PM60184-B-002-17

Phase II, Open-label, Multicenter Study of PM060184 in Patients with Advanced Colorectal Cancer after Standard Treatment

STATISTICAL ANALYSIS PLAN

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ABBREVIATIONS AND GLOSSARY

5-FU	5-fluorouracil
AE	Adverse Event
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical, Therapeutic, Chemical classification system
BSA	Body Surface Area
BSC	Best Supportive Care
CI	Confidence Interval
CIPN	Chemotherapy-induced Peripheral Neuropathy
CR	Complete Response
CRC	Colorectal Cancer
CRF	Case Report Form
d	Day
DOR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organisation for the Research and Treatment of Cancer
EOT	End of Treatment
FP	Fluoropyrimidine
GGT	Gamma-glutamyltransferase
IC	Informed Consent
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
MTI	Microtubule Inhibitor
MUGA	Multiple-gated Acquisition Scan
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOS	Not Otherwise Specified
OR	Objective Response
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PFS3	Progression-free Survival at 12 weeks (three months)

PGt	Pharmacogenetics
PGx	Pharmacogenomics
PK	Pharmacokinetics
PN	Peripheral Neuropathy
PR	Partial Response
PRO	Patient Reported Outcomes
PS	Performance Status
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
StD	Standard Deviation
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cells
WHO	World Health Organization

1. STUDY RATIONALE

Systemic 5-fluorouracil (5-FU)-based chemotherapy produces meaningful improvements in median survival and progression-free survival (PFS) compared with best supportive care (BSC) alone. These benefits are most pronounced with regimens containing irinotecan or oxaliplatin in combination with 5-FU, which represent the mainstay of advanced and metastatic colorectal cancer (CRC) chemotherapy.

Consequently, when patients with advanced or metastatic CRC have received prior FP (Fluoropyrimidine), irinotecan and oxaliplatin-based regimens (in addition to any ad hoc therapy targeting EGFR, and/or Vascular Endothelial Growth Factor (VEGF), according to tumor characteristics), clinical trials with investigational medicinal products (IMPs) are warranted.

PM060184 is a novel microtubule inhibitor (MTI), with a different, specific binding site on the β-tubulin, that is distinct from the vinca domain used by vinca alkaloids, as well as the taxane domain and binding site. PM060184 induces microtubule depolymerization and caspase-dependent, as well as non-classical apoptosis pathways. PM060184 has shown *in vitro* and *in vivo* antitumor activity at nanomolar concentrations in CRC. Thirteen evaluable CRC patients were treated with single-agent PM060184 to date and six (46%) had Stable Disease (SD) lasting three months or longer with a median PFS of 4.7 months (range, 3.7–12.8 months).

This trial will evaluate the efficacy of PM060184 in terms of progression-free survival at 12 weeks (PFS3) in advanced or metastatic CRC patients progressing after standard treatments (fluoropyrimidine, irinotecan, and oxaliplatin).

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

2. STUDY DESIGN

This is a phase II, multicenter, open-label, study of single-agent PM060184 to evaluate efficacy in patients with advanced CRC progressing after standard therapy.

Initially, 24 patients who are evaluable for the primary endpoint will be included and a futility analysis will be performed (first stage). If at least seven of these patients achieve PFS3, then the study will proceed to a second stage and 36 additional patients will be recruited.

An exploratory substudy will address pharmacogenomic and pharmacogenetic objectives. All patients who participate in the PM60184-B-002-17 clinical trial will be eligible for the substudy if they voluntarily sign a separate informed consent (IC). Refusal to participate in the substudy will not affect a patient's participation in the clinical trial.

3. OBJECTIVES AND ENDPOINTS

3.1. Primary Objective

- To evaluate the efficacy of PM060184 in terms of PFS3 in patients with advanced CRC after standard therapy.

3.2. Secondary Objectives

- To evaluate OS; PFS; overall response rate (ORR); and duration of response (DOR).
- To characterize the safety profile and feasibility of PM060184 in this population.
- To describe Peripheral Neuropathy (PN) and quality of life (QoL) profiles in this population using patient-reported outcomes (PRO) as measured by the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires (QLQ) for chemotherapy-induced peripheral neuropathy (QLQ-CIPN20) and general QoL (QLQ-C30).
- To characterize the Pharmacokinetics (PK) of PM060184 in this population.
- To characterize the metabolomics of PM060184, i.e. PM060184, i.e., systemic variations in the patient's pre- and post-treatment metabolic profile that allow the identification of potential biomarkers of PK, safety and/or efficacy response to PM060184.
- To characterize pharmacogenetics (PGt) of PM060184 in this population by identifying the presence or absence of germline mutations or polymorphisms that may help explain individual variability in the main PK parameters and safety outcomes.
- To characterize pharmacogenomics (PGx) of PM060184 in this population by analyzing the potential predictive factors (including BRAF-mutant-like gene expression subtypes) of sensitivity/resistance to PM060184 treatment.

3.3. Endpoints

Primary endpoint:

- Progression-free survival rate at twelve weeks, defined as the rate estimate of the percentage of patients who are alive and progression-free at 12 weeks (~3 months) after the first treatment administration.

Secondary endpoints:

- Overall Survival (OS), defined as the time from the first day of treatment to the date of death or last contact.
- Progression-free Survival (PFS), defined as the time from the first day of study treatment to the day of assessment of progression, death or last tumor evaluation.
- Overall Response Rate, defined as the percentage of patients with objective response (OR), either complete response (CR) or partial response (PR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1.
- Duration of Response, defined as the time between the date when response criteria (PR or CR, the first to be reached) are fulfilled and the first date when PD, recurrence or death is objectively documented.

- Treatment safety, including Adverse Events (AEs), Serious Adverse Events (SAEs), and laboratory abnormalities graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4. Dose reductions or delays required due to treatment-related AEs, and reasons for treatment discontinuations will also be analyzed.
- Profiles of peripheral neuropathy and quality of life as reported by patients using the EORTC QLQ-CIPN20 and QLQ-C30.
- Pharmacokinetics parameters will be evaluated in plasma by population PK modeling and/or standard non-compartmental analysis.
- Metabolomics of PM060184, i.e., intra- and inter-patient systemic variations in the patient's pre- and post-treatment metabolic profile.
- Pharmacogenetics of PM060184 will be evaluated to identify the presence or absence of germline mutations or polymorphisms that may help explain individual variability in the main PK parameters and safety outcomes.
- Pharmacogenomics of PM060184 will be evaluated to determine predictive/prognostic markers of response and/or resistance to PM060184 (including BRAF-mutant-like gene expression subtypes).

4. PATIENTS EVALUABILITY CRITERIA

Patients with relapsed, metastatic/locally advanced CRC with any KRAS-mutation status (wild-type, mutated, or status unknown), progressing after standard treatments (fluoropyrimidine, irinotecan, and oxaliplatin).

Patients must fulfill all the eligibility criteria to be eligible to participate in the study.

The study will include the following analysis population set definitions:

- "All Included Patients" analysis set is defined as all patients recorded in the database who have been included in the trial (excluding screening failures), 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 one (complete or incomplete) dose of the study drug.
- "All Evaluable Patients for Efficacy" analysis set is defined as all eligible patients who have at least one complete treatment cycle (or two PM060184 dose administrations over two cycles) and have, at least, one disease assessment at Week 6 and another one at Week 12. In addition, any patient who presents disease progression, symptomatic deterioration due to the disease or clinical progression, dies due to malignant disease, discontinues treatment due to unmanageable toxicity, or dies or discontinues treatment due to a treatment-related AE before evaluation of the response at Week 12 will also be considered evaluable for the primary endpoint and classified as a non-responder. Patients who have no disease assessment at Week 6 but remain on treatment and are assessed at Week 12 (or later, and with no evidence of disease progression) will be considered evaluable for efficacy. Patients who refuse further treatment before Week 12 due to reasons other than related AEs not considered unmanageable toxicity will be replaced.

- "All Responder Patients" analysis set is defined as all evaluable patients for efficacy who have had CR or PR as overall best response according to the RECIST v.1.1.
- "All Evaluable Quality of Life (QoL)" analysis set is defined as all patients who have fulfilled the EORTC-QLQ-C30 and EORTC-QLQ-CPIN20 questionnaires for at least two timepoints, one at baseline and at least one after the start of the therapy.

Patients must be replaced if they are considered not evaluable for efficacy for the primary endpoint (PFS3), i.e., if they are withdrawn from the study due to significant clinical deterioration of unknown reason, hypersensitivity reactions, unrelated AEs without any tumor assessments after the start of study treatment, if they refuse further treatment before Week 12 due to reasons other than related AEs not considered unmanageable toxicity, if they receive less than one complete treatment cycle (at least two PM060184 dose administrations over two cycles unless treatment discontinuation was due to unmanageable toxicity), or do not have the disease assessment at Week 12 (except in the cases outlined above).

4.1. Included Population

The "All included patients" analysis set will be used to show demographic and other baseline characteristics.

4.2. Efficacy Populations

The "All evaluable patients for efficacy" analysis set will be used for the primary endpoint analysis of PFS3 and secondary endpoint analyses of OS, PFS and ORR.

The secondary endpoint analysis of DOR will be based on the "All responder patients".

The "All evaluable QoL" set will be used for the secondary endpoint analysis of changes in patients QoL.

4.3. Safety Population

The safety analysis will be based on the "All treated patients" analysis set.

