A phase II study of Platinum-doublet chemotherapy in combination with nivolumab as first-line treatment, in subjects with unresectable, locally advanced or metastatic G3 Neuroendocrine Neoplasms (NENs) of the gastroenteropancreatic (GEP) tract or of unknown (UK) origin. (GETNE T1913).

NICE-NEC STUDY

FINAL STATISTICAL REPORT (2022)

9th of November 2022

1. Table of Contents

NICE-NEC a phase II study of Platinum-doublet chemotherapy in combination with nivolumab as first-line treatment, in subjects with unresectable, locally advanced or metastatic G3 Neuroendocrine Neoplasms (NENs) of the gastroenteropancreatic (GEP) tract or of unknown (UK) origin. (GETNE T1913).

Primary endpoint is 12 m OS.

Secondary endpoints include ORR, and PFS by RECIST 1.1 and safety.

The database for the results of the following report was locked down on the XXth of XX 202X.

2. PATIENTS RECRUITED AND STUDY POPULATIONS

2.1. SCREENING FAILURES

Table 2: List of patients: screening Failure Reasons

Patient number	Screening failure	Reason Screening failure

2.2. PATIENT POPULATIONS

Enrolled

All participants who signed informed consent and were registered.

Table 3: Enrolled population

	Overall (N=)
Enrolled	
Yes	
No	

Treated

All participants who received at least one dose of any study medication. This is the primary dataset for dosing and safety analysis.

Table 4: Treated population

	Overall (N=)
Treated	
Yes	
No	

Table 5: Treated population: Reason excluded

Patient number	Treated population	Reason excluded from Treated population

Response-Evaluable

All treated subjects who have a baseline and at least one on-treatment imaging evaluation or had progression or death prior to the first on-treatment scan.

REASON FOR EVALUATION

Table 6: Response-Evaluable population

	Overall (N=)
Response-Evaluable analysis set	
Yes	
No	

Table 7: Response-Evaluable population: Reason excluded

Patient number	Response-Evaluable population	Response reason	1st Tumor assessment measurement (lesions)	PD date	First FU	EOS reason	EOS date	First treatment admin

3. RESULTS

The database for the results of the following report was locked down on the XXth of XXX 202X.

3.1. EVALUABLE PATIENTS

Regarding the efficacy analysis the *Response-Evaluable* population will be used (n=).

Table 8: Populations and Hospital

Overall	Overall (N=)
Enrolled	
Yes	
No	
Treated	
Yes	
No	
Response-Evaluable analysis set	
Yes	
No	
Hospital	
CENTRO ONCOLÓGICO MD ANDERSON INTERNATIONAL ESPAÑA	
HOSPITAL RAMÓN Y CAJAL	
HOSPITAL UNIVERSITARI VALL D'HEBRON(*)	
HOSPITAL UNIVERSITARIO 12 DE OCTUBRE	
HOSPITAL UNIVERSITARIO CENTRAL DE ASTURIAS	
HOSPITAL UNIVERSITARIO LA PAZ	
HOSPITAL UNIVERSITARIO MIGUEL SERVET	
HOSPITAL VIRGEN DE LA VICTORIA	
HOSPITAL VIRGEN DEL ROCÍO	
INSTITUT CATALÀ D'ONCOLOGIA L'HOSPITALET (ICO)	

3.2. BASELINE CHARACTERISTICS

3.2.1. BASELINE - DEMOGRAPHIC DATA

Table 9: Baseline - Demographic Data

Overall	Overall (N=)
Gender	
Female	
Male	
Age at registration (year)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Race	
Caucasian	
Latin	
Unknown	
Weight (Kg)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Height (cm)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Systolic Blood Pressure (mmHg)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Diastolic Blood Pressure (mmHg)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Temperature (ºC)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	

Overall	Overall (N=)
Range	
Respiratory rate (bpm)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Pulse Rate (bpm)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
ECOG	
0	
1	
2	
Physical examination	
Normal	
Clinically relevant findings	

3.2.2. BASELINE - CANCER HISTORY

Table 10: Baseline - Cancer History (I)

Overall	Overall (N=)
Cancer Type	
Gastroenteropancreatic tract	
Primary Unknown	
Primary location	
Esophagus	
Gastric	
Pancreas	
Right colon	
Left colon	
Rectum	
Duodenum	
Ileum	
Prostate	
Inguinal	
Unknown	
Primary location (grouped)	
Duodenum/Ileum	
Esophagus/Gastric	
Pancreas	
Colon/Rectum	
Not specified/Others	
Primary location (Colon/Rectum vs Others)	
Colon/Rectum	
Others	
Initial T Stage	
T0	
T1	
T2	
T3	
T4	
Tx	
Initial N Stage	
N0	
N1	
N2	
Nx	
Initial M Stage	
M0	
M1	
Cancer Stage at diagnosis	
I	
III	
IV	
Histological grade	
3	
Ki-67 Index	
N	

Overall	Overall (N=)
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Ki-67 categorised	
<=20	
>20	
Ki-67 categorised	
<=50	
>50	
Ki-67 categorised	
<=55	
>55	
Mitotic Rate	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Differentiation	
Well differentiated	
Poorly differentiated	
Functional status	
Functioning	
Non-functioning	
Unknown	

Table 11: Baseline - Cancer History (II)

Overall	Overall (N=)
Primary surgery	
Yes	
No	
Unknown	
Time since Primary surgery to treatment initiation (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Primary Surgery Outcome	
Missing data	
R0	
R2	
UK	
Radiotherapy	
Yes	
No	
Other cancer history	
Yes	

Overall	Overall (N=)
No	
Unknown	
Other cancer history specify	
NA	
Breast	
Colorectal adenoma	
Prostate adenocarcinoma	

Table 12: Baseline - Current NEN

Overall	Overall (N=)
Current NEN T Stage	
T0	
T1	
T2	
T3	
T4	
Tx	
Current NEN N Stage	
N0	
N1	
N2	
Nx	
Current NEN M Stage	
M0	
M1	
Current NEN Stage	
III	
IV	

Table 13: Baseline - Metastatic disease location

Overall	Overall (N=)
Affected Organ Liver	
No	
Yes	
Affected Organ Lung	
No	
Yes	
Affected Organ Nodules	
No	
Yes	
Affected Organ Peritoneal	
No	
Yes	
Affected Organ Bone	

Overall	Overall (N=)
No	
Yes	
Affected Organ Spleen	
No	
Yes	
Affected Organ Soft tissue	
No	
Yes	
Affected Organ Others	
No	
Yes	
Affected Organs Number	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Affected Organs Number (categorised)	
1 Organ	
2 Organs	
3 Organs	
4 Organs	
5 Organs	
6 Organs	

3.3. BASELINE - ANALYTICS

3.4. BASELINE - HEMATOLOGY AND COAGULATION

Table 14: Baseline - Hematology and Coagulation

Overall	Overall (N=)
PTT Value	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Basophils (x 10e9/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Eosinophils (x 10e9/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Hematocrit (%)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Hemoglobine (g/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
INR Value	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Lymphocytes (x 10e9/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Monocytes (x 10e3/µL)	
N	
Mean (95%CI)	

Overall	Overall (N=)
SD	
Median (95%CI)	
Range	
Neutrophils (x 10e3/µL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Platelets (x 10e9/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
PT Value	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Red Blood Count (10e6/µL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
White Blood Count (10e3/µL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

3.5. Baseline - Biochemistry, Thyroid Function and Serology

Table 15: Baseline - Biochemistry, Thyroid Function and Serology

Overall	Overall (N=)
Albumin (g/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
ALT (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Amylase (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
AST (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
BUN (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
CGA (ng/mL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
CGA <> 2 x ULN	
Missing data	
CGA >= 2*ULN	
CGA < 2*ULN	
Calcium (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Overall	Overall (N=)
Creatinine Kinase (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Creatinine (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Direct Bilirubin (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Free T3 (pmol/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Free T4 (ng/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
GGT (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Glucose (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Indirect Bilirubin (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
IFNy (ng/mL)	
N	
Mean (95%CI)	

Overall	Overall (N=)
SD	
Median (95%CI)	
Range	
IL1 (pg/mL)	
N	
Mean	
SD	
Median	
Range	
IL6 (pg/mL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
LDH (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Lipase (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Magnesium (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Neuron-Specific Enolase (ng/mL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
NSE catgorised >2 x ULN	
Missing data	
NSE >= 2*ULN	
NSE < 2*ULN	
Phosphorus (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Phosphatase (U/L)	
N	

Overall	Overall (N=)
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Potassium (mmol/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Sodium (mmol/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
TNF-α Value	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Total Bilirubin (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Total Protein (g/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
TSH (mUI/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Urea (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Uric Acid (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	

Overall	Overall (N=)
Range	

3.6. Baseline - Other Determinations

Table 16: Baseline - Other Determinations

Overall	Overall (N=)
Protein	
Negative	
+1	
Traces	
+2	
+3	
Unknown	
Bilirubin	
Negative	
Positive	
Unknown	
ND	
Blood	
Negative	
Positive	
Unknown	
ND	
Color/appearence	
Normal	
Abnormal	
ND	
Unknown	
Glucose	
Normal	
Abnormal	
Unknown	
Leukocytes esterase	
Negative	
Positive	
ND	
Unknown	
Nitrite	
Negative	
Positive	
Unknown	
Urobilinogen	
Negative	
Positive	
ND	
Unknown	
Ketones	
Negative	
Positive	
Unknown	
Urine Analysis pH	
N	
Mean (95%CI)	

Overall	Overall (N=)
SD	
Median (95%CI)	
Range	
Urine Analysis Specific gravity	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
ECG	
Normal	
Clinically relevant findings	
Unknown	
Ecg QTc Value	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

4. Treatment exposure

Table 17: Patients in each phase

Overall	Overall (N=)
Starting Induction Phase	
No	
Yes	
Starting Maintenance Phase	
No	
Yes	

4.1. Induction Phase

Table 18: Adherence to Carboplatin, Etoposide and Nivolumab (Induction Phase)

	Carboplatin (N=)	Etoposide (N=)	Nivolumab (N=)
Time duration of in induction (months)			
N			
Mean (95%CI)			
SD			
Median (95%CI)			
Range			
Number of cycles administered (Induction phase)			
0			
1			
2			
3			
4			
5			
6			
Number of cycles administered (Induction phase)			
N			
Mean (95%CI)			
SD			
Median (95%CI)			
Range			
Omission (Induction phase)			
Yes			
No			
Omissions number (Induction phase)			
N			
Mean (95%CI)			
SD			
Median (95%CI)			

	Carboplatin (N=)	Etoposide (N=)	Nivolumab (N=)
Range			
Omissions number (Induction phase)			
0			
1			
2			
3			
Delay (Induction phase)			
Yes			
No			
Delay number (Induction phase)			
N			
Mean (95%CI)			
SD			
Median (95%CI)			
Range			
Delay number (Induction phase)			
0			
1			
2			
3			
4			

Table 19: Delay time Carboplatin (Induction Phase)

Patient Number	Carboplatin delay time - Induction phase C2 (days)	Carboplatin delay time - Induction phase C3 (days)	Carboplatin delay time - Induction phase C4 (days)	Carboplatin delay time - Induction phase C5 (days)	Carboplatin delay time - Induction phase C6 (days)	Carboplatin delay time - Induction phase C7 (days)	Carboplatin delay time - Induction phase C8 (days)	Carboplatin total delay time - Induction phase(days)

Table 20: Delay time Etoposide (Induction Phase)

Patient Number	Etoposide delay time - Induction phase C2 (days)	Etoposide delay time - Induction phase C3 (days)	Etoposide delay time - Induction phase C4 (days)	Etoposide delay time - Induction phase C5 (days)	Etoposide delay time - Induction phase C6 (days)	Etoposide delay time - Induction phase C7 (days)	Etoposide delay time - Induction phase C8 (days)	Etoposide total delay time - Induction phase(days)

Table 21: Delay time Nivolumab (Induction Phase)

Patient Number	Nivolumab delay time - Induction phase C2 (days)	Nivolumab delay time - Induction phase C3 (days)	Nivolumab delay time - Induction phase C4 (days)	Nivolumab delay time - Induction phase C5 (days)	Nivolumab delay time - Induction phase C6 (days)	Nivolumab delay time - Induction phase C7 (days)	Nivolumab delay time - Induction phase C8 (days)	Nivolumab total delay time - Induction phase(days)

4.2. Maintenance Phase

The following results are analyzed only in patients that started the maintenance phase.

Table 22: Adherence to Nivolumab (Maintenance Phase)

Overall	Overall (N=)
Time duration of Nivolumab in Maintenance (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Nivolumab number of cycles administered (Maintenance phase)	
0	
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
Nivolumab number of cycles administered (Maintenance phase)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Nivolumab omission (Maintenance phase)	
No	
Yes	

Overall	Overall (N=)
Nivolumab omissions number (Maintenance phase)	
0	
1	
Nivolumab omissions number (Maintenance phase)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Nivolumab delay (Maintenance phase)	
No	
Yes	
Nivolumab delay number (Maintenance phase)	
0	
1	
2	
3	
Nivolumab delay number (Maintenance phase)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Table 23: Delay time Nivolumab (Maintenance Phase)

Patient Number	Nivolumab delay time – Maintenance phase																										
	C2 (days)	C3 (days)	C4 (days)	C5 (days)	C6 (days)	C7 (days)	C8 (days)	C9 (days)	C10 (days)	C11 (days)	C12 (days)	C13 (days)	C14 (days)	C15 (days)	C16 (days)	C17 (days)	C18 (days)	C19 (days)	C20 (days)	C21 (days)	C22 (days)	C23 (days)	C24 (days)	C25 (days)	C26 (days)	C27 (days)	(days)

Table 24: List of administered dates Nivolumab (Maitenance Phase)

Patient Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27

4.3. Total duration of treatment with Nivolumab

Overall	Overall (N=)
Time duration of Nivolumab Induction + Maintenance (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

4.4. Cycles administered after progression

Table 25: Cycles administered after progression

	Nivolumab (N=)
Cycles after progression Nivolumab (Maintenance phase)	
Yes	
No	
Number of cycles after progression Nivolumab (Maintenance phase)	
0	
1	
2	
Number of cycles after progression Nivolumab (Maintenance phase)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

4.5. END OF TREATMENT - END OF STUDY - FOLLOW-UP

4.5.1. End of treatment

Table 26: End of Treatment reasons

Overall	Overall (N=)
Reason for End Of Treatment	
Progression	
Unnacceptable toxicity	
Investigator decision	
Study treatment completion	
Other	
Other reason for End Of Treatment specified	
Clinical impairment and death	
Death	
Esophageal mucositis	
Not applicable	
Not specified	

4.5.2. End of Study

Table 27: End of Study reasons

Overall	Overall (N=)
Reason for End Of Study	
Lost of follow-up	
Exitus	
Others	
Other reason for End Of Study specified	
End of study	
Not applicable	

4.5.3. Follow-up (all patients)

Table 28: Median follow-up (all patients)

Overall	Overall (N=)
Time since treatment started (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Time since treatment started (months) [> 24 months of follow-up]	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

4.5.4. Follow-up (only alive patients)

Table 29: Median follow-up (only alive patients)

Overall	Overall (N=)
Time since treatment started (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Time since treatment started (months) [> 24 months of follow-up]	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

The efficacy analyses are reported in those patients belonging to the response population as defined previously (n=).

4.6. PRIMARY ENDPOINT: OVERALL SURVIVAL (OS)

As specified in the protocol the **Primary endpoint is one year OS rate** with nivolumab plus chemotherapy. This is defined as the proportion of patients that remain alive at 12 months since the beginning of treatment. OS will be censored on the last date a participant was known to be alive.

Table 30: Events type OS

OS	N	%	95%CI
Alive			
Death			
Total			

Reason of death	N	%	95%CI
Clinical deterioration			
Clinical worsening.			
Not applicable			
Progression disease			
Sepsis			
Unknown			
Total			

Table 31: Median/mean OS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Overall survival				

Table 32: OS estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 12 months				
At 18 months				
At 24 months				
At 30 months				
At 36 months				

Figure 1: Overall survival

4.7. SECONDARY ENDPOINTS

4.7.1. PROGRESSION FREE SURVIVAL (PFS)

As specified in the protocol **PFS** is defined as the time from the enrollment date to the date of the first documented tumor progression per RECIST 1.1, or death due to any cause. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Participants who did not have any on study tumor assessments will be censored on the beginning of treatment date. PFS curves, PFS medians with 95% CIs, and PFS rates at 6, 12, 18, 24, 36, and 48 months with 95% CIs will be estimated using Kaplan-Meier methodology if follow-up requirements are met.

4.7.2. EVENTS: PROGRESSIONS/DEATHS

Table 33: Events type PFS

PFS (PD REcist 1.1 or Death)	N	%	95%CI
No			
PD (Recist 1.1)			
Death (without previous PD)			
Total			

Table 34: Median/mean PFS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Progression free survival				

Table 35: PFS estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 12 months				
At 18 months				
At 24 months				
At 30 months				
At 36 months				

Figure 2: Progression free survival

4.7.3. ORR: Objective Response Rate

BOR and **ORR** are determined based on RECIST 1.1.

4.7.4. Best Overall Response

Table 36: ORR

Overall Response Rate	N	%	95%CI
PR			
SD			
PD			
NE			
Total			

Table 37: BOR: Best Overall Response

Overall	Overall (N=)
Best Overall Response	
PR	
SD	
PD	
NE	

[+] *The X patients with **NE** had XXX*

4.7.5. Duration of Response

The duration of response is calculated in those patients with Best Response CR or PR.

Table 38: BOR: Best Overall Response

Overall	Overall (N=)
Duration of response (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

4.7.5.1. Figure: Waterfall plot. Maximum % total change with BOR

4.7.5.2 FIGURE: WATERFALL PLOT. MAXIMUM % TOTAL CHANGE VS BOR

4.7.5.3 FIGURE: WATERFALL PLOT. MAXIMUM % TOTAL CHANGE VS PRIMARY LOCATION

4.7.5.4 FIGURE: WATERFALL PLOT. MAXIMUM % TOTAL CHANGE VS KI67

4.7.5.4 FIGURE: WATERFALL PLOT. MAXIMUM % TOTAL CHANGE VS DIFFERENTATION TUMOUR

4.7.5.2. FIGURE: SPIDER PLOT. MAXIMUM % TOTAL CHANGE

4.7.5.5 Figure: Spider plot. Maximum % total change VS DIFFERENTIATION

4.7.5.6 Figure: Spider plot. Maximum % total change VS BOR

4.7.5.7 Figure: Spider plot. Maximum % total change VS CGA

4.7.5.8 Figure: Spider plot. Maximum % total change VS NSE

4.8. OS STRATIFIED BY FACTORS OF INTEREST: DIFFERENTIATED/ Ki67/ PRIMARY TUMOUR LOCATION / CGA / NSE

4.8.1. OS vs Differentiation

Two groups are defined (as reported in eCRD): Well and Poorly differientated

Table 39: OS vs Differentiation: Median estimation

	Median (months)	CI 95%	Mean	CI 95%
Well differentiated				
Poorly differentiated				

[1]*Estimated using Kaplan-Meier product-limit method*
[2] **Log rank test to compare categories: p-value=X**

Table 40: OS vs Differentiation: Survival ratio estimation

SG	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Well differentiated				
At 6 months				
At 12 months				
Poorly differentiated				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

4.8.1.1. Figure: OS vs Differentiation. Kaplan Meier graph

4.8.2. OS vs Ki67

Two groups are defined from the Ki67 values recorded at the eCRF: ≤ 55 and >55

Table 41: OS vs Ki67: Median estimation

	Median (months)	CI 95%	Mean	CI 95%
Ki67<=55				
Ki67>55				

[1]*Estimated using Kaplan-Meier product-limit method*
[2] **Log rank test to compare categories: p-value=X**

Table 42: OS vs Ki67: Survival ratio estimation

SG	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Ki67<=55				
At 6 months				
At 12 months				
Ki67>55				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

4.8.2.1. Figure: OS vs Ki67. Kaplan Meier graph

4.8.3. OS vs Location

Six groups are defined from the Location recorded at the eCRF: Esophagus/Gastric, Pancreas, Colon/Rectum, Duodenum/Ileum and Not specified/Others.

Table 43: OS vs Location: Median estimation

	Median (months)	CI 95%	Mean	CI 95%
Duodenum/Ileum				
Esophagus/Gastric				
Pancreas				
Colon/Rectum				
Not specified/Others				

[1]*Estimated using Kaplan-Meier product-limit method*
[2] Log rank test to compare categories: p-value=X

Table 44: OS vs Location Survival ratio estimation

SG	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Duodenum/Ileum				
At 6 months				
At 12 months				
Esophagus/Gastric				
At 6 months				
At 12 months				
Pancreas				
At 6 months				
At 12 months				
Colon/Rectum				
At 6 months				
At 12 months				
Not specified/Others				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

4.8.3.1. Figure: OS vs Location. Kaplan Meier graph

4.8.4. OS vs CGA

Two groups are defined from the CGA recorded at the eCRF: CGA < 2*ULN and CGA >= 2*ULN.

Table 45: OS vs CGA: Median estimation

	Median (months)	CI 95%	Mean	CI 95%
CGA < 2*ULN				
CGA >= 2*ULN				

[1]*Estimated using Kaplan-Meier product-limit method*
[2] **Log rank test to compare categories: p-value=X**

Table 46: OS vs CGA Survival ratio estimation

SG	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
CGA < 2*ULN				
At 6 months				
At 12 months				
CGA >= 2*ULN				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

4.8.4.1. Figure: OS vs CGA Kaplan Meier graph

4.8.5. OS vs NSE

Two groups are defined from the Location recorded at the eCRF: NSE < 2*ULN, NSE >= 2*ULN

Table 47: OS vs NSE: Median estimation

	Median (months)	CI 95%	Mean	CI 95%
NSE < 2*ULN				
NSE >= 2*ULN				

[1]*Estimated using Kaplan-Meier product-limit method*
[2] **Log rank test to compare categories: p-value=X**

Table 48: OS vs NSE Survival ratio estimation

SG	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
NSE < 2*ULN				
At 6 months				
At 12 months				
NSE >= 2*ULN				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

4.8.5.1. Figure: OS vs NSE Kaplan Meier graph

4.9. PFS STRATIFIED BY FACTORS OF INTEREST: DIFFERENTIATED/ KI67/ PRIMARY TUMOUR LOCATION / CGA / ENOLASE

4.9.1. PFS VS DIFFERENTIATION

Two groups are defined (as reported in eCRD): Well and Poorly differentiated

Table 49: PFS vs Differentiation: Median estimation

	Median (months)	CI 95%	Mean	CI 95%
Well differentiated				
Poorly differentiated				

[1]*Estimated using Kaplan-Meier product-limit method*
[2] **Log rank test to compare categories: p-value=X**

Table 50: PFS vs Differentiation: Survival ratio estimation

SG	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Well differentiated				
At 6 months				
At 12 months				
Poorly differentiated				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

4.9.1.1. FIGURE: PFS VS DIFFERENTIATION. KAPLAN MEIER GRAPH

4.9.2. PFS vs Ki67

Two groups are defined from the Ki67 values recorded at the eCRF: <=55 and >55

Table 51: PFS vs Ki67: Median estimation

	Median (months)	CI 95%	Mean	CI 95%
Ki67<=55				
Ki67>55				

[1]*Estimated using Kaplan-Meier product-limit method*
[2] **Log rank test to compare categories: p-value=X**

Table 52: PFS vs Ki67: Survival ratio estimation

SG	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Ki67<=55				
At 6 months				
At 12 months				
Ki67>55				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

4.9.2.1. Figure: PFS vs Ki67. Kaplan Meier graph

4.9.3. PFS vs Location

Six groups are defined from the Location recorded at the eCRF: Esophagus/Gastric, Pancreas, Colon/Rectum, Duodenum/Ileum and Not specified/Others.

Table 53: PFS vs Location: Median estimation

	Median (months)	CI 95%	Mean	CI 95%
Duodenum/Ileum				
Esophagus/Gastric				
Pancreas				
Colon/Rectum				
Not specified/Others				

[1]*Estimated using Kaplan-Meier product-limit method*
[2] Log rank test to compare categories: p-value= X

Table 54: PFS vs Location Survival ratio estimation

SG	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Duodenum/Ileum				
At 6 months				
At 12 months				
Esophagus/Gastric				
At 6 months				
At 12 months				
Pancreas				
At 6 months				
At 12 months				
Colon/Rectum				
At 6 months				
At 12 months				
Not specified/Others				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

4.9.3.1. Figure: PFS vs Location. Kaplan Meier graph

4.9.4. PFS vs CGA

4.9.4.1. PFS vs CGA (2)

Two groups are defined from the CGA at the eCRF: CGA < 2*ULN and CGA >= 2*ULN.

Table 55: PFS vs CGA: Median estimation

	Median (months)	CI 95%	Mean	CI 95%
CGA < 2*ULN				
CGA >= 2*ULN				

[1]*Estimated using Kaplan-Meier product-limit method*
[2] **Log rank test to compare categories: p-value=X**

Table 56: PFS vs CGA: Survival ratio estimation

SG	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
CGA < 2*ULN				
At 6 months				
At 12 months				
CGA >= 2*ULN				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

4.9.4.2. Figure: PFS vs CGA Kaplan Meier graph (2)

4.9.4.3. PFS vs CGA (3)

Two groups are defined from the CGA at the eCRF: CGA < 3·ULN and CGA >= 3· ULN.

Table 57: PFS vs CGA: Median estimation

	Median (months)	CI 95%	Mean	CI 95%
CGA < 3*ULN				
CGA >= 3*ULN				

[1]*Estimated using Kaplan-Meier product-limit method*
[2] **Log rank test to compare categories: p-value=X**

Table 58: PFS vs CGA: Survival ratio estimation

SG	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
CGA < 3*ULN				
At 6 months				
At 12 months				
CGA >= 3*ULN				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

4.9.4.4. Figure: PFS vs CGA Kaplan Meier graph (3)

4.9.4.5. PFS vs CGA (5)

Two groups are defined from the CGA at the eCRF: CGA < 5*ULN and CGA >= 5*ULN.

Table 59: PFS vs CGA: Median estimation

	Median (months)	CI 95%	Mean	CI 95%
CGA < 5*ULN				
CGA >= 5*ULN				

[1]*Estimated using Kaplan-Meier product-limit method*
[2] **Log rank test to compare categories: p-value=X**

Table 60: PFS vs CGA: Survival ratio estimation

SG	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
CGA < 5*ULN				
At 6 months				
At 12 months				
CGA >= 5*ULN				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

4.9.4.6. Figure: PFS vs CGA Kaplan Meier graph (5)

4.9.5. PFS vs Enolase

Two groups are defined from the Enolase values: NSE < 2*ULN and NSE >= 2*ULN

Table 61: PFS vs Enolase: Median estimation

	Median (months)	CI 95%	Mean	CI 95%
NSE < 2*ULN				
NSE >= 2*ULN				

[1]*Estimated using Kaplan-Meier product-limit method*
[2] **Log rank test to compare categories: p-value=X**

Table 62: PFS vs NSE: Survival ratio estimation

SG	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
NSE < 2*ULN				
At 6 months				
At 12 months				
NSE >= 2*ULN				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

4.9.5.1. Figure: PFS vs NSE Kaplan Meier graph

4.10. ORR STRATIFIED BY FACTORS OF INTEREST: DIFFERENTIATED/ Ki67/ PRIMARY TUMOUR LOCATION / CGA / NSE

Table 63: ORR vs Differentiation

	Well differentiated (N=)	Poorly differentiated (N=)	Total (N=)	p value
Best Overall Response				
PR				
SD				
PD				
NE				
Objective Response Rate (ORR): CR or PR (BOR)				
Yes (CR/PR)				
No				

1. Fisher's Exact Test for Count Data
2. Pearson's Chi-squared test

Table 64: ORR vs Ki67

	<=55 (N=)	>55 (N=)	Total (N=)	p value
Best Overall Response				
PR				
SD				
PD				
NE				
Objective Response Rate (ORR): CR or PR (BOR)				
Yes (CR/PR)				
No				

1. Fisher’s Exact Test for Count Data
2. Pearson’s Chi-squared test

Table 65: ORR vs Location

	Esophagus/ Gastric (N=)	Pancreas (N=)	Colon/Rectum (N=)	Duodenum/ Ileum (N=)	Not specified/Others (N=)	Total (N=)	p value
BOR							
PR							
SD							
PD							
NE							
Objective Response Rate (ORR): CR or PR (BOR)							
Yes (CR/PR)							
No							

1. Fisher's Exact Test for Count Data

Table 66: ORR vs Location

	Colon/Rectum (N=)	Others (N=)	Total (N=)	p value
Best Overall Response				
PR				
SD				
PD				
NE				
Objective Response Rate (ORR): CR or PR (BOR)				
Yes (CR/PR)				
No				

1. Fisher's Exact Test for Count Data

Table 67: ORR vs CGA

	CGA < 2*ULN (N=)	CGA >= 2*ULN (N=)	Total (N=)	p value
Best Overall Response				
PR				
SD				
PD				
NE				
Objective Response Rate (ORR): CR or PR (BOR)				
Yes (CR/PR)				
No				

1. Fisher's Exact Test for Count Data
2. Pearson's Chi-squared test

Table 68: ORR vs Enolase

	NSE < 2*ULN (N=)	NSE >= 2*ULN (N=)	Total (N=)	p value
Best Overall Response				
PR				
SD				
PD				
NE				
Objective Response Rate (ORR): CR or PR (BOR)				
Yes (CR/PR)				
No				

1. Fisher's Exact Test for Count Data
2. Pearson's Chi-squared test

4.10.1. MULTIVARIATE ANALYSIS OF PFS AND OS

4.10.1.1. FACTORS INCLUDED IN THE MULTIVARIATE ANALYSIS OF THE PFS (1)

Table 69: Factors included in the multivariate analysis of the PFS

PD/Exitus	No (N=)	Yes (N=)	Total (N=)	p value
CGA <> 2 x ULN				
Missing data				
CGA < 2*ULN				
CGA >= 2*ULN				
Enolase <> 2 x ULN				
Missing data				
NSE < 2*ULN				
NSE >= 2*ULN				
Primary neuroendocrine tumour				
Duodenum/Ileum				
Esophagus/Gastric				
Pancreas				
Colon/Rectum				
Not specified/Others				
Differentiation				
Well differentiated				
Poorly differentiated				
Ki-67 categorised				
<=55				
>55				
ECOG				
0				
1				
2				
Gender				
Female				
Male				
Age categorised by median (61 years)				
<=61y				
>61y				
LDH				
<= 2ULN				
> 2ULN				

1. Fisher's Exact Test for Count Data

Table 70: PFS univariate and multivariate Cox model

	Univariate Cox Regression					Multivariate Cox Regression				
Characteristic	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**
CGA <> 2 x ULN										
CGA < 2*ULN										
CGA >= 2*ULN										
Enolase <> 2 x ULN										
NSE < 2*ULN										
NSE >= 2*ULN										
Primary neuroendocrine tumour										
Duodenum/Ileum										
Esophagus/Gastric										
Pancreas										
Colon/Rectum										
Not specified/Others										
Differentiation										
Well differentiated										
Poorly differentiated										
Ki-67 categorised										
<=55										
>55										
ECOG										
0										
1										
2										
Gender										
Female										
Male										
Age categorised by median (61 years)										
<=61y										
>61y										
LDH										
<= 2ULN										

		Univariate Cox Regression					Multivariate Cox Regression				
Characteristic	**N**	**Event N**	**HR**[1]	**95% CI**[1]	**p-value**	**N**	**Event N**	**HR**[1]	**95% CI**[1]	**p-value**
> 2ULN										

[1]HR = Hazard Ratio, CI = Confidence Interval

Note: Los p-valores marcados en negrita indican que el valor es estadísticamente significativo <0.05

Figure 3: Forest plot PFS Multivariate Cox Regression

4.10.1.2. FACTORS INCLUDED IN THE MULTIVARIATE ANALYSIS OF THE PFS (2)

Table 71: Factors included in the multivariate analysis of the PFS

PD/Exitus	No (N=)	Yes (N=)	Total (N=)	p value
CGA <> 2 x ULN				
Missing data				
CGA < 2*ULN				
CGA >= 2*ULN				
Enolase <> 2 x ULN				
Missing data				
NSE < 2*ULN				
NSE >= 2*ULN				
Primary neuroendocrine tumour				
Colon/Rectum				
Others				
Differentiation				
Well differentiated				
Poorly differentiated				
Ki-67 categorised				
<=55				
>55				
ECOG				
0				
1				
2				
Gender				
Female				
Male				
Age categorised by median (x years)				
<=xy				
>xy				
LDH				
<= 2ULN				
> 2ULN				

1. Fisher's Exact Test for Count Data

Table 72: PFS univariate and multivariate Cox model

		Univariate Cox Regression					Multivariate Cox Regression			
Characteristic	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**
CGA <> 2 x ULN										
CGA < 2*ULN										
CGA >= 2*ULN										
Enolase <> 2 x ULN										
NSE < 2*ULN										
NSE >= 2*ULN										
Primary neuroendocrine tumour										
Colon/Rectum										
Others										
Differentiation										
Well differentiated										
Poorly differentiated										
Ki-67 categorised										
<=55										
>55										
ECOG										
0										
1										
2										
Gender										
Female										
Male										
Age categorised by median (x years)										
<=61y										
>61y										
LDH										
<= 2ULN										
> 2ULN										

[1]HR = Hazard Ratio, CI = Confidence Interval

Note: Los p-valores marcados en negrita indican que el valor es estadísticamente significativo <0.05

Figure 4: Forest plot PFS Multivariate Cox Regression

4.10.1.3. Factors included in the multivariate analysis of the OS (1)

Table 73: Factors included in the multivariate analysis of the OS

OS	Alive (N=)	Death (N=)	Total (N=)	p value
CGA <> 2 x ULN				
Missing data				
CGA < 2*ULN				
CGA >= 2*ULN				
Enolase <> 2 x ULN				
Missing data				
NSE < 2*ULN				
NSE >= 2*ULN				
Primary neuroendocrine tumour				
Duodenum/Ileum				
Esophagus/Gastric				
Pancreas				
Colon/Rectum				
Not specified/Others				
Differentiation				
Well differentiated				
Poorly differentiated				
Ki-67 categorised				
<=55				
>55				
ECOG				
0				
1				
2				
Gender				
Female				
Male				
Age categorised by median (x years)				
<=61y				
>61y				
LDH				

OS	Alive (N=)	Death (N=)	Total (N=)	p value
<= 2ULN				
> 2ULN				

1. Fisher’s Exact Test for Count Data
2. Pearson’s Chi-squared test

Table 74: OS univariate and multivariate Cox model

	Univariate Cox Regression					Multivariate Cox Regression				
Characteristic	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**
CGA <> 2 x ULN										
CGA < 2*ULN										
CGA >= 2*ULN										
Enolase <> 2 x ULN										
NSE < 2*ULN										
NSE >= 2*ULN										
Primary neuroendocrine tumour										
Duodenum/Ileum										
Esophagus/Gastric										
Pancreas										
Colon/Rectum										
Not specified/Others										
Differentiation										
Well differentiated										
Poorly differentiated										
Ki-67 categorised										
<=55										
>55										
ECOG										
0										
1										
2										
Gender										
Female										
Male										
Age categorised by median (x years)										
<=61y										
>61y										
LDH										

		Univariate Cox Regression				Multivariate Cox Regression				
Characteristic	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**
<= 2ULN										
> 2ULN										

[1]HR = Hazard Ratio, CI = Confidence Interval

Note: Los p-valores marcados en negrita indican que el valor es estadísticamente significativo <0.05

Figure 5: Forest plot OS Multivariate Cox Regression

4.10.1.4. Factors included in the multivariate analysis of the OS (2)

Table 75: Factors included in the multivariate analysis of the OS

OS	Alive (N=)	Death (N=)	Total (N=)	p value
CGA <> 2 x ULN				
Missing data				
CGA < 2*ULN				
CGA >= 2*ULN				
Enolase <> 2 x ULN				
Missing data				
NSE < 2*ULN				
NSE >= 2*ULN				
Primary neuroendocrine tumour				
Colon/Rectum				
Others				
Differentiation				
Well differentiated				
Poorly differentiated				
Ki-67 categorised				
<=55				
>55				
ECOG				
0				
1				
2				
Gender				
Female				
Male				
Age categorised by median (61 years)				
<=61y				
>61y				
LDH				
<= 2ULN				
> 2ULN				

1. Fisher’s Exact Test for Count Data
2. Pearson’s Chi-squared test

Table 76: OS univariate and multivariate Cox model

		Univariate Cox Regression					Multivariate Cox Regression			
Characteristic	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**
CGA <> 2 x ULN										
CGA < 2*ULN										
CGA >= 2*ULN										
Enolase <> 2 x ULN										
NSE < 2*ULN										
NSE >= 2*ULN										
Primary neuroendocrine tumour										
Colon/Rectum										
Others										
Differentiation										
Well differentiated										
Poorly differentiated										
Ki-67 categorised										
<=55										
>55										
ECOG										
0										
1										
2										
Gender										
Female										
Male										
Age categorised by median (61 years)										
<=61y										
>61y										
LDH										
<= 2ULN										
> 2ULN										

[1]HR = Hazard Ratio, CI = Confidence Interval

Note: Los p-valores marcados en negrita indican que el valor es estadísticamente significativo <0.05

Figure 6: Forest plot OS Multivariate Cox Regression

5. Safety analysis

Table 77: Overall safety

	Induction (N=)	Maintenance (N=)	General (N=)
Any AE			
Yes			
No			
AE grade >=3			
Yes			
No			
Toxicity: AE related to any treatment			
Yes			
No			
Toxicity: AE related to nivolumab			
Yes			
No			
Toxicity: AE related to carboplatin			
Yes			
No			
Toxicity: AE related to etoposide			
Yes			
No			
Toxicity: AE related to all treatments (induction)			
Yes			
No			
Toxicity grade >=3			
Yes			
No			
Toxicity related to nivolumab grade >=3			
Yes			
No			
Toxicity related to carboplatin grade >=3			
Yes			
No			
Toxicity related to etoposide grade >=3			
Yes			
No			
Toxicity related to all treatments grade >=3 (induction)			
Yes			
No			
SAE			
Yes			
No			

5.1. Induction

Table 78: Most frequent Toxicity with 5% threshold (induction)

Toxicity	Frequency	Percentage (%)

Table 79: Grade of most frequent toxicities with 5% threshold overall (induction)

Toxicity	No	G-UK	G-1	G-2	G-3	G-4	G-5

Table 80: List of toxicities grade >=3 in all patients (induction)

Patient Number	AE CTCAE	AE Grade	AE Related to

Table 81: Most frequent AEs with 5% threshold (induction)

AE	Frequency	Percentage (%)

Table 82: Grade of most frequent AEs with 5% threshold overall (induction)

AE	No	G-UK	G-1	G-2	G-3	G-4	G-5

Table 83: List of all SAEs (induction)

Patient Number	AE CTCAE	AE CTCAE Other	AE Grade	AE Start Date	AE Stop Date	AE Related	AE Intensity	AE Related to

Table 84: List of all toxicities (induction)

Patient Number	AE CTCAE	AE CTCAE Other	AE Grade	AE Start Date	AE Stop Date	AE SAE	AE Intensity	AE Related to

5.2. MAINTENANCE

Table 85: Most frequent Toxicity with 5% threshold (maintenance)

Toxicity	Frequency	Percentage (%)

Table 86: Grade of most frequent toxicities with 5% threshold overall (maintenance)

Toxicity	No	G-UK	G-1	G-2	G-3	G-4	G-5

Table 87: List of toxicities grade >=3 in all patients (maintenance)

Patient Number	AE CTCAE	AE Grade	AE Related to

Table 88: Most frequent AEs with 5% threshold (maintenance)

AE	Frequency	Percentage (%)

Table 89: Grade of most frequent AEs with 5% threshold overall (maintenance)

AE	No	G-UK	G-1	G-2	G-3	G-4	G-5

Table 90: List of all SAEs (maintenance)

Patient Number	AE CTCAE	AE CTCAE Other	AE Grade	AE Start Date	AE Stop Date	AE Related	AE Intensity	AE Related to

Table 91: List of all toxicities (maintenance)

Patient Number	AE CTCAE	AE CTCAE Other	AE Grade	AE Start Date	AE Stop Date	AE SAE	AE Intensity	AE Related to

5.3. General

Table 92: Most frequent Toxicity with 5% threshold

Toxicity	Frequency	Percentage (%)

Table 93: Grade of most frequent toxicities with 5% threshold overall

Toxicity	No	G-UK	G-1	G-2	G-3	G-4	G-5

Table 94: List of toxicities grade >=3 in all patients

Patient Number	AE CTCAE	AE Grade	AE Related to

Table 95: Most frequent AEs with 5% threshold

AE	Frequency	Percentage (%)

Table 96: Grade of most frequent AEs with 5% threshold overall

AE	No	G-UK	G-1	G-2	G-3	G-4	G-5

Table 97: List of all SAEs

Patient Number	AE CTCAE	AE CTCAE Other	AE Grade	AE Start Date	AE Stop Date	AE Related	AE Intensity	AE Related to

Table 98: List of all toxicities

Patient Number	AE CTCAE	AE CTCAE Other	AE Grade	AE Start Date	AE Stop Date	AE SAE	AE Intensity	AE Related to