GETNE 2411 - SPAINTRK

Retrospective analysis of the experience with Larotrectinib in patients with solid neoplasms with NTRK fusion in Spain

Statistical Analysis Plan

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GETNE
Grupo Español de Tumores Neuroendocrinos y Endocrinos

MFAR CLINICAL RESEARCH

1. TABLE OF CONTENTS

2. BASELINE

2.1. DEMOGRAPHIC DATA

Table 1: Demographic Data

	Total (N=)
Patient Age (years)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Sex	
N	
Female	
Male	
Race	
N	
Caucasian	
Latin	
Asian	
Maghreb	
African	
Other	
Text A	
Text B	
…	
Height (cm)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Weight (kg)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
BMI (kg/m²)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
BSA (m²)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

	Total (N=)
ECOG	
N	
0	
1	
2	

2.2. COMORBIDITIES

Table 2: Comorbidities and concomitant medication

	Total (N=)
Comorbidities	
N	
No	
Yes	

Table 3: List of Relevant Medical History

Comorbidities	Other Comorbidities	N (%)
Text A		
Text B		
Text C		
…		
Other Specified:	**Text A**	
	Text B	
	Text C	
	…	

2.3. BIOCHEMISTRY AND HEMATOLOGY

Table 4: Biochemistry

	Total (N=)
Albumin (g/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Albumin (g/L)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
ALT (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
ALT (U/L)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
Amylase (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Amylase (U/L)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
AST (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
AST (U/L)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	

	Total (N=)
Calcium (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Calcium (mg/dL)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
Creatinine Clearing (ml/min)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Creatinine Clearing (ml/min)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
Creatinine (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Creatinine (mg/dL)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
GGT (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
GGT (U/L)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	

	Total (N=)
Glucose (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Glucose (mg/dL)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
LDH (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
LDH (U/L)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
Lipase (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Lipase (U/L)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
Phosphatase (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Phosphatase (U/L)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	

	Total (N=)
Potassium (mmol/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Potassium (mmol/L)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
Sodium (mmol/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Sodium (mmol/L)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
Total Bilirubin (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Total Bilirubin (mg/dL)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
Total Protein (g/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Total Protein (g/dL)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	

Table 5: Hematology

	Total (N=)
Basophils (x 10e9/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Basophils (x 10e9/L)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
Eosinophils (x 10e9/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Eosinophils (x 10e9/L)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
Hematocrit (%)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Hematocrit (%)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
Hemoglobin (g/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Hemoglobin (g/dL)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	

	Total (N=)
Lymphocytes (x 10e9/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Lymphocytes (x 10e9/L)	
Missing	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
Monocytes (x 10e9/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Monocytes (x 10e9/L)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
Neutrophils (x 10e3/µL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Neutrophils (x 10e3/µL)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
Platelets (x 10e9/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Platelets (x 10e9/L)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	

	Total (N=)
Red Blood Count (10e6/µL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
Red Blood Count (10e6/µL)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	
White Blood Count (10e3/µL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
IQR	
Range	
White Blood Count (10e3/µL)	
N	
Below Normal (<LLN)	
Normal Range (LLN - ULN)	
Above Normal (>ULN)	

2[redacted]4. GENETIC ALTERATIONS

Table 6: Genetic Alterations

	Total (N=)
NTRK fusion Method	
N	
NGS (next-generation sequencing)	
FISH (fluorescence in situ hybridization)	
IHC (immunohistochemistry)	
Other	
Text A	
Text B	
…	
NTRK fusion gene	
N	
NTRK1	
NTRK2	
NTRK3	
NTRK fusion isoform	
N	
Text A	
Text B	
Text C	
…	

3. CANCER HISTORY

3.1. PRIMARY CANCER

Table 7: Primary Cancer Characteristics

	Total (N=)
Age at diagnose (years)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Cancer Type	
N	
Glioblastoma	
Lung	
Infant fibrosarcoma	
Breast cancer	
Thyroid	
Bronchus carcinoma	
Head and Neck	
Colon	
Other	
Cancer Type Specify	
Text A	
Text B	
…	
Primary tumor location	
N	
Brain	
Lung	
Breast	
Thyroid	
Head and Neck	
Colon	
Lower extremity	
Spinal cord	
Bronchus	
Upper extremity	
Shoulder	
Pelvis	
Other	
Text A	
Text B	
…	

	Total (N=)
Stage before larotrectinib	
N	
III	
IIIA	
IV	
IVA	
IVB	
Metastasis before larotrectinib	
N	
No	
Yes	
Time from initial diagnosis to the start of Larotrectinib (years)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Table 8: Primary Cancer Location

Metastasis Locations	Total (N=)
Anus	
Ascites	
Mouth	
Cecum	
Colon	
Pleural effusion	
Duodenum	
Esophagus	
Stomach	
Pharynx	
Liver	
Ileus	
Small intestine	
Large intestine	
Mediastinum	
Pancreas	
Peritoneum	
Pleura	
Lung	
Rectum	
Kidney	
Jejunum	
Lymph nodes	
Bone	
Ovarian	
Renal	
Skin	
Soft tissues	
Spleen	
CNS	
Brain	
Thyroid	
Other	
Text A	
Text B	
…	

3.2. BEFORE LAROTRECTINIB ANTICANCER TREATMENTS

Table 9: Prior Anticancer Treatments

	Total (N=)
Surgery	
N	
No	
Yes	
Radiotherapy	
N	
No	
Yes	
Previous treatment	
N	
No	
Yes	

Table 10: Number of Cycles of Radiotherapy

	Total (N=)
Radiotherapy cycles	
N	
1	
2	
3	
…	

Table 11: Previous Treatments, Treatment with Larotrectinib, and Post-Larotrectinib Therapies

	Total (N=)
Previous Treatment Type	
N	
Neoadjuvant	
Adjuvant	
1st line	
2nd line	
3rd line	

Table 12: Previous and current treatments therapies

	Total (N=)
Previous Treatment Treatment	
N	
Chemotherapy	
Targeted therapy	
Clinical trial	
SSA	
PRRT	
Locoregional therapies	
Other	
Text A	
Text B	
…	

3.3. BASELINE CHARACTERISTICS

3.3.1. GLIOBLASTOMA

Table 13: Baseline Characteristics for Glioblastoma

	Total (N=)
Glioblastoma Corticosteroids at inclusion	
N	
No	
Yes	
Glioblastoma Corticosteroid type	
N	
Text A	
Text B	
…	
Glioblastoma Corticosteroid Dose	
Text A	
Text B	
…	
Glioblastoma MGMT status	
N	
Unmethylated	
Methylated	
Glioblastoma IDH1 status	
N	
Native	
Mutated	
Glioblastoma IDH2 status	
N	
Native	
Mutated	
Glioblastoma Extent of resection	
N	
Biopsy	
Subtotal resection	
Complete resection	
Glioblastoma Barthel index	
N	
0	
5	
10	
…	
Glioblastoma Minimental test	
N	
1	
2	
3	
…	

3.3.2. LUNG

Table 14: Baseline Characteristics for Lung Cancer

	Total (N=)
Lung Cancer type	
N	
Non-small cell lung cancer (NSCLC)	
Lung carcinoid (Lung NET)	
Small cell lung cancer (SCLC)	
Mesothelioma	
Lung Cancer subtype	
N	
Adenocarcinoma	
Squamous cell carcinoma	
Large cell carcinoma	
Lung Smoking status	
N	
Former smoker	
Never smoker	
Smoker	
Lung Mitotic rate	
N	
Mean	
SD	
Median	
Range	
Lung Ki-67 index	
N	
Mean	
SD	
Median	
Range	
Lung Differentiation	
N	
Typical	
Atypical	
Lung WHO grade	
G1	
G2	
G3	

3.3.3. BREAST CANCER

Table 15: Baseline Characteristics for Breast Cancer

	Total (N=)
Breast Hormone receptor status	
N	
Triple negative	
HR+ and HER+	
HER +	
HR+ and HER2-	

3.3.4. INFANT FIBROSARCOMA

Table 16: Baseline Characteristics for Infant fibrosarcoma

	Total (N=)
Fibrosarcoma Time of illness	
N	
Less than 6 months	
6 months or more	
Fibrosarcoma Location	
N	
Trunk	
Lower extremities	
Head and neck	
Upper extremities	
Fibrosarcoma Tumor size	
N	
T1 (more than 5 cm)	
T0 (5 cm or less)	
Fibrosarcoma Distant metastasis	
N	
No	
Yes	
Fibrosarcoma Degree of differentiation	
1 (low)	
2 (intermediate)	
3 (high)	
Fibrosarcoma Ki differentiation grade	
N	
Mean	
SD	
Median	
Range	
Fibrosarcoma Type of treatment	
N	
Surgery + QT	
Surgery	
Surgery + RT	
RT	
QT	
Fibrosarcoma Type of surgery	
Missing	
Curative	
Palliative	
Fibrosarcoma Histological type	
Missing	
Ameloblastic fibrosarcoma	
Central odontogenic fibrosarcoma	
Dermatofibrosarcoma	
Facial fibrosarcoma	
Fibromyxosarcoma	
Periosteal fibrosarcoma	

3.3.5. THYROID

Table 17: Baseline Characteristics for Thyroid Cancer

	Total (N=)
Cancer Type	
N	
Differentiated thyroid carcinoma (DTC)	
Anaplastic thyroid carcinoma (ATC)	
Medullary thyroid carcinoma (MTC)	
Thyroid Cancer subtype	
N	
Follicular	
Poorly differentiated	
Papillary	
Hurtle cell	
Thyroid Histopathological grade	
N	
Well differentiated	
Poorly differentiated	

3.4. OTHER CANCER HISTORY

Table 18: Other Cancer History

	Total (N=)
Other cancer history	
N	
No	
Yes	

Table 19: Other Cancer History Type

	Total (N=)
Other Cancer Type	
N	
Text A	
Text B	
Text C	
…	
Other Cancer Treatment	
N	
Text A	
Text B	
Text C	
…	

4. TREATMENT WITH LAROTRECTINIB

Table 20: Characteristics of Initial Larotrectinib Dosing

	Total (N=)
End of Treatment Reason	
N	
Progression	
After complete response	
Clinical deterioration with no documented disease progression	
Lost of follow-up	
Toxicity	
Patient's decision	
Death	
Other	
Text A	
Text B	
…	
Larotrectinib Initial Dose	
Text A	
Text B	
…	
Larotrectinib Frequency	
N	
On Demand (PRN)	
Biweekly	
Weekly	
Three times per week	
Four times per week	
Once a day	
Twice daily	
Three times a day	
Four times a day	
Other	
Text A	
Text B	
…	
Pharmaceutical form	
N	
Vitrakvi 100 mg hard capsules	
Vitrakvi 20 mg/ml in 100ml glass bottle	
Vitrakvi 25mg hard capsules	
Other	
Text A	
Text B	
…	

4.1. OTHER TREATMENTS AFTER LAROTRECTINIB TREATMENT

Table 21: Other Treatments After Larotrectinib Treatment

	Total (N=)
Surgery	
N	
No	
Yes	
Radiotherapy	
N	
No	
Yes	
Systemic treatments	
N	
No	
Yes	

5. PRIMARY ENDPOINTS

5.1. DURATION OF RESPONSE (DOR)

Duration of Response (DoR): is defined as the time from first confirmed response (complete (CR) or partial (PR) response), according to Objective response rate (ORR) defined below, to the date of the documented progression of the disease (PD) as determined using RECIST V1.1 criteria or death due to any cause, whichever occurs first.

Those patients with response and without PD or death event will be censored on the date of their last tumor assessment.

Table 22: Duration of Response

	Total (N=)
DoR to Larotrectinib (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

5.2. TREATMENT DURATION

Table 23: Treatment Duration

	Total (N=)
Treatment Duration with Larotrectinib (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

5[redacted]. TREATMENT COMPLIANCE[redacted]

Table 24: Characteristics of Dose Reduction

	Total (N=)
Larotrectinib Incidence Reason	
N	
Toxicity	
AE	
Investigator's decision	
Patient's decision	
Other	
Text A	
Text B	
…	
Larotrectinib Dose	
Text A	
Text B	
…	

Table 25: Characteristics of Dose Interruption

	Total (N=)
Larotrectinib Incidence Reason	
N	
Toxicity	
AE	
Investigator's decision	
Patient's decision	
Other	
Text A	
Text B	
…	
Larotrectinib Dose	
Text A	
Text B	
…	

6. SECONDARY EFFECTIVENESS ENDPOINTS

6.1. OBJECTIVE RESPONSE RATE (ORR)

Objective response rate (ORR): is assessed by the investigator analysis of tumor growth through imaging follow-up (CT scan/MRI), using a method to evaluate it as RECIST V1.1. This will be considered as the number of patients with confirmed complete response (CR) or partial response (PR) as their overall best response throughout the period of treatment with [Larotrectinib].

Table 26: Best Response

	[Total (N=)]
Larotrectinib Best Response	
N	
PR	
CR	
SD	
PD	

Table 27: ORR

	[Total (N=)]
ORR	
Missing	
N	
CR or PR	
SD or PD	

6.2. P[redacted]OGRESSION FREE SURVIVAL (PF[redacted]S)

Progression free survival (PFS): Time from first dosing date to the date of confirmed PD according to RECIST 1.1. Patients alive and free of events at the date of the analysis will be censored at their last known tumor assessment. Patients who start a new treatment line without progression will be censored on the date of first dose of the subsequent anticancer treatment.

Table 28: Events PFS

	Total (N=)
PFS event	
N	
Alive free of event	N (%)
PD	N (%)
Death	N (%)

Table 29: Events type PFS

PFS event	N	%	95%CI
Death			
PD			
Total			

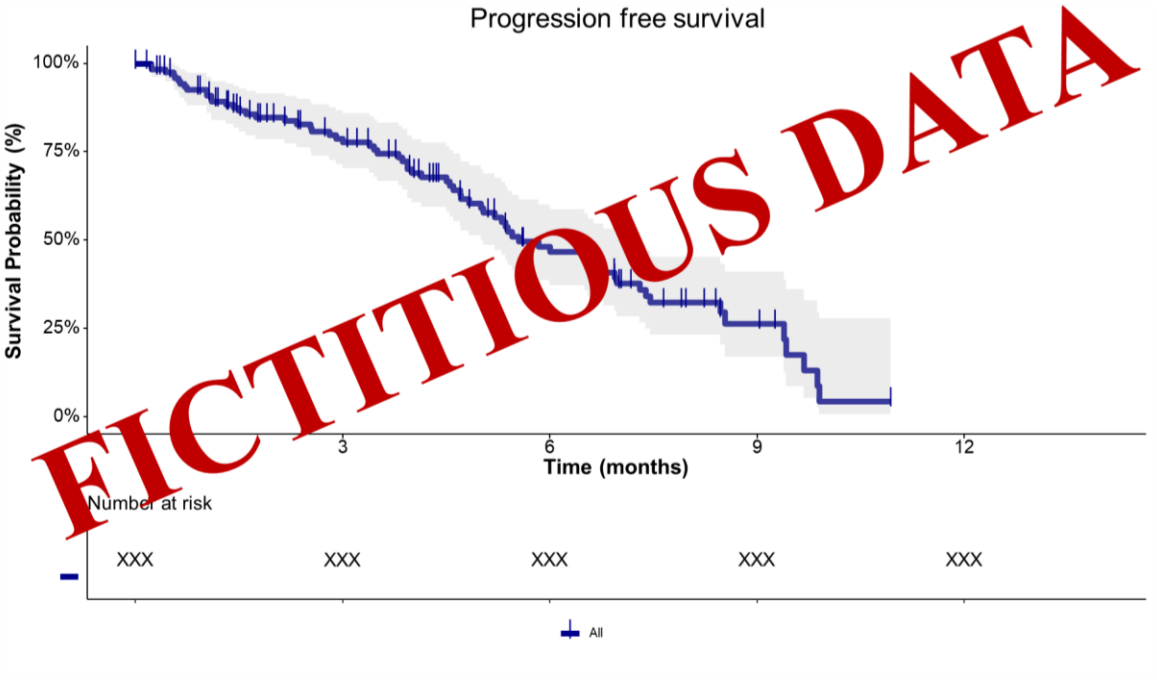
Table 30: M[redacted]dian/mean PFS (estimated by Kaplan-Me[redacted]r)

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

Table 31: PFS estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 3 months				
At 6 months				
At 9 months				
At 12 months				

Figure 1: PFS Overall



6.3. OVERALL SURVIVAL (OS)

Overall survival (OS): defined as the time elapsed from the first dose of study treatment until death from any cause. Patients alive and free of events at the date of the analysis will be censored at their last known contact. Survival will be assessed by recording patients' status at each visit.

Table 32: Follow up time (naive estimation)

	Total (N=)
Follow-up (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Table 33: Time to lost follow-up (estimated by Kaplan-Meier)

	Median (months)	CI 95%	RMST	CI 95%
Time to lost follow-up				

Table 14: Events

	Total (N=)
OS event	
N	
Alive	N (%)
Death	N (%)

Table 35: Events type OS

OS event	N	%	95%CI
Death			
Total			

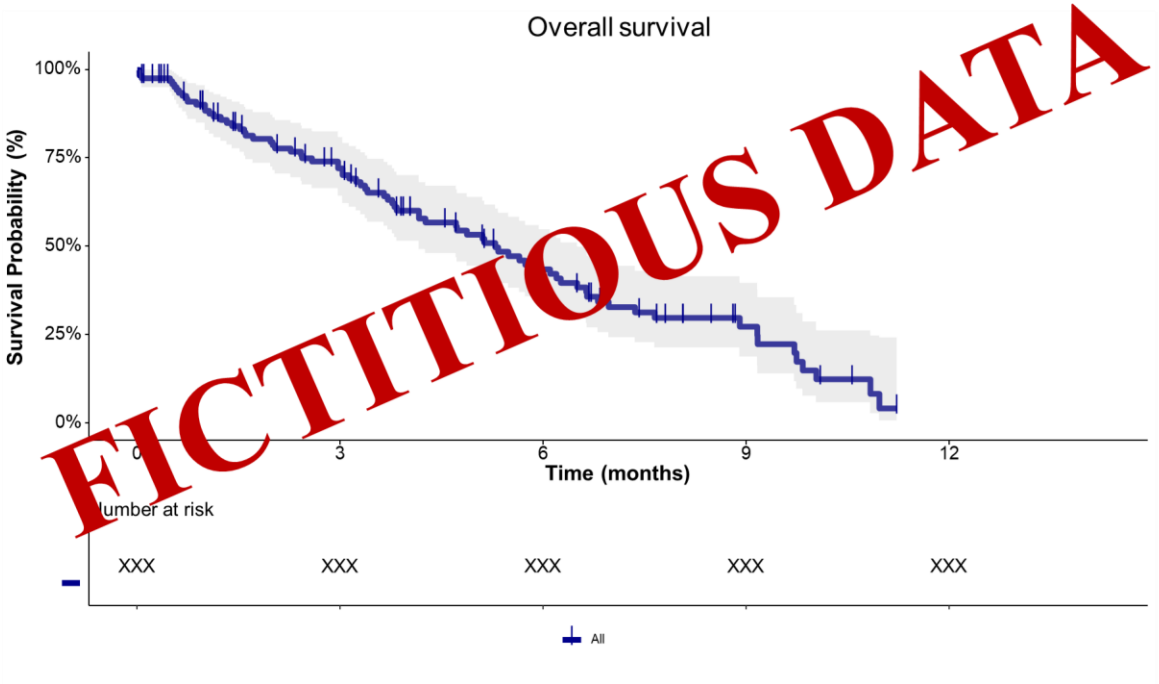
Table 36: Median/mean OS (estimated by Kaplan-Meier)

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

Table 37: OS estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 3 months				
At 6 months				
At 9 months				
At 12 months				

Figure 2: Overall survival



7. SAFETY ANALYSIS

In the following tables, the adverse events which are not completely ruled out as related to treatment are considered treatment-related.

Table 38: Overall safety

	Total (N=)
Adverse Events	
N	
No	
Yes	
AE Grade ≥ 3	
N	
No	
Yes	
AE related to any treatment	
N	
No	
Yes	
AE related grade ≥ 3	
N	
No	
Yes	
SAE	
N	
No	
Yes	

Table 39: Related AEs with 0% threshold

Related AE	Frequency	Percentage (%)
Text A		
Text B		
Text C		
…		

Table 40: Grade of related AEs with 0% threshold overall

Related AE	No	G-UK	G-1	G-2	G-3	G-4	G-5
Text A							
Text B							
Text C							
…							

Table 41: List of related AEs grade ≥ 3 in all patients

Patient Number	AE CTCAE	AE Grade	AE Related
Id A			
Id B			
Id C			
…			

Table 42: AEs with 0% threshold

AE	Frequency	Percentage (%)
Text A		
Text B		
Text C		
…		

Table 43: Grade of AEs with 0% threshold overall

AE	No	G-UK	G-1	G-2	G-3	G-4	G-5
Text A							
Text B							
Text C							
…							

Table 44: List of all SAEs

Patient Number	AE CTCAE	AE Grade	AE Start Date	AE Stop Date	AE Related AE SAE	AE Intensity
Id A						
Id B						
…						

1.1.1.ANNEX I

Table 45: List of all related AEs

Patient Number	AE CTCAE	AE Grade	AE Start Date	AE Stop Date	AE Related	AE SAE	AE Intensity
Id A							
Id B							
…							

7.1.2. ANNEX 2

Table 46: List of all non-serious AEs

Patient Number	AE CTCAE	AE Grade	AE Start Date	AE Stop Date	AE Related	AE SAE	AE Intensity
Id A							
Id B							
…							