

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

AuthorMariano Siguero, BiostatisticianVersion1.0Date28-07-09NCT Code00900562

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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 m².
 - *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/m²).
 - *Absolute dose intensity:* The actual cumulative dose divided by number of weeks of treatment. (Expressed in mg/m²/wk).
 - *Intended dose intensity*: The planned dose per cycle divided by the planned weeks by cycle. (Expressed in mg/m²/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 $\leq 10\%$ versus the alternative that ORR $\geq 30\%$ (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 (\geq 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 $\leq 5\%$ vs. ORR $\geq 20\%$ (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 (\geq 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 \geq 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 \geq 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 \leq 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 $\alpha = 5\%$. 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.

	Ins	titution 1	Inst	itution 2	Instit	ution	Г	otal
	Ν	%	Ν	%	Ν	%	Ν	%
N-included								
N-treated								

Table 10.1.1. 2. Disposition of patients.

Event	Date
Date first consent	
Date first dose of first patient	
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.

-		valuable efficacy		evaluable or safety	Total	
	Ν	%	Ν	%	Ν	%
N-included						
N-treated						

10.1.2 Reasons for treatment discontinuation.

Table 10.1.2. 1. Reasons for treatment discontinuation.

						Т	otal	
					Ν			%
Progressive disease								
Patient refusal								
Investigator decision								
Other*								
*See Listing 10.1.2.5								
Fable 10122 Descent for the								
Table 10.1.2. 2. Reasons for tree	eatment di	scontinuat	ion by nu		le (or Infu	sion)		
	C	ycle 1	(ycle 2	<u>Cycl</u>	,		Total
	N	<u>%</u>	N	<u>%</u>	N	%	Ν	%
Progressive disease								
Patient refusal								
Investigator decision								
Other*								
* See Listing 10.1.2.5								
Table 10.1.2. 3 Reason for end	of study							
Table 10.1.2. 5 Reason for end	of study.					7	otal	
						N I	otai	%
Progressive disease								,.
Toxicity (study drug)								
Death								
Other								
* See Listing 10.1.2.6								
Fable 10.1.2. 4. Time on treatment	nent (mon	the)						
Table 10.1.2. 4. Time on treating		N	N	Iedian	Ν	[in		Max
		11	10.	louiun	10			IVIUA
Listing 10.1.2. 5. Listing of rea	sons for t	reatment di	iscontinu	ation other th	nan progressiv	ve disease		
Patient ID				Reason			Specif	у
	C	. 1 1	<i></i>	a a	· ,			
Listing 10.1.2. 6. Listing of rea Patient ID	sons for s	tudy disco	ntinuation Reas		progressive d		oify	
Patient ID			Reas	011		Spe	city	
Listing 10.1.2. 7. Listing of trea	atment dis	scontinuati	on due to	AEs.				
Listing 10.1.2. 7. Listing of trea Patient Cycle PT M	atment dis [edDRA		on due to Literal		Relation	Actio	Sig	nificant

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
isting 10.1.3. 2 Protoco	l deviations: Patients d	eveloping withdrawal criteria but	were not
vithdrawn.		1 0	
Dose level	Patient id	Deviatio	n
isting 10 1 3 3 Protoco	l deviations: Patients w	vho received incorrect dose or sch	edule

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

	Dose level	Patient id	Deviation
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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 (1	N=XX)
	Ν	%
Race:		
Caucasian		
Black		
Other*		
Age grouped:		
18 - XX years		
XX – YY years		
\geq YY years		
* Patient id and race as a footnote.		
** Stands for Not Applicable. Specify details in the	ne footnote.	
Table 11.1.1. 2. Summary statistics: baseline characteristics.		

	Ν	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)	
	Ν	%
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		

* One table for each group. ** See listing 11.1.2.5

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

IA IB Table 11.1.2. 3. Sites for target and non-target lesions. Total Sites Total Bone N Lung Listing 11.1.2. 4. Listing of patient histology. Current stage Patient ID Tumor type Histology Grade Current stage Listing 11.1.2. 5. Listing of other tumor types. Patient ID Histology Patient ID Histology Specify Listing 11.1.2. 6. Listing of target and non target lesions. Patient ID Target/non-target Site Biopsy/FNA(V/N) Previously irradiated(V/N) Listing 11.1.2. 7. Listing of patients with only one single lesion. Patient ID Target/non-target Site Biopsy/FNA(V/N) Previously irradiated(V/N) Table 11.1.2. 8. Summary statistics of cancer diagnosis characteristics: Time from diagnosis and time from last PD. N Median Max Mean S Time from first diagnosis to first infusion (months)				N		%	
Total Total N % Bone Lung Lung							
Total Sites Total Sites N % Bone Lung	IB						
Sites Total Bone N % Bone Lung							
Sites N % Bone Lung	Table 11.1.2. 3. S	Sites for target and non-target	t lesions.				
Bone Lung Current stage isting 11.1.2. 4. Listing of patient histology. Tumor type Histology Grade Current stage isting 11.1.2. 5. Listing of other tumor types. Patient ID Histology Current stage isting 11.1.2. 6. Listing of other tumor types. Patient ID Histology Specify isting 11.1.2. 6. Listing of target and non target lesions. Patient ID Target/non-target Site/Subsite Method isting 11.1.2. 7. Listing of patients with only one single lesion. Patient ID Target/non-target Site/Subsite Method isting 11.1.2. 7. Listing of patients with only one single lesion. Previously irradiated(Y/N) Patient ID Target/non-target Site Biopsy/FNA(Y/N) Previously irradiated(Y/N) Fable 11.1.2. 8. Summary statistics of cancer diagnosis characteristics: Time from diagnosis and time from last PD. N Median Mean S Time from first diagnosis to first infusion (months) Time from last progression to fir infusion (months) Time from last progression to fir infusion (months) Time from anticancer therapy. 11.1.3 Prior anticancer therapy. Total (N=XX) Surgery.	Sites						
Lung	Bone				I	70	
isting 11.1.2. 4. Listing of patient histology. Patient ID Tumor type Histology Grade Current stage isting 11.1.2. 5. Listing of other tumor types. Patient ID Histology Specify isting 11.1.2. 6. Listing of target and non target lesions. Patient ID Target/non-target Site/Subsite Method isting 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) Fibel 11.1.2. 8. Summary statistics of cancer diagnosis characteristics: Time from diagnosis and time from last PD. Fable 11.1.2. 8. Summary statistics of cancer diagnosis characteristics: Time from diagnosis and time from last PD. Time from first diagnosis to first infusion (months) Time from last progression to fir infusion (months) *) SD stands for standard deviation LI.1.3 Prior anticancer therapy. Target. Surgery. Total (N=XX)							
Patient ID Tumor type Histology Grade Current stage .isting 11.1.2.5. Listing of other tumor types. Patient ID Histology	••••						
Patient ID Stage Current stage .isting 11.1.2. 5. Listing of other tumor types. Patient ID Histology	Listing 11.1.2. 4.	Listing of patient histology					
Stage Listing of other tumor types. Patient ID Histology Specify			y Grade	•••••		Current st	age
Patient ID Histology Specify sting 11.1.2. 6. Listing of target and non target lesions. Method Patient ID Target/non-target Site/Subsite Method sting 11.1.2. 7. Listing of patients with only one single lesion. Previously irradiated(Y/N) Patient ID Target/non-target Site Biopsy/FNA(Y/N) Previously irradiated(Y/N) Patient ID Target/non-target Site Biopsy/FNA(Y/N) Previously irradiated(Y/N) Fable 11.1.2. 8. Summary statistics of cancer diagnosis characteristics: Time from diagnosis and time from last PD. N Median Min Max Mean S Time from first diagnosis to first infusion (months) Time from last progression to fir infusion (months) *) SD stands for standard deviation *) SD stands for standard deviation Surgery. Total (N=XX)		Stage					8
Patient ID Histology Specify sting 11.1.2. 6. Listing of target and non target lesions. Method Patient ID Target/non-target Site/Subsite Method sting 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) Patient ID Target/non-target Site Biopsy/FNA(Y/N) Previously irradiated(Y/N) Fable 11.1.2. 8. Summary statistics of cancer diagnosis characteristics: Time from diagnosis and time from last PD. N Median Max Mean S 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. Total (N=XX)							
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Patient ID Target/non-target Site/Subsite Method Listing 11.1.2. 7. Listing of patients with only one single lesion. Target/non-target Site Biopsy/FNA(Y/N) Previously irradiated(Y/N) Patient ID Target/non-target Site Biopsy/FNA(Y/N) Previously irradiated(Y/N) Fable 11.1.2. 8. Summary statistics of cancer diagnosis characteristics: Time from diagnosis and time from last PD. N Median Min Max Mean S Time from first diagnosis to first infusion (months) Time from last progression to fir infusion (months) *) SD stands for standard deviation *1.1.3. Prior anticancer therapy. Total (N=XX) ************************************	I attent ID	Instology	•••••			peeny	
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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) Fable 11.1.2. 8. Summary statistics of cancer diagnosis characteristics: Time from diagnosis and time from last PD. Image: Contract of the state of the stat				e	Μ	ethod	
Patient ID Target/non-target Site Histology/Cytology Biopsy/FNA(Y/N) Previously irradiated(Y/N) Fable 11.1.2. 8. Summary statistics of cancer diagnosis characteristics: Time from diagnosis and time from last PD. N Median Min Max Mean S Time from first diagnosis to first infusion (months) Time from last progression to fir infusion (months) Time from last progression to fir Infusion (months) *) SD stands for standard deviation * Total (N=XX)							
Patient ID Target/non-target Site Histology/Cytology Biopsy/FNA(Y/N) Previously irradiated(Y/N) Fable 11.1.2. 8. Summary statistics of cancer diagnosis characteristics: Time from diagnosis and time from last PD. N Median Min Max Mean S Time from first diagnosis to first infusion (months) Time from last progression to fir infusion (months) Time from last progression to fir Infusion (months) *) SD stands for standard deviation Total (N=XX) Surgery	isting 1112 7	Listing of patients with only	y one single lesion				
Histology/Cytology N Fable 11.1.2. 8. Summary statistics of cancer diagnosis characteristics: Time from diagnosis and time from last PD. N Median Min Max Mean S Time from first diagnosis to first infusion (months) Time from last progression to fir infusion (months) Image: Cytology Image: C				′N)	Proviou	usly irradiated	
N Median Min Max Mean S Time from first diagnosis to first infusion (months) Time from last progression to fir infusion (months) Image: Comparison of the infusion (months) Image:	Dationt ID	ranged non tanget one			1 1 6 9 10 0	isly ill'aulateu	
N Median Min Max Mean S Time from first diagnosis to first infusion (months) Time from last progression to fir infusion (months) Time from last progression to fir infusion (months) Time from last progression to fir infusion (months) *) SD stands for standard deviation Time from anticancer therapy. Total (N=XX)							(Y/N)
Time from first diagnosis to first infusion (months) Time from last progression to fir infusion (months) *) SD stands for standard deviation I.1.3 Prior anticancer therapy. Fable 11.1.3.1 Surgery. Surgery. Total (N=XX)							l(Y/N)
infusion (months) Time from last progression to fir infusion (months) *) SD stands for standard deviation I.1.3 Prior anticancer therapy. Fable 11.1.3.1 Surgery. Total (N=XX)		Histology/Cytology			iagnosis and t		
Time from last progression to fir infusion (months) *) SD stands for standard deviation 11.1.3 Prior anticancer therapy. Fable 11.1.3. 1 Surgery. Surgery. Total (N=XX)	Tatlent ID] Fable 11.1.2. 8.	Histology/Cytology Summary statistics of cancer			iagnosis and t		
(*) SD stands for standard deviation (1.1.3 Prior anticancer therapy. Fable 11.1.3. 1 Surgery. Total (N=XX)	Tatlent ID Table 11.1.2. 8. S Time from firm	Histology/Cytology Summary statistics of cancer I st diagnosis to first			iagnosis and t		
11.1.3 Prior anticancer therapy. Fable 11.1.3. 1 Surgery. Surgery Total (N=XX)	Table 11.1.2. 8. S Time from fir infusion (mon Time from las	Histology/Cytology Summary statistics of cancer I st diagnosis to first aths) st progression to fir			iagnosis and t		
Table 11.1.3. 1 Surgery. Total (N=XX)	Tatlent ID Table 11.1.2. 8. S Time from firminfusion (mon Time from lass infusion (mon	Histology/Cytology Summary statistics of cancer I st diagnosis to first aths) st progression to fir aths)			iagnosis and t		
Table 11.1.3. 1 Surgery. Total (N=XX)	Tatlent ID Table 11.1.2. 8. S Time from firminfusion (mon Time from lass infusion (mon	Histology/Cytology Summary statistics of cancer I st diagnosis to first aths) st progression to fir aths)			iagnosis and t		
Surgery Total (N=XX)	Table 11.1.2. 8. S Time from firminfusion (mon Time from las infusion (mon (*) SD stands f	Histology/Cytology Summary statistics of cancer I st diagnosis to first aths) st progression to fir aths) For standard deviation			iagnosis and t		
	Table 11.1.2. 8. S Time from firminfusion (mon Time from las infusion (mon (*) SD stands f	Histology/Cytology Summary statistics of cancer I st diagnosis to first aths) st progression to fir aths) For standard deviation			iagnosis and t		
	Tatlent ID Table 11.1.2. 8. S Time from firminfusion (mon Time from lass infusion (mon (*) SD stands f 11.1.3 Prior a	Histology/Cytology Summary statistics of cancer I st diagnosis to first atths) st progression to fir atths) for standard deviation nticancer therapy.		Min	iagnosis and t Max	Mean	

Table 11.1.3. 2 Radiotherapy type.

		_		Total (N=XX		
			Ν	N	%	
External						
Brachythera	ру					
IORT						
Fable 11.1.3. 3 Rad	liotherapy setting					
				Total (N=XX)	
			Ν	N	%	
Radiotherapy						
Chemoradio	therapy					
Listing 11.1.3.4 Pa	tients with prior radi	iotherapy				
Patient ID	Туре	Setting	Site	First	Last date	
d	ate				Last uate	
Listing 11.1.3.5 Pa	atients with prior sur	erv.				
Patient ID	Intention	Site and Pr	ocedures	Residual diseas	Date	
N° of agents						
Table 11.1.3. 7 Nur	mber of lines and age	ents of systemic ant	icancer therapy.			
				Total (N=XX)		
			N	Total (N=XX)	%	
Number of line	'S		N	Total (N=XX)	%	
Number of line	'S		N	Total (N=XX)	%	
	'S		N	Total (N=XX)	%	
1	s		N	Total (N=XX)	%	
1 2	'S		N	Total (N=XX)	%	
1 2 3 > 3			N	Total (N=XX)	%	
1 2 3			N	Total (N=XX)	%	
1 2 3 > 3 Number agents 1			N	Total (N=XX)	%	
1 2 3 > 3 Number agents 1 2			N	Total (N=XX)	%	
1 2 3 > 3 Number agents 1			N	Total (N=XX)	%	
1 2 3 > 3 Number agents 1 2 3 > 3			N	Total (N=XX)	%	
1 2 3 > 3 Number agents 1 2 3 > 3 Table 11.1.3. 8 Price	or anticancer agents.					
1 2 3 > 3 Number agents 1 2 3 > 3 Table 11.1.3. 8 Price Antineoplastic	or anticancer agents.	odulating agen		Total (N=XX)	%	
1 2 3 > 3 Number agents 1 2 3 > 3 Fable 11.1.3. 8 Price Antineoplastic (ATC-clas. Let)	or anticancer agents. e and Immunom vels 1-4)	odulating agen				
1 2 3 > 3 Number agents 1 2 3 > 3 Table 11.1.3. 8 Price Antineoplastic	or anticancer agents. e and Immunom vels 1-4)	odulating agen				

Endocrine therapy (L02)

.....

11.1.4 Prior history.

Listing 11.1.4. 1. Prior history.

Eisting 11.1.1. 1. 1.1 nor mistory.			
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)	
			Ν	%
Physical Exami	nation:			
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 List	ing of abnormal ECO	G.		
Patient ID		ECG result	Spe	cify
Listing 11.1.5. 3 List	ing of LVEF.			
Patient ID	LVEF(%)	Method	Institutional normal range	Result

Table 11.1.5. 4 Vital signs.

	Ν	Missing	Median	Min	Max	Mean	SD
Heart Rate (beats/min)							
BPS (mmHg)							
BPD (mmHg)							
Temperature (°C)							

11.1.6 Hematological values at baseline.

Table 11.1.6. 1. Hematological abnormalities at baseline.

	Grade 1		Gra	Grade 2 Grad		de 3 Gr		ade 4	Total	
	N	%	Ν	%	Ν	%	Ν	%	Ν	%
Leukopenia										
Neutropenia										
Anemia										
Thrombocytopenia										
v 1										
Lymphopenia Table 11.1.6. 2. Hematolog						lin	Max	Mean		SD
Table 11.1.6. 2. Hematolog	gy at basel N		t value bef lissing	ore treatment Median		lin	Max	Mean		SD
Table 11.1.6. 2. Hematolog Leukocytes						lin	Max	Mean		SD
Table 11.1.6. 2. Hematolog Leukocytes Neutrophils						lin	Max	Mean		SD
Table 11.1.6. 2. Hematolog Leukocytes						lin	Max	Mean		SD

Patient ID.	Exam	

Listing 11.1.6.4. Hematolo	gy 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 bas	eline.
---	--------

	Gra	Grade 1		Grade 2 Grade 3		nde 3	Grade 4		Total	
	Ν	%	Ν	%	Ν	%	Ν	%	Ν	%
AST										
ALT										
Total Bilirubin										
Direct Bilirubin										
				C						
Table 11.1.7. 2. Biochem	nstry at ba N		Last value be Missing	Median		Ain	Max	Mean	1	Max
A OT	I		wiissing	Median	I	/11/1	wax	Mean		viax
AST										
ALT										
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 Biochem	stry at baseline. Abnormalities gr	rade >=2	
		2.	
Patient ID.	Parameter	Value	Grade
i aucit iD.	i ai allieter	value	Graue

11.1.8 Other metabolic values at baseline.

Table 11.1.8. 1. Other metabolic abnormalities at baseline.

		Gr	ade 1	Gra	de 2	Gra	de 3	Gra	de 4	To	otal
		Ν	%	Ν	%	Ν	%	Ν	%	Ν	%
1	•										

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.

	Ν	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/MedI	ORA Preferr	Gi	rade 1	Gr	ade 2	Gra	de 3	Gra	de 4	Τα	otal
term		1	%	Ν	%	Ν	%	Ν	%	Ν	%
General Disorders	Abdominal Distension										
 Pain											

Ν	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.

Total (N=XX) Total (N=XX)	Concomitant n	nedication (ATC	C1/ATC4)				
Total (N=XX) Number of Systems (ATC1) 1 2 3 3 able 11.1.10. 3. Concomitant therapy started at baseline. Summary of number of agents involved (ATC1). 1 Median Max Mean SD* 11.1.10. 5. Listing of Baseline characteristics: Concomitant therapy. 11 11.1.10. S. Listing of patients excluded from the efficacy a	(ATC level 1)	(ATC lev	vel 4)		Ν		%
Total (N=XX) Number of Systems (ATC1) N % 1 2 3 > > 3 > 3 > 3 Number of agents (ATC4) 1 1 2 1 2 3 > 3 > 3 > 3 > 3 > able 11.1.10. 3. Concomitant therapy started at baseline. Summary of number of systems involved (ATC1). M Median Max Mean SD* able 11.1.10. 4. Concomitant therapy started at baseline. Summary of number of agents involved (ATC4). N Median Max Mean SD* able 11.1.10. 5. Listing of Baseline characteristics: Concomitant therapy. attient ID Start date ATC code Route Reason for use 1.2 Efficacy.							
Total (N=XX) Number of Systems (ATC1) N % 1 2 3 > > 3 > 3 > 3 Number of agents (ATC4) 1 1 2 1 2 3 > 3 > 3 > 3 > 3 > able 11.1.10. 3. Concomitant therapy started at baseline. Summary of number of systems involved (ATC1). M Median Max Mean SD* able 11.1.10. 4. Concomitant therapy started at baseline. Summary of number of agents involved (ATC4). N Median Max Mean SD* able 11.1.10. 5. Listing of Baseline characteristics: Concomitant therapy. attient ID Start date ATC code Route Reason for use 1.2 Efficacy.							
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Number of Systems (ATC1) N % 1 2 3 > 3 Number of agents (ATC4) 1 2 3 2 3 > 3 > 3 able 11.1.10. 3. Concomitant therapy started at baseline. Summary of number of systems involved (ATC1). N Median Max Mean SD ² able 11.1.10. 4. Concomitant therapy started at baseline. Summary of number of agents involved (ATC4). N Median Max Mean SD ² able 11.1.10. 5. Listing of Baseline characteristics: Concomitant therapy. atient ID Start date ATC code Route Reason for use 1.2 Efficacy, Reason	able 11.1.10. 2. C	oneonnant medicati	ion enaracteristics at	basenne.	Tota	I (N=XX)	
1 2 3 > 3 Number of agents (ATC4) 1 1 2 3 > 3 'able 11.1.10.3. Concomitant therapy started at baseline. Summary of number of systems involved (ATC1). N Median Min Max Mean SD* able 11.1.10.4. Concomitant therapy started at baseline. Summary of number of agents involved (ATC4). N Median Min Max Mean SD* able 11.1.10.4. Concomitant therapy started at baseline. Summary of number of agents involved (ATC4). N Median Min Max Mean SD* atient ID Start date ATC code Route Reason for use 1.2 Efficacy. 1.2 Efficacy. atient ID Reason atient ID Reason atient ID Reason atient ID Reason able 11.2.1. 1. Listing of patients excluded from the efficacy analysis. atient ID Reason able 11.2.1. 2. Patients e				Ν			/0
2 3 Number of agents (ATC4) 1 2 3 able 11.1.10. 3. Concomitant therapy started at baseline. Summary of number of systems involved (ATC1). Median Min Max Mean SD ⁴ able 11.1.10. 4. Concomitant therapy started at baseline. Summary of number of agents involved (ATC4). N Median Min Max Mean SD ⁴ able 11.1.10. 5. Listing of Baseline characteristics: Concomitant therapy. atient ID Start date ATC code Route Reason for use 1.2 Efficacy. 1.2.1 Response. isting 11.2.1. 1. Listing of patients excluded from the efficacy analysis. atient ID Reason able 11.2.1. 2. Patients evaluable for efficacy. Evaluable <u>Total (N=XX)</u> N %	Number of Syst	tems (ATC1)					
3 > 3 Number of agents (ATC4) 1 2 3 > 3 > 3 able 11.1.10. 3. Concomitant therapy started at baseline. Summary of number of systems involved (ATC1). N Median Min Max able 11.1.10. 4. Concomitant therapy started at baseline. Summary of number of agents involved (ATC4). N Median Min Max Median Min Max Mean SD* able 11.1.10. 4. Concomitant therapy started at baseline. Summary of number of agents involved (ATC4). N Median Min Max Mean SD* able 11.1.10. 5. Listing of Baseline characteristics: Concomitant therapy. attent ID Start date ATC code Route Iter to be the second for use Iter to be the second for the efficacy analysis. attent ID Reason able 11.2.1. 2. Patients evaluable for efficacy. Total (N=XX) N <td< td=""><td>1</td><td></td><td></td><td></td><td></td><td></td><td></td></td<>	1						
> 3 Number of agents (ATC4) 1 2 3 > 3 able 11.1.10. 3. Concomitant therapy started at baseline. Summary of number of systems involved (ATC1). N Median Min Max Mean SD ⁴ able 11.1.10. 4. Concomitant therapy started at baseline. Summary of number of agents involved (ATC4). N Median Min Max Mean SD ⁴ able 11.1.10. 5. Listing of Baseline characteristics: Concomitant therapy. atient ID Start date ATC code Route Reason for use 1.2 Efficacy. 1.2.1 Response. isting 11.2.1. 1. Listing of patients excluded from the efficacy analysis. atient ID Reason able 11.2.1. 2. Patients evaluable for efficacy. Evaluable <u>Total (N=XX)</u> N %							
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3 >3 'able 11.1.10. 3. Concomitant therapy started at baseline. Summary of number of systems involved (ATC1). N Median Min Max Mean SD* 'able 11.1.10. 4. Concomitant therapy started at baseline. Summary of number of agents involved (ATC4). N Median Min Max Mean SD* 'able 11.1.10. 4. Concomitant therapy started at baseline. Summary of number of agents involved (ATC4). N Median Min Max Mean SD* 'able 11.1.10. 5. Listing of Baseline characteristics: Concomitant therapy.							
> 3 iable 11.1.10. 3. Concomitant therapy started at baseline. Summary of number of systems involved (ATC1). N Median Min Max Mean SD ² 'able 11.1.10. 4. Concomitant therapy started at baseline. Summary of number of agents involved (ATC4). N Median Min Max Mean SD ² 'able 11.1.10. 5. Concomitant therapy started at baseline. Summary of number of agents involved (ATC4). N Median Min Max Mean SD ² 'able 11.1.10. 5. Listing of Baseline characteristics: Concomitant therapy. ATC code Route Reason for use 1.2 Efficacy. Reason for use							
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N Median Min Max Mean SD* able 11.1.10. 4. Concomitant therapy started at baseline. Summary of number of agents involved (ATC4). N Median Min Max Mean SD* isting 11.1.10. 5. Listing of Baseline characteristics: Concomitant therapy. atient ID Start date ATC code Route Reason for use 1.2 Efficacy. I.2.1. Response. isting 11.2.1. 1. Listing of patients excluded from the efficacy analysis. atient ID Reason able 11.2.1. 2. Patients evaluable for efficacy. Total (N=XX) N %	> 3						
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isting 11.1.10. 5. Listing of Baseline characteristics: Concomitant therapy. atient ID Start date ATC code Route Reason for use 1.2 Efficacy. 1.2.1 Response. isting 11.2.1.1. Listing of patients excluded from the efficacy analysis. atient ID Reason 'able 11.2.1.2. Patients evaluable for efficacy. Evaluable Total (N=XX) N %		N	Median	Min	Max	Mean	SD*
atient ID Start date ATC code Route Reason for use 1.2 Efficacy. 1.2.1 Response. isting 11.2.1.1. Listing of patients excluded from the efficacy analysis. atient ID Reason Yable 11.2.1.2. Patients evaluable for efficacy. Evaluable Total (N=XX) N %		N oncomitant therapy	Median started at baseline. S	Min ummary of numbe	Max er of agents	Mean involved (ATC4).	
atient ID Start date ATC code Route Reason for use 1.2 Efficacy. 1.2.1 Response. isting 11.2.1.1. Listing of patients excluded from the efficacy analysis. atient ID Reason Yable 11.2.1.2. Patients evaluable for efficacy. Evaluable Total (N=XX) N %		N oncomitant therapy	Median started at baseline. S	Min ummary of numbe	Max er of agents	Mean involved (ATC4).	SD [*]
1.2 Efficacy. 1.2.1 Response. isting 11.2.1. 1. Listing of patients excluded from the efficacy analysis. atient ID Reason Table 11.2.1. 2. Patients evaluable for efficacy. Evaluable Total (N=XX) N %	àble 11.1.10.4. Co	N oncomitant therapy N	Median started at baseline. S Median	Min ummary of numbe Min	Max er of agents	Mean involved (ATC4).	
1.2.1 Response. .isting 11.2.1. 1. Listing of patients excluded from the efficacy analysis. Patient ID Reason Yable 11.2.1. 2. Patients evaluable for efficacy. Evaluable Total (N=XX) N %	`able 11.1.10. 4. Co .isting 11.1.10. 5. 1	N oncomitant therapy N Listing of Baseline c	Median started at baseline. S Median characteristics: Conco	Min ummary of numbe Min omitant therapy.	Max er of agents Max	Mean involved (ATC4). Mean	SD*
1.2.1 Response. .isting 11.2.1. 1. Listing of patients excluded from the efficacy analysis. Patient ID Reason Yable 11.2.1. 2. Patients evaluable for efficacy. Evaluable Total (N=XX) N %	`able 11.1.10. 4. Co .isting 11.1.10. 5. 1	N oncomitant therapy N Listing of Baseline c	Median started at baseline. S Median characteristics: Conco	Min ummary of numbe Min omitant therapy.	Max er of agents Max	Mean involved (ATC4). Mean	SD*
1.2.1 Response. isting 11.2.1. 1. Listing of patients excluded from the efficacy analysis. atient ID Reason Yable 11.2.1. 2. Patients evaluable for efficacy. Evaluable Total (N=XX) N %	able 11.1.10.4. Co	N oncomitant therapy N Listing of Baseline c	Median started at baseline. S Median characteristics: Conco	Min ummary of numbe Min omitant therapy.	Max er of agents Max	Mean involved (ATC4). Mean	SD*
isting 11.2.1. 1. Listing of patients excluded from the efficacy analysis. Patient ID Reason Pable 11.2.1. 2. Patients evaluable for efficacy. Evaluable Total (N=XX) N %	`able 11.1.10. 4. Constrained in the second seco	N oncomitant therapy N Listing of Baseline c	Median started at baseline. S Median characteristics: Conco	Min ummary of numbe Min omitant therapy.	Max er of agents Max	Mean involved (ATC4). Mean	SD*
atient ID Reason Yable 11.2.1. 2. Patients evaluable for efficacy. Evaluable Total (N=XX) N %	Table 11.1.10. 4. Constrained isting 11.1.10. 5. I atient ID 1.2 Efficacy.	N oncomitant therapy : N Listing of Baseline of Start date	Median started at baseline. S Median characteristics: Conco	Min ummary of numbe Min omitant therapy.	Max er of agents Max	Mean involved (ATC4). Mean	SD*
atient ID Reason Yable 11.2.1. 2. Patients evaluable for efficacy. Evaluable Total (N=XX) N %	Table 11.1.10. 4. Constrained isting 11.1.10. 5. I atient ID 1.2 Efficacy.	N oncomitant therapy : N Listing of Baseline of Start date	Median started at baseline. S Median characteristics: Conco	Min ummary of numbe Min omitant therapy.	Max er of agents Max	Mean involved (ATC4). Mean	SD*
Total (N=XX) Evaluable N<%	`able 11.1.10. 4. Constrained in the second seco	N oncomitant therapy in N Listing of Baseline of Start date	Median started at baseline. Si Median characteristics: Conco ATC code	Min ummary of numbe Min omitant therapy. Route	Max er of agents Max	Mean involved (ATC4). Mean	SD*
Evaluable Total (N=XX) N %	Table 11.1.10. 4. Constraints	N oncomitant therapy in N Listing of Baseline of Start date	Median started at baseline. Si Median characteristics: Conco ATC code	Min ummary of numbe Min omitant therapy. Route	Max er of agents Max	Mean involved (ATC4). Mean	SD*
Evaluable Total (N=XX) N %	Table 11.1.10. 4. Constraint Constraint 11.1.10. 5. In the second sec	N oncomitant therapy in N Listing of Baseline of Start date	Median started at baseline. Si Median characteristics: Conco ATC code	Min ummary of numbe Min omitant therapy. Route	Max er of agents Max	Mean involved (ATC4). Mean	SD*
Evaluable N %	Table 11.1.10. 4. Constrained for the second sec	N oncomitant therapy in N Listing of Baseline of Start date	Median started at baseline. So Median characteristics: Conco ATC code	Min ummary of numbe Min omitant therapy. Route	Max er of agents Max	Mean involved (ATC4). Mean	SD*
	Table 11.1.10. 4. Constrained for the second sec	N oncomitant therapy in N Listing of Baseline of Start date	Median started at baseline. So Median characteristics: Conco ATC code	Min ummary of numbe Min omitant therapy. Route	Max er of agents Max	Mean involved (ATC4). Mean Reason for use	SD*
No	Table 11.1.10. 4. Co Listing 11.1.10. 5. I Patient ID 11.2 Efficacy. 11.2.1 Response Listing 11.2.1. 1. Lis Patient ID Fable 11.2.1. 2. Pati Evaluable Yes	N oncomitant therapy in N Listing of Baseline of Start date	Median started at baseline. So Median characteristics: Conco ATC code	Min ummary of numbe Min omitant therapy. Route cy analysis. Reason	Max er of agents Max	Mean involved (ATC4). Mean Reason for use (N=XX)	SD*

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 \geq 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	Ν	%	CI (95%)
Complete Response (CR)			
Partial Response (PR)			
Stable Disease ≥ 4 months*			
Stable Disease (SD)			
Progression Disease (PD)**			
Not evaluable			
Programming Notes: Percentage is base	ed on total patient of p	atients treated	
(*)Patients who are free from progressi			
(**) Detionts with Early DD will also h	a included in this acto	corry (provided the	t thay reacive at

(**) 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	Tota	I (N=XX)
FF 54	Ν	% (95% CI)
Yes		
No		
Total		

Table 11.2.1.6. Progression Free Survival status at 4 months (PFS4) in all treated patients.

DECA	Tota	l (N=XX)
PFS4	Ν	% (95% CI)
Yes		
No		
No Total		

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

PFS6	Tota	I (N=XX)
F F 50	Ν	% (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)
FF 50	Ν	% (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*.

Pa	tient charact	eristics	Outcome prior treatment			PM00104				
treatme	nt									
Patient	Sex/Age/PS	Histology	N°	Prior	Last prior	Cycles	Best	TTP	Cyc	PFS
OS										
			CT	Lines	Treatment	received	Respon	ise		

(*) 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	•••••
Ν					
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	admiı	nistered.	
~	-				

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

Table 12.1.1. 2. Summary of cycles administered.

N	Median	Min	Max	Mean	SD*
(*) SD stands for standard deviati	on				
Table 12.1.1. 3. Dose intensity.					
	N	Med	lian Min	ı N	Max
Cumulative dose (mg/ m ²)					
Treatment duration (wk)					
Dose intensity (mg/m ² wk)					
Relative dose intensity (%)					
12.1.2 Dose delays.					
Гаble 12.1.2. 1. Dose delay.					
		Ν		(%
Number of patients treated					
Number of patients with any dos	e delay				
Number of cycles administered					
Number of cycles susceptible to	be delayed				
Patients with					
No delays					
1 cycle delayed					
2 cycles delayed					
\geq 3 cycles delayed					
Number of cycles with dose d					
Programming Notes: Percentage i		-	*	e delayed.	
* Denominator = Number of o	cycles susceptil	ble to be delaye	ed.		
	4	4			
Table 12.1.2. 2. Dose delay according to			4~d**	Non Treat	nont volate
	1	reatment rela N	<u>%</u>	<u>Non – Treatr</u> N	<u>nent retate</u> %
Patients with		1 N	/0	1 N	/0
No delays					
1 cycle delayed					
2 cycles delayed					
\geq 3 cycles delayed					
<u>2</u> 5 cycles delayed	1-1				

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.

	Treatmo	ent relat	ed* No	on – Trea	tment re	late	To	tal
	Ν	%) D	Ν	%		Ν	%
Lenght of delay								
1-7 days								
7 – 14 days								
> 14 days								
Programming Notes:								
* Denominator = Number of cy	cles susc	eptible t	o be del	ayed.				
** Hematological reason / Non		1						
e		C						
Fable 12.1.2.4 Dose delay and reason by	cycle							
Fable 12.1.2. 4 Dose delay and reason by	•	rle ?		cle 3				[ata]
Fable 12.1.2. 4 Dose delay and reason by	•	cle 2 %	U	cle 3	 N			Fotal %
	•	cle 2 %	Cy N	cle 3 %	 N	%	N N	<u>fotal</u> %
Number of delays	•		U					
Number of delays Treatment related*	•		U					
Number of delays Treatment related* Hematological reason	•		U					
Number of delays Treatment related*	•		U					
Number of delays Treatment related* Hematological reason Non hematological reason Non Treatment related*	Cyo N	%	N	%	N	⁰ / ₀		
Number of delays Treatment related* Hematological reason Non hematological reason Non Treatment related*	Cyo N	%	N	%	N	⁰ / ₀		
Number of delays Treatment related* Hematological reason Non hematological reason	Cyo N or = Num	%	N	%	N	⁰ / ₀		

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.

	Ν	%
Number of patients treated		
Number of patients with dose reduced		
Number of cycles administered		
Patients with		
N° reductions		
1 cycle reduction		
2 cycle reductions		
\geq 3 cycle reductions		
Number of cycles with dose reduction		
	1 C 1 (11)	1 1 1

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

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

		Freatment rela		Non – Tre	eatment 1	
		Ν	%	Ν		%
Patients with						
N° reductions						
1 reduction						
2 reductions						
\geq 3 reductions						
Number of cycles with dose						
Programming Notes:* Denom ** Hematolo	iinator = Number gical reason / Nor			educed.		
Table 12.1.3.3 Dose reduction and		Carala 2			Т	4-1
-	Cycle 2	Cycle 3				otal
	N %	N º	/0 N	%	Ν	
Number of patients						
Number of delays						
Treatment related*						
Hematological reason						
Non hematological reason Non Treatment related*						
Programming Notes:* Denom						
Patient ID Cycle Rea	ason of reductio		mments	Г	Reduction	u (/
12.1.4 Skipped doses.				1		
						n (70
12.1.4 Skipped doses.		N				n (74
12.1.4 Skipped doses. Fable 12.1.4. 1 Skipped doses.						<u>n (</u> 20
12.1.4 Skipped doses.						
12.1.4 Skipped doses. Fable 12.1.4. 1 Skipped doses. Number of patients treated wi	th at least 2					u (//
12.1.4 Skipped doses. Fable 12.1.4. 1 Skipped doses. Number of patients treated winfusions Number of patients with any s Number of patients with any s	th at least 2 skipped dos					u (
12.1.4 Skipped doses. Fable 12.1.4. 1 Skipped doses. Number of patients treated wi nfusions Number of patients with any s	th at least 2 skipped dos					
12.1.4 Skipped doses. Fable 12.1.4. 1 Skipped doses. Number of patients treated winfusions Number of patients with any s Number of patients with any s	th at least 2 skipped dos skipped dos					
I2.1.4 Skipped doses. Fable 12.1.4. 1 Skipped doses. Number of patients treated winfusions Number of patients with any s	th at least 2 skipped dos skipped dos					
I2.1.4 Skipped doses. Fable 12.1.4. 1 Skipped doses. Number of patients treated winfusions Number of patients with any s Number of patients with any s Skipped doses.	th at least 2 skipped dos skipped dos					
I2.1.4 Skipped doses. Fable 12.1.4.1 Skipped doses. Number of patients treated winfusions Number of patients with any s Number of patients with any s Number of patients with any s Number of cycles administere Number of cycles susceptible Number of cycles susceptible Sumber of cycles with at leas	th at least 2 skipped dos skipped dos ed to have any					
I2.1.4 Skipped doses. Fable 12.1.4. 1 Skipped doses. Number of patients treated winfusions Number of patients with any statements with any sta	th at least 2 skipped dos skipped dos ed to have any					
I2.1.4 Skipped doses. Fable 12.1.4. 1 Skipped doses. Number of patients treated winfusions Number of patients with any s Number of patients with any s State of patients with any s Number of patients with any s State of patients with any s Number of patients with any s State of patients with any s Number of cycles administere Number of cycles susceptible Number of cycles with at lease State of cycles with at lease Jose (drug related) Day 8	th at least 2 skipped dos skipped dos ed to have any					
I2.1.4 Skipped doses. Fable 12.1.4. 1 Skipped doses. Number of patients treated winfusions Number of patients with any s Number of patients with any s Stream of patients with any s Number of patients with any s Stream of cycles administere Number of cycles susceptible Stream of cycles with at leas Number of cycles with at leas Stream of cycles with at leas Jose (drug related) Day 8 Day 15 Day 15	th at least 2 skipped dos skipped dos ed to have any					
I2.1.4 Skipped doses. Fable 12.1.4. 1 Skipped doses. Number of patients treated winfusions Number of patients with any s Number of patients with any s State of patients with any s Number of patients with any s State of patients with any s Number of patients with any s State of patients with any s Number of cycles administere Number of cycles susceptible Number of cycles with at lease State of cycles with at lease Jose (drug related) Day 8	th at least 2 skipped dos skipped dos ed to have any t one skipp	N		%	· · · · · · · · · · · · · · · · · · ·	
I2.1.4 Skipped doses. Fable 12.1.4. 1 Skipped doses. Number of patients treated winfusions Number of patients with any s Number of patients with any s Stream of patients with any s Number of patients with any s Stream of cycles administere Number of cycles susceptible Stream of cycles with at leas Number of cycles with at leas Stream of cycles with at leas Jose (drug related) Day 8 Day 15 Day 15	th at least 2 skipped dos skipped dos ed to have any t one skipp Treatn	N	No	%	ent relat	ed
12.1.4 Skipped doses. Fable 12.1.4. 1 Skipped doses. Number of patients treated winfusions Number of patients with any s Number of patients with any s Number of patients with any s Ourgerelated) Number of cycles administere Number of cycles susceptible Dission Number of cycles with at leas dose (drug related) Day 8 Day 15 Day 8+15	th at least 2 skipped dos skipped dos ed to have any t one skipp Treatn	N	No	%	· · · · · · · · · · · · · · · · · · ·	ed
I2.1.4 Skipped doses. Fable 12.1.4. 1 Skipped doses. Number of patients treated winfusions Number of patients with any s Number of patients with any s Stream of patients with any s Number of patients with any s Stream of cycles administere Number of cycles susceptible Stream of cycles with at leas Number of cycles with at leas Stream of cycles with at leas Jose (drug related) Day 8 Day 15 Day 15	th at least 2 skipped dos skipped dos ed to have any t one skipp Treatn	N	No	%	ent relat	ed

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	Gr	ade 1	Gra	ade 2	Gra	ade 3	Gra	ide 4	Т	otal
	Ν	%	Ν	%	Ν	%	Ν	%	Ν	%
System Organ Class 1 Preferred Term										
System Organ Class 2 Preferred Term										

* 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.

	Gro	up XX
	Ν	% (*)
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	Grade	Relation with		Onset date	End Date	
Patient ID	preferred term	Grade	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 ter	m Gra	de Relation with the study drug	••••	Start date	End Date
Listing 12.2.3.	2. Listing of death	is related to st	udy drug.			

12.3 Laboratory evaluation.

12.3.1 Hematological abnormalities.

Table 12.3.1.1 Hematology worst grade per patient.

	Gi	rade 1	Grade 2	Gr	ade 3	<u> </u>	ide 4	To	otal
	Ν	%	N %	Ν	%	Ν	%	Ν	%
Leukopenia									
Neutropenia									
Anemia									
Thrombocytop	penia								
Lymphopenia									
Programming	Notes: Percer	ntages ar	e based on the	safety popu	ulation.				
Table 12.3.1. 2	Hematology wor	st grade po	er cycle.						
		rade 1	Grade 2	Gr	ade 3	Gra	de 4	To	otal
	Ν	%	N %	Ν	%	Ν	%	Ν	%
Leukopenia									
Neutropenia									
Anemia									
T1 1 (ania								
Ihrombocytop	benna								
	benna								
Lymphopenia		ntages ar	e based on the	safety pop	ulation.				
Lymphopenia Programming	Notes: Percer	C				de 3-4			
Lymphopenia Programming Table 12.3.1. 3	Notes: Percer Supportive lis	ting: Patie	nts with any hema	ological abn	ormalities gra			Grade N	CI
Lymphopenia Programming	Notes: Percer	C		ological abn			KLLN	Grade N CTCAE	
Lymphopenia Programming Table 12.3.1. 3	Notes: Percer Supportive lis	ting: Patie	nts with any hema	ological abn	ormalities gra		KLLN		
Lymphopenia Programming Table 12.3.1. 3	Notes: Percer Supportive lis	ting: Patie	nts with any hema	ological abn	ormalities gra		xLLN		
Lymphopenia Programming Table 12.3.1. 3 Patient	Notes: Percer Supportive lis Lab. test	ting: Patie Cycle	nts with any hema Examination	ological abn	ormalities gra Std. valu		KLLN		
Table 12.3.1. 3	Notes: Percer Supportive lis Lab. test	ting: Patie Cycle	nts with any hema	ological abn	ormalities gra Std. valu		XLLN		

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

	N	All c	ycles
	Ν	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 nations w	ith Grade 3-4		

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

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

			Wo	orst grad	e per p	atient		
	Gra	de 0-	Gra	nde 2	Gra	ide 3	Gra	ade 4
	Ν	%	Ν	%	Ν	%	Ν	%
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 v	worst grade per	patient.
-----------------	----------------	-----------------	----------

	Gr	ade 1	Gra	de 2	Gra	de 3	Gra	de 4	To	otal
	Ν	%	Ν	%	Ν	%	Ν	%	Ν	%
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.

	G	Frade 1	Grad	e 2	Gra	ide 3		Grade 4	<u>ا</u>	Tota	ıl
	Ν	%	Ν	%	Ν	%	N	9	/o	N	%
AST											
ALT											
Total Bilirul	oin										
Direct Bilir	ubin										
Programming	Notes: Perce	entages are	e based on	the safe	ety popu	lation.					
-0	,	0			J I - I -						
Table 12.3.2. 3	Supportive listing	ng: Patients			y abnorma	lities grad	des 3-4.				_
Patient ID	Lab. test	Cycle	Examin dat		Ν	Std.	valı	xLLN		Grade	
			uat	.e							-
											-
Listing 1222 4	Listing of pat	tionto with h	io ob omistry .	avaluatio	na miasina						
				evaluatio	ns missing	5.	_				
Patient	Cycle	Lal	b. tes								
Patient	Cycle	Lal	b. tes				-				
Patient	Cycle	Lal	b. tes				-				
Patient	Cycle	Lat	b. tes				_				
	•						-				
Patient Table 12.3.2. 5	•			istry toxic	cities.		-				
	•			istry toxic	cities.	N	-	All c	ycles		
	•			istry toxic	cities.	N	- - Mee		-	ge	
Table 12.3.2. 5	•			istry toxic	cities.	N	_ Mee	All c lian	ycles Ran	ge	
Table 12.3.2. 5	Time course and	l recovery fr		istry toxic	cities.	N	_ Mee		-	ge	
Table 12.3.2. 5 ALT Day of po	Time course and	l recovery fr		istry toxic	cities.	N	_ Mee		-	ge	
Table 12.3.2. 5 ALT Day of po Nadir of	Time course and eak ALT cour ALT count (/:	l recovery fr nt 'mm3)		istry toxic	cities.	N	_ 		-	ge	
Table 12.3.2. 5 ALT Day of po Nadir of Day of A	Time course and eak ALT cour ALT count (/ LT G3-4 onse	l recovery fr nt (mm3) et		istry toxic	cities.	N	_ Med		-	ge	
Table 12.3.2. 5 ALT Day of po Nadir of Day of A	Time course and eak ALT cour ALT count (/:	l recovery fr nt (mm3) et		istry toxic	cities.	N	_ 		-	ge	
Table 12.3.2. 5 ALT Day of po Nadir of Day of A Day of re	Time course and eak ALT cour ALT count (/ LT G3-4 onsecovery to gra	l recovery fr nt 'mm3) et ade ≤2	om biochemi	istry toxic	cities.	N	_ Mee		-	ge	
Table 12.3.2. 5 ALT Day of po Nadir of Day of A Day of re N° of day	Time course and eak ALT cour ALT count (/ LT G3-4 onsecovery to gra ys with grade	l recovery fr nt 'mm3) et ade ≤2 3-4 ALT	om biochemi	istry toxic	cities.	N	Mee		-	ge	
Table 12.3.2. 5 ALT Day of po Nadir of Day of A Day of re N° of day Day of re	Time course and eak ALT cour ALT count (/ LT G3-4 onsecovery to gra	l recovery fr nt 'mm3) et ade ≤2 3-4 ALT	om biochemi	istry toxic	cities.	N	Mee		-	ge	
Table 12.3.2. 5 ALT Day of po Nadir of Day of A Day of re N° of day Day of re AST	Time course and eak ALT cour ALT count (/ LT G3-4 onse ecovery to gra ys with grade ecovery to gra	I recovery fr nt (mm3) et ade ≤ 2 3-4 ALT ade ≤ 1	om biochemi	istry toxic	cities.	N	Mee		-	ge	
Table 12.3.2. 5 ALT Day of po Nadir of Day of A Day of re N° of day Day of re AST Day of po	Time course and eak ALT cour ALT count (/: LT G3-4 onsecovery to gra ys with grade ecovery to gra eak AST cour	l recovery fr nt 'mm3) et ade ≤2 3-4 ALT ade ≤ 1 nt	om biochemi	istry toxic	cities.	N	Mee		-	ge	
Table 12.3.2. 5 ALT Day of po Nadir of Day of A Day of re N° of day Day of re AST Day of po Nadir of	Time course and eak ALT cour ALT count (// LT G3-4 onsecovery to gra ys with grade ecovery to gra eak AST cour AST count (//	I recovery fr nt (mm3) et ade ≤ 2 3-4 ALT ade ≤ 1 nt mm3)	om biochemi	istry toxic	pities.	N	_ 		-	ge	
Table 12.3.2. 5 ALT Day of po Nadir of Day of A Day of re N° of day Day of re AST Day of po Nadir of	Time course and eak ALT cour ALT count (/: LT G3-4 onsecovery to gra ys with grade ecovery to gra eak AST cour	I recovery fr nt (mm3) et ade ≤ 2 3-4 ALT ade ≤ 1 nt mm3)	om biochemi	istry toxic	cities.	N	- 		-	ge	
Table 12.3.2. 5 ALT Day of po Nadir of Day of A Day of re N° of day Day of re AST Day of po Nadir of Day of A	Time course and eak ALT count ALT count (/: LT G3-4 onse ecovery to gra ys with grade ecovery to gra eak AST count AST count (/i ST G3-4 onse	I recovery fr nt (mm3) et ade ≤ 2 3-4 ALT ade ≤ 1 nt mm3) et	om biochemi	istry toxic	cities.	N	- 		-	ge	
Table 12.3.2. 5 ALT Day of po Nadir of Day of A Day of re N° of day Day of re AST Day of po Nadir of Day of A Day of re	Time course and eak ALT coun ALT count (/: LT G3-4 onse ecovery to gra ys with grade ecovery to gra eak AST count AST count (/i ST G3-4 onse ecovery to gra	I recovery fr nt (mm3) et ade ≤ 2 3-4 ALT ade ≤ 1 nt mm3) et ade ≤ 2	om biochemi	istry toxic	cities.	N	- 		-	ge	
Table 12.3.2. 5 ALT Day of po Nadir of Day of A Day of re N° of day Day of re AST Day of po Nadir of Day of A Day of re N° of day	Time course and eak ALT count ALT count (/: LT G3-4 onse ecovery to gra ys with grade ecovery to gra eak AST count AST count (/i ST G3-4 onse	I recovery fr nt (mm3) et ade ≤ 2 3-4 ALT ade ≤ 1 nt mm3) et ade ≤ 2 3-4 AST	om biochemi	istry toxic	cities.	N	 		-	ge	

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

	Worst grade per patient							
	Grade 0-1		Grade 2		Grade 3		Grade 4	
	Ν	%	Ν	%	Ν	%	Ν	%
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								

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

12.3.3 Other metabolic abnormalities.

 Table 12.3.3. 7
 Metabolic abnormalities worst grade per patient.

Hyperglycemia	N	%	Grade 2		Grade 3		Grade 4		Total	
Hyperglycemia			Ν	%	Ν	%	Ν	%	Ν	%
* All metabolic parar	meters s	suscentibl	e to be o	oraded as	ner NCI	-CTCA	F v 3 0			
7 minetabolie para		susception				-010/1	L VJ.0			
Fable 12.3.3. 8 Metaboli	ic abnorm	nalities grad	e ner cvc	le						
		ade 1		de 2	Gra	de 3	Grad	le 4	Т	otal
-	Ν	%	Ν	%	Ν	%	Ν	%	Ν	%
Hyperglycemia										
Hypergrycenna										
••••										
* All metabolic parar	meters s	susceptibl	e to be s	graded as	per NCI	-CTCA	E v3.0			
1		1			1					
Table 12.3.3. 9 Supportiv	ve listing	: Patients w	rith any m	etabolic abr	normalities	s grades 3	3-4.			
				ination		-				
	tost	Cycle		ate	Ν	S	td. value	xLL	N	Grad
Patient ID Lab.	. iesi	•	u	au						Ulau

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 Listi	ng of abnormal ECG.			
Patient id	Result	Sp	ecify	

12.5 Concomitant medication during treatment.

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

Concomitant me	dication (ATC1/ATC4)		
(ATC level 1)	(ATC level 4)	Ν	%

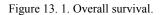
 Table 12.5.1. 2. Concomitant medication characteristics during treatment.

		Total (N=XX)				
	—	Ν	,	%		
Number of Systems (ATC	C1)					
1	,					
2						
3						
> 3						
Number of agents (ATC4)					
1	, ,					
2						
3						
> 3						
-	entage is based on to	otal patient includ	ed.			
> 3 Programming Notes: Perce	entage is based on to	otal patient includ	ed.			
-	C			C1).		
Programming Notes: Perce Table 12.5.1. 3. Concomitant th	C			C1). Mean	SD*	
Programming Notes: Perce Table 12.5.1. 3. Concomitant th	erapy during treatment.	Summary of systems	involved (ATC		SD,	
Programming Notes: Perce Table 12.5.1. 3. Concomitant th	erapy during treatment. N Median	Summary of systems	involved (ATC		SD,	
Programming Notes: Perce Table 12.5.1. 3. Concomitant th	erapy during treatment. N Median	Summary of systems	involved (ATC		SD;	
Programming Notes: Perce Table 12.5.1. 3. Concomitant th	erapy during treatment. N Median deviation	Summary of systems Min	involved (ATC 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.



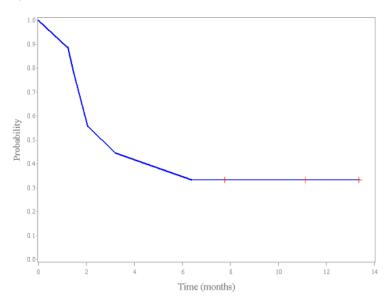
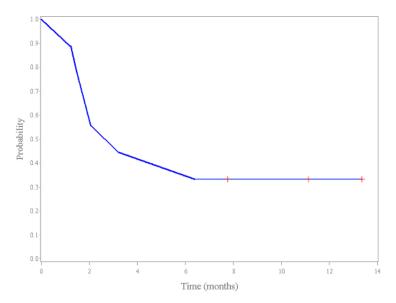
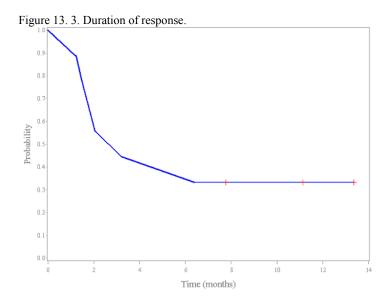


Figure 13. 2. Progression-free survival.





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

Figure 13. 4. CA-125 for responders.

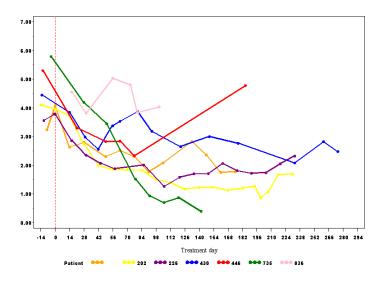
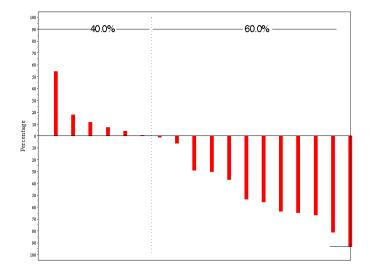
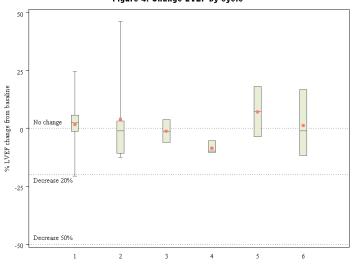


Figure 13. 5. Waterfall plots.



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.





Boxplot showing the change by cycle in LVEF from baseline.