pattern (freqs)

	Dose received						*Total*	
	7 mg FD / 3.5 mg/m²		*6 mg FD / 2.6 mg/m²*		*5 mg FD/ 2.0 mg/m²*			
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Baseline grade 0								
1st cycle								
Onset day grade 3/4								
≤ 7								
8-14								
≥ 15								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 3/4								
≤ 7								
8-14								
≥ 15								
...								
Total								
Onset day grade 3/4								
≤ 7								
8-14								
≥ 15								
...								
Baseline grade 1, 2								
...								
Total								
1st cycle								
Onset day grade 3/4								
≤ 7								
8-14								
≥ 15								
...								
2nd cycle, 3rd cycle ….								
Onset day grade 3/4								
≤ 7								
8-14								
≥ 15								
...								
Total								
Onset day grade 3/4								
≤ 7								
8-14								
≥ 15								
Peak day grade 3/4								
≤ 7								
8-14								
≥ 15								
Recovery day to grade ≤ 2								
≤ 22								
23-28								
≥ 29								
Duration in days to grade 2								
≤ 5								
6-10								
≥ 11								
Recovery day to grade ≤ 1								
≤ 22								

	Dose received						*Total*	
	7 mg FD / 3.5 mg/m²		*6 mg FD / 2.6 mg/m²*		*5 mg FD/ 2.0 mg/m²*			
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
23-28								
≥ 29								
Duration in days to grade 1								
≤ 5								
6-10								
≥ 11								

Listing 12.5.2.3 Troponin I and Troponin T values. Evolution during the study.

Original listing:

Patient id.	Cycle	Value	ULN

Changed to:

Patient id.	Cycle	***Test***	Value	ULN

Table 12.6.1 Concomitant medication during treatment (ATC1, ATC2 and ATC4 levels)

Original table:

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		
…		

Changed to:

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 12.6.2 Summary of concomitant medication during treatment

Original table:

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

Changed to:

	N	%
No. of systems ~~***at BL***~~ (ATC1 level) 0 1 2 ≥ 3 Median (range)		
No. of indications ~~***at BL***~~ (ATC2 level) 0 1 2 ≥ 3 Median (range)		
No. of agent families ~~***at BL***~~ (ATC4 level) 0 1 2 ≥ 3 Median (range)		
No. of agents ~~***at BL***~~ (PN level) 0 1 2 ≥ 3 Median (range)		

Table 12.6.5 Transfurions and G-CSF by dose

Table added:

Table 12.6.5 Transfusions and G-CSF by dose

	7 mg FD		*3.5 mg/m²*		*Total*	
	N	*%*	*N*	*%*	*N*	*%*
Transfusions						
RBC						
Platelets						
G-CSF						

Rest of tables in this section has been renumbered.

Section 13 DB Listings

Original title:

Listing 13.1.1: Cover

Changed to:

Listing 13.1.1: Investigator comments

Added:

ICH Listings.

-Listing 16.2.1 Discontinued patients
-Listing 16.2.2 Protocol deviations
-Listing 16.2.3 Patients excluded from the efficacy analysis
-Listing 16.2.4 Demographic data
-Listing 16.2.5 Compliance and-or Drug Concentration Data
-Listing 16.2.6 Individual Efficacy Response data
-Listing 16.2.7 Adverse event listings
-Listing 16.2.8 Individual laboratory measurements