PM60184-A-003-14

Phase I Multicenter, Open-label, Clinical and Pharmacokinetic Study of PM060184 in Combination with Gemcitabine in Selected Patients with Advanced Solid Tumors

STATISTICAL ANALYSIS PLAN

Version	Date	Description
V1.0	23-Dec-2014	Version 1.0

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LIST OF ABBREVIATIONS

AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
aPTT	Activated Plasma Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under The Concentration vs. Time Curve
BSA	Body Surface Area
CL	Clearance
Cmax	Maximum Plasma Concentration
CR	Complete Response
d/D	Day(s)
DI	Dose Intensity
DL	Dose level
DLT	Dose-limiting Toxicity
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
e-CRF	Electronic Case Report Form
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
FUP	Follow-up
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GIST	Gastrointestinal Stromal Tumor
hCG	Human Chorionic Gonadotropin
ICH	International Conference on Harmonization
IEC	Independent Ethics Committees
IRB	Institutional Review Board
i.v.	Intravenous (intravenously)
LVEF	Left Ventricular Ejection Fraction
ml	Milliliter
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition Scan
NCA	Non-compartmental Analysis
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PhV	Pharmacovigilance
PK	Pharmacokinetic(s)
PR	Partial Response

PRE TT	Pre-treatment
PS	Performance Status
PT	Prothrombin Time
q3wk	Every Three Weeks
q4wk	Every Four Weeks
RD	Recommended Dose
RECIST	Response Evaluation Criteria In Solid Tumors
SAE(s)	Serious Adverse Event(s)
SD	Stable Disease
SUSAR/SUA	Suspected Unexpected Serious Adverse Reaction
TTP	Time To Progression
Uk	Unknown
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO	World Health Organization
wk/wks	Week/weeks
WMA	World Medical Association

1. INTRODUCTION

This document (Statistical Analysis Plan) explains in detail the statistical analyses that will be carried out for the PharmaMar PM60184-A-003-14 study.

The analyses described in this Statistical Analysis Plan are based upon and supplement those described in the Clinical Trial Protocol, version 1.0 (dated 28-Jul-2014).

2. STUDY OBJECTIVES

The Clinical Trial Protocol states the following:

2.1. Primary Objective

- To determine the maximum tolerated dose (MTD) and the recommended dose (RD) of PM060184 in combination with gemcitabine in selected patients with advanced solid tumors.

2.2. Secondary Objectives

- To characterize the safety profile and feasibility of this combination in this study population.
- To characterize the pharmacokinetics (PK) of this combination and to detect major drug-drug PK interactions.
- To obtain preliminary information on the clinical antitumor activity of this combination.

3. STUDY DESIGN

Prospective, open-label, dose-ranging, uncontrolled phase I study with escalating doses of PM060184 in combination with gemcitabine in selected patients with advanced solid tumors.

Following a classical 3+3 design, successive cohorts of patients will receive escalating doses of intravenous (i.v.) gemcitabine over 30 minutes, followed by i.v. PM060184 over 10 minutes on Day 1 and Day 8 every three weeks (q3wk), until the RD is reached. All evaluable patients within a dose level (DL) must be followed for at least one full cycle (i.e., three weeks) before dose escalation may proceed to the next DL.

The MTD will be the lowest DL explored during dose escalation at which more than one third of evaluable patients experienced a DLT during Cycle 1. The RD will be the highest DL explored at which less than one third of evaluable patients experienced a DLT during Cycle 1. Dose escalation will cease immediately once the MTD is reached. Intermediate DLs can be tested, if deemed appropriate upon the Sponsor's and Investigators' agreement.

At least nine evaluable patients will be treated in an expansion cohort at the RD in order to evaluate its tolerability and feasibility. The tumor type(s) and/or target subpopulations to be included once the RD has been defined will be chosen according to the preliminary efficacy observed among patients treated during dose escalation, and will be discussed and agreed between the Investigators and the Sponsor, as appropriate.

4. SAMPLE SIZE AND DOSE ESCALATION

4.1. Sample size

The number of patients may vary depending both on the tolerability of PM060184 combined with gemcitabine and the number of dose levels required to identify the MTD. Approximately between six and 36 evaluable patients are planned to be included in this study.

4.2. Dose escalation schedule

The starting dose (DL1) for gemcitabine will be 800 mg/m^2. This corresponds to a dose intensity (DI) of 533.33 mg/m^2/week, and is equivalent to 80% of the RD with this schedule. This is the minimal gemcitabine dose accepted in clinical practice.

The DL1 for PM060184 will be 6.0 mg/m^2. This corresponds to a DI of 4.0 mg/m^2/week, and is equivalent to 64% of the RD determined for PM060184 given as single agent with this schedule.

The dose escalation scheme will follow pre-defined dose levels, starting at DL1, as summarized in the following table:

DL	No. of patients	Relative DI (%) of gemcitabine / PM060184	Gemcitabine dose (mg/m^2) on Day 1 and Day 8 q3wk	PM060184 dose (mg/m^2) on Day 1 and Day 8 q3wk
DL-1	0-6	80/53	800	**5.0**
DL1	3-6	80/64	800	**6.0**
DL2	3-6	80/74	800	**7.0**
DL3	3-6	100/74	1000	**7.0**
DL4 and beyond	3-6		No further dose increases beyond 1000 mg/m^2	**Further dose increases of 0.5 or 1.0 mg/m^2, according to observed toxicities**
DI, dose intensity; DL, dose level; MTD, maximum tolerated dose.				

- Cohorts of at least three fully evaluable patients will be treated at each cohort.
- The second and third patients of a cohort may be included simultaneously after the first patient has completed the first cycle, except if a DLT is reported in the first patient, in which case the third patient of the cohort will be included once the second patient has received a complete treatment cycle with no reported DLTs. All patients will have to be fully evaluable (3-week period) prior to any further dose escalation. Patients not fully evaluable will be replaced.
- Dose escalation will continue if no DLT is observed.
- Subsequent dose levels will enroll three patients, and up to six fully evaluable patients if one DLT is observed in any of the first three fully evaluable patients.
- Once a DLT is observed, further patients will be included up to **six** fully evaluable patients in this dose cohort.

No. of patients evaluable for DLT	No. of patients with DLTs in Cycle 1	Action
3	0	Escalate DL
	1	Add 3 patients
	>1	MTD
6	1	Escalate DL
	>1	MTD
DL, dose level; DLT, dose-limiting toxicities; MTD, maximum tolerated dose.		

- **For gemcitabine**: two doses (800 mg/m^2 and 1000 mg/m^2) will be initially tested. If the toxicity observed during dose escalation is clearly related to gemcitabine (i.e. neutropenia and/or thrombocytopenia), intermediate gemcitabine doses might be tested after agreement between the Investigators and the Sponsor.

- **For PM060184:** pre-established PM060184 doses have been set for the first three DLs. After DL3, dose increments of 1.0 mg/m^2 will be tested if toxicity at each previous DL is acceptable. These dose increments may be of 0.5 mg/m^2, according to the toxicity observed. In the event of toxicities specifically related with PM060184 (i.e. peripheral neuropathy, post-infusion abdominal pain and/or diarrhea), intermediate PM060184 doses might be tested after agreement between the Investigators and the Sponsor.

Both the PM060184 and the gemcitabine doses may be rounded to the first decimal.

If more than one of three or six evaluable patients at any DL experience a DLT during Cycle 1, dose escalation will be terminated. The MTD will be the lowest level at which more than one third of evaluable patients experienced a DLT in Cycle 1. The RD will be the highest DL explored with less than one third of evaluable patients experiencing a DLT during Cycle 1.

If two or more evaluable patients (of 3-6 patients) at any DL experience a dose delay > 7 (+1) days from the theoretical due date (conforming or not to DLT criteria) and/or dose omissions exclusively related to PM060184 toxicity during Cycle 1, the cohort should be expanded as shown in the table below. If more than 50% of evaluable patients in a cohort experience dose delays and/or omissions, dose escalation will be terminated and this DL will be considered the MTD. An alternative schedule could then be explored after discussion between the Investigators and with the Sponsor's agreement. The starting dose of the new schedule will be the DL immediately below the MTD.

Dose delays	**Dose omissions**	Action
1	-	None
-	1	None
1	1	Add 3 more patients
≥ 2	-	Add 3 more patients
-	≥ 2	Add 3 more patients
If more than 50% evaluable patients in a cohort have dose delays and/or omissions		MTD
DLT, dose-limiting toxicities; MTD, maximum tolerated dose.		

An expansion cohort of a minimum of nine evaluable patients will be treated at the RD once it has been determined; this is to confirm its feasibility and tolerability. The tumor type(s) and/or target subpopulations that will be eligible to be included in this expansion cohort will be chosen according to the preliminary efficacy observed among those previously treated during dose escalation, and will be discussed and agreed between the Investigators and the Sponsor.

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

5. POPULATION AND ENDPOINTS

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

5.1. Patient evaluability criteria

Analysis sets definitions:

"All Included Patients": it is defined as all patients who are included in the trial, independently of whether they have received the study drugs or not, excluding screen failure patients (Potential patient who did not meet one or more criteria at screening that was required for participation in the study).

All Evaluable Patients for the Assessment of the Primary Endpoint": A patient evaluable for the primary endpoint should have received at least one complete cycle (including the observation period). Patients who are discontinued early or miss/delay doses and/or assessments will be evaluable if these events are the consequence of treatment-related toxicity (excluding hypersensitivity reactions and/or extravasations).

"All Treated Patients (safety)":it is defined as all included patients who have received at least part of one infusion of PM060184/Gemcitabine.

"All Evaluable for Efficacy Patients": although it is not the main objective of this study, antitumor activity will be evaluated according to the RECIST v.1.1 in all patients with measurable disease, according to Choi criteria and/or EORTC metabolic response criteria for solid tumors in GIST patients, or by evaluation of serum tumor markers if applicable (e.g., ovarian cancer) every two cycles (i.e., approximately every six weeks) ± one week after treatment initiation until Cycle 4. Patients continuing treatment after Cycle 4 will have the assessments performed every three cycles (i.e., approximately every nine weeks) ± one week from Cycle 4 while on treatment, unless otherwise is clinically indicated. Patients included in the expansion cohort at the RD must be evaluable as per RECIST v.1.1 (or Choi criteria and/or EORTC metabolic response criteria for solid tumors, in the case of GIST), or by tumor markers

All analyses will be based on the actual treatment received by each patient rather than by the intended treatment. Any departures from the planned treatment according to the study schedule will be listed and documented in the clinical study report.

5.2. Replacement of patients

Patients must be replaced if they are not evaluable for the assessment of the primary endpoint, i.e. if:

- They are withdrawn from the study before receiving at least one evaluable cycle for any reason other than treatment-related toxicity (excluding hypersensitivity and/or extravasations reactions). An evaluable cycle is defined as: gemcitabine followed by PM060184 on Day 1 and Day 8, with the corresponding 2-week observation period during the first cycle.
- They require RT or other therapeutic procedure within three weeks after the first study drug dose, unless they previously had another treatment-related AE included in the definition of DLT.

- There is a protocol violation resulting in an impossibility of concluding anything regarding the safety of the study therapy.

All replaced patients will be included in the general safety analysis and in the efficacy analysis (if appropriate).

5.3. Endpoints

5.3.1. Primary endpoint

5.3.1.1. Determination of MTD and RD

The MTD will be the lowest DL explored during dose escalation at which more than one third of evaluable patients experienced a DLT during Cycle 1.

The RD will be the highest DL explored at which less than one third of evaluable patients experience a DLT during Cycle 1. This RD will be confirmed if less than one third of the first nine evaluable patients treated during expansion have DLTs during their Cycle 1.

A patient evaluable for the primary endpoint should have received at least one complete cycle (including the observation period). Patients who are discontinued early or miss/delay doses and/or assessments will be evaluable if these events are the consequence of treatment-related toxicity (excluding hypersensitivity reactions and/or extravasations).

5.3.1.2. DLT criteria

DLTs are defined as AEs and laboratory abnormalities related to the study treatment that occurred during Cycle 1 and fulfilled at least one of the following criteria:

- Grade 4 neutropenia (ANC $< 0.5 \times 10^9$/l) lasting > 3 days.
- Grade ≥ 3 febrile neutropenia of any duration or neutropenic sepsis.
- Grade 4 thrombocytopenia (platelet count $< 25 \times 10^9$/l) or grade 3 with any major bleeding episode requiring a platelet transfusion.
- Grade 4 ALT and/or AST increase, or grade 3 lasting > 7 days.
- Treatment-related grade ≥ 2 ALT or AST increase concomitantly with ≥ 2 x ULN total bilirubin increase and normal AP.
- Any other grade 3/4 non-hematological AE that is suspected to be related to study drug(s), except nausea/vomiting (unless the patient is receiving an optimal anti-emetic regimen), hypersensitivity reactions, extravasations, grade 3 asthenia lasting less than one week, anorexia, and non-clinically relevant isolated biochemical abnormalities [e.g., isolated increase in gamma-glutamyltransferase (GGT)]. In any case, the clinical relevance should be discussed between the Investigators and the Sponsor's representatives.

- Delay in the administration of Cycle 2 of the combination exceeding seven (+1) days of the treatment due date (i.e., Day 22), due to any AEs related to study drug(s).

The following circumstances will be discussed between the Principal Investigator and the Sponsor, and the final consensus will be documented:

- ✓ DLTs with delayed onset (i.e., that occur after Cycle 1).
- ✓ Non-compliance with the intended dose intensity (DI) in more than half of patients at any dose level (i.e., missing infusions on Day 8 or frequent dose delays due to treatment-related toxicity despite not conforming to a formal DLT definition).

5.3.2. Secondary endpoints

- **Safety:** patients will be evaluable for safety if they have received at least one partial or complete infusion of PM060184 and one partial or complete infusion of gemcitabine. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4.

- **Pharmacokinetics:** PK analyses will be evaluated in plasma by standard non-compartmental analysis (NCA) (compartmental modeling may be performed if appropriate).

- **Pharmacogenetics:** a blood sample will be collected to evaluate the presence or absence of known polymorphisms that may explain individual variability in main PK parameters.

- **Efficacy:** although it is not the main objective of this study, antitumor activity will be evaluated according to RECIST v.1.1 in all patients with measurable disease, according to Choi criteria and/or EORTC metabolic response criteria for solid tumors, in GIST patients, or by evaluation of serum tumor markers if applicable (e.g., ovarian cancer), every two cycles (i.e., approximately every six weeks) ± one week after treatment initiation until Cycle 4. Patients continuing treatment after Cycle 4 will have the assessments performed every three cycles (i.e., approximately every nine weeks) ± one week from Cycle 4 while on treatment, unless otherwise is clinically indicated. Patients included in the expansion cohort at the RD must be evaluable as per RECIST v.1.1 (or Choi criteria and/or EORTC metabolic response criteria for solid tumors, in GIST patients) or by tumor markers.

Safety endpoints include:

- Adverse events (AEs).
- Hematology.
- Clinical chemistry.
- Coagulation tests.
- Vital signs.

- ECG and LVEF.
- Physical examinations.

Efficacy endpoints include:

Best overall response: defined as the best response achieved during the study according to RECIST / GCIG (ovarian cancer) / Choi criteria and/or EORTC metabolic response criteria for solid tumors (GIST), before disease progression, administration of subsequent anticancer treatment or study discontinuation.

Response rate (RR): defined as the ratio of patients with any response (CR or PR) divided by the total number of patients included in the efficacy population. The number of patients with SD ≥ 4 months will also be shown.

Duration of overall response: calculated from the date of first documentation of response (CR or PR, whichever comes first) to the date of documented PD or death. The censoring rules defined for PFS will be used for duration of response.

Progression-free survival: calculated as the time from the date of first drug administration to the date of documented progression or death (regardless of the cause of death). If the patient receives further antitumor therapy or is lost to follow-up before PD, PFS will be censored at the date of last tumor assessment before the date of subsequent antitumor treatment.

In patients with disease evaluable by serum markers, tumor assessments will be obtained every two cycles (i.e., every six weeks) and tumor response will be evaluated by GCIG specific criteria in patients with ovarian cancer. (see details in study protocol, Appendices 3 and 6).

6. GENERAL ANALYSIS METHODS

6.1. Statistical software

Medidata Rave® electronic data capture (EDC) will be used for data entry and clinical data management. SAS® Software v9.2 (or above) will be used for all statistical analyses.

7. STATISTICAL ANALYSIS

7.1. Patient disposition and protocol deviations

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

- All included patients.
- All treated patients.
- All patients evaluable for the primary endpoint.
- All patients evaluable for efficacy.

Reasons for not belonging to any of these populations will be detailed.

The accrual and study discontinuation details will be presented descriptively.

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

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

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

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

- Ineligible patients as per protocol.
- Patients not withdrawn as per protocol.
- Excluded concomitant medications.
- Incorrect dose or schedule, including patients not meeting re-treatment criteria on Day 1 and 8 of subsequent cycles.
- Failure to comply with study procedures.

7.2. Baseline characteristics

7.2.1. Demographics

Demographics and baseline characteristics will be summarized for all patients. All subject characteristics descriptions will be performed by dose level (or most adequate dose grouping).

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

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

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

Baseline 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 will be calculated based on the date of birth and the date of informed consent. Age categories and race will be summarized with frequency counts.

$$Age = \frac{(\text{date of informed consent}) - (\text{date of birth})}{365.25}$$

Baseline body mass index (BMI) will be calculated, using the formula:

$$BMI = \frac{weight(kg)}{height(m)^2}$$

Baseline ECOG will be summarized with frequency counts.

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

Primary tumor sites and baseline lesions will be recoded by the Sponsor's physicians to categorize them accurately in the analysis.

Previous relevant medical history (other than cancer) will be listed by dose level (or most adequate dose grouping) and patient.

A frequency tabulation of the different types of previous cancer surgery, radiotherapy, or anticancer systemic therapy (number of lines and number of agents) will be given. Chemotherapy agents and lines will be recoded by the Sponsor's physicians to categorize them accurately in the analysis.

Signs and symptoms, hematology and serum biochemistry abnormalities at baseline will be displayed by tabulation of frequencies according to NCI-CTCAE v4.03 toxicity grades. Signs and symptoms and laboratory abnormalities of grade ≥2 at baseline will be listed by dose level (or most adequate dose grouping) and patient.

7.3. Statistical analysis for safety

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

The safety population consists of all patients who receive at least part of a PM060184/Gemcitabine infusion. The safety patient population will be used for the general safety presentations.

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

7.3.1. Treatment administration

Exposure to treatment will be described by dose level for all patients who have received at least one of the study drugs.

Total cumulative dose, expressed in mg /m², is the sum of all the product doses from Cycle 1 until the dose received in the last cycle.

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

Absolute dose intensity is the total cumulative dose divided by the duration of the treatment. As a convention, the duration of the last cycle is considered to be 21 days (planed cycle duration) even if the patient dies or receives another anticancer therapy before the end of the cycle.

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

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

The number of cases, median, standard deviations, minimum and maximum values for the parameters defined above will be tabulated by dose level (or most adequate dose grouping).

7.3.1. Cycle delays

The item "Infusion skipped/delayed: No/Yes" in the E-CRF will be used to calculate the delay. For doses considered as delayed by the Investigator, the delay will be calculated as:

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

The first cycle is excluded from all calculation of cycle delay (and the denominator used for calculations will be equal to the number of cycles susceptible to be delayed).

A second analysis taking into account the drug administration dates rather than the item “dose delay” completed by the Investigator will be performed in order to know the calculated delay in days.

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

7.3.1. Dose omissions

Infusions not administered on Day 8 of a cycle will be considered skipped doses.

The distribution of omissions will be studied by means of counts and percentages. The reasons for infusion omission will be detailed, specifying how many were due to treatment and how many were not. Within omissions attributable to treatment, hematological and non-hematological reasons will be outlined, and the specific reasons will be detailed.

7.3.2. Dose modifications

All dose reductions will be considered and described (per cycle and patient), specifying the magnitude and the reason for reduction (hematological toxicity, non-hematological toxicity or other causes not due to treatment).

7.3.1. Adverse events

Toxicity will be evaluated according to the NCI-CTCAE v4.03 and the events will be coded and classified using the MedDRA dictionary.

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

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

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

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

Additional safety analyses may be determined at any time, in order to most clearly enumerate rates of toxicities and to further define the safety profile of PM060184. In order to categorize accurately the safety information, additional classifications other than SOC/PT could be populated in order to understand better the safety drug profile.

7.3.1. Serious adverse event (SAE)

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

7.3.1. Laboratory evaluations

7.3.1.1. Hematology

Hematological toxicities classified according to the NCI-CTCAE v4.03 will be calculated in all cycles by dose level (or most adequate dose grouping). Separate analyses will be carried out for Cycle 1. The worst grade reached by each patient during treatment and Cycle 1 will also be calculated.

If serious toxicities occur, special follow-up including calculation of median and range of nadir values and median time to recover to baseline values and descriptive tables will be made to find out the pattern of thrombocytopenia and neutropenia within and between the different cycles.

If appropriate, these tables might be complemented with boxplots for the nadir of neutrophils and platelets count by cycle along the treatment by dose level (or most adequate dose grouping). Furthermore, graphs of the inter-cycle time course of neutropenia, thrombocytopenia or any other considered parameter will be provided. Eventually, graphs comparing the time course during the first and second cycles will be created.

7.3.1.2. Serum biochemistry and coagulation tests

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

If serious toxicities occur, special follow-up including calculation of median and range of peak values and median time to recover to baseline values and descriptive tables will be made to find out the pattern of the involved toxicities within and between the different cycles.

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

7.3.1. Physical examination

The results of the physical examination (normal/abnormal) will be summarized with frequency counts. All data will be listed by dose level.

7.3.2. ECG / LVEF

The results of the baseline ECG evaluation (normal/abnormal) will be summarized with frequency counts.

Continuous variables (PR Interval, QT Interval, QRS Complex, Ventricular Rate, QTc (Fridericia's), LVEF and LVEF Normal Range) will be summarized and presented with summary statistics, i.e., mean, standard deviation, median and range. Tabulation of baseline values and evolution during treatment will be presented with summary statistics.

$$QTcF = \frac{QT}{\sqrt[3]{\frac{60}{HR}}}$$

HR = Heart Rate

QTc (Fridericia's) will be graded using NCI-CTCAE v4.03.

7.3.3. Vital signs

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

7.3.4. Concomitant medication

Concomitant therapies will be coded using WHO-ATC dictionary and categorized per ATC (levels 1, 2 and 4) class. The number of patients receiving each type of therapy will be tabulated in two separated tables: a frequency tabulation of the therapies that started before the study, and a frequency tabulation of those that started during the study. The accompanying listing will contain all concomitant therapies.

Additional listings for patients taking medications / therapies that were prohibited by protocol will be provided.

7.4. Statistical analysis for efficacy

7.4.1. Exploratory analysis of antitumor activity

Response rates as per RECIST v1.1 (and as per Choi criteria or EORTC metabolic response criteria for ovarian cancer and GIST patients, respectively) [percentage of patients with any response [PR, CR or the sum of both being the overall response rate (ORR)], percentage of patients with clinical benefit [i.e., patients with any response, or with stable disease (SD) ≥ 4 months], will be characterized using descriptive statistics (95% exact binomial confidence interval) and according to primary tumor type. Time-related parameters (e.g., PFS) will also be analyzed according to the Kaplan-Meier method, if appropriate. If any specific tumor type subset is adequately represented, exploratory subgroup analyses will be performed. The characteristics of the patients achieving an objective response or SD ≥ 4 months by RECIST v1.1 will be displayed.

7.4.2. Level of significance

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

7.5. Pharmacokinetics

Methods used and results will be provided in a separate document prepared by the Clinical Pharmacology department.

8. OTHER STATISTICAL ANALYSIS

8.1. Stratification and covariate analysis

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

8.2. Multivariate analysis

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

8.3. Subgroup analysis

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

8.4. Interim analysis

The patient's safety will be assessed on a regular basis prior to each dose escalation upon completion of a cohort. No formal interim analyses are planned.

8.5. Missing values management

Missing laboratory values will be subtracted from the tables.

8.5.1. Imputation of incomplete dates

Dates before randomization

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

Dates after end of treatment

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

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10. APPENDIX I. PATIENTS DISPOSITION

10.1. General characteristics

10.1.1. Patients treated, eligible and evaluable

Table 10.1.1. 1 Patient accrual by Institution and dose level

Institution	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
Institution 1					
Institution 2					
…..					
Total					

Note: Percentage is based on number of patients by dose level.

Table 10.1.1. 2 Disposition of patients

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

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

Table 10.1.1. 3 Time on treatment by dose level

Median and range of time on treatment (weeks)	DL 1	DL 2	DL 3	…..	Total
N					
Median (range)					
Mean (std)					

Table 10.1.1. 4 Number of patients evaluable for analysis

	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
All included patients					
Evaluable for DLT					
Evaluable for safety					
Evaluable for efficacy					

Table 10.1.1. 5 Number of patients evaluable for analysis

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

10.1.2. Treatment discontinuations

Table 10.1.2. 1 Treatment discontinuation by dose level

	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
Progressive disease					
Patient refusal					
Death					
Investigator's decision					
Treatment-related adverse event					
Non treatment-related adverse event					
Other					
Total					

Notes: Percentage is based on number of patients by dose level.

Table 10.1.2. 2 Treatment discontinuation details

Dose level	Patient No.	Last cycle infused	Treatment discontinuation reason	Details

Table 10.1.2. 3 Treatment discontinuation due to adverse events

Dose level	Patient No.	SOC / Group	PT / sub-group	Relationship	…

Table 10.1.2. 4 Reasons for treatment discontinuation other than progressive disease

Dose level	Patient No.	Last cycle infused	Off Study reason	Specify

Table 10.1.2. 5 Reasons for study discontinuation by dose level

	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
Study termination (clinical cut-off)					
Patient's follow-up completed					
Patient's refusal					
Death					
Never treated					
Lost to follow up					
Other					
Total					

Note: Percentage is based on number of patients by dose level.

10.1.3. Protocol deviations

Table 10.1.3. 1 Protocol deviations

Dose level	Patient No.	Protocol deviation type	Specify

10.2. Patient characteristics

10.2.1. Patient characteristics at baseline

Table 10.2.1. 1 Age at entry by dose level

	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
Age at entry					
18 - XX years					
XX-YY years					
. . .					
>= ZZ years					
Total					
Age median and range					
N					
Median (Range)					
Mean (std)					
Gender					
Male					
Female					
Total					

Notes: Percentage is based on number of patients by dose level.

Table 10.2.1. 2 Supportive listing: Baseline demographics characteristic

Dose level	Patient No.	Gender	Age at study entry (calculated)

10.2.2. Cancer history

Table 10.2.2. 1 Primary tumor by dose level

	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
Breast cancer					
Epithelial ovarian cancer					
Head and neck					
NSCLC					
Germ cell tumors					
Biliary tract adenocarcinoma					
UKPS					
Cervix carcinoma					
GIST					
Urothelial cancer					
Total					

Table 10.2.2. 2 Prior cancer history time differences

	DL 1	DL 2	DL 3	…..	Total
Time from diagnosis to first infusion (months)					
N					
Median (range)					
Mean (std)					
Time from last PD to first infusion (months)					
N					
Median (range)					
Mean (std)					
TTP of last prior therapy (months)					
N					
Median (range)					
Mean (std)					

Table 10.2.2. 3 Other cancer history characteristics

Note: According to each tumor type.

	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
Histology grade					
Well differentiated					
Moderately differentiated					
….					
Total					
Current stage					
Early					
Locally advanced					
Metastatic					
Total					
TNM					
T1N1M1					
—					
—					
Total					

10.2.3. Sites involved

Table 10.2.3. 1 Supporting listing: Evaluation method

	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
No. of sites					
1 site					
2 sites					
…..					
Total					
No. of sites					
N					
Median (range)					
Mean (std)					
Sites					
Lung					
Liver					
…..					
Bulky disease					
> 50 mm					
≤ 50 mm					
Total					

Table 10.2.3. 2 Supportive listing: Sites of disease (RECIST v1.1)

Dose level	Patient No.	Tumor assessment date	Type*	Method	Site	Longest diameter

(*) Target lesion / Non target lesion.

10.2.4. Previous treatment summary

Table 10.2.4. 1 Previous treatment summary by dose level

	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
Systemic therapy					
Surgery					
Radiotherapy					

Notes: Percentage is based on number of patients by dose level.

Table 10.2.4. 2 Previous surgery by dose level

	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
Previous surgery					
Yes					
No					
Total					

Notes: Percentage is based on number of patients by dose level.

Table 10.2.4. 3 Previous radiotherapy by dose level

	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
Previous radiotherapy					
Yes					
No					
Total					

Notes: Percentage is based on number of patients by dose level.

Table 10.2.4. 4 Agents of previous anticancer therapies (ATC 1 & 4) by dose level

	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
ATC level 1					
ATC level 2					
ATC level 4					
. . .					
ATC level 4					

Notes: Percentage is based on number of patients by dose level.

Table 10.2.4. 5 No. of lines/agent of prior anticancer therapies by dose level

	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
No. of lines					
1 line					
2 lines					
3 lines					
≥4 lines					
Total					
N					
Median (range)					
No. of agents					
0 agents					
1 agent					
2 agents					
3 agents					
≥4 agents					
Total					
N					
Median (range)					
Mean (std)					

Notes: Percentage is based on number of patients by dose level.

10.2.5. Physical examination, vital signs, electrocardiogram and other tests

Table 10.2.5. 1 Physical examination by dose level

	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
Physical examination					
Normal					
Abnormal					
Total					
Weight (kg)					
N					
Median (range)					
Height (cm)					
N					
Median (range)					
BSA (m^2 - calculated by Dubois & Dubois formula)					
N					
Median (range)					
BMI					
N					
Median (range)					

Notes: Percentage is based on number of patients by dose level.

Table 10.2.5. 2 ECOG performance status by dose level

PS (ECOG)	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
0					
1					
. . .					
Total					

Notes: Percentage is based on number of patients by dose level.

Table 10.2.5. 3 Supportive listing: Patients with PS ≥ 2

Dose level	Patient No.	Performance status (ECOG)

Table 10.2.5. 4 ECG by dose level

	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
ECG result					
Abnormal					
Normal					
Total					
PR interval					
N					
Median (range)					
Mean (std)					
QT interval					
N					
Median (range)					
Mean (std)					
Ventricular rate					
N					
Median (range)					
Mean (std)					
QTc interval					
N					
Median (range)					
Mean (std)					

Table 10.2.5. 5 LVEF by dose level

	DL 1	DL 2	DL 3	…..	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
LVEF result					
Normal					
Abnormal					
Total					
LVEF method					
ECHO					
MUGA					
Total					
LVEF value					
N					
Median (range)					
Mean (std)					

Table 10.2.5. 6 Vital signs by dose level

	DL 1	DL 2	DL 3	…..	Total
Pulse (beats / minute):					
N					
Median (range)					
Mean (std)					
Temperature (ºC):					
N					
Median (range)					
Mean (std)					
Blood pressure systolic (mmHg):					
N					
Median (range)					
Mean (std)					
Blood pressure diastolic (mmHg):					
N					
Median (range)					
Mean (std)					

10.2.6. Hematological evaluation at baseline

Table 10.2.6. 1 Hematological abnormalities by dose level

					DL n				
Event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1-2	Grade 3-4	Grade 1-4	N
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	
Anemia									
Leukopenia									
Neutropenia									
Lymphopenia									
Thrombocytopenia									

Notes: Percentage is based on number of patients by dose level.

Table 10.2.6. 2 Median and range for hematological parameters by dose level

Parameter	DL 1	DL 2	DL 3	…..	Total
Hemoglobin					
N					
Median (range)					
Mean (std)					
WBC:					
N					
Median (range)					
Mean (std)					
Lymphocytes					
N					
Median (range)					
Mean (std)					
XXXXX					
N					
Median (range)					
Mean (std)					

Table 10.2.6. 3 Supportive listing: Patients with grade ≥2 hematological abnormalities

Dose level	Patient No.	Lab. test	Cycle	Examination date	Std. value	NCI-CTCAE V4.03 grade

Table 10.2.6. 4 Supportive listing: Patients with missing grade for hematological abnormalities

Dose level	Patient No.	Lab. test	Cycle	Examination date	Std. value	NCI-CTCAE v4.03 grade

10.2.7. Biochemical evaluation at baseline

Table 10.2.7. 1 Biochemical abnormalities by dose level

	DL n								
Event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1-2	Grade 3-4	Grade 1-4	N
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	
AP increase									
ALT increase									
AST increase									
XXXXX									

Notes: Percentage is based on number of patients by dose level.

Table 10.2.7. 2 Median and range for biochemical parameters by dose level

Parameter	DL I	DL II	DL III	...	...	DL n	Total
AP							
N							
Median (range)							
Mean (std)							
ALT							
N							
Median (range)							
Mean (std)							
AST							
N							
Median (range)							
Mean (std)							
XXXXXXX							
N							
Median (range)							
Mean (std)							

Table 10.2.7. 3 Supportive listing: Patients with grade ≥2 biochemical abnormalities

Dose level	Patient No.	Lab. test	Cycle	Examination date	Std. value	xULN	NCI-CTCAE V4.03 grade

Table 10.2.7. 4 Supportive listing: Patients with missing grade for biochemical abnormalities

Dose level	Patient No.	Lab. test	Cycle	Examination date	Std. value	NCI-CTCAE V4.03 grade

10.2.8. Signs and symptoms at baseline

Table 10.2.8. 1 Signs and symptoms by dose level

MedDRA System Organ Class / Preferred Term	DL I		DL II		DL III		...		...		DL n		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%

Notes: Percentage is based on number of patients by dose level.

Table 10.2.8. 2 Listing of grade ≥2 and not disease-related signs and symptoms

Dose level	Patient No.	Literal	MedDRA Preferred Term	NCI-CTCAE V4.03 grade	Start date	Disease-related

Dose level	Patient No.	Literal	MedDRA Preferred Term	NCI-CTCAE V4.03 grade	Start date	Disease-related

Table 10.2.8. 3 Incidence of signs and symptoms by dose level

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

Notes: Percentage is based on number of patients by dose level.

10.2.9. Concomitant medication starting pre-study

Table 10.2.9. 1 Concomitant medication starting pre-study (ATC 1 and 4) by dose level

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

Notes: Percentage is based on number of patients by dose level.

Table 10.2.9. 2 Concomitant medication starting pre-study (Transfusions and/or EPO)

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

Notes: Percentage is based on number of patients by dose level

Table 10.2.9. 3 Supportive listing: Patients with transfusions and/or EPO (pre-study)

Dose level	Patient No.	Cycle	Type	Literal term	ATC 4	ATC 2	ATC 1	Route	Dose	Unit	Start date	End date	Reason for use

11. APPENDIX II. SAFETY EVALUATION

11.1. Extent of exposure

11.1.1. Cumulative Dose, Dose Intensity and Relative Dose Intensity: PM060184

Table 11.1.1. 1 No. of cycles administered (PM060184)

		Patients		Cycles	
Dose level	No. of cycles infused	No. of patients	No. of patients (accumulated)	No. of cycles	No. of cycles (accumulated)
I	1 cycle				
	2 cycles				
II	1 cycle				
	2 cycles				
III	1 cycle				
	2 cycles				
. . .	. . .				
	. . .				
N	1 cycle				
	2 cycles				
Total	1 cycle				
	2 cycles				
	3 cycles				
	. . .				
	N cycles				

Table 11.1.1. 2 No. of cycles administered by dose level (PM060184)

No. of cycles	DL I		DL II		DL III		. . .		. . .		DL n		Total	
administered per patient	N	%	N	%	N	%	N	%	N	%	N	%	N	%
1 cycle														
2 cycles														
3 cycles														
. . .														
N cycles														
N														
Median (range)														
Mean (std)														

Notes: Percentage is based on number of patients by dose level.

Table 11.1.1. 3 Cumulative dose, DI and RDI by dose level (PM060184)

	DL I	DL II	DL III	. . .	. . .	DL n	Total
Cumulative dose (mg/m²)							
N							
Median (range)							
Mean (std)							
Dose intensity (mg /m²/week)							
N							
Median (range)							
Mean (std)							
Relative dose intensity (%)							
N							
Median (range)							
Mean (std)							

Table 11.1.1. 4 Supportive listing: Patients with less than 60% of RDI (PM060184)

Dose level	Patient No.	Cycle	Date	Intended dose (mg /m²)	Total dose (mg)	Delay/Omission	Delay/Omission specify	Dose modification	Dose modification specify

11.1.2. Cumulative Dose, Dose Intensity and Relative Dose Intensity: Gemcitabine

Table 11.1.2. 1 No. of cycles administered (gemcitabine)

		Patients		Cycles	
Dose level	No. of cycles infused	No. of patients	No. of patients (accumulated)	No. of cycles	No. of cycles (accumulated)
I	1 cycle				
	2 cycles				
II	1 cycle				
	2 cycles				
III	1 cycle				
	2 cycles				
. . .	. . .				
	. . .				
N	1 cycle				
	2 cycles				
Total	1 cycle				
	2 cycles				
	3 cycles				
	. . .				
	N cycles				

Table 11.1.2. 2 No. of cycles administered by dose level (gemcitabine)

No. of cycles	DL I		DL II		DL III		. . .		. . .		DL n		Total	
administered per patient	N	%	N	%	N	%	N	%	N	%	N	%	N	%
1 cycle														
2 cycles														
3 cycles														
. . .														
N cycles														
N														
Median (range)														
Mean (std)														

Notes: Percentage is based on number of patients by dose level.

Table 11.1.2. 3 Cumulative dose, DI and RDI by dose level (gemcitabine)

	DL I	DL II	DL III	· · ·	· · ·	DL n	Total
Cumulative dose (mg/m²)							
N							
Median (range)							
Mean (std)							
Dose intensity (mg /m²/week)							
N							
Median (range)							
Mean (std)							
Relative dose intensity (%)							
N							
Median (range)							
Mean (std)							

Table 11.1.2. 4 Supportive listing: Patients with less than 60% of RDI (gemcitabine)

Dose level	Patient No.	Cycle	Date	Intended dose (mg /m²)	Total dose (mg)	Delay	Delay specify	Dose modification	Dose modification specify

11.1.3. Cycle Delays: PM060184

Note: "Dose Delayed: No/Yes" in the CRF will be used to calculate the delay. For cycles considered as delayed by the Investigator, the delay will be calculated as:

Delay = (Date of current drug administration) - (Date of previous drug administration) - theoretical cycle duration in days (21))

A second internal analysis taking into account the drug administration dates rather than the item "dose delay" completed by the Investigator will be performed in order to know the real delay occurred, in days.

Note: The distribution of delays according to the administered cycle will be studied by means of counts and percentages. The reason for cycle delay will be detailed, specifying how many delays were due to treatment and how many were not. Within delays attributable to the study drug, hematological and non-hematological reasons will be outlined and the exact reason will be stated (specific data listings will be provided).

Table 11.1.3. 1 Summary of dose delay by dose level (PM060184)

Dose delay	DL I	DL II	DL III	· · ·	Total
No. of patients					
No. of patients susceptible to be delayed					
No. of patients with delay (n,%)					
==> Hematological tox (n,%)					
==> Non-hematological tox (n,%)					
==> Both (n,%)					
==> Non drug-related (n,%)					
Patients with 1 cycle delayed (n,%)					
Patients with 2 cycles delayed (n,%)					
Patients with 3 cycles delayed (n,%)					
Patients with 4 cycles delayed (n,%)					
Summary statistics no. of cycles delayed					
No. of cycles					
No. of cycles susceptible to be delayed					
No. of cycles with delay (n,%)					
==> Hematological tox (n,%)					
==> Non-hematological tox (n,%)					
==> Both (n,%)					
==> Non drug-related (n,%)					

Notes: Percentage is based on number of patients by dose level.
* Drug-related.
** Non drug-related.

Table 11.1.3. 2 Supportive listing: Dose delays (PM060184)

Dose level	Patient No.	Cycle / Day	Date	Intended dose (mg /m²)	Total dose (mg)	Length of delay	Delay reason	Delay specify

Table 11.1.3. 3 Supportive listing: Dose delays excluding administrative reasons (PM060184)

Dose level	Patient No.	Cycle / Day	Date	Intended dose (mg /m²)	Total dose (mg)	Length of delay	Delay reason	Delay specify

(*) Excluding administrative reasons.

11.1.4.

Cycle Delays: Gemcitabine

Table 11.1.4. 1 Summary of dose delay by dose level (gemcitabine)

Dose delay	DL I	DL II	DL III	· · ·	Total
No. of patients					
No. of patients susceptible to be delayed					
No. of patients with delay (n,%)					
==> Hematological tox (n,%)					
==> Non-hematological tox (n,%)					
==> Both (n,%)					
==> Non drug-related (n,%)					
Patients with 1 cycle delayed (n,%)					
Patients with 2 cycles delayed (n,%)					
Patients with 3 cycles delayed (n,%)					
Patients with 4 cycles delayed (n,%)					
Summary statistics no. of cycles delayed					
No. of cycles					
No. of cycles susceptible to be delayed					
No. of cycles with delay (n,%)					
==> Hematological tox (n,%)					
==> Non-hematological tox (n,%)					
==> Both (n,%)					
==> Non drug-related (n,%)					

Notes: Percentage is based on number of patients by dose level.
* Drug-related.
** Non drug-related.

Table 11.1.4. 2 Supportive listing: Dose delays (gemcitabine)

Dose level	Patient No.	Cycle / Day	Date	Intended dose (mg /m²)	Total dose (mg /m²)	Length of delay	Delay reason	Delay specify

Table 11.1.4. 3 Supportive listing: Dose delays excluding administrative reasons (gemcitabine)

Dose level	Patient No.	Cycle / Day	Date	Intended dose (mg /m²)	Total dose (mg /m²)	Length of delay	Delay reason	Delay specify

(*) Excluding administrative reasons.

11.1.5. Dose Omission: PM060184

Table 11.1.5. 1 Summary of dose omission by dose level (PM060184)

Dose omission	DL I	DL II	DL III	· · ·	Total
No. of patients					
No. of patients susceptible to be omitted					
No. of patients with omission (n,%)					
==> Hematological tox (n,%)					
==> Non-hematological tox (n,%)					
==> Both (n,%)					
==> Non drug-related (n,%)					
Patients with 1 cycle omitted (n,%)					
Patients with 2 cycles omitted (n,%)					
…...					
Summary statistics no. of cycles omitted					
No. of cycles					
No. of cycles susceptible to be omitted					
No. of cycles with omission (n,%)					
==> Hematological tox (n,%)					
==> Non-hematological tox (n,%)					
==> Both (n,%)					
==> Non drug-related (n,%)					

Notes: Percentage is based on number of patients by dose level.
* Drug-related.
** Non drug-related.

Table 11.1.5. 2 Listing of dose omissions (PM060184)

Dose level	Patient No.	Cycle / Day	Infusion No.	Reason for omission	Specify

11.1.6. Dose Omission: Gemcitabine

Table 11.1.6. 1 Summary of dose omission by dose level (gemcitabine)

Dose omission	DL I	DL II	DL III	· · ·	Total
No. of patients					
No. of patients susceptible to be omitted					
No. of patients with omission (n,%)					
==> Hematological tox (n,%)					
==> Non-hematological tox (n,%)					
==> Both (n,%)					
==> Non drug-related (n,%)					
Patients with 1 cycle omitted (n,%)					
Patients with 2 cycles omitted (n,%)					
…..					
Summary statistics no. of cycles omitted					
No. of cycles					
No. of cycles susceptible to be omitted					
No. of cycles with omission (n,%)					
==> Hematological tox					
==> Non-hematological tox (n,%)					
==> Both (n,%)					
==> Non drug-related (n,%)					

Notes: Percentage is based on number of patients by dose level.
* Drug-related.
** Non drug-related.

Table 11.1.6. 2 Listing of dose omissions (gemcitabine)

Dose level	Patient No.	Cycle / Day	Infusion No	Reason for omission	Specify

11.1.7. Dose Modification: PM060184

All dose modifications will be considered and described, specifying the reason for change (hematological toxicity, non-hematological toxicity or other causes not due to the study drug) and the exact reason will be stated (specific data listings will be provided).

Table 11.1.7. 1 Summary of reduced cycles by dose level (PM060184)

Dose reduction	DL I	DL II	DL III	···	Total
No. of patients					
No. of patients susceptible to be reduced					
No. of patients with reduction (n,%)					
==> Hematological tox (n,%)					
==> Non-hematological tox (n,%)					
==> Both (n,%)					
==> Non drug-related (n,%)					
Patients with 1 cycle reduced (n,%)					
Patients with 2 cycles reduced (n,%)					
Summary statistics no. of cycles reduced					
No. of cycles					
No. of cycles susceptible to be reduced					
No. of cycles with reduction (n,%)					
==> Hematological tox (n,%)					
==> Non-hematological tox (n,%)					
==> Both (n,%)					
==> Non drug-related (n,%)					

Notes: Percentage is based on number of patients by dose level.

Table 11.1.7. 2 Listing of dose reductions (PM060184)

Dose level	Patient No.	Cycle / Day	Start date	Is infusion reduced?	Reduce reason	Specify

11.1.8. Dose Modification: Gemcitabine

All dose modifications will be considered and described, specifying the reason for change (hematological toxicity, non-hematological toxicity or other causes not due to the study drug) and the exact reason will be stated (specific data listings will be provided).

Table 11.1.8. 1 Summary of reduced cycles by dose level (gemcitabine)

Dose reduction	DL I	DL II	DL III	···	Total
No. of patients					
No. of patients susceptible to be reduced					
No. of patients with reduction (n,%)					
==> Hematological tox (n,%)					
==> Non-hematological tox (n,%)					
==> Both (n,%)					
==> Non drug-related (n,%)					
Patients with 1 cycle reduced (n,%)					
Patients with 2 cycles reduced (n,%)					
Summary statistics no. of cycles reduced					
No. of cycles					
No. of cycles susceptible to be reduced					
No. of cycles with reduction (n,%)					
==> Hematological tox (n,%)					
==> Non-hematological tox (n,%)					
==> Both (n,%)					
==> Non drug-related (n,%)					

Notes: Percentage is based on number of patients by dose level.

Table 11.1.8. 2 Listing of dose reductions (gemcitabine)

Dose level	Patient No.	Cycle / Day	Start date	Is infusion reduced?	Reduce reason	Specify

11.2. Dose-limiting toxicities (DLT)

11.2.1. Dose-limiting toxicities

Table 11.2.1. 1 Summary of patients with DLT by dose level

Dose level	Escalation factor	N	DLT

Note: Each row shows the number of patients of that dose level, the number of cases with defined DLTs of the N patients.

Table 11.2.1. 2 Details of DLT

Dose level	Patient No.	Cycle	DLT description	NCI-CTCAE V4.03 grade	Comments

11.3. Adverse events (AEs)

11.3.1. Display of adverse events

Table 11.3.1. 1 Drug-related (or relationship UK) AEs. Worst grade by patient

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

Table 11.3.1. 2 Drug-related (or relationship UK) AEs in the first cycle

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

Table 11.3.1. 3 Drug-related (or relationship UK) AEs. Worst grade per cycle

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

Table 11.3.1. 4 Drug related (or relationship UK) AEs in ≥10% of patients

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

Notes: Percentage is based on number of patients by dose level.

Table 11.3.1. 5 Drug related (or relationship UK) AEs in ≥10% of patients. Worst grade per cycle

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

Notes: Percentage is based on number of cycles by dose level.

Table 11.3.1. 6 AEs regardless of relationship. Worst grade by patient

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

Notes: Percentage is based on number of patients by dose level.

Table 11.3.1. 7 AEs regardless of relationship in the first cycle

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

Notes: Percentage is based on number of patients by dose level.

Table 11.3.1. 8 AEs regardless of relationship. Worst grade per cycle

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

Notes: Percentage is based on number of cycles by dose level.

Table 11.3.1. 9 AEs observed in ≥10% of cycles

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

Notes: Percentage is based on number of patients by dose level.

Table 11.3.1. 10 AEs observed in ≥10% of patients. Worst grade per cycle

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

Notes: Percentage is based on number of cycles by dose level.

Table 11.3.1. 11 Supportive listing: Drug-related (or relationship UK) grade 2-4 AEs

Dose level	Patient No.	Cycle	SOC	MedDRA Preferred Term	Literal term	NCI-CTCAE V4.03 grade	SAE (Y/N)	Onset date	Resolved date	Relationship to study drug	Action taken	Main consequence

Table 11.3.1. 12 Supportive listing: All AEs regardless of relationship

Dose level	Patient No.	Cycle	SOC	MedDRA Preferred Term	Literal term	NCI-CTCAE V4.03 grade	SAE (Y/N)	Onset date	Resolved date	Relationship to study drug	Action taken	Main consequence

11.4. Deaths and other serious adverse events

11.4.1. Deaths

Table 11.4.1. 1 Patients who died while on treatment

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

Note: Patient with Death reported as End of Treatment Reason.

Table 11.4.1. 2 Patients who died within 30 days of last drug administration

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

Table 11.4.1. 3 Listing of all deaths

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

11.4.2. Serious adverse events

Table 11.4.2. 1 Drug-related (or relationship UK) SAEs. Worst grade by patient

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

Table 11.4.2. 2 Drug-related (or relationship UK) SAEs in the first cycle

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

Table 11.4.2. 3 Drug-related (or relationship UK) SAEs. Worst grade per cycle

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

Table 11.4.2. 4 Drug related (or relationship UK) SAEs in ≥10% of patients

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

Notes: Percentage is based on number of patients by dose level.

Table 11.4.2. 5 Drug related (or relationship UK) SAEs in ≥10% of patients. Worst grade per cycle

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

Notes: Percentage is based on number of cycles by dose level.

Table 11.4.2. 6 SAEs regardless of relationship. Worst grade by patient

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

Notes: Percentage is based on number of patients by dose level.

Table 11.4.2. 7 SAEs regardless of relationship in the first cycle

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

Notes: Percentage is based on number of patients by dose level.

Table 11.4.2. 8 SAEs regardless of relationship. Worst grade per cycle

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

Notes: Percentage is based on number of cycles by dose level.

Table 11.4.2. 9 SAEs observed in ≥10% of cycles

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

Notes: Percentage is based on number of patients by dose level.

Table 11.4.2. 10 SAEs observed in ≥10% of patients. Worst grade per cycle

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

Notes: Percentage is based on number of cycles by dose level.

Table 11.4.2. 11 All SAEs

Dose level	Patient No.	Cycle	MedDRA System Organ Class	Preferred Term	NCI-CTCAE V4.03 grade	AE Status	AE relationship	AE consequences	SAE	Onset date	Resolved date

11.5. Clinical laboratory evaluation

11.5.1. Hematological abnormalities

Table 11.5.1. 1 Hematological abnormalities: Worst grade per patient

	DL n								
Event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1-2	Grade 3-4	Grade 1-4	N
Anemia									
Leukopenia									
Neutropenia									
Lymphopenia									
XXXXX									

Notes: Percentage is based on number of patients by dose level.

Table 11.5.1. 2 Hematological abnormalities: Worst grade per cycle

	DL n								
Event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1-2	Grade 3-4	Grade 1-4	N
Anemia									
Leukopenia									
Neutropenia									
Lymphopenia									
XXXXX									

Notes: Percentage is based on number of patients by dose level.

Table 11.5.1. 3 Supportive listing: Patients with grade ≥3 hematological abnormalities

Dose level	Patient No.	Lab. test	Cycle	Examination date	N	Std. value	Normal range	NCI-CTCAE V4.03 grade

Table 11.5.1. 4 Supportive listing: Patients with missing grade for hematological abnormalities

Dose level	Patient No.	Lab. test	Cycle	Examination date	N	Std. value	Normal range	NCI-CTCAE V4.03 grade

11.5.2. Biochemical abnormalities

Table 11.5.2. 1 Biochemical abnormalities: Worst grade per patient

Event	DL n Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1-2	Grade 3-4	Grade 1-4	N
AP increase									
ALT increase									
AST increase									
Amylase increase									
XXXXX									

Notes: Percentage is based on number of patients by dose level.

Table 11.5.2. 2 Biochemical abnormalities: Worst grade per cycle

Event	DL n Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1-2	Grade 3-4	Grade 1-4	N
AP increase									
ALT increase									
AST increase									
Amylase increase									
XXXXX									

Notes: Percentage is based on number of patients by dose level.

Table 11.5.2. 3 Supportive listing: Patients with grade ≥3 biochemical abnormalities

Dose level	Patient No.	Lab. test	Cycle	Examination date	N	Std. value	Value (xULN)	NCI-CTCAE V4.03 grade

Table 11.5.2. 4 Supportive listing: Patients with missing grade for biochemical abnormalities

Dose level	Patient No.	Lab. test	Cycle	Examination date	N	Std. value	Value (xULN)	NCI-CTCAE V4.03 grade

11.5.3. Laboratory Values over Time

Table 11.5.3. 1 Shift of hematological abnormalities. Baseline grade vs worst grade on treatment

			Worst grade on treatment							
		Baseline grade	Gr.1		Gr. 2		Gr. 3		Gr. 4	
			N	%	N	%	N	%	N	%
DL I	Anemia	0								
		…								
		4								
	Leukopenia	0								
		…								
		4								
	—	0								
		…								
		4								
…	Anemia	0								
		…								
		4								
	Leukopenia	0								
		…								
		4								
	—	0								
		…								
		4								
DL n	Anemia	0								
		…								
		4								
	Leukopenia	0								
		…								
		4								
	—	0								
		…								
		4								
All treated population	Anemia	0								
		…								
		4								
	Leukopenia	0								
		…								
		4								
	—	0								
		…								
		4								

Notes: Percentage is based on number of patients by dose level.

Table 11.5.3. 2 Shift of biochemical abnormalities. Baseline grade vs worst grade on treatment

			Worst grade on treatment							
		Baseline grade	Gr.1		Gr. 2		Gr. 3		Gr. 4	
			N	%	N	%	N	%	N	%
DL I	AP increase	0								
		…								
		4								
	ALT increase	0								
		…								
		4								
	…	0								
		…								
		4								
…	AP increase	0								
		…								
		4								
	ALT increase	0								
		…								
		4								
	…	0								
		…								
		4								
DL n	AP increase	0								
		…								
		4								
	ALT increase	0								
		…								
		4								
	…	0								
		…								
		4								
All Treated Population	AP increase	0								
		…								
		4								
	ALT increase	0								
		…								
		4								
	…	0								
		…								
		4								

Notes: Percentage is based on number of patients by dose level.

Table 11.5.3. 3 Worst severity of hematological abnormalities during the first and later cycles

Over time	Toxicity	DL I	DL II	DL III	...	...	DL n
Cycle 1	Anemia/…						
	Grade 1 - 4, n(%)						
	Grade 1						
	Grade 2						
	Grade 3						
	Grade 4						
Cycle >1	Anemia/…						
	Grade 1 - 4, n(%)						
	Grade 1						
	Grade 2						
	Grade 3						
	Grade 4						

Notes: Percentage is based on number of patients by dose level.

Table 11.5.3. 4 Worst severity of biochemical abnormalities during the first and later cycles

Over time	Toxicity	DL I	DL II	DL III	...	...	DL n
Cycle 1	AP increase/…						
	Grade 1 - 4, n(%)						
	Grade 1						
	Grade 2						
	Grade 3						
	Grade 4						
Cycle >1	AP increase/…						
	Grade 1 - 4, n(%)						
	Grade 1						
	Grade 2						
	Grade 3						
	Grade 4						

Notes: Percentage is based on number of patients by dose level.

Table 11.5.3. 5 Pattern of neutropenia/thrombocytopenia

Dose level (X)				Day of recovery to XX x ULN			Days to recovery		
Laboratory abnormalities NEU (N= XX) PLAT (N= XX)	Onset day grade 3/4	Day of recovery to grade 1	Days to recovery	<=21	22-28	>28	<=15	16-24	>=25

Table 11.5.3. 6 Pattern of hepatobiliary parameters

Dose level (X)				Day of recovery to XX x ULN			Days to recovery		
Laboratory abnormalities ALT (N= XX) AST (N= XX)	Onset day grade 3/4	Day of recovery to 3 x ULN	Days to recovery	<=21	22-28	>28	<=15	16-24	>=25

11.6. Other observation related to safety

11.6.1. Vital signs, physical findings and other observations related to safety

Table 11.6.1. 1 Performance status during the study by cycle and dose level

		Baseline	Cycle 1	Cycle 2	· · ·	Cycle N
Dose level	Patient No.	PS	PS	PS		PS
DL I (N = XX)						
DL II (N = XX)						
· · ·						
DL N (N = XX)						
				.		.

Table 11.6.1. 2 Physical examination during the study by cycle and dose level

		Baseline	Cycle 1	Cycle 2	· · ·	Cycle N
Dose level	Patient No.	Physical exam	Physical exam	Physical exam	Physical exam	Physical exam
DL I (N = XX)						
DL II (N = XX)						
· · ·						
DL N (N = XX)						
				.		.

Table 11.6.1. 3 Weight gain-loss during the study by dose level

Dose level	Patient No.	Weight at baseline (kg)	Cycle 1	Cycle 2	···	Cycle N
			% change	% change	% change	% change
DL I (N = XX)						
DL II (N = XX)						
···						
DL N (N = XX)						

Table 11.6.1. 4 Vital sign (pulse) during the study by cycle and dose level

Dose level	Patient No.	Baseline Pulse	Cycle 1 Pulse	Cycle 2 Pulse	··· Pulse	Cycle N Pulse
DL I (N = XX)						
DL II (N = XX)						
···						
DL N (N = XX)						

Table 11.6.1. 5 Vital sign (temperature) during the study by cycle and dose level

Dose level	Patient No.	Baseline Temperature	Cycle 1 Temperature	Cycle 2 Temperature	··· Temperature	Cycle N Temperature
DL I (N = XX)						
DL II (N = XX)						
···						
DL N (N = XX)						

Table 11.6.1. 6 Vital sign (BPS) during the study by cycle and dose level

		Baseline	Cycle 1	Cycle 2	· · ·	Cycle N
Dose level	Patient No.	BPS	BPS	BPS	BPS	BPS
DL I (N=XX)						
DL II (N=XX)						
· · ·						
DL N (N=XX)						
				.		.

Table 11.6.1. 7 Vital sign (BPD) during the study by cycle and dose level

		Baseline	Cycle 1	Cycle 2	· · ·	Cycle N
Dose level	Patient No.	BPD	BPD	BPD	BPD	BPD
DL I (N=XX)						
DL II (N=XX)						
· · ·						
DL N (N=XX)						
				.		.

Table 11.6.1. 8 ECG during the study by cycle and dose level

		Baseline	Cycle 1	Cycle 2	· · ·	Cycle N
Dose level	Patient No.	ECG	ECG	ECG	ECG	ECG
DL I (N=XX)						
DL II (N=XX)						
· · ·						
DL N (N=XX)						
				.		.

Table 11.6.1. 9 ECG (PRI) during the study by cycle and dose level

		Baseline	Cycle 1	Cycle 2	···	Cycle N
Dose level	Patient No.	PRI	PRI	PRI	PRI	PRI
DL I (N=XX)						
DL II (N=XX)						
···						
DL N (N=XX)						
				.		.

Table 11.6.1. 10 ECG (QTI) during the study by cycle and dose level

		Baseline	Cycle 1	Cycle 2	···	Cycle N
Dose level	Patient No.	QTI	QTI	QTI	QTI	QTI
DL I (N=XX)						
DL II (N=XX)						
···						
DL N (N=XX)						
				.		.

Table 11.6.1. 11 ECG (QTc) during the study by cycle and dose level

		Baseline	Cycle 1	Cycle 2	···	Cycle N
Dose level	Patient No.	QTc	QTc	QTc	QTc	QTc
DL I (N=XX)						
DL II (N=XX)						
···						
DL N (N=XX)						
				.		.

Table 11.6.1. 12 ECG (VR) during the study by cycle and dose level

		Baseline	Cycle 1	Cycle 2	· · ·	Cycle N
Dose level	Patient No.	VR	VR	VR	VR	VR
DL I (N = XX)						
DL II (N = XX)						
· · ·						
DL N (N = XX)						

11.7. Concomitant medication

11.7.1. Concomitant medication during study

Table 11.7.1. 1 Concomitant medication during study (ATC 1 and 4) by dose level

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

Notes: Percentage is based on number of patients by dose level.

Table 11.7.1. 2 Transfusions / EPO (Patients with transfusions and/or EPO)

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

Notes: Percentage is based on number of patients by dose level.

12. APPENDIX III. EFFICACY EVALUATION

12.1. Efficacy analysis

All efficacy tables and graphs will be split by type of evaluation criteria, if appropriate, and any group of interest will be adequately represented as shown in Table 12.1.1.1. Otherwise, listings with individual patient responses will be produced and additional details for patients responding or showing stabilizations ≥ 4 months will be provided.

12.1.1. Response

Table 12.1.1. 1 Overall response by dose level. Treated patients

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

Notes: Percentage is based on number of patients by dose level.
* Patients not qualifying for response or progression disease.

Table 12.1.1. 2 Overall response by dose level. Evaluable patients

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

Notes: Percentage is based on number of patients by dose level.

Table 12.1.1. 3 Tumor marker evolution during the study

			Baseline	Cycle 1	···		
Dose level	Patient No.	Tumor type/Tumor marker	Value	Value		Best change during treatment (%)	Time to best change during treatment
I							
···							
N							

Table 12.1.1. 4 Progression-free survival. Treated population

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

Table 12.1.1. 5 Progression-free survival. Evaluable population

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

Table 12.1.1. 6 Duration of response

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

Table 12.1.1. 7 Characteristics of patients with evidence of clinical benefit*

Dose level	Patient No.	Gender	Age	PS	Tumor type	No. of previous lines of CT	Agents (previous CT)	Best response previous CT	to TTP previous CT (months)	Cycles received PM060184	Overall response	PFS (months)	Reason for treatment discontinuation	Cause of death

(*) "Evidence of clinical benefit" is defined as response (CR, PR) or SD>4 months and/or no evidence of PD with decreasing tumor markers, if not evaluable per RECIST.

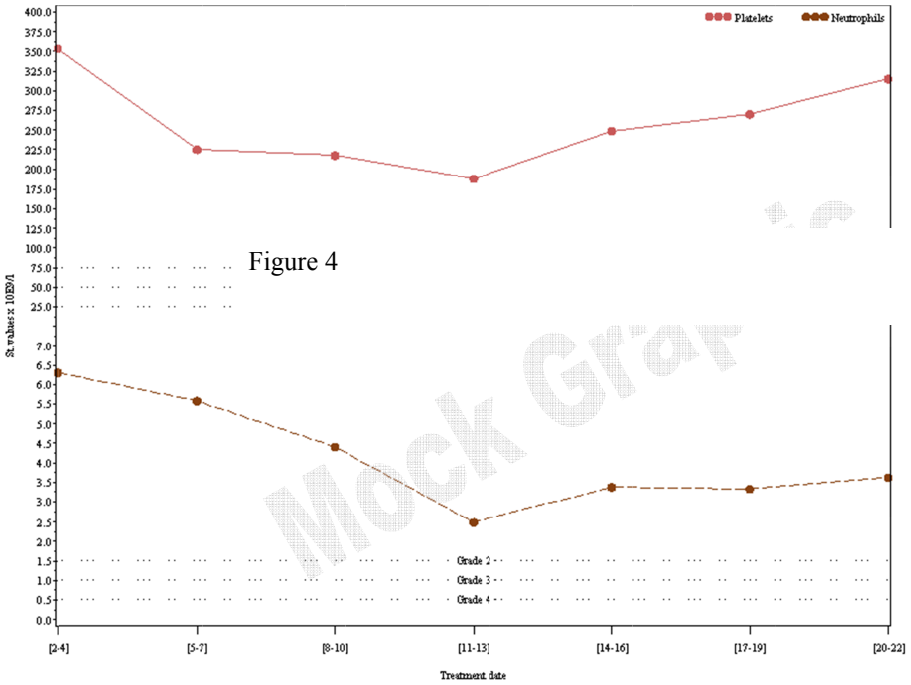
Table 12.1.1. 8 Supportive listing: efficacy dataset analyzed

Dose level	Patient No.	Tumor type	Evaluable	Evaluation criteria	Best response	Progression	Progression date	Death	Death date

13. FIGURES

13.1. Hematological profile

Figure 13.1. 1 Pattern of hematological/non-hematological DLTs in individual patients



13.2. Transaminase Profile

Figure 13.2. 1 Transaminase series. Patient XX

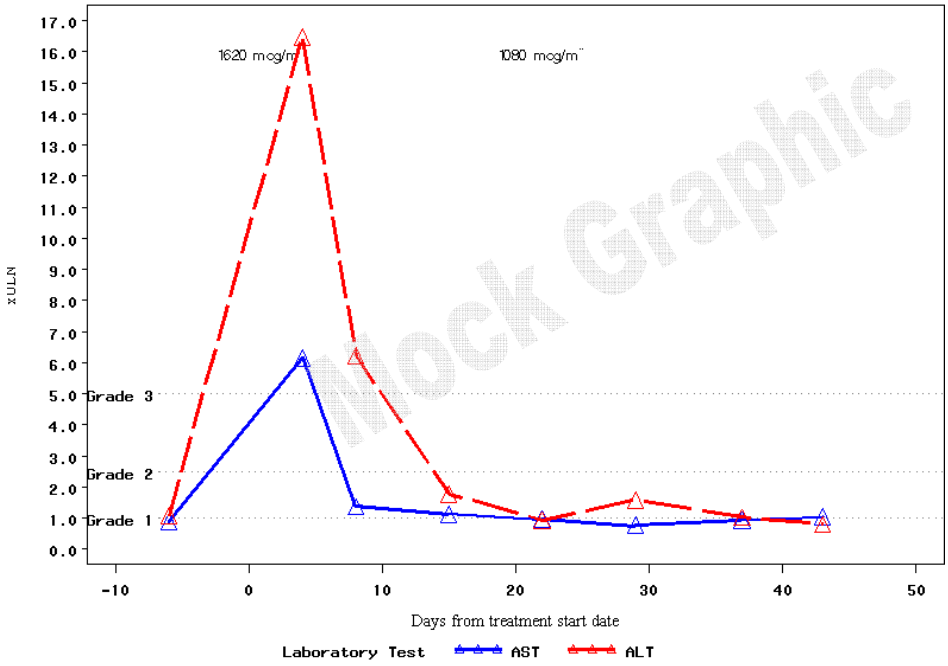


Figure 13.2. 2 Bar charts of hematological/biochemical laboratory abnormalities by dose level

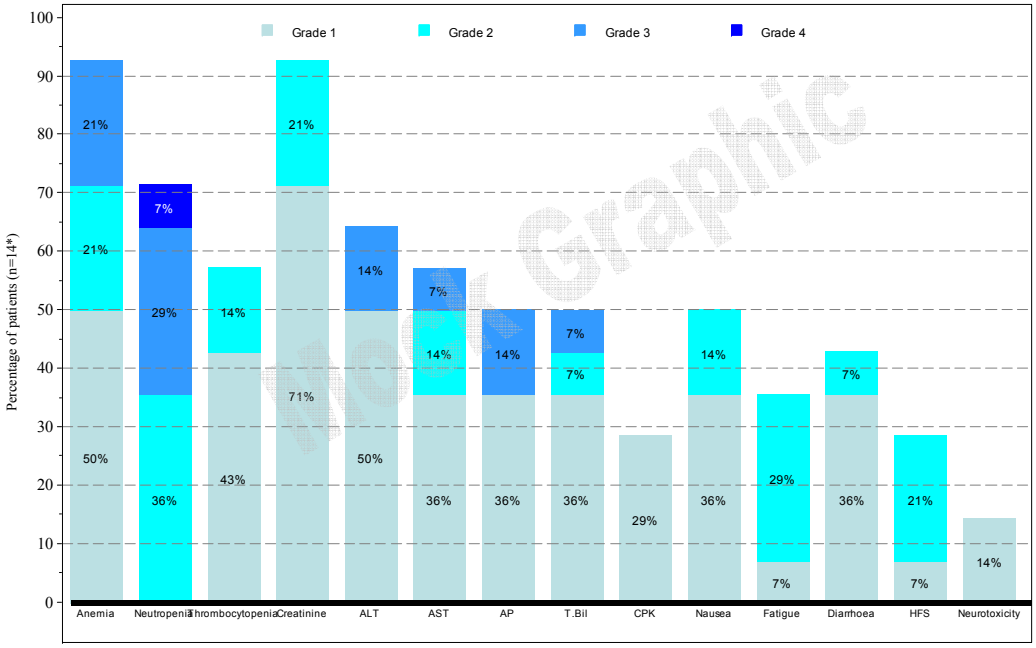
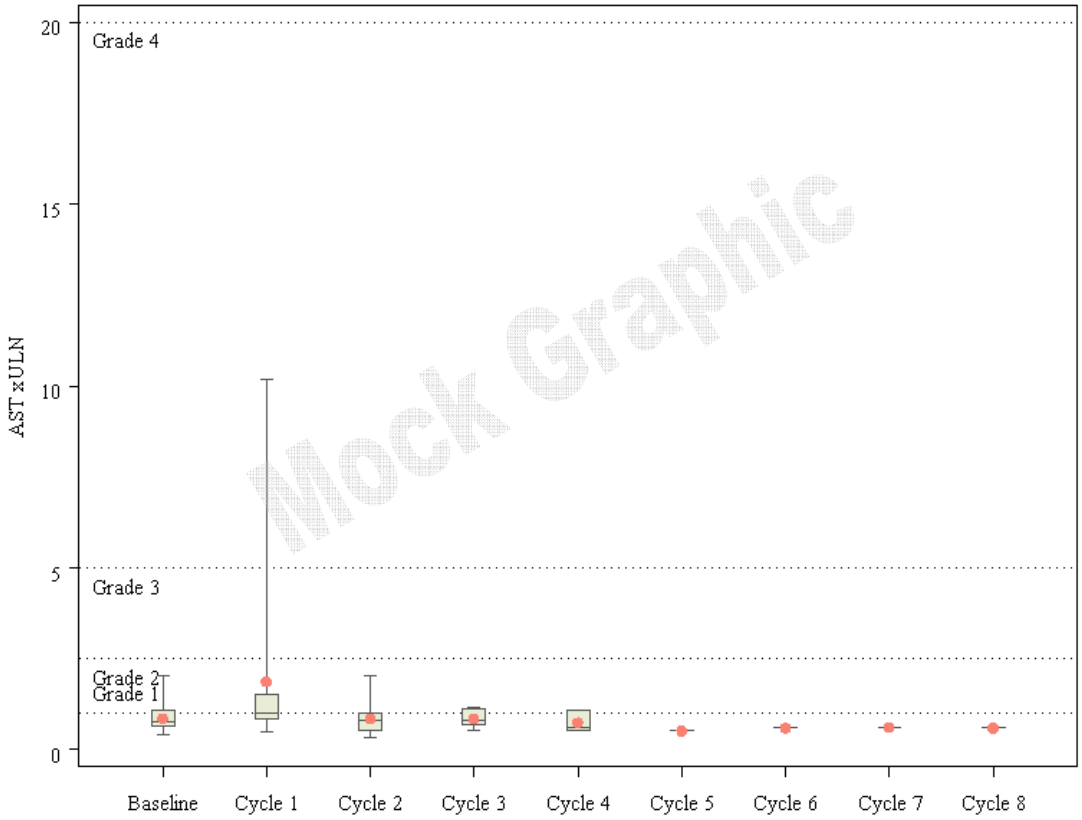
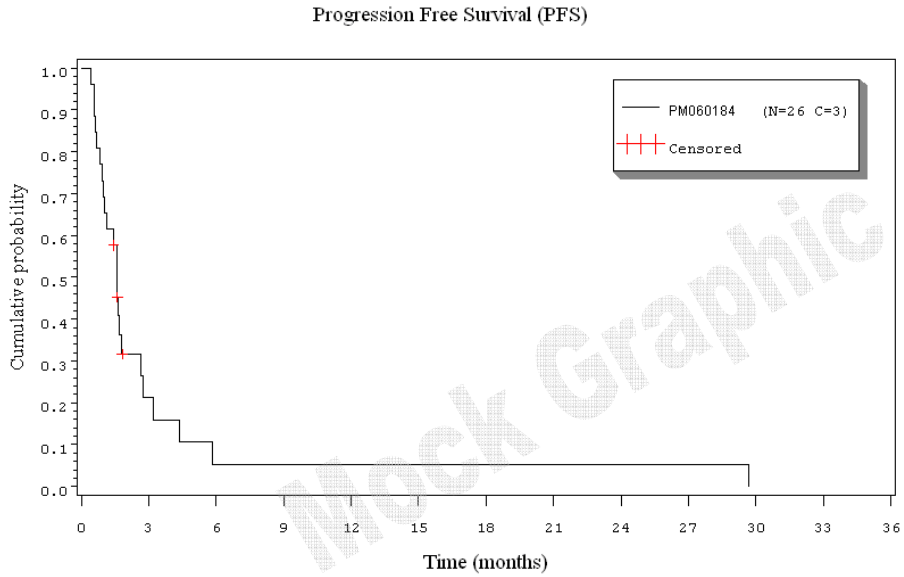


Figure 13.2. 3 Hematology / Transaminase. Worst severity by cycle



13.3. Time to event graphs

Figure 13.3. 1 Progression-free survival (PFS)



Median 1.6 95% CI (1.0-2.7)
PFS at 3 months 21.2% 95% CI (3.9%-38.4%)
PFS at 6 months 5.3% 95% CI (0%-15.3%)
PFS at 12 months 5.3% 95% CI (0%-15.3%)

14. DATABASE LISTINGS

Listing 14.1 Patient registration

Listing 14.2 Demography

Listing 14.3 Birth control and pregnancy test

Listing 14.4 Relevant prior history

Listing 14.5 Cancer history

Listing 14.6 Prior surgery

Listing 14.7 Prior radiotherapy

Listing 14.8 Prior anticancer therapy

Listing 14.9 Drug administration

Listing 14.10 End of treatment

Listing 14.11 Adverse events

Listing 14.12.1 Hematology

Listing 14.12.2 Serum biochemistry

Listing 14.12.3 Coagulogram

Listing 14.12.4 Other tests

Listing 14.13 Physical examination

Listing 14.14 Performance status (PS)

Listing 14.15 Vital signs

Listing 14.16 Electrocardiogram

Listing 14.17 Left ventricular ejection fraction (LVEF) results

Listing 14.18 Concomitant therapy

Listing 14.19 Tumor assessment

Listing 14.20 Tumor response cycles

Listing 14.21 Clinical response cycles

Listing 14.22 Best response

Listing 14.23 Summary efficacy

Listing 14.24 Follow-up status

Listing 14.25 Follow-up: Antitumor therapy

Listing 14.26 Death report

Listing 14.27 Off study

Listing 14.28 Signature report