Clinical trial results:
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.

Summary

EudraCT number	2019-001546-18
Trial protocol	ES
Global end of trial date	09 June 2023

Results information

Result version number	v1 (current)
This version publication date	18 October 2024
First version publication date	18 October 2024
Summary attachment (see zip file)	NICE-NEC Scientific Manuscript (s41467-024-50969-8.pdf)

Trial information

Trial identification

Sponsor protocol code	GETNE-T1913

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03980925
WHO universal trial number (UTN)	-
Other trial identifiers	CA209-73D: BMS protocol identification number

Notes:

Sponsors

Sponsor organisation name	Grupo Español de Tumores Neuroendocrinos y Endocrinos
Sponsor organisation address	C/ Balmes 243, Escalera A, 5º1ª, Barcelona, Spain, 08006
Public contact	Federico Nepote, MFAR Clinical Research, 34 93 434 44 12, investigacion@mfar.net
Scientific contact	Federico Nepote, MFAR Clinical Research, 34 93 434 44 12, investigacion@mfar.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 November 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 June 2023
Global end of trial reached?	Yes
Global end of trial date	09 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the overall survival patients with advanced G3 NENs treated with nivolumab + platinum-based chemotherapy.

Protection of trial subjects:

The eligibility criteria were designed to only include patients who can receive the experimental treatment without unacceptable toxicities, according to clinical data available at the moment. The protocol was approved by an independent ethics committee and study was performed according to Declaration of Helsinki and GCPs.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 September 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 37
Worldwide total number of subjects	37
EEA total number of subjects	37

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	37
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

37 patients were recruited between 4/11/2019 and 26/01/2021 in a total of 12 sites in Spain

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	38[1]
Number of subjects completed	37

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One patient was not eligible

Period 1

Period 1 title	Overall study period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not blinded

Arms

Arm title	Nivolumab + platinum-doublet chemotherapy

Arm description:

1. Induction Phase: Nivolumab 360 mg IV plus Carboplatin IV (AUC=5) plus Etoposide 10mg/m2/day on days 1-3D, all every 3 weeks up to 6 cycles followed by Nivolumab 480mg for 24 months or until PD, death or toxicity.

Order of administration: Nivolumab, Carboplatin, Etoposide

2. Maintenance Phase Nivolumab 480 mg IV will be administered every 4 weeks (±3 days) for 2 years.

Arm type	Experimental
Investigational medicinal product name	Nivolumab Solution for Injection
Investigational medicinal product code	
Other name	BMS-936558-01
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1. Induction Phase: Nivolumab 360 mg IV first day all every 3 weeks up to 6 cycles followed by Nivolumab 480mg for 24 months or until PD, death or toxicity.
2. Maintenance Phase Nivolumab 480 mg IV will be administered every 4 weeks (±3 days) for 2 years.

Investigational medicinal product name	Carboplatin Solution for injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin IV infusion first day all every 3 weeks up to 6 cycles

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Etoposide 100 mg/m2/day IV infusion on days 1-3D, all every 3 weeks up to 6 cycles

Number of subjects in period 1	Nivolumab + platinum-doublet chemotherapy
Started	37
Completed	37

Baseline characteristics

Reporting groups	
Reporting group title	Overall study period

Reporting group description: -

Reporting group values	Overall study period	Total	
Number of subjects	37	37	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age at registration			
Units: years			
median	61		
full range (min-max)	28 to 84	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	25	25	
ECOG			
Eastern Cooperative Oncology Group scale			
Units: Subjects			
ECOG 0	11	11	
ECOG 1	22	22	
ECOG 2	4	4	
Stage at diagnosis Units: Subjects			
Stage I	1	1	
Stage III	1	1	
Stage IV	35	35	
Differentiation Units: Subjects			
NET	12	12	
NEC	25	25	
Ki 67 Units: Subjects			
21 - 55%	12	12	
> 55%	25	25	

Primary site Units: Subjects			
Esophageal	2	2	
Gastric	6	6	
Pancreatic	14	14	
Colonic	4	4	
Rectal	2	2	
Small intestine	2	2	
Other	2	2	
Unknown	5	5	
Metastatic sites number Units: Subjects			
= 1	10	10	
≥ 2	27	27	
Previous surgery Units: Subjects			
Yes	6	6	
No	30	30	
Unknown	1	1	
CgA			
Chromogranin A. Definitions: upper limit of normal (ULN)			
Units: Subjects			
< 2x ULN	7	7	
≥ 2x ULN	27	27	
Unknown	3	3	
Enolase			
Definitions: upper limit of normal (ULN)			
Units: Subjects			
< 2x ULN	13	13	
≥ 2x ULN	21	21	
Unknown	3	3	
LDH			
Definitions: upper limit of normal (ULN)			
Units: Subjects			
> 2x ULN	9	9	
≤ 2x ULN	28	28	

End points

End points reporting groups

Reporting group title	Nivolumab + platinum-doublet chemotherapy

Reporting group description:

1. Induction Phase: Nivolumab 360 mg IV plus Carboplatin IV (AUC=5) plus Etoposide 10mg/m2/day on days 1-3D, all every 3 weeks up to 6 cycles followed by Nivolumab 480mg for 24 months or until PD, death or toxicity.

