Clinical trial results:
Phase II multicenter single-arm study evaluating the safety and efficacy of everolimus as a first-line treatment in newly-diagnosed patients with advanced GI neuroendocrine tumors.

Summary

EudraCT number	2011-006160-48
Trial protocol	GR
Global end of trial date	06 August 2019

Results information

Result version number	v1 (current)
This version publication date	21 August 2020
First version publication date	21 August 2020

Trial information

Trial identification

Sponsor protocol code	HE 67/12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01648465
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hellenic Cooperative Oncology Group
Sponsor organisation address	Messoghion Avenue 41, Athens, Greece, 11526
Public contact	Clinical Trials, Hellenic Cooperative Oncology Group, 0030 2106912520, hecogoff@otenet.gr
Scientific contact	Clinical Trials, Hellenic Cooperative Oncology Group, 0030 2106912520, hecogoff@otenet.gr

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	19 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 August 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the safety and efficacy of Everolimus (as first-line treatment) and 15month progression-free survival rate (15month PFS rate) (according to RECIST 1.1) in newly-diagnosed patients with advanced or unresectable GI and pancreatic neuroendocrine tumors

Protection of trial subjects:

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines and the local regulatory requirements

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 August 2012
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	Greece: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	19
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled between 6 August 2012 and 29 October 2015 in 8 sites in Greece

Pre-assignment

Screening details:

Patients were screened for eligibility before entering the study and signed the informed consent form which was obtained before any study procedure.

Period 1

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

Arms

Arm title	Everolimus

Arm description:

Everolimus, which is a selective mTOR inhibitor, was administered as a first-line treatment at the dose of 10mg (2x5mg) orally once daily until disease progression, unacceptable toxicity, consent withdrawal or completion of 15 months of treatment.

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	Afinitor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus was administered at the dose of 10mg (2x5mg) orally (tablet) once daily, until disease progression, unacceptable toxicity, consent withdrawal or completion of 15 months of treatment

Number of subjects in period 1	Everolimus
Started	25
Completed	5
Not completed	20
Physician decision	1
Consent withdrawn by subject	5
Disease progression	10
Adverse event, non-fatal	2
Second malignancy of urothelial carcinoma	1
6 weeks without therapy	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	25	25	
Age categorical Units: Subjects			
Adults (18-64 years)	19	19	
From 65-84 years	6	6	
Age continuous Units: years			
median	56.9		
full range (min-max)	37.6 to 79.9	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	10	10	

End points

End points reporting groups

Reporting group title	Everolimus

Reporting group description:

Everolimus, which is a selective mTOR inhibitor, was administered as a first-line treatment at the dose of 10mg (2x5mg) orally once daily until disease progression, unacceptable toxicity, consent withdrawal or completion of 15 months of treatment.

Primary: 15-month PFS rate

End point title	15-month PFS rate[1]

End point description:

The primary endpoint was to evaluate the 15-month progression-free survival rate (15month PFS rate) (according to RECIST 1.1) in newly-diagnosed patients with advanced or unresectable GI and pancreatic neuroendocrine tumors treated with Everolimus, as a first-line treatment. Prorgession-free survival was calculated as the time (in months) from study entry to the date of the first documented disease progression, death , or last contact (whichever occurred first).

End point type	Primary

End point timeframe:

CT / MRI was done during the screening period and in a maximum period of up to 28 days before the first dose of the drug. Then it was repeated on Day 1 of Cycle 3, in each three subsequent cycles (every 12 weeks) and at the end of the study.

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: No statistical analyses for this end point

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: percentage of patients	48			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival was defined as the time from study entry to the date of death from any cause or last contact in newly-diagnosed patients with advanced or unresectable GI and pancreatic neuroendocrine tumors treated with Everolimus as a first-line treatment

End point type	Secondary

End point timeframe:

Patients were followed-up for a median of 76.6 months (95% CI 62.6-79.5).

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: number of deaths	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression free survival was calculated from the date of patient's entry into the study until the first documented disease progression, death or last contact in newly-diagnosed patients with advanced or unresectable GI and pancreatic neuroendocrine tumors treated with everolimus, as a first-line treatment

End point type	Secondary

End point timeframe:

Patients were followed up for a median of 76.6 months (95% CI 62.6-79.5).