5. SAMPLE CONSIDERATIONS

5.1. Sample Size

The primary endpoint of this phase II study is PFS3. Patients will be treated with PM060184 to test the null hypothesis (H_0) that 30% or less patients are alive and free of progression at twelve weeks according to RECIST v.1.1 ($p \leq 0.30$) versus the alternative hypothesis (H_1) that 50% or more patients are alive and free of progression at 12 weeks according to the aforementioned criteria ($p \geq 0.50$). The variance of the standardized test is based on the null hypothesis. The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is 0.1; hence, statistical power is 90%. Sixty evaluable patients are necessary to test the hypothesis. If at least 25 of 60 evaluable patients are alive and free of progression at 12 weeks then the null hypothesis can be rejected and PM060184 considered active and deserving potential development in this setting.

5.2. Early Stopping Rule for Futility

A futility analysis using O'Brien-Fleming boundaries is planned when 24 patients can be evaluated (first stage). If there are seven or more patients achieving PFS3 in the first stage then the trial will proceed to a second stage and a total of 60 patients will be recruited.

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 mean, standard deviation (StD), median, minimum, and maximum values of each variable.

For main efficacy results patients included in the first stage will be summarized together with patients included in the second stage.

6.1. Planned Analyses and Definitions

Primary endpoint

Progression-free survival rate at 12 weeks, defined as the rate estimate of the percentage of patients who are alive and progression-free at 12 weeks (~3 months) after the first treatment administration.

Secondary endpoints

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

- ***Overall Survival***, defined as the time from the first day of treatment to the date of death or last contact.
- ***Progression-free Survival***, defined as the time from the first day of study treatment to the day of assessment of progression, death or last tumor evaluation.
- ***Overall Response Rate***, defined as the percentage of patients with objective response (OR), either complete response or partial response according to the RECIST v.1.1.
- ***Duration of Response***, defined as the time between the date when response criteria (PR or CR, the first to be reached) are fulfilled and the first date when PD, recurrence or death is objectively documented.
- ***Profiles of peripheral neuropathy and quality of life*** as reported by patients using the EORTC QLQ-CIPN20 and QLQ-C30.

6.2. Efficacy Analysis Methods

6.2.1. Primary Endpoint

For the evaluation of the primary endpoint (PFS3), the efficacy population and the exact binomial estimator (count and percentage) including its 95% confidence interval will be used.

6.2.2. Secondary Endpoints

Time-to-event variables (DOR, PFS and OS) and their fixed time estimates will be analyzed according to the Kaplan-Meier method. Kaplan-Meier curves will be plotted.

For categorical variables, comparisons will be carried out by a Fisher exact test and a multivariate analysis by logistic regression. For time-to-event variables, comparisons will be carried out by a log-rank test and by a Cox regression analysis. No formal conclusions will be expected on these grounds. Exploratory comparisons will be performed at a 0.05 level.

If appropriate, exploratory multivariate models (main effects or including interaction terms) will include all prognostic factors/covariates widely reported and recognized by oncologists: age, age at diagnosis, baseline ECOG PS (Eastern Cooperative Oncology Group Performance Status), stage at diagnosis, Tumor primary location: right vs left side tumors; sites of metastasis; visceral vs non visceral, body mass index (BMI), body surface area (BSA), time from diagnosis to first infusion, time from diagnostic of metastatic disease to first infusion, prior advanced treatment lines, last prior therapy PFS, prior oxaliplatin exposure, KRAS status, BRAF-like expression, any relevant concomitant medication at baseline; EORTC-QLQ-C30 and QLQ-CPN20 score at baseline and other prognostic/predictive factors determined by the oncologist. The total number of variables included in the final model will always be in accordance with the number of events and the sample size, thus, whenever possible, no more than one variable per ten events will be included. The parameter estimates, hazard ratios and p-values of the variables retained in the model will be presented.

A sensitivity analysis for PFS including all treated patients will be performed. Event will be defined as progression or death irrespective of the subsequent therapies received for this analysis.

Waterfall plots will be used to describe the best variation of the sum of target lesions during treatment. Questionnaires scores over time will be described by time series charts, if appropriate.

6.2.2.1. QoL Analysis Methods

Changes in QoL will be followed using the EORTC-QLQ-C30 and EORTC-QLQ-CPIN20 questionnaires scores over time.

- **EORTC-QLQ-C30**

  General QoL will be evaluated through EORTC QLQ-C30. These include 30 items, which transformation produces five functional scales, three symptom scales, a global health status / QoL scale, and six single items.

  All of the scales and single-item measures range in score from 0 to 100, using the scoring procedures described in the manual (1). A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL but a high score for a symptom scale / item represents a high level of symptomatology / problems.

- **EORTC-QLQ-CIPN20**

  Peripheral neuropathy will be evaluated through EORTC QLQ-CIPN20, a 20-item quality of life questionnaire for the patients' self-reported neurotoxicity, targeting symptoms and patient concerns specifically associated with treatment-induced PN and potential activity impairment.

  The EORTC QLQ CIPN20 consists of three subscales: sensory scale, motor scale and autonomic scale. For all of them, the individual items and the multi-item scale should be scored such that higher scores represent more symptoms/problems (i.e., higher score = worse).

  If forming a scale appears to be justified, then the same algorithm can be used as is applied in the scoring manual for the QLQ-C30 for linearly converting items and/or scales to 0-100 scales.

The module items will be reported both individually and in the form of mean scores. If item mean scores are being presented, the items should first be linearly converted to a 0 to 100 scale, whilst it will be reported the percentage of patients endorsing each of the response categories for the first case. It could be displayed by dichotomize scores also, if appropriate, for example by grouping scores into 'Not at all' vs. 'Any extent'.

Finally, QoL and PN will be evaluated by changes in the EORTC QLQ-CIPN20 and QLQ-C30 scores over time and tested for statistical significance by means of repeat-measure analyses of variance. The scores will be compared at the pre-specified time points using a T-test for related samples to establish differences, if any, between pairs of assessments. A p-value of < 0.05 is considered statistically significant for the exploratory comparisons.

7. STATISTICAL METHODOLOGY FOR SAFETY

Safety analyses will consider AEs and SAEs, according to their relationship with study treatment, as well as analytical results, deaths and the reasons for treatment discontinuations, delays and/or dose reductions. All AEs and SAEs will be graded according to NCI-CTCAE v.4., and they will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Safety profiles will be described by bar charts. If serious toxicities happen, special follow-up -with descriptive statistics and graphs (boxplots, line plots) - will be made to find out the pattern of the event.

7.1. Toxicity and Adverse Events

All the AEs will be coded using the MedDRA.

The toxicity evaluation will be coded with the NCI-CTCAE v.4. Toxicities will be described according to the worst NCI-CTCAE grade.

Summary of overall AEs will be done by System Organ Class (SOC) and Preferred Term (PT), by severity (worst toxicity grade) and by relationship to the study drug. 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. AEs 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 v.4.

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

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

If a grade 3/4 neutropenia or thrombocytopenia increase occurs during a treatment cycle, the first day the onset value is reached (counting from the start of the cycle) will be tabulated.

Time to recovery of the abnormality (i.e., grade 3/4 neutropenia or thrombocytopenia) will be assessed and defined as the time, in days, from the start of the grade 3/4 abnormality until the abnormality is recovered (grade ≤ 2). The analysis will be carried out taking into account all events, including those that occur in a same cycle. The information will be shown by means of median and range.

Likewise, the following biochemical values (worst grade per patient and per cycle during treatment) will be displayed: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, alkaline phosphatase (AP), creatinine, creatinine clearance, calcium (corrected by albumin levels), potassium (K), sodium (NA), glucose and albumin.

Time to recovery of the abnormality (grade 3/4 AST or ALT) will be assessed and defined as the time, in days, from the start of the grade 3/4 abnormality until recovery to grade ≤ 2. The analysis will be carried out taking into account all events, including those that occur in a same cycle. The information will be shown by means of median and range.

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

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

Summary tables will be prepared with the performance status, physical examination, 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 following the same pattern than AEs.

8. OTHER ANALYSES

Continuous variables will be tabulated and presented with summary statistics (i.e., mean, StD, 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 deviations regarding patients' eligibility, 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 World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system, will be described following standard tables detailed in Appendix I.

Age, baseline weight, height, and BSA values will be summarized descriptively. Age categories, race and baseline ECOG PS score will be summarized with frequency counts.

Baseline weight and height are recorded on the Case Report Form (CRF). If BSA value is missing, it will be calculated using the Dubois & Dubois formula:

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

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 other characteristics of the primary and current disease will be described using standard tables detailed in Appendix I.

Previous relevant medical history (other than cancer) will be tabulated by SOC and PT.

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

Signs and symptoms, defined as AEs reported at baseline, will be displayed by tabulation of frequencies according to NCI-CTCAE v.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 last value prior to or on the first day of treatment will be considered the baseline measurement.

8.4. Treatment Administration

Total cumulative dose, dose intensity and relative dose intensity, administration times, time on treatment, cycle delays, dose reductions and omissions will be described using 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 the last cycle.

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

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

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

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

$$Delay = Date\ of\ current\ drug\ administration - Date\ of\ previous\ drug\ administration - 21$$

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 Analyses

This analysis will be detailed in a separate document.

8.7. Pharmacogenetic Analyses

This analysis will be detailed in a separate document.

8.8. Pharmacogenomic Analyses

This analysis will be detailed in a separate document.

8.9. Metabolomics (Biomarkers)

This analysis will be detailed in a separate document.

8.10. 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 as duration and time to certain event. However, when all of them, day, month and year are missing no imputation will be done.

Before registration/treatment start

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

Between treatment start and end of treatment

All date variables during treatment for which information is needed and is not fully available, for example AEs or concomitant medications, will be subjected to imputation by means of SAS programming. If the day of a date is unknown then the imputed day will be the 1st of the month, if the month and/or year are also unknown then the imputed date will be the 1st of January. This assumption will be valid if the imputed date is earlier than the treatment start date; otherwise, the imputed date will be the treatment start date.

After end of treatment

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 PM060184), except if the patient dies before, in which case the date of death minus 1 will be used.

8.11. Decimal Places

By default, all numeric results will be rounded to one decimal, except when variables are integer; in that case, they will be reported without decimals, for example, age in years, number of sites, etc. or in the case of p-values and Hazard Ratio values where four decimals will be used.

8.12. Subgroup Analyses

If applicable, specific analyses for different subgroups determined by the following factors will be developed: prior oxaliplatin exposure, tumor primary location: right vs left side tumors, KRAS status, BRAF-like expression, MSI phenotype and other relevant factors determined by the oncologist.

No differentiation by center is planned.

8.13. Methods for Handling Missing Data

Missing values will not be included in the calculation of outputs.

8.14. First Stage Analysis

A futility analysis will be performed once the first 24 evaluable patients complete the Week 12 (± 5 days) tumor assessment; progress; die due to PD; or discontinue treatment due to unmanageable toxicity (whichever occurs first). If seven patients or more achieve PFS3, then 36 additional patients will be recruited (second stage).

8.15. Identification of Fixed or Random Effects Models

Not applicable.

8.16. Data Analysis Conventions

All data analysis conventions, data calculations and grouping needed to perform the statistical analysis will be described in a separate document.

9. STATISTICAL SOFTWARE

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

EAST v.6 has been used to calculate sample size.

SAS v.9.4 or superior will be used for all statistical analysis outputs.

I. APPENDIX: TABLES, LISTINGS AND GRAPHS

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

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

10.Study Patients

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

10.1. Patient Disposition

Patient disposition analysis will be based in the "All included patients" population.

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 inclusion criteria or meet any exclusion criteria.

Patient id.	Criterion number(s) and description

Listing 10.1.3 Screening failures.

Patient	Inclusion/Exclusion criterion not met

Listing 10.1.4 Non-evaluable patients for efficacy.

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 country/institution.

Country/Institution	No. of patients included		No. of patients treated	
	N	%	N	%
Institution 1 Institution 2 …				

Table 10.1.7 Relevant study dates.

	Total
Date of first patient's informed consent	
Date of first dose of the first patient	
Date of last patient's informed consent	
Date of first dose of the last patient	
Date of last dose	
Date of last follow-up*	

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

10.2. Discontinuations

Treatment discontinuation tables and listings will be based on "All treated patients", whereas study discontinuation tables and listings will be based on "All included patients".

10.2.1. Treatment discontinuations

Table 10.2.1 Treatment discontinuation.

Reason	N	%
Progressive disease		
Patient refusal to treatment		
Death (due to toxicity)*[1]		
Death (non-treatment-related)*[2]		
Investigator's decision*[3]		
Treatment-related AE		
Non treatment-related AE		
Other*[3]		
Total		

(*[1]) Cause of death = Study drug related AE; (*[2]) Cause of death = Malignant disease, Non study drug related AE or Other; (*[3]) See Listing 10.2.2.

Listing 10.2.2 Reasons for treatment discontinuation other than progressive disease.

Patient id.	Reason	Last cycle	Comments

When the reason for discontinuation is a study treatment-related adverse event or death due to toxicity, patients will be identified and described in depth in Listing 10.2.3.

Listing 10.2.3 Treatment discontinuation due to AEs.

Patient id.	Last cycle	Preferred term code	AE reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Seriousness criteria

10.2.2. Study discontinuation

Table 10.2.4 Study discontinuation.

Reason	N	%
Never treated*[1] Withdrawal of consent Death (due to toxicity)*[2] Death (non-treatment-related) *[3] Lost to follow-up Other *[4] Total		

(*[1]) See Listing 10.1.5; (*[2]) Cause of death = Study drug related AE or UK relationship; (*[3]) Cause of death = Malignant disease, Non study drug related AE or Other; (*[4]) Specified in Listing 10.2.5.

Listing 10.2.5 Study discontinuation due to other reason.

Patient id.	Specify

10.3. Protocol Deviations

Protocol deviations of "All included patients" population will be shown.

Listing 10.3.1 Protocol deviations.

Patient id.	Deviation type	Description

11. Efficacy Evaluation

11.1. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of "All Included Patients" population will be shown.

11.1.1. Patient Characteristics at Baseline

Table 11.1.1 Baseline characteristics.

	N	%
Number of patients		
Gender Female Male		
Age Median (range) Mean (StD)		
Age group 18-49 50-69 ≥70		
Race American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander White Other (specify)*		

(*) See Listing 11.1.2.

Listing 11.1.2 Race (other).

Patient	Race	Specify

11.1.2. Disease at diagnosis and current disease

Table 11.1.3 Disease at diagnosis and current disease.

	N	%
Time from first diagnosis to first infusion Median (range) Mean (StD)		
Primary tumor side Rigth Left		
Primary tumor site Cecum Ascending Transverse Descending Sigmoid Rectum …		
Histology grade G1. Well differentiated		

	N	%
G2. Moderately differentiated G3. Poorly differentiated G4. Undifferentiated GX. Grade cannot be evaluated		
KRAS mutational status Wild type Not done UK Mutated, specify*[1]		
NRAS mutational status Wild type Not done UK Mutated, specify*[2]		
BRAF mutational status Wild type Not done UK Mutated, specify*[3]		
MSI status Done Not done/UK MSI phenotype*[4] MSI Stable MSI-H MSI-L		
Stage at diagnosis I …		
TNM …		
Dukes A B …		
MAC A B1 …		

(*[1]) See Listing 11.1.4 (*[2]) See Listing 11.1.5 (*[3]) See Listing 11.1.6 (*[4]) Listing 11.1.7.

Listing 11.1.4 KRAS mutational status (mutated).

Patient	Specify

Listing 11.1.5 NRAS mutational status (mutated).

Patient	Specify

Listing 11.1.6 BRAF mutational status (mutated).

Patient	Specify

Listing 11.1.7 MSI phenotype (gene affected).

Patient	MSI phenotype (MSI Stable/MSI-H/MSI-L)	Gen affected

Table 11.1.8 Current disease.

	N	%
Current disease status Locally recurrent disease Metastasis Both		
Time from diagnosis of advanced disease to study entry Median (range) Mean (StD)		
Time from prior last progression before study entry Median (range) Mean (StD)		
Time from stop date of prior chemotherapy to study entry Median (range) Mean (StD)		
Site of current disease Primary tumor site/ Local relapse Lung …		
Number of sites involved 1 2 … Median (range) Mean (StD)		

11.1.3. Prior Relevant Medical History

Table 11.1.9 Prior medical history.

SOC	Preferred term		
		N	%
Patients with any past and/or concomitant disease or past surgeries			
Gastrointestinal disorders	Constipation		
	Diarrhoea		
	…		
…	…		
	…		

Listing 11.1.10 Prior medical history (ongoing events).

Patient id.	Description (Literal)	SOC	PT	Onset date

11.1.4. Prior Anticancer Therapy

Table 11.1.11 Prior surgery (major surgical procedures for study disease only).

	N	%
Surgery (Y/N) Residual disease Yes No UK		

Table 11.1.12 Prior radiotherapy.

	N	%
Radiotherapy (Y/N) Type External Brachytherapy IORT IMRT Intention Curative Palliative Concurrent		

Table 11.1.13 Prior anticancer medical therapy.

	N	%
Number of prior lines (including neo/adjuvant) 1 …		
Number of prior lines for advanced disease 1 …		
Number of prior agents (including neo/adjuvant) 1 …		
Number of prior agents for advanced disease 1 …		
Prior agents (ATC coded) Fluoropyrimidine Irinotecan Oxaliplatin …		
Last prior agents (ATC coded) …		
Progression free interval* Median (range)		
Progression free interval to Oxaliplatin Median (range)		
Best response to last prior therapy Complete Response Partial Response Stable Disease Progressive Disease NE/UK/NA		

(*) Time from last prior therapy to first infusion of PM60184.

11.1.5. Physical Examination and performance status

Table 11.1.14 Baseline ECOG Performance Status.

	N	%
ECOG PS 0 1		

Table 11.1.15 Baseline physical examination.

	N	%
Physical examination abnormalities (Y/N)		
Weight (kg) Median (range) Mean (StD)		
Height (cm) Median (range) Mean (StD)		
Body surface area (m^2) Median (range) Mean (StD)		
BMI (kg/m^2) Median (range) Mean (StD) ≤ 20 21-25 26-30 > 30		

11.1.6. Vital signs, Electrocardiogram, LVEF and other tests

Table 11.1.16 Vital signs, Electrocardiogram, LVEF and other tests.

	N	%
Vital signs Heart rate (Beats/minute) Median (range) Mean (StD) Systolic blood pressure (mmHg) Median (range) Mean (StD) Diastolic blood pressure (mmHg) Median (range) Mean (StD) Temperature (ºC) Median (range) Mean (StD)		
ECG Normal Significant abnormalities Non significant abnormalities		
LVEF Method ECHO MUGA Result Normal Non-significant abnormalities Significant abnormalities		
Pregnancy test Positive Negative NA*		

(*) See Listing 11.1.17.

Listing 11.1.17 Patients with not applicable pregnancy test.

Patient	Specify

Listing 11.1.18 Other tests/ procedures.

Patient	Test name	Result	Comments

11.1.7. Hematological Values at Baseline

Table 11.1.19 Hematological abnormalities at baseline*.

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1/4		Total
	N	%	N	%	N	%	N	%	N	%	N
Anaemia											
Leukopenia											
Neutropenia											
Lymphopenia											
Thrombocytopenia											

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

Table 11.1.20 Hematological values at baseline*.

	Median (range)
Hemoglobin (g/dL)	
WBC (10^9/L)	
Neutrophils (10^9/L)	
Lymphocytes (10^9/L)	
Platelets (10^9/L)	

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

Listing 11.1.21 Hematological abnormalities at baseline* (grade >1).

Patient	Test	Grade

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

Listing 11.1.22 Hematological tests not assessed at baseline*.

Patient	Test
…	
…	

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

11.1.8. Biochemical Values at Baseline

Table 11.1.23 Biochemical abnormalities at baseline*.

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1/4		Total
	N	%	N	%	N	%	N	%	N	%	N
ALT increased											
AP increased											
AST increased											
Creatinine increased											

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

Table 11.1.24 Biochemistry values at baseline*.

	Median (range)
ALT (IU/L)	
AP (IU/L)	
AST (IU/L)	
Creatinine (mg/dL)	
Creatinine Clearance (mg/min)	
Direct bilirubin (mg/dL)	
GGT (U/L)	
Glucose (mmol/L)	
K (mmol/L)	
LDH (IU/L)	
Na (mmol/L)	
Total bilirubin (mg/dL)	

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

Listing 11.1.25 Biochemical abnormalities at baseline* (grade >1).

Patient	Test	Grade

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

Listing 11.1.26 Biochemical tests not assessed at baseline*.

Patient	Test
…	
…	

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

Table 11.1.27 Other metabolic abnormalities at baseline*.

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1/4		Total
	N	%	N	%	N	%	N	%	N	%	N
GGT increased											
Hypercalcemia[*2]											
Hyperglycemia											
Hyperkalaemia											
Hypernatremia											
Hypoalbuminaemia											
Hypocalcemia[*2]											
Hypoglycemia											
Hypokalaemia											
Hyponatremia											

(*) Defined as the last value recorded before or on the date of first infusion.
(*[2]) Total plasmatic calcium corrected by albumin.

Listing 11.1.28 Other metabolic abnormalities at baseline* (grade >1).

Patient	Test	Grade

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

11.1.9. Signs and Symptoms at Baseline

Table 11.1.29 Signs and symptoms at baseline*.

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

(*) AEs with onset day previous to first administration of the study treatment.

Table 11.1.30 Signs and symptoms at baseline.

MedDRA SOC/PT*	N	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1/4	
		N	%	N	%	N	%	N	%	N	%
Constipation											
Diarrhoea											
Dyspnea											
Pain											
…											

(*) Sorted by frequency.

Table 11.1.31 Disease related signs and symptoms at baseline.

MedDRA SOC/PT*	N	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1/4	
		N	%	N	%	N	%	N	%	N	%
Constipation											
Diarrhoea											
Dyspnea											
Pain											
…											

(*) Sorted by frequency.

Listing 11.1.32 Signs and symptoms at baseline.

Patient	Sign/symptom	Grade	Onset date	Relationship	Treated

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

11.1.10. Peripheral Neuropathy

Table 11.1.33 Peripheral neuropathy.

	N	%
Peripheral neuropathy (Y/N)		
Type of peripheral neuropathy Sensory Motor Both		
Location Hands Feet Arms Legs …		
Worst grade observed (NCI-CTCAE v.4) Grade 1 Grade 2 Grade 3 Grade 4 UK		
Outcome of the overall grade Complete recovery Recovered with sequelae		
Neuropathy due to prior chemotherapies or biological treatments: agents Oxaliplatin Other		
Neuropathy due to prior chemotherapies or biological treatments: dose modification / discontinuation Yes No UK		

11.1.11. Concomitant Therapy and Procedures at Baseline

Table 11.1.34 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 11.1.35 Summary of concomitant medication at baseline.

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

Listing 11.1.36 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.

11.2. Measurements of Treatment Compliance

Compliance of individual patients with the treatment regimen under study will be measured and tabulated in Appendix I.12.1 and listed in Appendix III (ICH listings).

11.3. Efficacy Analysis

Efficacy analysis will be carried out on the "All Evaluable Patients" population except duration of response analysis which will be carried out on the "All Responding Patients" population and QoL analysis, which will be carried out on the "All evaluable QoL" population.

11.3.1. Primary Analysis

Patients who are evaluable for efficacy but have not been followed-up for at least 12 weeks (+/- 5 days) will be categorized as PFS3=No.

Table 11.3.1 PFS3 rate (binomial exact estimator and 95% confidence interval).

	Proportion	Lower 95% limit	Upper 95% limit
PFS3*			

(*) Progression-free-survival rate at 12 weeks (+/- 5 days).
Binomial exact estimator and 95% CI.

Listing 11.3.2 Censored patients.

Patient	PFS3 rate	PFS (months)	Reason for censoring

11.3.2. Secondary Analyses

Table 11.3.3 Overall survival.

	PM060184
N	
Events	
Censored	
Median OS	
OS at 12 months	

A Kaplan-Meier plot will also be shown (see Figure 11.3.4).

See Figure 11.3.8 as an example of Kaplan Meier plot.

Table 11.3.5 Progression-free survival.

	PM060184
N	
Events	
Censored	
Median PFS	
PFS at 3 months	
PFS at 6 months	
PFS at 12 months	

A Kaplan-Meier plot will also be shown (see Figure 11.3.8).

Figure 11.3.6 Kaplan-Meier plot of PFS.

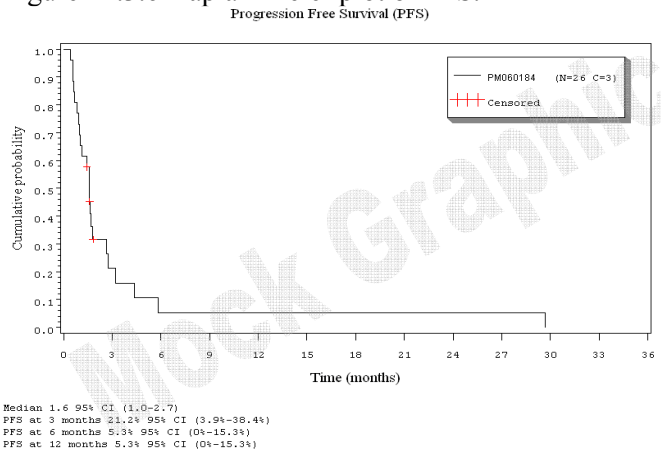


Table 11.3.7 Sensitive analysis of Progression-free survival.

	PM060184
N	
Events	
Censored	
Median PFS	
PFS at 3 months	
PFS at 6 months	
PFS at 12 months	

A Kaplan-Meier plot will also be shown (see Figure 11.3.8).

Figure 11.3.8 Kaplan-Meier plot of sensitivity analysis of PFS.

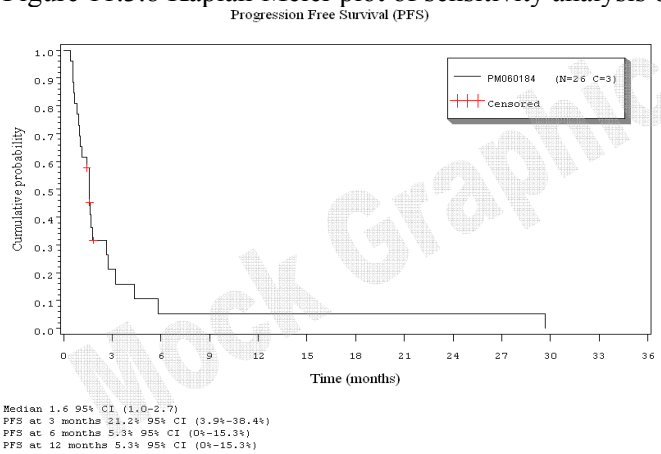


Table 11.3.9 Overall response as per RECIST v1.1.

Response	N	%
Complete response		
Partial response		
Stable disease		
SD < 3 months		
SD ≥ 3 months		
Progressive disease		
Non-evaluable for efficacy*		

(*) Treatment failures.

Table 11.3.10 Overall response rate.

	Proportion	Lower 95% limit	Upper 95% limit
Response rate*			
Response rate or PFS3			

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

Figure 11.3.11 Best RECIST efficacy assessment in evaluable patients.

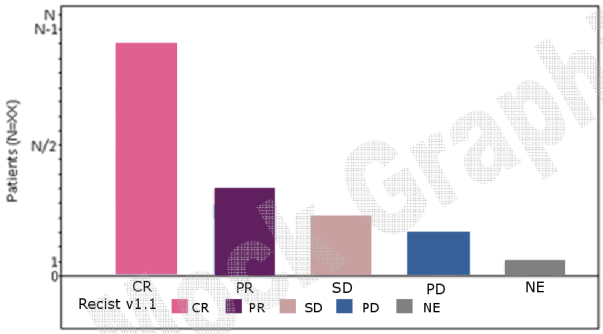


Figure 11.3.12 Waterfall plot of best reduction in sum of diameters of target lesions from baseline (RECIST v1.1).

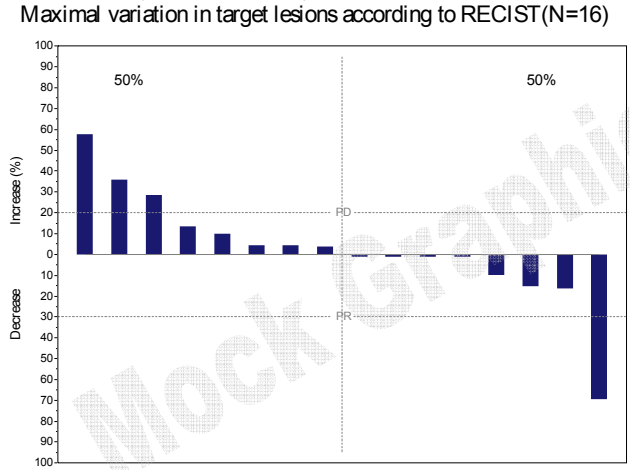


Table 11.3.13 Duration of response.

	PM060184
N	
Events	
Censored	
Median DOR	

A Kaplan-Meier plot will also be shown (see Figure 11.3.14).

An example of Kaplan Meier plot could be seen in Figure 11.3.8.

A summary of the main characteristics of responding patients or PFS3 will be performed.

Listing 11.3.15 Characteristics of patients with response.

Patient	Race	ECOG PS	Age	Primary tumor side	Primary site	Number of prior lines	Last prior treatment		
							Agent	Best response	PFI

Patient	N Metastatic sites	Cycles received	Best response	Tumor shrinkage	PFS (months)	TTP (months)	PFS3	DOR	OS

Table 11.3.16 Median follow up.

Follow-up*	PM060184	
	Median	95% CI
PFS		
OS		

(*) Calculated using the Kaplan-Meier method reversing the censored values and the usual descriptive way.

11.3.3. QoL analyses

11.3.3.1. General QoL (QLQ-C30)

Table 11.3.17 Raw data for individual items* of EORTC QLQ-C30 over time.

	Baseline N (%)	Cycle 1 N (%)	Cycle X N (%)	EOT N (%)	Follow up N (%)
Item 1 Not at all A little Quite a bit Very much					
…					
Item 30 Not at all A little Quite a bit Very much					

(*) Could also be displayed by dichotomized scores, if appropriate, by for example grouping scores into 'Not at all' vs. 'Any extent'.

Table 11.3.18 Over time scores of EORTC QLQ-C30.

Scale / Item	Baseline Mean (StD)	Cycle 1 Mean (StD)	Cycle X Mean (StD)	EOT Mean (StD)	Follow up Mean (StD)
Global health status / QoL					
Functional scales					
Physical functioning					
Role functioning					
Emotional functioning					
Cognitive functioning					
Social functioning					
Symptom scales					
Fatigue					
Nauseas and vomiting					
Pain					
Dyspnoea					
Insomnia					
Appetite loss					
Constipation					
Diarrhoea					
Financial difficulties					

A time series chart will also be shown (see Figure 11.3.19).

See Figure 11.3.24 as an example of Time serie chart to describe over time scores of EORTC QLQ-C30.

Table 11.3.20 Changes in scores of EORTC QLQ-C30 over time from baseline.

Scale / Item	Cycle 1		Cycle X		EOT		Follow up	
	Mean (StD)	p-value	Mean (StD)	p-value	Mean (StD)	p-value	Mean (StD)	p-value
Global health status / QoL								
Functional scales								
Physical functioning								
Role functioning								
Emotional functioning								
Cognitive functioning								
Social functioning								
Symptom scales								
Fatigue								
Nauseas and vomiting								
Pain								
Dyspnoea								
Insomnia								
Appetite loss								
Constipation								
Diarrhoea								
Financial difficulties								

Table 11.3.21 Changes in scores of EORTC QLQ-C30 over time (Repeated Measures Analysis of Variance).

Source	DF	Mean Square	F value	p-value

11.3.3.2. Chemotherapy-induced Peripheral Neuropathy (QLQ-CIPN20)

Table 11.3.22 Raw data for individual items* of EORTC QLQ-CIPN20 over time.

	Baseline N (%)	Cycle 1 N (%)	Cycle X N (%)	EOT N (%)	Follow up N (%)
Item 1 Not at all A little Quite a bit Very much					
…					
Item 20 Not at all A little Quite a bit Very much					

(*) Could also be displayed by dichotomized scores, if appropriate, by for example grouping scores into 'Not at all' vs. 'Any extent'.

Table 11.3.23 Over time scores of EORTC QLQ-CIPN20.

Scale / Item	Baseline Mean (StD)	Cycle 1 Mean (StD)	Cycle X Mean (StD)	EOT Mean (StD)	Follow up Mean (StD)
Sensory scale					
Motor scale					
Autonomic scale					

A Time serie chart will also be shown (see Figure 11.3.24).

Figure 11.3.24 Time serie chart of mean and 95% CI for scales of EORTC QLQ-CIPN20.

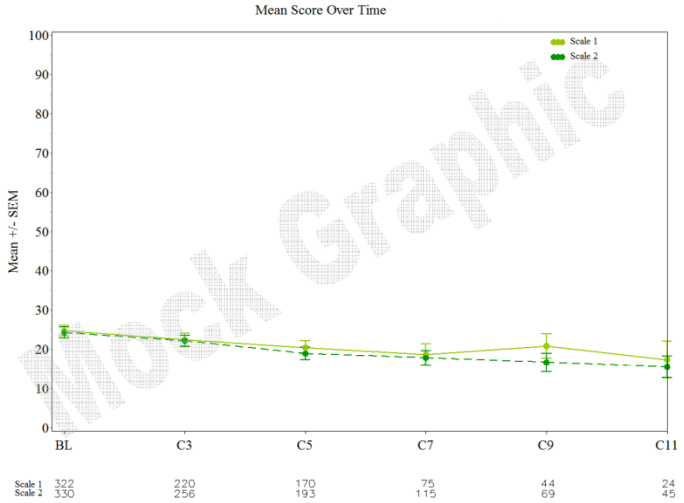


Table 11.3.25 Changes in scores of EORTC QLQ-CIPN20 from baseline over time.

Scale / Item	Cycle 1		Cycle X		EOT		Follow up	
	Mean (StD)	p-value	Mean (StD)	p-value	Mean (StD)	p-value	Mean (StD)	p-value
Sensory scale								
Motor scale								
Autonomic scale								

Table 11.3.26 Changes in scores of EORTC QLQ-CIPN20 over time (Repeated Measures Analysis of Variance).

Source	DF	Mean Square	F value	p-value

11.3.4. Exploratory Analyses

Table 11.3.27 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).

Table 11.3.28 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).

Table 11.3.29 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 11.3.30 Multivariate analysis of PFS3 (Yes/No).

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).

11.3.4.1. Subgroup Analysis

Table 11.3.31 Subgroup analysis of PFS3 rate (binomial exact estimator and 95% confidence interval).

		Proportion (95% CI)		
Oxaliplatin exposure	Subgroup		Yes	No
	PFS3*			
Tumor primary location	Subgroup		Right	Left
	PFS3*			
KRAS status (mutated)	Subgroup		Yes	No
	PFS3*			
BRAF-like expression (mutated)	Subgroup		Yes	No
	PFS3*			
MSI phenotype	Subgroup	MSI Stable	MSI-H	MSI-L
	PFS3*			

(*) Progression-free-survival rate at 12 weeks (+/- 5 days). Binomial exact estimator and 95% CI.

Table 11.3.32 Subgroup analysis of Overall survival.

Oxaliplatin exposure	Subgroup		Yes	No
	N			
	Events			
	Censored			
	Median OS			
	OS at 12 months			
Tumor primary location	Subgroup		Right	Left
	N			
	Events			
	Censored			
	Median OS			
	OS at 12 months			
KRAS status (mutated)	Subgroup		Yes	No
	N			
	Events			
	Censored			
	Median OS			
	OS at 12 months			
BRAF-like expression (mutated)	Subgroup		Yes	No
	N			
	Events			
	Censored			
	Median OS			
	OS at 12 months			
MSI phenotype	Subgroup	MSI Stable	MSI-H	MSI-L
	N			
	Events			
	Censored			
	Median OS			
	OS at 12 months			

A Kaplan-Meier plot will also be shown (see Figure 11.3.33).

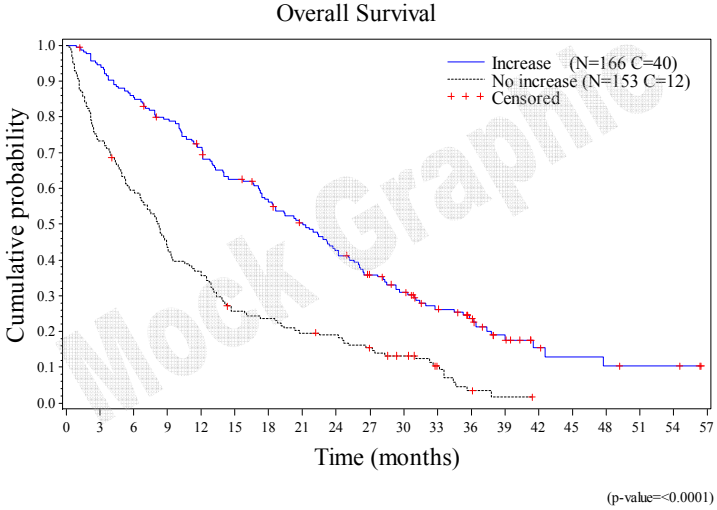
See Figure 11.3.8 as an example of Kaplan Meier plot.

Table 11.3.34 Subgroup analysis of progression-free survival.

Oxaliplatin exposure	Subgroup		Yes	No
	N			
	Events			
	Censored			
	Median PFS			
	PFS at 3 months			
	PFS at 6 months			
	PFS at 12 months			
Tumor primary location	Subgroup		Right	Left
	N			
	Events			
	Censored			
	Median PFS			
	PFS at 3 months			
	PFS at 6 months			
	PFS at 12 months			
KRAS status (mutated)	Subgroup		Yes	No
	N			
	Events			
	Censored			
	Median PFS			
	PFS at 3 months			
	PFS at 6 months			
	PFS at 12 months			
BRAF-like expression (mutated)	Subgroup		Yes	No
	N			
	Events			
	Censored			
	Median PFS			
	PFS at 3 months			
	PFS at 6 months			
	PFS at 12 months			
MSI phenotype	Subgroup	MSI Stable	MSI-H	MSI-L
	N			
	Events			
	Censored			
	Median PFS			
	PFS at 3 months			
	PFS at 6 months			
	PFS at 12 months			

A Kaplan-Meier plot will also be shown (see Figure 11.3.8).

Figure 11.3.35 Kaplan-Meier plot of PFS by subgroups*.



(*) (A) Oxaliplatin exposure (Yes/No), (B) Tumor primary location (Right/Left), (C) KRAS status (mutated) (Yes/No), BRAF-like expression (mutated) (Yes/No) and (D) MSI phenotype (MSI Stable/MSI-H/MSI-L).

Table 11.3.36 Subgroup analysis of overall response as per RECIST v1.1.

		N (%)	
Oxaliplatin exposure	Subgroup	Yes	No
	Response		
	Complete response		
	Partial response		
	Stable disease		
	SD < 3 months		
	SD ≥ 3 months		
	Progressive disease		
	Non-evaluable for efficacy*		
Tumor primary location	Subgroup	Right	Left
	Response		
	Complete response		
	Partial response		
	Stable disease		
	SD < 3 months		
	SD ≥ 3 months		
	Progressive disease		
	Non-evaluable for efficacy*		
KRAS status (mutated)	Subgroup	Yes	No
	Response		
	Complete response		
	Partial response		
	Stable disease		
	SD < 3 months		
	SD ≥ 3 months		
	Progressive disease		
	Non-evaluable for efficacy*		
BRAF-like expression (mutated)	Subgroup	Yes	No
	Response		
	Complete response		
	Partial response		
	Stable disease		
	SD < 3 months		
	SD ≥ 3 months		

	Progressive disease			
	Non-evaluable for efficacy*			
MSI phenotype	Subgroup	MSI Stable	MSI-H	MSI-L
	Response			
	Complete response			
	Partial response			
	Stable disease			
	SD < 3 months			
	SD ≥ 3 months			
	Progressive disease			
	Non-evaluable for efficacy*			

(*) Treatment failures.

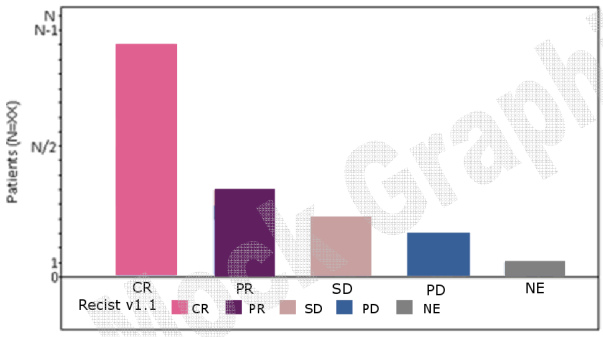
Table 11.3.37 Subgroup analysis of overall response rate.

		Proportion (95% CI)	
Oxaliplatin exposure	Subgroup	Yes	No
	Response rate*		
	Response rate or PFS3		
Tumor primary location	Subgroup	Right	Left
	Response rate*		
	Response rate or PFS3		
KRAS status (mutated)	Subgroup	Yes	No
	Response rate*		
	Response rate or PFS3		
BRAF-like expression (mutated)	Subgroup	Yes	No
	Response rate*		
	Response rate or PFS3		
MSI phenotype	Subgroup	MSI Stable	MSI-H	MSI-L
	Response rate*			
	Response rate or PFS3			

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

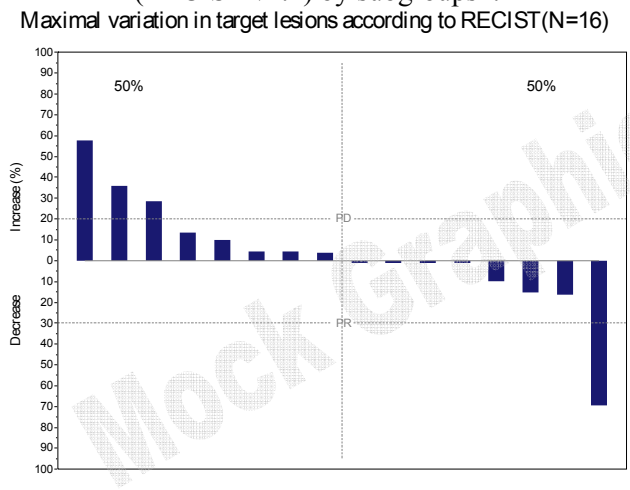
If appropriate, grouping of other similar or clinically related items will be made at the time of the analysis.

Figure 11.3.38 Best RECIST efficacy assessment in evaluable patients by subgroups*.



(*) (A) Oxaliplatin exposure (Yes/No), (B) Tumor primary location (Right/Left), (C) KRAS status (mutated) (Yes/No), BRAF-like expression (mutated) (Yes/No) and (D) MSI phenotype (MSI Stable/MSI-H/MSI-L).

Figure 11.3.39 Waterfall plot of best reduction in sum of diameters of target lesions from baseline (RECIST v1.1) by subgroups*.



(*) (A) Oxaliplatin exposure (Yes/No), (B) Tumor primary location (Right/Left), (C) KRAS status (mutated) (Yes/No), BRAF-like expression (mutated) (Yes/No) and (D) MSI phenotype (MSI Stable/MSI-H/MSI-L).

Table 11.3.40 Duration of response.

Oxaliplatin exposure	Subgroup		Yes	No
	N			
	Events			
	Censored			
	Median DOR			
Tumor primary location	Subgroup		Right	Left
	N			
	Events			
	Censored			
	Median DOR			
KRAS status (mutated)	Subgroup		Yes	No
	N			
	Events			
	Censored			
	Median DOR			
BRAF-like expression (mutated)	Subgroup		Yes	No
	N			
	Events			
	Censored			
	Median DOR			
MSI phenotype	Subgroup	MSI Stable	MSI-H	MSI-L
	N			
	Events			
	Censored			
	Median DOR			

A Kaplan-Meier plot will also be shown (see Figure 11.3.41).

An example of Kaplan Meier plot could be seen in Figure 11.3.8.

12.Safety Evaluation

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

12.1. Extent of Exposure

12.1.1. Treatment Administration

Table 12.1.1 Number of cycles administered and dose intensity.

	N	%
No. of cycles administered per patient 1 2 3 … Median (range) Mean (Std)		
Time on treatment* (weeks) Median (range) Mean (Std)		
Cumulative dose (mg) Median (range) Mean (Std)		
Dose intensity (mg/wk) Median (range) Mean (Std)		
Relative dose intensity (%) Median (range) Mean (Std)		

(*) 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

Listing 12.1.2 Delays.

Patient id.	Delayed cycle	Delayed cycle start date	Previous cycle	Previous cycle start date	Calculated dose delay (days)	Reason for dose delay	Specify reason for dose delay

Table 12.1.3 Number of patients and cycles with dose delay, any relationship.

	N	%
Patients treated		
Patients with any dose delay		
Cycles administered		
Cycles susceptible to be delayed*[1]		
Cycles with dose delay[*2]		
Patients with No cycles delayed 1 cycle delayed 2 cycles delayed ≥ 3 cycles delayed		

(*[1]) All cycles excluding first cycle. (*[2]) Denominator= Number of cycles susceptible to be delayed.

Table 12.1.4 Number of patients and cycles with dose delay according to relationship with study treatment.

	Treatment-related[*2]		Non-treatment-related	
	N	%	N	%
Patients with No cycles delayed 1 cycle delayed 2 cycles delayed ≥ 3 cycles delayed				
Cycles with dose delay*[1]				

(*[1]) Denominator= Number of cycles susceptible to be delayed. (*[2]) Hematological reason, non-hematological reason or both.

Table 12.1.5 Number of patients and cycles with dose delay according to relationship with study treatment.

Reasons for treatment-related delays	N	%
Cycles with dose delays* Hematological Non-hematological Both		
Patients with dose delays Hematological No cycles delayed 1 cycle delayed 2 cycles delayed ≥ 3 cycles delayed Non-hematological No cycles delayed 1 cycle delayed 2 cycles delayed ≥ 3 cycles delayed Both No cycles delayed 1 cycle delayed 2 cycles delayed ≥ 3 cycles delayed		

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

Table 12.1.6 Length of dose delay.

		Treatment-related[*2]		Non-treatment-related		Total	
Length of delay	Median (range)						
Length of delay*[1]		N	%	N	%	N	%
<= 7 days							
>7 days and <=14 days							
> 14 days							

(*[1]) Denominator= Number of cycles susceptible to be delayed. (*[2]) Hematological reason, Non-hematological reason or both.

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 12.1.7 Cycle delays due to AEs.

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

AEs with action = 'Dose delayed', 'Dose delayed/ reduced', 'Dose delayed/omitted' or 'Dose delayed/ omitted/ reduced'.

12.1.3. Dose Omission

Listing 12.1.8 Dose omission.

Patient id.	Cycle	Reason for dose omission	Dose omission Spec.

Table 12.1.9 Number of patients and infusions with dose omissions, any relationship.

	N	%
Patients treated		
Patients with any dose omitted		
Infusions susceptible to be omitted		
Infusions omitted Treatment-related Hematological Non-hematological Both Non-Treatment-related		
Patients with No cycles delayed 1 cycle delayed 2 cycles delayed ≥ 3 cycles delayed		

(*) Denominator= Number of infusions susceptible to be omitted.

Listing 12.1.10 Dose omissions due to AEs.

Patient id.	Cycle	Preferred term code	AE reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Action taken	Significant consequences

AEs with action = 'Dose omitted', 'Dose omitted/ reduced', 'Dose delayed/omitted' or 'Dose delayed/ omitted/ reduced'.

12.1.4. Dose Reductions

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

Listing 12.1.11 Dose reductions.

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

Table 12.1.12 Number of patients and infusions with dose reduction, any relationship.

	N	%
Patients treated		
Patients with any dose reduced		
Cycles susceptible to be reduced in dose		
Patients with No dose reductions 1 cycle with dose reduced 2 cycles with dose reduced ≥ 3 cycles with dose reduced		
Cycles administered		
Cycles susceptible to have any dose reduced*[1]		
Cycles with dose reduced *[2]		
Cycles with dose reduced (Treatment-related)*[2]		

(*[1]) All cycles. (*[2]) Denominator= Number of cycles susceptible to have a dose reduction.

Table 12.1.13 Number of patients and cycles with dose reduction according to the relationship.

	Treatment-related*[2]		Non-treatment-related	
	N	%	N	%
Patients with No dose reductions 1 cycle with dose reduced 2 cycles with dose reduced ≥ 3 cycles with dose reduced				
Cycles with dose reduction*[1]				

(*[1]) Denominator= Number of cycles susceptible to be delayed. (*[2]) Hematological reason, non-hematological reason or both.

Table 12.1.14 Number of patients and cycles with dose reduction according to the reason of the relationship.

Reasons for treatment-related reduction	N	%
Cycles with dose reduction* Hematological Non-hematological Both		
Patients with dose reduction Hematological No dose reductions 1 cycle with dose reduced 2 cycles with dose reduced ≥ 3 cycles with dose reduced Non-hematological No dose reductions 1 cycle with dose reduced 2 cycles with dose reduced ≥ 3 cycles with dose reduced Both No dose reductions 1 cycle with dose reduced 2 cycles with dose reduced ≥ 3 cycles with dose reduced		

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

Listing 12.1.15 Dose reductions due to AEs.

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

AEs with action = 'Dose reduced', 'Dose omitted/ reduced', 'Dose delayed/reduced' or 'Dose delayed/ omitted/ reduced'.

12.1.5. Temporarily Interrupted Infusions

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

Listing 12.1.16 Interrupted infusions.

Patient id.	Cycle	Reason

12.1.6. Prophylactic Medication Administration

A listing of the patients who did not receive, as required per protocol, corticosteroids, 5-HT antagonists and other antiemetic prophylaxis (or equivalents), will be reported with the corresponding reason.

Listing 12.1.17 Patients and cycles with prophylactic medication not taken per protocol.

Patient id.	Cycle	Prophylactic medication not taken*	Reason
…			

(*) Corticosteroids, 5-HT antagonists and other antiemetic prophylaxis

12.2. Adverse Events

As far as all toxicities are concerned, the NCI-CTCAE v.4 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, as described in NCI-CTCAE.

AEs will be described in this section; treatment-related events (stated as related to the study drug or of unknown relationship) will be tabulated. AEs regardless relationship will be tabulated in two different ways as any AE reported or as treatment emergent AEs (excluding AEs present before drug administration and without increase in severity grade along the treatment).

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.

12.2.1. Display of Adverse Events

Table 12.2.1 Summary of AEs.

Category*	N (%)
Any AE	
Any drug-related AE	
Any grade 3/4 AE	
Any grade 3/4 drug-related AE	
Any treatment emergent AE*[2]	
Any SAE in clinical database	
Any drug-related SAE in clinical database	
Any grade 3/4 SAE in clinical database	
Any grade 3/4 drug-related SAE in clinical database	
Deaths associated with AEs	
Deaths associated with drug-related AEs	
Treatment discontinuations associated with AEs	
Treatment discontinuations associated with drug-related AEs	

(*) Drug-related: AEs drug-related and unknown relationship.
(*[2]) excluding AEs present before drug administration and without increase in severity grade along the treatment.

Table 12.2.2 Treatment-related AEs. Worst grade by patient.

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anaemia Not Otherwise Specified (NOS)							
	...							
	…							
Cardiac disorders	Neuropathy peripheral							
	…							

(*) Any grade.

Table 12.2.3 Treatment-related AEs. Worst grade by cycle.

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anaemia NOS							
	...							
	…							
Cardiac disorders	Neuropathy peripheral							
	…							

(*) Any grade.

Table 12.2.4 Adverse Event regardless of relationship. Worst grade by patient.

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anaemia NOS							
	...							
	…							
Cardiac disorders	Neuropathy peripheral							
	…							

(*) Any grade.

Table 12.2.5 Adverse Event regardless of relationship. Worst grade by cycle.

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anaemia NOS							
	...							
	…							
Cardiac disorders	Neuropathy peripheral							
	…							

(*) Any grade.

Table 12.2.6 Treatment emergent AEs. Worst grade by patient.

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anaemia NOS							
	...							
	…							
Cardiac disorders	Neuropathy peripheral							
	…							

(*) Any grade.

Table 12.2.7 Treatment emergent AEs. Worst grade by cycle.

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anaemia NOS							
	...							
	…							
Cardiac disorders	Neuropathy peripheral							
	…							

(*) Any grade.

Listing 12.2.8 Treatment-related grade 3/4 AEs. Worst grade per patient.

Patient id.	Cycle	SOC Name	Preferred term	Grade

Listing 12.2.9 Treatment-related grade 3/4 AEs. Worst grade by cycle.

Patient id.	Cycle	SOC Name	Preferred term	Grade

Listing 12.2.10 Grade 3/4 adverse events regardless of relationship. Worst grade per patient.

Patient id.	Cycle	SOC Name	Preferred term	Grade

Listing 12.2.11 Grade 3/4 adverse events regardless of relationship. Worst grade by cycle.

Patient id.	Cycle	SOC Name	Preferred term	Grade

Listing 12.2.12 Grade 3/4 treatment emergent AEs. Worst grade per patient.

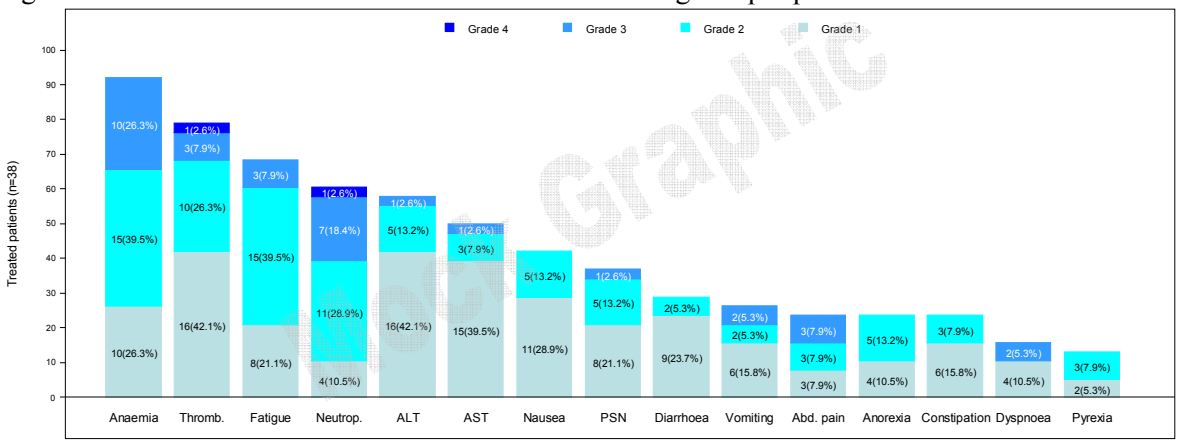
Patient id.	Cycle	SOC Name	Preferred term	Grade

Listing 12.2.13 Grade 3/4 treatment emergent AEs. Worst grade by cycle.

Patient id.	Cycle	SOC Name	Preferred term	Grade

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

Figure 12.2.14 Bar chart of treatment-related AEs. Worst grade per patient.



12.3. Serious Adverse Events and Deaths

12.3.1. Serious Adverse Events

Table 12.3.1 Treatment-related SAEs. Worst grade by patient.

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anaemia NOS							
	...							
	…							
Nervous system disorders	Neuropathy peripheral							
	…							

(*) Any grade.

Table 12.3.2 Treatment-related SAEs. Worst grade by cycle.

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anaemia NOS							
	...							
	…							
Cardiac disorders	Neuropathy peripheral							
	…							

(*) Any grade.

Table 12.3.3 SAEs regardless of relationship. Worst grade by patient.

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anaemia NOS							
	...							
	…							
Cardiac disorders	Neuropathy peripheral							
	…							

(*) Any grade.

Table 12.3.4 SAEs regardless of relationship. Worst grade by cycle.

SOC	Preferred Term	Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anaemia NOS							
	...							
	…							
Cardiac disorders	Neuropathy peripheral							
	…							

(*) Any grade.

Listing 12.3.5 Serious Adverse Events.

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

12.3.2. Deaths

Table 12.3.6 Cause of death.

	N	%
Deaths		
Reason* Malignant disease Study drug related AE Non-study drug related AE Other		

(*) Denominator=Number of patients who died.

Listing 12.3.7 Death.

Patient id.	Date of death	Cause	Comments	Autopsy	Number of cycles administered	Date of last infusion	Time on treatment*[1]	Time from last dose*[2]

(*[1]) Time on treatment: defined as date of last infusion plus 30 days, or date of death or subsequent therapy (whichever comes first) minus date of first infusion. (*[2]) Time from last dose defined as date of death minus date of last infusion.

Listing 12.3.8 AEs with an outcome of death.

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

12.4. Clinical Laboratory Evaluation

12.4.1. Hematological Abnormalities During Treatment

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

Table 12.4.1 Hematological abnormalities during treatment, worst grade per patient.

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

(*) Any grade

Table 12.4.2 Hematological abnormalities during treatment, worst grade per cycle.

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

(*) Any grade.

Listing 12.4.3 Grade 3/4 hematological abnormalities. Worst grade per patient.

Patient id.	Test	Grade

Listing 12.4.4 Grade 3/4 hematological abnormalities. Worst grade by cycle.

Patient id.	Cycle	Test	Grade

Listing 12.4.5 Hematological tests not assessed per patient.

Patient id.	Lab. test

Listing 12.4.6 Hematological tests not assessed by cycle.

Patient id.	Cycle	Lab. test

12.4.2. Biochemical Abnormalities During Treatment

Table 12.4.7 Biochemical abnormalities during treatment, worst grade per patient.

	N	Grade 1		…	Grade 4		All*[1]	
		N	%	…	N	%	N	%
ALT increased								
AP increased								
AST increased								
Creatinine increased								
Hyperglycemia								
Hypernatremia								
Hypercalcemia*[2]								
Hyperkalaemia								
Hypoglycemia								
Hyponatremia								
Hypocalcemia*[2]								
Hypokalaemia								
Hypoalbuminaemia								
GGT increased								

(*[1]) Any grade. (*[2]) Total plasmatic calcium corrected by albumin.

Table 12.4.8 Biochemical abnormalities during treatment, worst grade by cycle.

	N	Grade 1		…	Grade 4		All*[1]	
		N	%	…	N	%	N	%
ALT increased								
AP increased								
AST increased								
Creatinine increased								
Hyperglycemia								
Hypernatremia								
Hypercalcemia*[2]								
Hyperkalaemia								
Hypoglycemia								
Hyponatremia								
Hypocalcemia*[2]								
Hypokalaemia								
Hypoalbuminaemia								
GGT increased								

(*[1]) Any grade. (*[2]) Total plasmatic calcium corrected by albumin.

Listing 12.4.9 Grade 3/4 biochemical abnormalities. Worst grade per patient.

Patient id.	Test	Grade

Listing 12.4.10 Grade 3/4 biochemical abnormalities. Worst grade by cycle.

Patient id.	Cycle	Test	Grade

Listing 12.4.11 Biochemical tests not assessed per patient.

Patient id.	Lab. test

Listing 12.4.12 Biochemical tests not assessed by cycle.

Patient id.	Cycle	Lab. test

12.4.3. Laboratory abnormalities Over Time

Table 12.4.13 Evolution of hematological abnormalities from baseline, worst case per patient.

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

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

Table 12.4.14 Evolution of biochemical abnormalities from baseline, worst case per patient.

			Worst grade per patient						Total	
			0		1		…			
			N	%	N	%	N	%	N	%
Baseline*	AST increased	Grade 0								
		Grade 1								
		……								
	ALT increased	Grade 0								
		Grade 1								
		……								
	….	Grade 0								
		Grade 1								
		……								

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

Table 12.4.15 Platelet count and neutrophil count time course pattern (summary).

Laboratory abnormalities	Onset day grade 3/4	Days with grade 3/4	Time to recovery*
			Median (range)
Platelet count			
Neutrophil count			

(*) Defined as the time, in days, from the start of the grade 3/4 abnormality until the abnormality is recovered (grade ≤ 2).

Table 12.4.16 ALT and AST time course pattern (summary).

Laboratory abnormalities	Onset day grade 3/4	Days with grade 3/4	Time to recovery*
			Median (range)
ALT			
AST			

(*) Defined as the time, in days, from the start of the grade 3/4 abnormality until the abnormality is recovered (grade ≤ 2).

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

12.5.1. Physical Findings and ECOG PS

Table 12.5.1 ECOG performance status during the study.

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

(*) Worst ECOG PS of the cycle determinations.

Table 12.5.2 Physical examination during the study.

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

(*) Worst result per cycle.

Table 12.5.3 Weight by patient per cycle.

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

(*) % of changes compared to baseline.

12.5.2. LVEF, ECG and Other Related Tests

Listing 12.5.4 LVEF evolution during the study.

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

(*) LVEF (%) value and method.

Listing 12.5.5 Electrocardiogram results. Evolution during the study.

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

(*) Worst result of the cycle measurements.

12.6. Concomitant Therapy / Procedures According to the ATC Classification

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

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

Table 12.6.2 Summary of concomitant medication during treatment.

	N	%
No. of systems (ATC1 level) 0 1 2 ≥ 3 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	Treatment	Drug dose in the previous cycle	Platelets / RBC	Date of first transfusion	Date of last transfusion	No. of units required*

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

Table 12.6.4 Subsequent therapy.

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

II. APPENDIX: DATABASE LISTINGS

CRF Listings.

-Listing II.1.1.: Cover
-Listing II.1.2.: Screening
-Listing II.1.3.: Demography
-Listing II.1.4.: Pregnancy test and adequate contraception
-Listing II.1.5.: Prior medical history
-Listing II.1.6.: Cancer history: First diagnosis
-Listing II.1.7.: Cancer history: Current disease
-Listing II.1.8.: Prior surgery
-Listing II.1.9.: Prior radiotherapy
-Listing II.1.10.: Prior anticancer medical therapy
-Listing II.1.11.: Peripheral Neuropathy
-Listing II.1.12.: Prophylactic medication
-Listing II.1.13.: Drug administration
-Listing II.1.14.: Hematology laboratory values
-Listing II.1.15.: Biochemistry laboratory values
-Listing II.1.16.: Other metabolic laboratory values
-Listing II.1.17.: Performance status
-Listing II.1.18.: Physical examination
-Listing II.1.19.: Vital signs
-Listing II.1.20.: Electrocardiogram
-Listing II.1.21.: LVEF
-Listing II.1.22.: Other tests/ procedures
-Listing II.1.23.: Tumor assessment
-Listing II.1.24.: Evaluation of response by cycle
-Listing II.1.25.: Best study overall response
-Listing II.1.26.: Concomitant medication/ procedures
-Listing II.1.27.: End of treatment
-Listing II.1.28.: EORTC QLQ C30
-Listing II.1.29.: EORTC QLQ CIPN20
-Listing II.1.30.: Adverse events (including signs and symptoms)
-Listing II.1.31.: Follow up
-Listing II.1.32.: Surgery procedures (after end of treatment)
-Listing II.1.33.: Radiotherapy (after end of treatment)
-Listing II.1.34.: Medical treatment (after end of treatment)
-Listing II.1.35.: Death report form
-Listing II.1.36.: Off study
-Listing II.1.37.: Signature report

III. APPENDIX: ICH LISTINGS

In accordance with ICH E-3 guidelines, the patient listings specified as Section 16.2 will be prepared.

- 16.2.1 Discontinued Patients
- 16.2.2 Protocol Deviations
- 16.2.3 Patients Not Included in the Efficacy Analysis
- 16.2.4 Demographic Data
- 16.2.5 Compliance and/or Drug Concentration Data
- 16.2.6 Individual Efficacy Response Data
- 16.2.7 Adverse Event Listing (each patient)
- 16.2.8 Listing of Individual Laboratory Measurements by Patient

13.REFERENCES

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