Order of administration: Nivolumab, Carboplatin, Etoposide

2. Maintenance Phase Nivolumab 480 mg IV will be administered every 4 weeks (±3 days) for 2 years.

Primary: 12-month Overall Survival rate

End point title	12-month Overall Survival rate[1]

End point description:

End point type	Primary

End point timeframe:

12 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The NICE-NEC trial is a singñe arm trial. Staistical comparison was not applicable

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

End point type	Secondary

End point timeframe:

30 months

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

End point type	Secondary

End point timeframe:

30 months

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

End point type	Secondary

End point timeframe:

30 months

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:
overall study

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 30 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	NCI CTCAE
Dictionary version	5.0

Reporting groups	
Reporting group title	Nivolumab + platinum-doublet chemotherapy

Reporting group description:

1. Induction Phase: Nivolumab 360 mg IV plus Carboplatin IV (AUC=5) plus Etoposide 10mg/m2/day on days 1-3D, all every 3 weeks up to 6 cycles followed by Nivolumab 480mg for 24 months or until PD, death or toxicity.

Order of administration: Nivolumab, Carboplatin, Etoposide

2. Maintenance Phase Nivolumab 480 mg IV will be administered every 4 weeks (±3 days) for 2 years.

Serious adverse events	Nivolumab + platinum-doublet chemotherapy		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 37 (48.65%)		
number of deaths (all causes)	25		
number of deaths resulting from adverse events	4		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Alkaline phosphatase increased			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood lactate dehydrogenase increased			

subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Inguinal hernia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cognitive disturbance			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysarthria			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			

subjects affected / exposed	1 / 37 (2.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General clinical deterioration				
subjects affected / exposed	1 / 37 (2.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Multi-organ failure				
subjects affected / exposed	1 / 37 (2.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 37 (2.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bowel subocclusion				
subjects affected / exposed	1 / 37 (2.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 37 (2.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhea				
subjects affected / exposed	1 / 37 (2.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Esophageal hemorrhage				
subjects affected / exposed	1 / 37 (2.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Esophageal mucositis				

subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Nausea			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal hemorrhage			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune-mediated nephritis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract obstruction			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusion			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue			

disorders			
Bone pain			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteremia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Covid-19			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hepatic infection			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Nivolumab + platinum-doublet chemotherapy		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 37 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
General disorders and administration site conditions			

Edema limbs			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	29 / 37 (78.38%)		
occurrences (all)	29		
Fever			
subjects affected / exposed	7 / 37 (18.92%)		
occurrences (all)	7		
General disorders and administration site conditions			
subjects affected / exposed	5 / 37 (13.51%)		
occurrences (all)	5		
Pain			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Dysgeusia			

subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3 2 / 37 (5.41%) 2 2 / 37 (5.41%) 2		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) White blood cell decreased subjects affected / exposed occurrences (all)	 18 / 37 (48.65%) 18 2 / 37 (5.41%) 2 21 / 37 (56.76%) 21 9 / 37 (24.32%) 9 3 / 37 (8.11%) 3		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhea subjects affected / exposed occurrences (all) Gastrointestinal disorders	 4 / 37 (10.81%) 4 9 / 37 (24.32%) 9 14 / 37 (37.84%) 14		

subjects affected / exposed	7 / 37 (18.92%)		
occurrences (all)	7		
Mucositis oral			
subjects affected / exposed	7 / 37 (18.92%)		
occurrences (all)	7		
Nausea			
subjects affected / exposed	19 / 37 (51.35%)		
occurrences (all)	19		
Vomiting			
subjects affected / exposed	9 / 37 (24.32%)		
occurrences (all)	9		
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	12 / 37 (32.43%)		
occurrences (all)	12		
Dry skin			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	6 / 37 (16.22%)		
occurrences (all)	6		
Rash acneiform			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Endocrine disorders			

Endocrine disorders subjects affected / exposed occurrences (all) Hyperthyroidism subjects affected / exposed occurrences (all) Hypothyroidism subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3 2 / 37 (5.41%) 2 3 / 37 (8.11%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Musculoskeletal and connective tissue disorder subjects affected / exposed occurrences (all)	 3 / 37 (8.11%) 3 2 / 37 (5.41%) 2 4 / 37 (10.81%) 4		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	 2 / 37 (5.41%) 2		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all) Hypomagnesemia subjects affected / exposed occurrences (all)	 10 / 37 (27.03%) 10 2 / 37 (5.41%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2019	Investigator Brochure amendment
27 November 2020	Investigator Brochure amendment
01 February 2022	Investigator Brochure amendment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported