GEM-1202
(GRAY-B)

STATISTICAL PLAN

Statistical Results Report Version 1.8

November 28, 2013

TITLE: Single-group, multicenter Phase II Clinical Trial on the combination of Radiotherapy and Ipilimumab for the treatment of patients with melanoma and brain metastases.
(GEM STUDY: RADIATION AND YERVOY IN PATIENTS WITH MELANOMA AND BRAIN METASTASES)

PROMOTER: GEM Study [redacted]

STUDY COORDINATOR:
[redacted]

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1. RESULTS

1.1. PATIENTS ASSESSED

POPULATIONS (following definitions in section 9.2 of the protocol)

- **included patients and patients (safety population):** Of the **58 patients**included,all patients were considered within the population of **patients treated** since allthem had received the minus one dose of Ipilimumab. Baseline characteristics, drug exposure analysis, and safety are presented in this population (n = 58).

- **EVALUABLE PATIENTS:** will include all patients who have received at least one dose of ipilimumab and complete treatment with RTCT.

Table 1. Populations

		N (%)
Patients included	**Yes**	
	Total	
Patients treated (Safety Population)	**Yes**	
	Total	
Evaluable patients	**Yes**	
	No	
	Total	

Table 2. Evaluable patients for the study according to hospital

		No	Yes	Total
		N (%)	N (%)	N (%)
Hospital				

Table 3. List of NON-evaluable

patients Patient	Hospital	RDT duration	Total number of Ipilimumab cycles	Reason not evaluable / excluded

1.2. BASELINE CHARACTERISTICS

The database was closed on XX-XX-XXXX and based on the population of **XX patients** included / treated in the study, the baseline characteristics are presented:

Table 4. Baseline characteristics (I)

	N	Mean (SD	Median (Min-Max)
Age (years)			
Karnofsky functional status (0-100)			
Barthel index (0-20)			

Table 5. Baseline characteristics (II)

		N (%[1])
Sex	**Male**	
	Female	
	Total	
KPS	**70-80**	
	90-100	
	Not specified	
	Total	
Barthel Index	**<15**	
	15-20	
	Total	
Status B-Raf (Current Melanoma)	**Mutated**	
	Native	
	Not specified	
	Total	
Nº of lines of previous treatment	**0**	
	1	
	> 1	
	Total	
Status B-Raf (Previous Melanoma)	**Mu tado**	
	Native	
	Not specified	
	Total	
Brain M1	**Multiple**	
	Single	
	Not specified	
	Total	
No. of organs with metastatic disease	**1**	
	2	
	3	
	4	
	5	
	Total	
No. of organs with metastatic disease	**≤2**	
	> 2	
	Total	
Brain metastases	**Yes**	
	Total	
Pulmonary metastases	**No**	
	Yes	
	Total	
Hepatic metastases	**No**	
	Yes	
	Total	

Metastasis Skin	**No**	
	Yes	
	Total	
Gastrointestinal metastases	**No**	
	Yes	
	Total	
Locoregional lymph node metastases	**No**	
	Yes	
	Total	
Distant lymph node metastases	**No**	
	Yes	
	Total	

1:% with respect to ***included patients*** with available data.

Table 6. Use of previous BRAF inhibitors

		N (%[1])
Use of previous BRAF inhibitors	**No**	
	Yes	
	Total	
Type of treatment lines BRAF inhibitor	**BRAFi**	
	BRAFi + MEKi	
	Vemurafenib + Pembrolizumab	
	Total	

1:% with respect to ***included patients*** with available data.

Table 7. Corticosteroids at baseline and / or cycle 1

		N (%[1])
Corticosteroids at baseline and / or C1	**No**	
	Yes	
	Total	

1:% with respect to ***included patients*** with available data.

Table 8. Mean daily dose (dexamethasone reference)

	N	Mean (SD	Median (Min-Max)
Mean daily dose (Dexamethasone)			

1:% with respect to the ***patients included*** with available data (patients who received corticosteroids and for whom the dose)

Table 9.: Hematology

	N	Mean (SD	Median (Min-Max)
Leukocytes x10 ^ 3 / uL			
Eosinophils			
Baseline laboratory testsBasophils			
Monocytes			
Neutrophils			
Lymphocytes			
Neutrophils Total x10 ^ 3 / uL			
Eosinophils Total x10 ^ 3 / uL			
Basophils Total x10 ^ 3 / uL			
Total Monocytes x10 ^ 3 / uL			
Total Lymphocytes x10 ^ 3 / uL			
Hemoglobin g / dl			
Platelets x10 ^ 3 / uL			
Neutrophil / Lymphocyte Ratio			

The mean baseline LDH value was 420.3 U / L.Baseline blood tests

Table 10.: Biochemistry

	N	Mean (SD	Median (Min-Max)
Creatinine (mg / dl)			
Creatinine Clearance (ml / min)			
SGOT / AST (U / L)			
SGTP / ALT (U / L)			
Total Bilirubin (mg / dL)			
CRP			
Ureic Nitrogen or Urea (mg / dL)			
Glucose (mg / dL)			
Sodium (mmol / L)			
Chloride (mmol / L)			
Bicarbonate (mmol / L)			
Baseline LDH (U / L)			

Table 11. LDH categorized

		N (%[1])
Value of LDH> ULN	**No**	
	Yes	
	Total	
LDH value> 1.5 * ULN	**No**	
	Yes	
	Total	

1:% with respect to ***included patients*** with available data.

Table 12. Baseline analysis: Endocrine

	N	Mean (SD	Median (Min-Max)
Cortisol (ug / dl)			
ACTH (pg / mL)			
T4 (ug / mL)			
T3 (ug / mL)			
TSH (ulU / mL)			
Prolactin (ng / ml)			

1.3. TREATMENT EXPOSURE

Table 13. IPI treatment (I)

		N (%)
Total number of Ipilimumab cycles	1	
	2	
	3	
	4	
	Total	
	Total	
number of omissions	0	
	1	
	2	
	3	
	Total	
	Total	
number of reductions	0	
	1	
	2	
	3	
	4	
	Total	
	Total	
number of delays	0	
	1	
	2	
	3	
	Total	

1:% with respect to ***patients included*** with available data

Table 14. RDT treatment (I)

		N (%)
Premature end of RDT	No	
	Yes	
	Total	
		N (%)
Reason for interruption of RDT treatment		

1:% with respect to ***patients included*** with available data

Table 15. Duration of RDT

	N	Mean (SD	Median (Min-Max)
Duration of RDT			

Table 16. Patients with no end date of RDT

	Patient code	Duration RDT	EndRDT	date ofStart date of RDT
1				

1.4. Screening of all patients

median follow-up for ***the patient population treated, n = XX,*** was XXmonths.

Table 17. Time tracking all patients

	N	Mean (SD)	median (Me n-Max)
Follow-up time (months from 1st cycle of Ipilimumab)			

1.5. EFFECTIVENESS ANALYSIS

Following the protocol, the population ofwas used for the efficacy analysis evaluable patients: n = XX (see section 1.1)

1.5.1. OVERALL SURVIVAL (Evaluable)

Survival Overall (OS) is presented for evaluable patients (n = XX). The estimated overall survival at one year (calculated using Kaplan-Meier) was X% (with a 95% CI: XX%) with a median OS of X months (95% CI XX months).

Table 18. Overall survival (evaluable)

Estimated overall survival	N events	N at risk	% of patients without death	95% CI	% with death
at 6 months					
to 12 months					
	N (%)	**Median**	**Min-Max**	**Standard Error**	**95% Confidence interval**
Overall survival Estimated					

Table 19. Overall survival: Events and OS at 1 year (Evaluable)

		N (%; 95% CI)
Overall survival	**Live**	
	Exitus	
	Total	
OS at 1 year (*crude*)	**No**	
	Yes	
	No follow-up at 1 year (or death)	
	Total	
OS at 1 year (*gross*) (excluding patients with follow-up <1 year and without previous death)	**No**	
	Yes	
	Total	

Figure 1. Estimated overall survival (Evaluable)

Table 20. Time to Exitus (only in patients with death)

	N	Mean (SD)	Median (Min-Max)
Time to Exitus			

.

Table 21. Reasons for leaving the study (evaluable)

		N (%)
Reason Exitus	**Progression of the disease**	

1.5.1.1. OS RATE AT 1 YEAR vs BASAL CHARACTERISTICS

A univariate and multivariate analysis of the possible association between baseline characteristics and the rate was presented below. of global survival per year, using logistic regression models taking death per year as an event.

Table 22. Univariate analysis: 1-year OS rate vscharacteristics baseline

		1-yearOS			Univariate logistic regression	
		No (death) N (%)	Yes (alive) N (%)	Total N (%)	OR (95% CI)	p -value
Age categorized according to median (66 years)	<66 years					
	≥66 years					
	Total					
Sex	Female					
	Male					
	Total					
KPS	90-100					
	70-80					
	Total					
Barthel Index	15-20					
	<15					
	Total					
Status B-Raf (Current Melanoma)	Native					
	Mutated					
	Total					
No. of lines of previous treatment	> 1					
	1					
	0					
	Total					
Status B-Raf (previous Melanoma)	Native					
	Mutated					
	Total					
Type of locations M1 Current	brain Single					
	Multiple					
	Total					
Location M1 Current liver	No					
	Yes					
	Total					
Corticosteroids at baseline and / or C1	No					
	Yes					
	Total					
No. of organs with metastatic disease	1					
	2					
	3					
	4					

Total		
No. of organs with metastatic disease	**≤2**	
	> 2	
	Total	
Neutrophil /Ratio Lymphocyte(quantitative)		
Neutrophil /ratio Lymphocyte> 3 (high risk)	**No**	
	Yes	
	Total	
Previous BRAF Inhibitor	**No**	
	Yes	
	Total	
CRP value		
Hemoglobin value		
LDH value		
LDH value> ULN	**No**	
	Yes	
	Total	

LDH value> 1.5 * ULN	**No**	
	Yes	
	Total	

1.5.1.2. 1-YEAR OS RATE vs BASAL CHARACTERISTICS. MULTIVARIATE ANALYSISBaseline

Table 23. Multivariate analysis: 1-year OS rate vscharacteristics

			Multivariate logistic regression	
		N[1]	OR (95% CI)	p-value
XXXXX	No			
	Yes			
Constant				

1: patients for whom no data were available are excluded from the model data in all variables included in the multivariate model (n = X).

In the table below, the variables that were not significant have been excluded:

Table 24. Multivariate analysis: 1-year OS rate vscharacteristics[2]

			Multivariate logistic regression	
		N[1]	OR (95% CI)	p-value
BaselineXXXXXl	No			
	Yes			

1: patients for whom data were not available on all variables included in the multivariate model (n = X) are excluded from the model.
2: IMPORTANT NOTE: Those variables that were not significant but that were used for the construction of the multivariate model shown in thetable are not shown in the table ***previous.***

-

Table 25. Multivariate analysis: 1-year OS rate vscharacteristics baseline

			Multivariate logistic regression	
		N[1]	OR (95% CI)	p-value
XXX	No			
	Yes			
Constant				

1: patients for whom no data was available in all variables included in the multivariate model (n = X).

1.5.1.3. 1-YEAR SG RATE vs BASAL CHARACTERISTICS. MULTIVARIATE ANALYSIS. GOODNESS OF FIT

Table 26. Goodness of fit: Hosmer-Lemeshow

	Chi-square test	Degrees of freedom	p-value
Hosmer and Lemeshow Test			

Table 27. Goodness of fit: Classification table

		Predicted		
		OS at 1 year		
Observed		No (death)	Yes (alive)	% correct
OS at 1 year	No (death)			
	Yes (alive)			

	% Total	

Table 28. Goodness of fit: Area under thecurve

AUC	Standard error	p-value	95% CI

Figure 2. Goodness of fit: ROC curve

1.5.2. PROGRESSION-FREE SURVIVAL (Evaluables)

Following the protocol, the population ofwas used for the efficacy analysis evaluable patients: n = X (see section 1.1)

According to protocol: PFS is defined in each patient as the time between the date of the first dose of ipilimumab and the date on which progression is determined or death occurs, whichever occurs first. If a patient dies without prior notification of progression, progression will be considered to have occurred on the date of death. For a patient who undergoes tumor resection during the study, the PFS will be censored on the date of the last tumor evaluation prior to resection. In the case of patients who remain alive and do not show progression, the PFS will be censored on the date of the last tumor evaluation. For patients in whom PE has been determined before week 12 and a subsequent evaluation of EE, PR, or CR is obtained, the date of PE after response (if available) will be used in the analysis. of the SLP; otherwise, these patients will be censored on the date of their last tumor evaluation.

Table 29. Progression-free survival (evaluable)

Estimated progression-free survival	N events	N at risk	% of patients without progression	95% CI	with progression
at 6 months					
to 12 months					
	N (%)	Median	Min-Max	Standard Error	Confidence interval 95%
Estimated progression-free survival					

Table 30. Progression-free survival and PFS at 6 months (Evaluable)

		N (%; 95% CI)
Progression-free survival	Alive (without PE)	
	PE	
	Exitus (without prior PE)	
	Total	
PFS at 6 months (*crude*)	No	
	Yes	
	No follow-up at 6 months (or PE before 6m)	
	Total	
PFS at 6 months (*crude*) (excluding patients with follow-up <6 months and no PE / previous death)	No	
	Yes	
	Total	

Figure 3. Survival free of Estimated progression (Evaluable)

Table 31. Time to PE (only in patients with PE)

	N	Mean (SD)	Median (Min-Max)
Time to PFS (months from 1st cycle of Ipilimumab) (only patients with PE)			

1.5.2.1. PFS RATE A 6 MONTHS vs BASAL CHARACTERISTICS

Next, a univariate and multivariate analysis was proposed. e the possible association between the baseline characteristics and the 6-month progression-free survival rate, using logistic regression models taking PD or death as an event at 6-month follow-up.

A univariate analysis was carried out in which none of the following variables showed a statistically significant association (p <0.1) with PFS at 6 months of follow-up and therefore multivariate analysis was not carried out.

Table 32. Univariate analysis: PFS rate at 6m vs Baselinecharacteristics

		PFSat 6m			Univariate logistic regression	
		No (without PD or death) N (%)	Yes (living without PD) N (%)	Total N (%)	OR (95% CI)	p-value
Age categorized according to median (66 years)	<66 years					
	≥66 years					
	Total					
Sex	Female					
	Male					
	Total					
KPS	90-100					
	70-80					
	Total					
Barthel Index	15-20					
	<15					
	Total					
Status B-Raf (Current Melanoma)	Native					
	Mutated					
	Total					
No. of lines of previous treatment	0					
	1					
	> 1					
	Total					
Status B-Raf (previous Melanoma)	Native					
	Mutated					
	Total					
Type of locations M1 Current Brain	Single					
	Multiple					
	Total					
Location M1 Current liver	No					
	Yes					
	Total					
Corticosteroids at baseline and / or C1	No					
	Yes					
	Total					

No. of organs with metastatic disease	1	
	2	
	3	
	4	
	Total	
No. of organs with metastatic disease	≤2	
	> 2	
	Total	
Neutrophil / Lymphocyte(quantitative)		
RatioNeutrophil /Ratio Lymphocyte> 3 (high risk)	No	
	Yes	
	Total	
Previous BRAF Inhibitor	No	
	Yes	
	Total	
CRPvalue		
Hemoglobinvalue		
LDH valueLDH value		
> ULN	No	
	Yes	
	Total	
LDH value> 1.5 * ULN	No	
	Yes	
	Total	

-

Table 33 Multivariate analysis: PFS rate at 6m vs Baseline characteristics

			Multivariate logistic regression	
		N[1]	OR (95% CI)	p-value
XXXXX	No			
	Yes			
XXXXX	No			
	Yes			
Constant				

1: patients for whom data were not available in all variables included in the multivariate model (n = X).

1.5.3. BEST RESPONSE (Evaluable)

Following the protocol, for the efficacy analysis the population ofwas used evaluable patients: n = X (see section 1.1)

Table 34. Best response (Evaluable)

		N (%; 95% CI)
Best response (Criteria modified from WHO)	CR	
	PR	
	EE	
	PE	
	NE (Not evaluated)	
	Total	
Best response (Response Criteria related to immunity. CRri)	RCri	
	RPri	
	EEri	
	PEri	
	NEri (Not evaluated)	
	Total	

According to protocol: **Overall best response rate (TMRG)**

The MRG is defined by a population subgroup as the total number of patients treated in the subgroup whose MRG is CR or PR, divided by the total number of patients treated in the subgroup.

Table 35. TMRG (Evaluables)

		N (%; 95% CI)
TMRG: CR or PR (Modified WHO Criteria)	No	
	Yes	
	Not evaluated	
	Total	
TMRG: CR or PR (Response Criteria related to immunity. CRri)	No	
	Yes	
	Not evaluated	
	Total	

According to protocol: **Disease control rate (TBI)**

TBI is defined as the total number of patients treated in each subgroup whose GRM is CR, PR or EE, divided by the total number of patients treated in the subgroup.

Table 36. TBI (Evaluable)

		N (%; 95% CI)
TCE: CR or PR or EE (Modified WHO Criteria)	No	
	Yes	
	Not evaluated	
	Total	
TCE: CR or PR or EE (Response Criteria related to immunity. CRri)	No	
	Yes	
	Not evaluated	
	Total	

Table 37. Time to best response (evaluable)

	N[1]	Mean (SD)	Median (Min-Max)
Time to best WHO response (months from 1st cycle of ipilimumab)			
Time to best response CRri (months from 1st cycle of ipilimumab)			

1: Patients with response recorded in CRDe

Table 38. Time to best response (Evaluable) according to MRG

Time to best response		N[1]	Mean (SD)	Median (Min-Max)
Best global response (modified WHO criteria)	**CR**			
	PR			
	EE			
	PE			
Time to best response		**N[1]**	**Mean (SD)**	**Median (Min-Max)**
Best Overall response (Response Criteria related to immunity. CRri)	**RCri**			
	RPri			
	EEri			
	PEri			

1: Patients with response recorded in CRDe

According to protocol: Duration of response

The duration of a patient's response is defined as the time elapsed between the date on which the measurement criteria for an overall response of PR or CR are first met (whichever response is recorded first, and if confirmed later) and the date of disease progression or death , whichever comes first. For patients undergoing tumor resection during the study, the duration of response will be censored on the date of the last tumor evaluation prior to resection. In the case of patients who remain alive and do not show progression, the duration of the response will be censored on the date of the last tumor evaluation.

Table 39. Duration of response (Evaluable)

	N[1]	Mean (SD)	Median (Min-Max)
Duration of response (modified WHO criteria), months			
Duration of response (Response Criteria related to immunity. CRri) , months			

1: Patients with response recorded in CRDe

According to protocol: Duration of Stable Disease

The duration of stable disease is defined in patients whose MRG is EE as the time that elapses between the moment when the disease was documented for the first time. EE and date of PE or death (whichever occurs first). In the case of a patient who undergoes tumor resection after week 12 but before disease progression occurs, the duration of stable disease will be censored on the date of the last evaluable tumor evaluation prior to resection. In patients with an EE MRG at week 12, the date of PE after this time (if available) will be used in the analysis of the duration of stable disease. In patients with an EE MRG who have not shown subsequent progression and remain alive, the duration of stable disease will be censored on the date of the last evaluable tumor evaluation.

Table 40. Duration of stable disease (Evaluable)

	N[1]	Mean (SD)	Median

	(Min-Max)
Duration of stable disease (modified WHO criteria), months	
Duration of stable disease (Response Criteria related to immunity . CRri), months	

1: Patients with response recorded in CRDe

1.5.4. GRAPHIC REPRESENTATIONS RESPONSE (Evaluable)

Following the researcher's instructions, different graphic representations have been elaborated to evaluate the results of the response (WHO).

Figure 4. Spider plot: Absolute change in the measurements of the lesions with respect to baseline

Figure 6. Waterflow plot: Absolute change in the measurements of the lesions with respect to baseline (according to the use of corticosteroids)

Figure 7. Waterflow plot: Absolute change in the measurements of the lesions with respect to baseline (excluding extreme value) (according to the use of corticosteroids)

Figure 8. Waterflow plot:% change in the measurements of the lesions with respect to baseline (according to the use of corticosteroids)

Figure 9. Waterflow plot:% change in the measurements of lesions with respect to baseline (according to use of corticosteroids) cut by 200%

Figure 10. Waterflow plot:% change in the measurements of lesions with respect to baseline (excluding extreme value) (according to use of corticosteroids)

Figure 11. Waterflow plot:% change in lesion measurements with respect to baseline (according to response)

Figure 12. Waterflow plot:% change in lesion measurements with respect to baseline (excluding extreme value) (according to answer)

Figure 13. Swimmerplot: follow-up Entity of each patient with corticosteroids, response and status at the end of follow-up

1.6. TOXICITIES (Treatment-related AEs)

As specified in the protocol for this analysis,was used <u>the population of treated patients, n = XX.</u>

Table 41. Toxicities

		N (%[1]; 95% CI)
Patients with at least one toxicity, any grade	**No**	
	Yes	
	Total	
Patients with at least one gradetoxicity≥3	**No**	
	Yes	
	Total	
Patients with grade 3 toxicities	**No**	
	Yes	
	Total	
Patients with grade toxicities 4	**No**	
	Yes	
	Total	
Patients with grade 5 toxicities	**No**	
	Total	
No. of gradetoxicities≥3per patient[1]	**None**	
	1 toxicity	
	2 toxicities	
	3 toxicities	
	4 toxicities	
	Total	

1: Patients could present more than one toxicity of the same grade

Table 42. Time between initiation of treatment and toxicity (days)

	Mean (SD)	Median (Min-Max)
Time between initiation of treatment and toxicity (days)		

The frequencies of toxicities with grade ≥3 are shown below.

Table 43. Toxicities with grade ≥3

Type of Toxicity	Grade 3 N (%[1])	Grade 4 N (%[1])

1:% calculated with respect to the total number of patients evaluable for safety (n = XX)

Below is a list of the toxicities with grade≥3 per patient with their characteristics.

Table 44. List of grade ≥3 toxicities (patients may present more than one toxicity)

Patient code	Toxicity and Grade	SAE	Relationship with treatment	Start	date AE End date AE

The most frequent toxicities with their degrees and in ANNEX I : LIST OF TOXICITIES A list of all toxicities is presented.

Table 45. Most frequent toxicities (> 10% on = 5) and their grade

		N (%)
XXXX	Absence	
	Presence	
XXXX	Absence	
	Presence	

Table 46. Median time between initiation of treatment and toxicity in the most frequent toxicities (days)

	Time between initiation of treatment and toxicity
Type of toxicity (most frequent)	Median (days)

Table 47. Median time between the start of treatment and toxicity in the most frequent toxicities (days) as a function of the MRG rate

	Type of Toxicity	Rate of best global response TMRG (PR or CR) (modified WHO criteria)	Median (days)
Adverse Event	XXXX	No	
		Yes	
		Total	
	XXXX	No	
		Yes	
		Not evaluated	
		Total	

1.7. AEs

As specified in the protocol for this analysis,was used <u>the population of treated patients, n = XX.</u>

Table 48. AEs

		N (%[1]95% CI)
Patients with at the least one AE, any grade	No	
	Yes	
	Total	
Patients with at the least one AE grade≥3	No	
	Yes	
	Total	
Patients with AEs grade 3	No	
	Yes	
	Total	
Patients with AEs grade 4	No	
	Yes	
	Total	
Patients with Grade 5 AEs	No	
	Total	
No. of GradeAEs≥3per patient[1]	None	
	1 AE	
	2 AEs	
	3 AEs	
	4 AEs	
	5 AEs	
	11 AEs	
	Total	

1: Patients could present more than one AE of the same grade

. present the frequencies of AEs with grade ≥3.

Table 49.with grade ≥3

AEType of AE	Grade 3 N (%[1])	Grade 4 N (%[1])

1:% calculated with respect to the total number of patients evaluable for safety (n = XX)

Table 50. Time between start of treatment and AE

	Mean (SD)	Median (Min-Max)
Time between initiation of treatment and AE		

Below are the most frequent AEs with their grades and in ANNEX II: LIST OF ALL AEsAEs a list of allis presented.

Table 51. AEs most frequent (> 10% or= 5) and its grade

		nN (%)
XXXX	**Absence**	49 (84.5%)
	Presence	9 (15.5%)
XXXX	**Absence**	43 (74.1%)
	Presence	15 (25.9%)

1.8. SAE

ALL / Related

As specified in the protocol,was used for this analysis <u>the treated patient population, n = XX,.</u>

Table 52. SAEs

		N (%[1]; 95% CI)
At least one SAE	**No**	
	Yes	
	Total	

1:% with respect to ***included patients*** with available data.

The SAEs with their details are presented below:

Table 53. List of SAEs with details

Relationship with AE treatment	No.	Patient code	SAE and grade	Specify relationship AE	Start	date AE End date AE
No	1					
	2					
	3					
Yes	1					
	2					
	3					

The following are the frequencies of SAEs not related to grade ≥3.

Table 54. Unrelated SAEs with grade ≥3

Type of unrelated SAE	Grade 3 N (%[1])	Grade 4 N (%[1])

1:% with respect to ***included patients*** with available data.

Below are the frequencies of unrelated SAEs of any grade.

Table 55. List of unrelated SAEsunrelated

Type ofSAE	N (%[1])

1:% with respect to ***included patients*** with available data.

1.9. DEATHS

As specified in the protocol for this analysis, the treated patient population, n = XX, was used.
Deaths in the study or within 30 days after the last dose: ALL / drug related

Table 56. Deaths during the study

		N (%[1]; 95% CI)
Deaths during the study or within 30 days after the last dose	**No (Exitus but considered out of study)**	
	Yes	
	Not applicable (no death)	
	Total	

1:% regarding the ***patients included*** with available data.

Table 57.list

ExitusExitus during the study or in the 30 days after the last dose	No.	Patient code	Exitus reason Exitus	reason other	Date of last Ipilimumab cycle	Date Exitus	OS time (months since 1st ipilimumab cycle)
No (exitus considered out of study)	1						
	2						
	3						
Yes	1						
	2						
	3						

2. ANNEXES

2.1. ANNEX I: TOXICITY LIST

The frequencies of all the toxicities listed in the DB are detailed below.

Table 58. List of all toxicities

Toxicities	N (%)
Total	

2.2. ANNEX II: LIST OF ALL AEs

Below frequencies of all AEs collected in the DB are detailed (toxicities included).

Table 59. List of all AEs

AEs	N (%)
Total	