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: months				
median (confidence interval 95%)	14.6 (5.8 to 15.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response

End point title	Best overall response

End point description:

Best overall response was defined as the best response for each patient during the treatment period of everolimus, according to RECIST 1.1 criteria in newly-diagnosed patients with advanced or unresectable GI and pancreatic neuroendocrine tumors, treated with Everolimus, as a first-line treatment

End point type	Secondary

End point timeframe:

CT / MRI was done during the screening period and in a maximum period of up to 28 days before the first dose of the drug. Then was repeated on Day 1 of Cycle 3, in each three subsequent cycles (every 12 weeks) and at the end of the study.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: number of patients				
CR	1			
PR	6			
SD	12			
PD	4			
Treatment discontinuation prior to evaluation	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety profile

End point title	Safety profile

End point description:

Safety was assessed in the safety population consisting of all patients that received at least one dose of the study drug

End point type	Secondary

End point timeframe:

Assessment of adverse events (AEs) was performed every 28 days (per cycle) throughout the course of treatment with Everolimus

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	25[2]			
Units: number of patients				
Any adverse event	24			
Fatal adverse event	0			
Serious adverse event	9			

Notes:

[2] - All 25 patients received at least one dose of everolimus and were assessed for safety.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to best response

End point title	Time to best response

End point description:

Time to best response was estimated from the date of study entry until the date of best response throughout the study in newly-diagnosed patients with advanced or unresectable GI and pancreatic neuroendocrine tumors treated with Everolimus, as a first-line treatment

End point type	Secondary

End point timeframe:

CT/MRI was performed during the screening period and in a maximum of up to 28 days before the first dose and repeated on Day 1 of Cycle 3, in each three subsequent cycles (every 12 weeks) and at the end of the study. Median follow-up 76.6 months.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: months				
median (confidence interval 95%)				
Among patients with objective response	2.6 (1.8 to 4.7)			
Among patients with CR/PR/SD	2.3 (1.8 to 2.6)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Evaluation of possible association between biomarkers and disease progression

End point title	Evaluation of possible association between biomarkers and disease progression

End point description:

The differences in the levels of Chromogranin-A (CgA) were assessed at baseline and at the last treatment cycle.

End point type	Other pre-specified

End point timeframe:

Analysis of biological markers should be performed at study initiation, on Day 1 of cycle 3 and then every 3 cycles (every 12 weeks) as well as at the end of the study.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	12[3]			
Units: nmol/l				
median (full range (min-max))				
Baseline	3.5 (1.57 to 102)			
Last cycle	4.0 (2.30 to 91.6)			

Notes:
[3] - In total, 24 patients had available CgA data at baseline and 12 at both baseline and last cycle.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Assessment of adverse events will be performed every 28 days (per cycle) during treatment with Everolimus.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Everolimus

Reporting group description:

Everolimus 10mg (5x2 mg) was administered orally once daily, until disease progression, unacceptable toxicity, consent withdrawal or completion of 15 months of treatment.

Serious adverse events	Everolimus		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 25 (36.00%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	0		
Investigations			
Blood creatinine phosphokinase increased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Wound abscess			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			

Allergic reaction				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Mucositis oral				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bacteraemia				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral	Additional description: H1N1			
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Biliary tract infection				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Everolimus		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 25 (96.00%)		
Investigations			
Alkaline phosphatase increased			
subjects affected / exposed	8 / 25 (32.00%)		
occurrences (all)	16		
Alanine aminotransferase increased			
subjects affected / exposed	11 / 25 (44.00%)		
occurrences (all)	75		
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 25 (40.00%)		
occurrences (all)	37		
CPK increased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	11		
Cholesterol high			
subjects affected / exposed	8 / 25 (32.00%)		
occurrences (all)	21		
Creatinine increased			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	13		
Gamma-glutamyltransferase increased			
subjects affected / exposed	10 / 25 (40.00%)		
occurrences (all)	25		
Platelet count decreased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Neutrophil count decreased			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	11		
Weight loss			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	5		
White blood cell count decreased			

subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	22		
LDH increased			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	5		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	12		
Thromboembollic Event			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 25 (36.00%)		
occurrences (all)	33		
General disorders and administration site conditions			
Oedema	Additional description: limbs		
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	11		
Fatigue			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences (all)	14		
Flu-like symptoms			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		

Fever subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 18		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Dyspesia subjects affected / exposed occurrences (all) Mycositis oral subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1 1 / 25 (4.00%) 1 5 / 25 (20.00%) 14 1 / 25 (4.00%) 3 8 / 25 (32.00%) 27 1 / 25 (4.00%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 4 1 / 25 (4.00%) 1 1 / 25 (4.00%) 1		

Pneumonitis			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Nail dystrophy			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Rash	Additional description: Head and hair		
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Rash acneiform			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences (all)	8		
Dry skin			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Nail loss			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	2		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	15		
Skin hypopigmentation			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	15		
Infections and infestations			

Viral infection	Additional description: Upper respiratory		
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Papulopustular rash			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Upper respiratory infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
Hyperglycaemia			
subjects affected / exposed	17 / 25 (68.00%)		
occurrences (all)	69		
Hyperkalaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	5		
Hypertriglyceridaemia			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences (all)	24		
Hyperuricaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	7		
Hypoglycaemia			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	10		
Hypomagnesaemia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Hypophosphataemia			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	15		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported