PM104-B-001-09

Phase II Clinical and Pharmacokinetic Trial of Zalypsis® in Patients with Advanced and/or Metastatic Endometrial or Cervical Cancer Treated with at least One Line of Systemic Therapy

Statistical Analysis Plan

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1 Introduction

1.1 Study rationale

This Statistical Analysis Plan (SAP) explains in detail the statistical analyses that will be carried out for Pharmamar in PM104 – B – 001 – 09 study. The analyses described in this SAP are based upon and supplement those described in the study protocol (dated 27-Jan-2009).

1.2 Information on Study Drug

PM00104 is a new synthetic alkaloid that has been selected for clinical development based on its in vitro activity against human solid and non-solid tumor cell lines, its in vivo activity in xenografted human tumors, as well as an acceptable non-clinical toxicology profile.

2 Objectives

The study protocol states the following:

2.1 Primary

- To evaluate the antitumor activity of PM00104 administered as a 1-hour intravenous (i.v) infusion on Day 1, 8 and 15 every four weeks (d1, d8 and d15; q4wk) to patients with advanced and/or metastatic endometrial or cervical cancer previously treated with one line of systemic chemotherapy.

2.2 Secondary

- To determine the safety profile of this PM00104 regimen in these patients.
- To determine the pharmacokinetic (PK) profile of this PM00104 regimen in these patients.
- To determine the pharmacogenomic (PGx) profile of this PM00104 regimen in these patients. Hypothesis-generating exploratory PGx analyses will be conducted to correlate the molecular parameters found in the tumor samples of the patients with the clinical results achieved with PM00104.

3 Study design

Multicenter, open label, phase II clinical trial with single-agent PM00104 given as a as a 1-hour i.v. infusion on d1, d8 and d15 q4wk to patients with advanced and/or metastatic endometrial or cervical cancer progressing after at least one line of systemic chemotherapy.

The primary endpoint of the study is the overall response rate (ORR), defined as the percentage of patients with objective response (OR; complete or partial response) as defined by the Response Evaluation Criteria in Solid Tumors (RECIST).

4 Study populations

4.1 Analysis populations

Female adult patients with endometrial (Group 1) or cervical cancer (Group 2) progressing after at least one previous line of systemic chemotherapy are eligible for this trial. To be included in the study, patients have to fulfill all inclusion criteria and none of the exclusion criteria.

4.1.1 Efficacy population

To be evaluable for efficacy, patients must have received at least four infusions of the six infusions in the first two cycles and at least one disease measurement recorded not less than six weeks after treatment onset will be evaluable for efficacy.

In addition, any eligible patient who receives at least two of the three infusions in one treatment cycle and experience disease progression or die due to progressive disease (PD) prior to response evaluation will be considered evaluable for the main endpoint (ORR) and will be categorized as an "early progression".

Patients withdrawn due to toxicity without any tumor assessment after the start of study treatment will be considered as "treatment failures" and will not be replaced.

Patients withdrawn due to significant clinical deterioration of unknown reason, hypersensitivity reactions, refusal to continue on study for any reason or unrelated AEs without any tumor assessment after the start of study treatment will be considered not evaluable for efficacy and will be replaced.

4.1.2 Safety population

All patients who have received at least one complete or partial infusion of PM00104 infusion will be included in the safety analysis.

5 Endpoints

5.1 Primary endpoints

Overall response rate (ORR), defined as the percentage of patients with confirmed objective response (OR), either complete (CR) or partial (PR) response according to the RECIST.

5.2 Secondary endpoints

- Progression-free survival at four months (PFS4 rate), defined as the percentage of patients who are alive and with no evidence of disease progression at four months after the first study drug administration.

- Progression-free survival rate at six months (PFS6), defined as the percentage of patients who are alive and with no evidence of disease progression at six months after the first study drug administration.

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

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

- Overall survival (OS), defined as the time from the first day of treatment to the date of death (or the last day when the patient is known to be alive). Survival will be followed for up to six months after the treatment discontinuation of the last patient.

- Safety profile: AEs, SAEs, laboratory evaluations, deaths and the reason for study discontinuations, dose delays, modifications or omissions will be analyzed. All AEs and SAEs will be classified according to the NCI-CTCAE, version 3.0, and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 10.0.

- Treatment exposure:

    - *Date of treatment start***:** Date of treatment dose at cycle 1.

    - *Date of last dose*: Date of last treatment dose at last cycle.

    - *Date of treatment discontinuation (for the purpose of exposure calculations)*: The minimum date between the death date and the date of the first infusion of last cycle + 28 days.

    - *Body Surface Area (BSA):* The calculated surface of a human body measured in m^2.

    - *Treatment duration*: The time between the day of the first dose and the day of treatment discontinuation (in weeks).

    - *Total cumulative dose*: The sum of all the PM00104 doses from the first cycle until last cycle including the dose received in last cycle. (Expressed in mg/m^2).

    - *Absolute dose intensity:* The actual cumulative dose divided by number of weeks of treatment. (Expressed in $mg/m^2/wk$).

    - *Intended dose intensity*: The planned dose per cycle divided by the planned weeks by cycle. (Expressed in $mg/m^2/wk$).

    - *Relative dose intensity*: The ratio of absolute dose intensity (x100) divided by the intended dose intensity. (Expressed in percentage).

- Pharmacokinetic/Pharmacodynamic parameters.

- Pharmacogenomic profile

6 Sample size

6.1 Sample size determination

In this phase II trial, efficacy of PM00104 will be evaluated in two different groups of patients with endometrial or cervical cancer.

Group 1 (endometrial cancer): A Simon two-stage design will be adopted in this group to test the null hypothesis that the ORR by RECIST is ≤ 10% versus the alternative that ORR ≥ 30% (two-sided test; alpha=0.1 and beta=0.1).

A maximum of 30 evaluable patients will be included in this group. In a first stage, 10 evaluable patients will be recruited. If one or more (≥ 1) patients achieve an objective response, the accrual in this group will be expanded with 20 additional evaluable patients.

If the total number of patients with objective response is 6 or more (≥ 6) in 30 evaluable patients (i.e., an ORR in the whole study of at least 20%), the null hypothesis will be rejected and PM00104 will be considered for further clinical development in endometrial cancer.

Group 2 (cervical cancer): Also a Simon two-stage design where the null hypothesis ORR by RECIST is ≤ 5% vs. ORR ≥ 20% (two-sided test; alpha=0.1 and beta=0.1).

A maximum of 32 evaluable patients will be included in this group. In a first stage, 18 evaluable patients will be recruited. If one or more (≥ 1) patients achieve an objective response, the accrual in this group will be expanded with 14 additional evaluable patients.

If the total number of patients with objective response is 4 or more (≥ 4) in 32 evaluable patients (i.e., an ORR in the whole study of at least 12.5%), the null hypothesis will be rejected and PM00104 will be considered for further clinical development in cervical cancer.

6.2 Interim analyses

Interim efficacy analysis will be performed when the 10 first evaluable patients have been recruited in the group 1 and 18 patients have been recruited in the group 2. In addition, a safety evaluation will be performed when 10 patients in each group will be recruited and followed for at least four weeks. The study will be stopped, and the recommended dose re-evaluated if the stopping rule described below is met in any of the groups.

Other non-scheduled interim analyses might be performed exclusively for enhancing the safety of the patients.

Early stopping rule:

An early stopping rule for excessive toxicity will be evaluated when ten patients in each group will be recruited and followed for at least four weeks. A "serious toxicity" rate (STR) of 40% or more will be considered inadequate. The following are considered serious toxicities:

- Drug-related grade 4 neutropenia lasting for more than seven days.
- Grade 4 thrombocytopenia.
- Grade 3/4 nausea/vomiting despite adequate prophylaxis.
- Grade 3/4 transaminase increase lasting for more than seven days.
- Grade 3/4 fatigue.
- Any other grade 3/4 drug-related event leading to early study discontinuation.

If ≥ 4 patients of the first 10 patients had one of these serious toxicities, the trial will be stopped and the recommended dose and/or administration schedule for phase II will be re-evaluated.
With this stopping rule, the probability of ≥4/10 STR in the sample (if the true probability of STR is <1/6) is 0.0697. On the other hand, the probability of observing ≤3/10 STR in the sample (if the true probability of STR is >40%) would be 0.3822.

7 Statistical analysis

7.1 Treatment discontinuation and protocol deviations management

The accrual and study discontinuation details will be presented descriptively. The reasons for treatment discontinuation will be described by counts and percentages, overall and by number of cycles received. Reasons of treatment discontinuation other than disease progression will be detailed.

A study of the protocol deviations deemed relevant according to the Data Management Plan and Oncology review will be made following the ICH guidelines. The protocol deviations will be listed by type of deviation:

- Patients entered but not satisfying entry criteria
- Patients developing withdrawal criteria but not withdrawn
- Patients receiving incorrect dose or schedule
- Patients receiving excluded concomitant treatment

7.2 Demographic analysis

Demographics and baseline characteristics will be summarized by group for all recruited patients.

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

Age, sex, race, baseline weight, height, body surface area (BSA), PS, pulse, BPS, BPD, temperature, LVEF, ECG and X-ray results will be summarized descriptively. Age is calculated based on the date of birth at the time date of registration date.

For solid tumors, histology diagnosis, number of organs involved and sites of disease will be described following standard tables detailed in section 10 (Appendix I).

A frequency tabulation of the number of patients with the different types of previous cancer surgery, radiotherapy and systemic therapy will be given.

A summary of prior relevant history and signs and symptoms will be presented per patient.

Laboratory values at baseline will be tabulated. Median values, ranges and CTC grades will be displayed by laboratory parameters.

Concomitant therapies will be categorized per ATC (level 1 and 4) class and coded term. The number of patients receiving each type of therapy during the treatment phase will be tabulated in 2 separate tables: a frequency tabulation of the different therapies that started pre-study, and a frequency tabulation of the different therapies that started during the study. Each table will be

generated once by class, and once by coded term. The accompanying listing will contain all concomitant therapies.

7.3 Exposure

Cumulative dose, dose intensity and relative dose intensity, cycle delay, and dose modifications or omissions will be described following standard tables detailed in section 12 (Appendix III).

7.4 Statistical methodology for efficacy

Binomial estimates with exact 95% CIs will be calculated for the analysis of the main endpoint (ORR) and the secondary endpoints PFS4 and PFS6 rates. Time-to-event endpoints (DR, PFS and OS) will be analyzed according to the Kaplan-Meier method.

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

The characteristics of patients with complete response, partial response, or free from progression at 4 months, will be described.

Statistical tests, if and when they are carried out, will only have an exploratory purpose and have a threshold of α = 5%. Exact binomial Confidence Intervals will be calculated with the same significance level.

See section 11 (Appendix II) for further details on the efficacy analysis.

7.5 Statistical methodology for safety

Descriptive statistics, tabulation and graphic representation will be used for the evaluation of safety by tumor type in this phase II study, as described in section 12 (Appendix III).

If the safety profile of PM00104 is similar in both study groups (endometrial and cervical cancer), a pooled analysis for all included patients regardless its tumor type could be performed for safety.

Adverse events will be graded according to NCI-CTCAE version 3.0. The incidence and grade of adverse events and laboratory abnormalities will be calculated considering the most severe grade per patient and cycle.

Descriptive statistics will be used to present the profiles of drug-related adverse events, drug-related deaths, SAE and drug-related treatment discontinuation and the observed grade 1-4 toxicities, per patient and per cycle.

The shift of severity grades from baseline to the worst occurrence during treatment will be tabulated. The time to onset and recovery from neutrophils, platelets and hepatic enzymes elevations will be illustrated by means of descriptive statistics.

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, significant consequences and actions taken.

PS, weight gain – loss and LVEF measurements evolution during the study will be summarized by frequency tabulation.

See section 12 (Appendix III) for further details on the safety analysis.

7.6 Missing values management

In case of missing values in the determination of protocol deviations (i.e. time from last anticancer treatment to start of treatment with PM00104) the most conservative approach will be taken for the evaluation.

If a date is missing, the worst case will be taken into account when calculating the difference between two dates. In such a case, this will be specified in the table footnote.

The cycles with missing information regarding laboratory values or adverse events will be subtracted from the denominator of the tables.

As regards of the analysis of Time to Progression, in case of more than one missing tumor scan between the last evaluation without progression and the documentation of progressive disease, the time to progression will be censored at the day of the last tumor evaluation without progression.

8 Pharmacokinetic (PK) and pharmacogenomic (PGx) evaluation

These analysis will be described in two different documents not included in this SAP.

9 Statistical software

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

SAS v8.2 will be used for all the statistical analysis.

TABLES, LISTINGS AND FIGURE SHELLS

NOTE: All tables, listings and figures described in this section will be duplicated in two different groups. First, patients with endometrial cancer (group 1) and secondly, patients with cervical cancer (group 2).

If appropriate, a pooled analysis for all included patients regardless its tumor type (group 1 + group 2) could be performed for Safety as in Sections 12.2 and 12.3.

Each particular table, listing and figure will have a comprehensive header and/or footnotes, identifying the group of treatment and/or relevant specifications.

10 Appendix I. Patients disposition.

10.1 General characteristics.

10.1.1 Patients treated, eligible and evaluable.

Table 10.1.1. 1. Patients accrual by institution.

	Institution 1		Institution 2		Institution ..		Total	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
N-included								
N-treated								

Table 10.1.1. 2. Disposition of patients.

Event	**Date**
Date first consent	
Date first dose of first patien	
Date last consent	
Date first dose of last patient	
Date last dose	
Last follow up date	

Table 10.1.1. 3. Number of patients evaluable for analysis.

	N. evaluable for efficacy		N.evaluable for safety		Total	
	N	**%**	**N**	**%**	**N**	**%**
N-included						
N-treated						

10.1.2 Reasons for treatment discontinuation.

Table 10.1.2. 1. Reasons for treatment discontinuation.

	Total	
	N	%
Progressive disease		
Patient refusal		
Investigator decision		
…..		
Other*		

*See Listing 10.1.2.5

Table 10.1.2. 2. Reasons for treatment discontinuation by number of cycles received.

	Last Cycle (or Infusion)							
	Cycle 1		Cycle 2		Cycle (X)		Total	
	N	%	N	%	N	%	N	%
Progressive disease								
Patient refusal								
Investigator decision								
……								
Other*								

* See Listing 10.1.2.5

Table 10.1.2. 3 Reason for end of study.

	Total	
	N	%
Progressive disease		
Toxicity (study drug)		
Death		
….		
Other		

* See Listing 10.1.2.6

Table 10.1.2. 4. Time on treatment (months).

	N	Median	Min	Max

Listing 10.1.2. 5. Listing of reasons for treatment discontinuation other than progressive disease.

Patient ID	Reason	Specify

Listing 10.1.2. 6. Listing of reasons for study discontinuation other than progressive disease.

Patient ID	Reason	Specify

Listing 10.1.2. 7. Listing of treatment discontinuation due to AEs.

Patient	Cycle	PT MedDRA Code	AE Literal	Grade	Relation	Action	Significant consequences

10.1.3 Protocol deviations.

Listing 10.1.3. 1 Elegibility: Patients who entered the study even though they did not satisfy the entry criteria.

Dose level	Patient id	I-E criteria no fulfilled	Deviation

Listing 10.1.3. 2 Protocol deviations: Patients developing withdrawal criteria but were not withdrawn.

Dose level	Patient id	Deviation

Listing 10.1.3. 3 Protocol deviations: Patients who received incorrect dose or schedule.

Dose level	Patient id	Deviation

Listing 10.1.3. 4 Protocol deviations: Patients who received an excluded concomitant medication.

Dose level	Patient id	Deviation

11 Appendix II. Efficacy evaluation.

11.1 Baseline characteristics.

11.1.1 Patients characteristics at baseline.

Table 11.1.1. 1. Baseline characteristics: Summary statistics.

	Total (N=XX)	
	N	%
Race:		
Caucasian		
Black		
……		
Other*		
Age grouped:		
18 – XX years		
XX – YY years		
≥ YY years		

* Patient id and race as a footnote.
** Stands for Not Applicable. Specify details in the footnote.

Table 11.1.1. 2. Summary statistics: baseline characteristics.

	N	Missing	Median	Min	Max	Mean	SD
Age (years)							
Weight (Kg)							

11.1.2 Histology and time from diagnosis.

Table 11.1.2. 1. Cancer diagnosis at baseline.

	Total (N=XX)	
	N	**%**
Tumor type*:		
Endometrial		
Endometroid		
Papillary Serous		
Mixed		
Clear cell		
Other**		
Cervix		
Squamus cells carcinoma		
Adenocarcinoma		
Adenosquamus		
Other**		
Histology Grade:		
Well differentiated		
Moderately differentiated		
Poorly differentiated		
Undifferentiated		
Unknown		
Current Disease		
Locally advanced		
Metastatic		
Number of Sites involved (target-non target):		
1		
2		
3		
> 3		
Summary Statistics of Number of Sites involved (target-non target):		
N		
Median		
Minimum		
Maximum		

Programming Notes: Percentage is based on total patient included.
* One table for each group. ** See listing 11.1.2.5

Table 11.1.2. 2. Stage at baseline (FIGO criteria).

	N	%
IA		
IB		
…		

Table 11.1.2. 3. Sites for target and non-target lesions.

Sites	**Total**	
	N	**%**
Bone		
Lung		
….		

Listing 11.1.2. 4. Listing of patient histology.

Patient ID	**Tumor type**	**Histology**	**Grade**	**……**	**Current stage**
	Stage				

Listing 11.1.2. 5. Listing of other tumor types.

Patient ID	**Histology**	**……**	**Specify**

Listing 11.1.2. 6. Listing of target and non target lesions.

Patient ID	**Target/non-target**	**Site/Subsite**	**Method**

Listing 11.1.2. 7. Listing of patients with only one single lesion.

Patient ID	**Target/non-target**	**Site**	**Biopsy/FNA(Y/N)**	**Previously irradiated(Y/N)**
	Histology/Cytology			

Table 11.1.2. 8. Summary statistics of cancer diagnosis characteristics: Time from diagnosis and time from last PD.

	N	**Median**	**Min**	**Max**	**Mean**	**SD**
Time from first diagnosis to first infusion (months)						
Time from last progression to fir infusion (months)						

(*) SD stands for standard deviation

11.1.3 Prior anticancer therapy.

Table 11.1.3. 1 Surgery.

Surgery	**Total (N=XX)**	
	N	**%**

Table 11.1.3. 2 Radiotherapy type.

	Total (N=XX)	
	N	%
External		
Brachytherapy		
IORT		

Table 11.1.3. 3 Radiotherapy setting

	Total (N=XX)	
	N	%
Radiotherapy		
Chemoradiotherapy		

Listing 11.1.3. 4 Patients with prior radiotherapy

Patient ID	Type	Setting	Site	First date	Last date

Listing 11.1.3. 5 Patients with prior surgery.

Patient ID	Intention	Site and Procedures	Residual diseas	Date

Table 11.1.3. 6 Summary statistics of prior systemic anticancer therapy.

	N	Median	Min	Max	Mean	SD
Nº of lines						
Nº of agents						

Table 11.1.3. 7 Number of lines and agents of systemic anticancer therapy.

	Total (N=XX)	
	N	%
Number of lines		
1		
2		
3		
> 3		
Number agents		
1		
2		
3		
> 3		

Table 11.1.3. 8 Prior anticancer agents.

Antineoplastic and Immunomodulating agents (ATC-clas. Levels 1-4)	N	%
Antineoplastic Agents (L01)		
…..		
Endocrine therapy (L02)		
…..		

11.1.4 Prior history.

Listing 11.1.4. 1. Prior history.

Patient ID.	Description	Onset da	Resolved date

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

Table 11.1.5. 1 Physical examination at baseline.

	Total (N=XX)	
	N	%
Physical Examination:		
Normal		
Abnormal		
ECOG-PS:		
0		
1		
ECG:		
Normal		
Abnormal		
LVEF		
Normal		
Abnormal		
Adequate birth control:		
Yes		
No		
NA*		
Pregnancy test		
Positive		
Negative		

* NA stands for “Not applicable”

Listing 11.1.5. 2 Listing of abnormal ECG.

Patient ID	ECG result	Specify

Listing 11.1.5. 3 Listing of LVEF.

Patient ID	LVEF(%)	Method	Institutional normal range	Result

Table 11.1.5. 4 Vital signs.

	N	Missing	Median	Min	Max	Mean	SD
Heart Rate (beats/min)							
BPS (mmHg)							
BPD (mmHg)							
Temperature (ºC)							

11.1.6 Hematological values at baseline.

Table 11.1.6. 1. Hematological abnormalities at baseline.

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

Table 11.1.6. 2. Hematology at baseline. Last value before treatment.

	N	Missing	Median	Min	Max	Mean	SD
Leukocytes							
Neutrophils							
Hemoglobin							
Platelets							
Lymphocytes							

Listing 11.1.6. 3. Hematology at baseline. Patients with hematological parameters missing.

Patient ID.	Exam

Listing 11.1.6. 4. Hematology at baseline. Abnormalities grade >=2.

Patient ID.	Parameter	Value	Grade

11.1.7 Biochemical values at baseline

Table 11.1.7. 1. Biochemical abnormalities at baseline.

	Grade 1		Grade 2		Grade 3		Grade 4		Total	
	N	%	N	%	N	%	N	%	N	%
AST										
ALT										
Total Bilirubin										
Direct Bilirubin										
….										

Table 11.1.7. 2. Biochemistry at baseline. Last value before treatment.

	N	Missing	Median	Min	Max	Mean	Max
AST							
ALT							
Total Bilirubin							
Direct Bilirubin							
….							

Listing 11.1.7. 3 Biochemistry at baseline. Patients with biochemical parameters missing.

Patient ID.	Exam

Listing 11.1.7. 4. Biochemistry at baseline. Abnormalities grade >=2.

Patient ID.	Parameter	Value	Grade

11.1.8 Other metabolic values at baseline.

Table 11.1.8. 1. Other metabolic abnormalities at baseline.

	Grade 1		Grade 2		Grade 3		Grade 4		Total	
	N	%	N	%	N	%	N	%	N	%
Hyperglycemia										
….										

* All metabolic parameters susceptible to be graded as per NCI-CTCAE v3.0

Table 11.1.8. 2. Other metabolic abnormalities at baseline (Hyper-Hypo). Last value before treatment.

	N	Missing	Median	Min	Max	Mean	SD
Glucose							
*….							

* Glucose (Hyper-Hypo), Albumin, lipase, Total proteins, Troponin I ,LDH, CPK,CPK-MB

Listing 11.1.8. 3. Patients with metabolic parameters missing.

Patient ID.	Exam

Listing 11.1.8. 4. Other metabolic at baseline. Abnormalities grade >=2.

Patient ID.	Parameter	Value	Grade

11.1.9 Signs and symptoms at baseline.

Table 11.1.9. 1. Summary statistics: Signs and symptoms.

SOC/MedDRA Preferr term		Grade 1		Grade 2		Grade 3		Grade 4		Total	
		N	%	N	%	N	%	N	%	N	%
General Disorders	Abdominal Distension										
	…..										
… Pain											

Table 11.1.9. 2. Median of signs and symptoms by dose level.

	N	Median	Min	Max	Mean	SD*

(*) SD stands for standard deviation

Listing 11.1.9. 3. Listing of Baseline characteristics: Signs and symptoms.

Patient ID	SOC	Sign/symptom	Grade	Onset date

11.1.10 Concomitant therapy.

Table 11.1.10. 1. Agents of Concomitant therapy started at baseline.

Concomitant medication (ATC1/ATC4)			
(ATC level 1)	**(ATC level 4)**	**N**	**%**
…			

Table 11.1.10. 2. Concomitant medication characteristics at baseline.

	Total (N=XX)	
	N	**%**
Number of Systems (ATC1)		
1		
2		
3		
> 3		
Number of agents (ATC4)		
1		
2		
3		
> 3		

Table 11.1.10. 3. Concomitant therapy started at baseline. Summary of number of systems involved (ATC1).

	N	**Median**	**Min**	**Max**	**Mean**	**SD***

Table 11.1.10. 4. Concomitant therapy started at baseline. Summary of number of agents involved (ATC4).

	N	**Median**	**Min**	**Max**	**Mean**	**SD***

Listing 11.1.10. 5. Listing of Baseline characteristics: Concomitant therapy.

Patient ID	**Start date**	**ATC code**	**Route**	**….**	**Reason for use**

11.2 Efficacy.

11.2.1 Response.

Listing 11.2.1. 1. Listing of patients excluded from the efficacy analysis.

Patient ID	**Reason**

Table 11.2.1. 2. Patients evaluable for efficacy.

Evaluable	Total (N=XX)	
	N	**%**
Yes		
No		
Total		

Programming Notes: Percentage is based on total patient included (ITT)

Table 11.2.1. 3. Best response in all evaluable patients.

Response	N	%	CI (95%)
Complete Response (CR)			
Partial Response (PR)			
Stable Disease ≥ 4 months*			
Stable Disease (SD)			
Progression Disease (PD)**			

Programming Notes: Percentage is based on the total of patient evaluable for efficacy
(*) Patients who are free from progression in the tumor evaluation at 4 months
(**) Patients with Early PD will also be included in this category (provided that they receive at least two infusions of PM00104)
NOTE: An analysis of best response in the 10 and 18 first evaluable patients in the group 1 and group 2 respectively will also be performed. Table 11.2.1.3 will be repeated at this interim analysis and at the end of the study.

Table 11.2.1. 4. Best response in all treated patients.

Response	N	%	CI (95%)
Complete Response (CR)			
Partial Response (PR)			
Stable Disease ≥ 4 months*			
Stable Disease (SD)			
Progression Disease (PD)**			
Not evaluable			

Programming Notes: Percentage is based on total patient of patients treated
(*)Patients who are free from progression in the tumor evaluation at 4 months
(**) Patients with Early PD will also be included in this category (provided that they receive at least two infusions of PM00104)

Table 11.2.1. 5. Progression Free Survival status at 4 months (PFS4) in all evaluable patients.

PFS4	Total (N=XX)	
	N	% (95% CI)
Yes		
No		
Total		

Table 11.2.1. 6 . Progression Free Survival status at 4 months (PFS4) in all treated patients.

PFS4	Total (N=XX)	
	N	% (95% CI)
Yes		
No		
Total		

Table 11.2.1. 7. Progression Free Survival status at 6 months (PFS6) in all evaluable patients.

PFS6	Total (N=XX)	
	N	% (95% CI)
Yes		
No		
Total		

Table 11.2.1. 8. Progression Free Survival status at 6 months (PFS6) in all treated patients.

PFS6	Total (N=XX)	
	N	% (95% CI)
Yes		
No		
Total		

11.2.2 Time-to-event variables.

Table 11.2.2. 1. Duration of response.

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

Table 11.2.2. 2. Progression Free Survival (Kaplan-Meier estimates in all evaluable patients).

Summary
N=XX
Events X (XX.X%)
Censored X (XX.X%)
Median X.X 95% CI (X.X-X.X)
PFS rate at 4 months XX.X% 95% CI XX.XX%-XX.X%)
PFS rate at 6 months XX.X% 95% CI XX.XX%-XX.X%)

Table 11.2.2. 3. Progression Free Survival (Kaplan-Meier estimates in all treated patients).

Summary
N=XX
Events X (XX.X%)
Censored X (XX.X%)
Median X.X 95% CI (X.X-X.X)
PFS rate at 4 months XX.X% 95% CI XX.XX%-XX.X%)
PFS rate at 6 months XX.X% 95% CI XX.XX%-XX.X%)

Table 11.2.2. 4. Overall Survival. Evaluable population.

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

Table 11.2.2. 5. Overall Survival. Treated population.

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

Table 11.2.2. 6. Follow-up period.

Parameter	**Median**	**95% CI Lower bound**	**95% CI Upper bou**
PFS			
OS			

11.2.3 Patients with clinical benefit.

Listing 11.2.3. 1. Characteristics of patients with clinical benefit*.

Patient characteristics				**Outcome prior treatment**				**PM00104 treatment**		
Patient	**Sex/Age/PS**	**Histology**	**Nº Prior CT Lines**	**Last prior Treatment**	**Cycles received**	**Best Response**	**TTP**	**Cyc**	**PFS**	**OS ...**

(*) Clinical benefit defined as patients who experience any of the following CR or PR or PFS4.

11.2.4 Tumor marker evolution/response (group 1).

Table 11.2.4. 1 CA-125 evolution summary.

	Baseline	**Cyc 1**	**Cyc 2**	**Cyc 3**	**……**
N					
Median					
Max					
Min					

Table 11.2.4. 2 CA-125 evolution during treatment per patient.

Patient ID	**Baseline**	**Cycle 1**	**Cycle 2**	**……..**

12 Appendix III. Safety evaluation.

12.1 Extent of exposure.

12.1.1 Treatment administration.

Table 12.1.1. 1. Cycles administered.

Cycles per patient: n (%)	**N**	**%**
1		
2		
3		
>3		

Table 12.1.1. 2. Summary of cycles administered.

	N	Median	Min	Max	Mean	SD*

(*) SD stands for standard deviation

Table 12.1.1. 3. Dose intensity.

	N	Median	Min	Max
Cumulative dose (mg/ m²)				
Treatment duration (wk)				
Dose intensity (mg/m² wk)				
Relative dose intensity (%)				

12.1.2 Dose delays.

Table 12.1.2. 1. Dose delay.

	N	%
Number of patients treated		
Number of patients with any dose delay		
Number of cycles administered		
Number of cycles susceptible to be delayed		
Patients with		
No delays		
1 cycle delayed		
2 cycles delayed		
≥ 3 cycles delayed		
Number of cycles with dose delay*		

Programming Notes: Percentage is based on number of cycle susceptible to be delayed.
* Denominator = Number of cycles susceptible to be delayed.

Table 12.1.2. 2. Dose delay according to their relationship to study drug.

	Treatment related**		Non – Treatment related	
	N	%	N	%
Patients with				
No delays				
1 cycle delayed				
2 cycles delayed				
≥ 3 cycles delayed				
Number of cycles with dosing delay				

Programming Notes:
* Denominator = Number of cycles susceptible to be delayed.
** Hematological reason / Non hematological reason.

Table 12.1.2. 3. Length of dose delay.

	Treatment related*		Non – Treatment relate		Total	
	N	%	N	%	N	%
Lenght of delay						
1 – 7 days						
7 – 14 days						
> 14 days						

Programming Notes:
* Denominator = Number of cycles susceptible to be delayed.
** Hematological reason / Non hematological reason.

Table 12.1.2. 4 . Dose delay and reason by cycle.

	Cycle 2		Cycle 3		…		Total	
	N	%	N	%	N	%	N	%
Number of delays								
Treatment related*								
Hematological reason								
Non hematological reason								
Non Treatment related*								

Programming Notes: * Denominator = Number of cycles susceptible to be delayed.

Listing 12.1.2. 5. Listing of patient with dose delay.

Patient II	Cycle	Reason of delay	Comments	Delay (days)

12.1.3 Dose reduction.

Note: All dose reductions will be considered and described, specifying the reason for reduction (hematological toxicity, non hematological toxicity or other causes not due to study drug).

Table 12.1.3. 1 Dose reduction.

	N	%
Number of patients treated		
Number of patients with dose reduced		
Number of cycles administered		
Patients with		
Nº reductions		
1 cycle reduction		
2 cycle reductions		
≥ 3 cycle reductions		
Number of cycles with dose reduction		

Programming Notes: Percentage is based on number of cycle susceptible to be reduced.

Table 12.1.3. 2 Dose reduction according to their relationship to study drug.

	Treatment related**		Non – Treatment related	
	N	%	N	%
Patients with				
Nº reductions				
1 reduction				
2 reductions				
≥ 3 reductions				
Number of cycles with dose reduction*				

Programming Notes:* Denominator = Number of cycles susceptible to be reduced.
** Hematological reason / Non-hematological reason.

Table 12.1.3. 3 Dose reduction and reason by cycle.

	Cycle 2		Cycle 3		…		Total	
	N	%	N	%	N	%	N	%
Number of patients								
Number of delays								
Treatment related*								
Hematological reason								
Non hematological reaso								
Non Treatment related*								

Programming Notes:* Denominator = Number of cycles susceptible to be reduced.

Listing 12.1.3. 4 Patient with dose reduction.

Patient ID	Cycle	Reason of reductio	Comments	Reduction (%)

12.1.4 Skipped doses.

Table 12.1.4. 1 Skipped doses.

	N	%
Number of patients treated with at least 2 infusions		
Number of patients with any skipped dos		
Number of patients with any skipped dos (drug related)		
Number of cycles administered		
Number of cycles susceptible to have any omission		
Number of cycles with at least one skipp dose (drug related)		
Day 8		
Day 15		
Day 8+15		

	Treatment related**		Non – Treatment related	
	N	%(of all cycles)	N	%(of all cycles)
Day 8				
Day 15				
Day 8+15				

Listing 12.1.4.3. Listing of patients with skipped doses.

Patient ID	Cycle/infusion (skipped dose)	Reason (drug related/other)	Comments

12.2 Toxicity.

12.2.1 Adverse events.

Table 12.2. 1 Drug related adverse events. Worst case per patient.
Table 12.2. 2 Drug related adverse events occurring in > 10% of all patients. Worst case per patient.
Table 12.2. 3 All adverse events regardless relationship. Worst case per patient.
Table 12.2. 4 All adverse events regardless relationship occurring in > 10% of all patients. Worst case per patient.
Table 12.2. 5 Drug related adverse events. Worst case per cycle.
Table 12.2. 6 Drug related adverse events occurring in > 10% of all cycles. Worst case per cycle.
Table 12.2. 7 All adverse events regardless relationship. Worst case per cycle.
Table 12.2. 8 All adverse events regardless relationship occurring in > 10% of all cycles. Worst case per cycle.

System Organ Class/ Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Total	
	N	%	N	%	N	%	N	%	N	%
System Organ Class 1										
Preferred Term 1										
……..										
System Organ Class 2										
Preferred Term 1										
……..										

* Percentages are based on the safety population. Table shows number of distinct patients with events.

12.2.2 Serious toxicity rate.

Table 12.2.2. 1 Serious toxicity rate by group.

	Group XX	
	N	% (*)
Yes		
No		

(*) Based on the first 10 consecutive patients by group.

Listing 12.2.2. 1 Listing of patients with any serious toxicity rate (grades 3-4) by group.

Patient ID	MedDRA preferred term	Grade	Relation with the study drug	……	Onset date	End Date

12.2.3 Serious adverse events.

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

Listing 12.2.3. 1. Listing of SAEs

Patient ID	MedDRA preferred term	Grade	Relation with the study drug	….	Start date	End Date

Listing 12.2.3. 2. Listing of deaths related to study drug.

Patient ID	Cause of death	Death date	Time from last infusion (days)	Autopsy (Y/N)	Autopsy report available (Y/N)

12.3 Laboratory evaluation.

12.3.1 Hematological abnormalities.

Table 12.3.1. 1 Hematology worst grade per patient.

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

Programming Notes: Percentages are based on the safety population.

Table 12.3.1. 2 Hematology worst grade per cycle.

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

Programming Notes: Percentages are based on the safety population.

Table 12.3.1. 3 Supportive listing: Patients with any hematological abnormalities grade 3-4.

Patient	Lab. test	Cycle	Examination dat	N	Std. value	xLLN	Grade NCI CTCAE v3.0

Listing 12.3.1. 4 Listing of patients with haematology evaluations missing.

Patient	Cycle	Lab. test

Table 12.3.1. 5 Time course and recovery from hematological toxicities.

	N	All cycles	
		Median	Range
Neutrophils			
Day of nadir neutrophils count			
Nadir of neutrophils count (/mm3)			
Day of neutropenia G3-4 onset			
Day of recovery to grade ≤2			
N° of days with grade 3-4 neutropenia			
Day of recovery to grade ≤ 1			
Platelets			
Day of nadir platelets count			
Nadir of platelets count (/mm3)			
Day of thrombopenia G3-4 onset			
Day of recovery to grade ≤2			
N° of days with grade 3-4 thrombopenia			
Day of recovery to grade ≤ 1			

Programming notes: (*)Denominator = N of patients with Grade 3-4

Table 12.3.1. 6 Baseline grade and evolution of hematological toxicities.

	Worst grade per patient							
	Grade 0-		Grade 2		Grade 3		Grade 4	
	N	%	N	%	N	%	N	%
Anemia (Baseline)								
Grade 0-1								
Grade 2								
Grade 3								
Grade 4								
Neutropenia (Baseline)								
Grade 0-1								
Grade 2								
Grade 3								
Grade 4								
……								
Grade 0-1								
Grade 2								
Grade 3								
Grade 4								

12.3.2 Biochemistry abnormalities.

Table 12.3.2. 1 Biochemistry worst grade per patient.

	Grade 1		Grade 2		Grade 3		Grade 4		Total	
	N	%	N	%	N	%	N	%	N	%
AST										
ALT										
Total Bilirubin										
Direct Bilirubin										
….										

Programming Notes: Percentages are based on the safety population.

Table 12.3.2. 2 Biochemistry worst grade per cycle.

	Grade 1		Grade 2		Grade 3		Grade 4		Total	
	N	%	N	%	N	%	N	%	N	%
AST										
ALT										
Total Bilirubin										
Direct Bilirubin										
….										

Programming Notes: Percentages are based on the safety population.

Table 12.3.2. 3 Supportive listing: Patients with any Biochemistry abnormalities grades 3-4.

Patient ID	Lab. test	Cycle	Examination date	N	Std. valu	xLLN	Grade

Listing 12.3.2. 4 Listing of patients with biochemistry evaluations missing.

Patient	Cycle	Lab. tes

Table 12.3.2. 5 Time course and recovery from biochemistry toxicities.

	N	All cycles	
		Median	Range
ALT			
Day of peak ALT count			
Nadir of ALT count (/mm3)			
Day of ALT G3-4 onset			
Day of recovery to grade ≤2			
N° of days with grade 3-4 ALT increase			
Day of recovery to grade ≤ 1			
AST			
Day of peak AST count			
Nadir of AST count (/mm3)			
Day of AST G3-4 onset			
Day of recovery to grade ≤2			
N° of days with grade 3-4 AST increase			
Day of recovery to grade ≤ 1			

Programming notes: (*) Denominator= N of patients with Grade 3-4.

Table 12.3.2. 6 Baseline grade and evolution of Biochemical toxicities.

	Worst grade per patient							
	Grade 0-1		Grade 2		Grade 3		Grade 4	
	N	%	N	%	N	%	N	%
ALT (Baseline)								
Grade 0-1								
Grade 2								
Grade 3								
Grade 4								
AST (Baseline)								
Grade 0-1								
Grade 2								
Grade 3								
Grade 4								
……								
Grade 0-1								
Grade 2								
Grade 3								
Grade 4								

12.3.3 Other metabolic abnormalities.

Table 12.3.3. 7 Metabolic abnormalities worst grade per patient.

	Grade 1		Grade 2		Grade 3		Grade 4		Total	
	N	%	N	%	N	%	N	%	N	%
Hyperglycemia										
….										

* All metabolic parameters susceptible to be graded as per NCI-CTCAE v3.0

Table 12.3.3. 8 Metabolic abnormalities grade per cycle.

	Grade 1		Grade 2		Grade 3		Grade 4		Total	
	N	%	N	%	N	%	N	%	N	%
Hyperglycemia										
….										

* All metabolic parameters susceptible to be graded as per NCI-CTCAE v3.0

Table 12.3.3. 9 Supportive listing: Patients with any metabolic abnormalities grades 3-4.

Patient ID	Lab. test	Cycle	Examination date	N	Std. value	xLLN	Grade

Listing 12.3.3. 10 Listing of patients with metabolic evaluations missing.

Patient	Cycle	Lab. test

12.4 Vital Signs.

Table 12.4. 1 Vital signs.

Vital Signs	Baseline	Cycle 1	Cycle 2	…	Cycle (X)
PS					
Weigth (Kg)					
LVEF (%)					

Table 12.4. 2 Listing of abnormal ECG.

Patient id	Result	Specify

12.5 Concomitant medication during treatment.

Table 12.5.1. 1. Agents of Concomitant therapy started during treatment.

Concomitant medication (ATC1/ATC4)			
(ATC level 1)	**(ATC level 4)**	**N**	**%**
…			

Table 12.5.1. 2. Concomitant medication characteristics during treatment.

	Total (N=XX)	
	N	**%**
Number of Systems (ATC1)		
1		
2		
3		
> 3		
Number of agents (ATC4)		
1		
2		
3		
> 3		

Programming Notes: Percentage is based on total patient included.

Table 12.5.1. 3. Concomitant therapy during treatment. Summary of systems involved (ATC1).

	N	Median	Min	Max	Mean	SD*

(*) SD stands for standard deviation

Table 12.5.1. 4. Concomitant therapy during treatment. Summary of agents involved (ATC4).

	N	Median	Min	Max	Mean	SD

Table 12.5.1. 5. Listing of Baseline characteristics: Concomitant therapy.

Patient ID	Start date	ATC code	Route	….	Reason for use

13 Figures.

NOTE: Figures will be showed for “all evaluable patients” and “all treated patients” by group when applicable. Also in case of patients with STR individual figures for the specific toxicity will be shown.

Figure 13. 1. Overall survival.

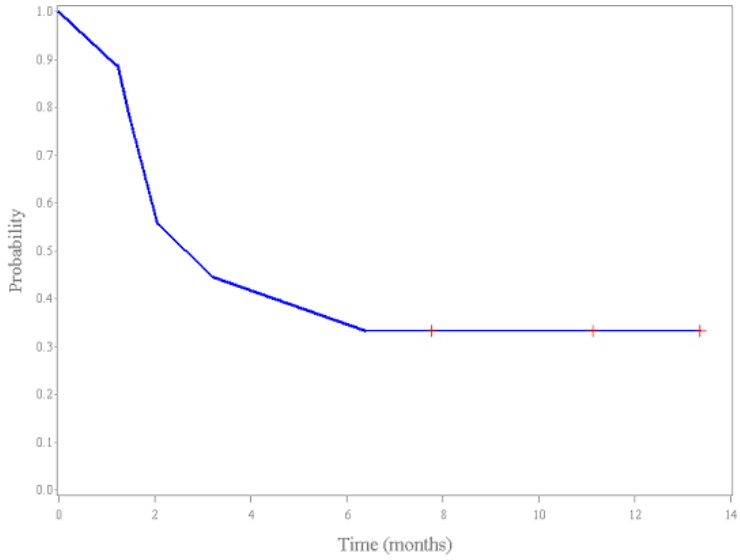


Figure 13. 2. Progression-free survival.

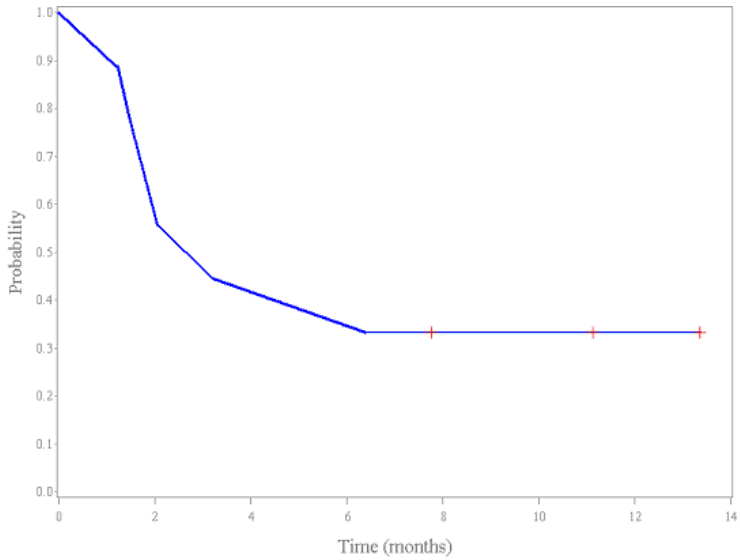
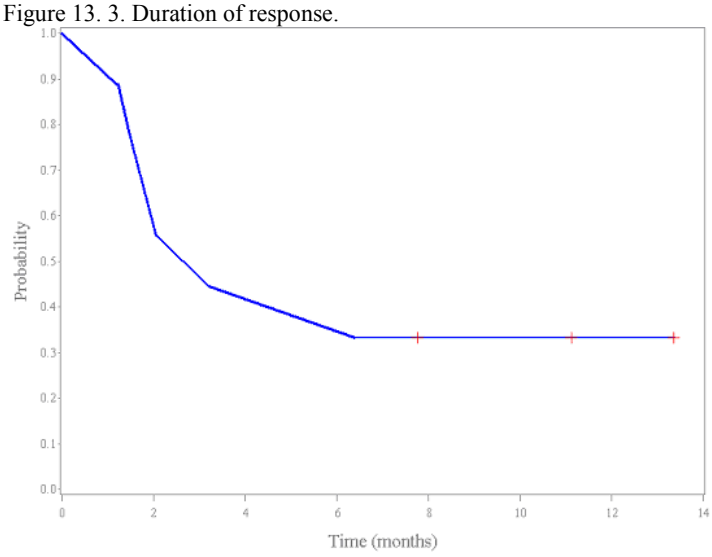


Figure 13. 3. Duration of response.



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

Figure 13. 4. CA-125 for responders.

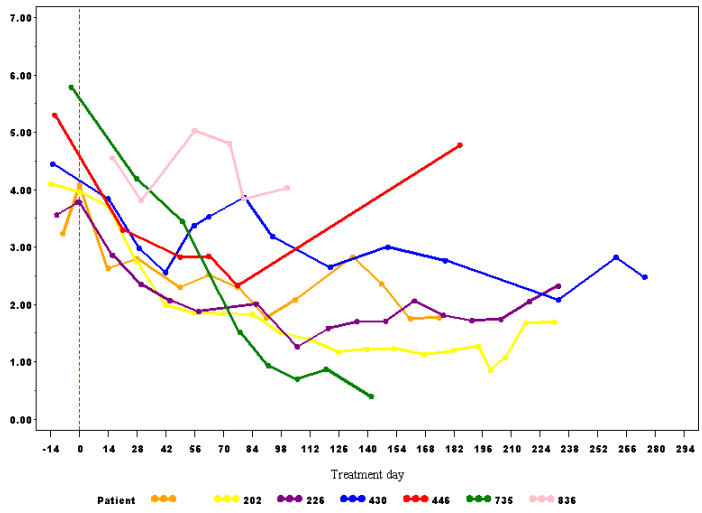
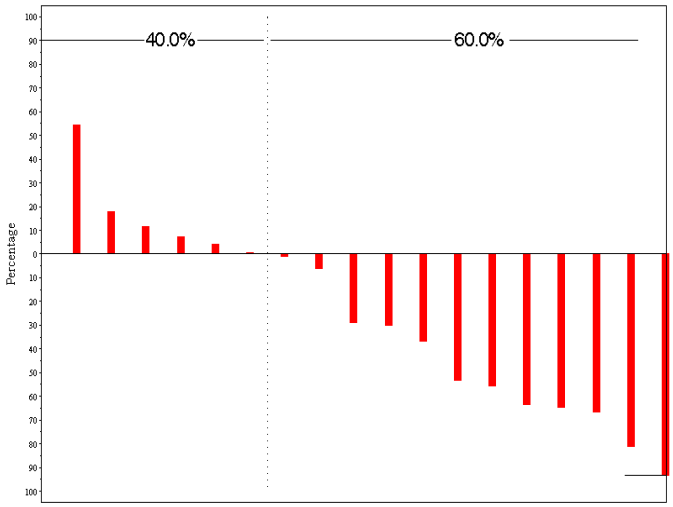
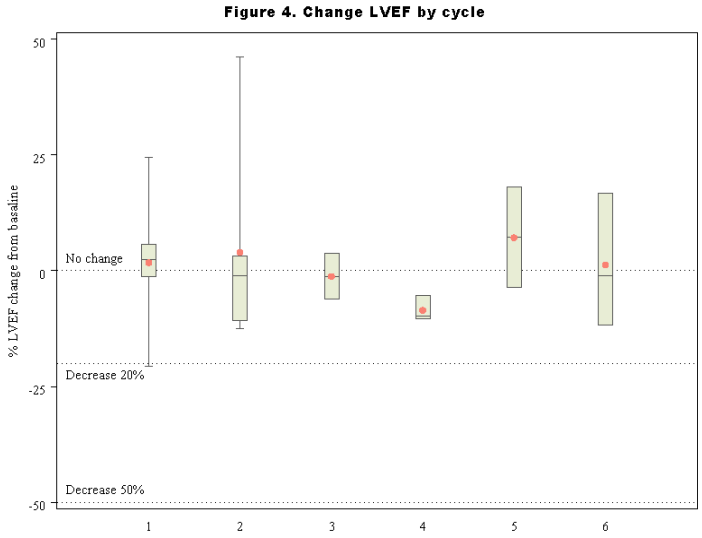


Figure 13. 5. Waterfall plots.



Maximum tumor shrinkage in measurable lesions by RECIST will be displayed. Additional graphs by tumour type and RECIST/CA-125 response will also be provided when applicable.

Figure 13. 6. Boxplot of LVEF evolution from BL .



Boxplot showing the change by cycle in LVEF from baseline.