



## Clinical trial results:

**Randomized open label study to compare the efficacy and safety of everolimus followed by chemotherapy with STZ-5FU upon progression or the reverse sequence, chemotherapy with STZ-5FU followed by everolimus upon progression, in advanced progressive pNETs (SEQTOR study)**

### Summary

EudraCT number	2013-000726-66
Trial protocol	SE DE IT ES DK NL FR GB
Global end of trial date	12 July 2021

### Results information

Result version number	v1 (current)
This version publication date	12 March 2025
First version publication date	12 March 2025

### Trial information

#### Trial identification

Sponsor protocol code	GETNE1206
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02246127
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE)
Sponsor organisation address	Velazquez St, 7-3o, Madrid, Spain,
Public contact	Trial Lead Coordinator, Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE), 34 934344412, getne@getne.org
Scientific contact	Trial Lead Coordinator, Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE), 34 934344412, getne@getne.org

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:

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## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 July 2021
Global end of trial reached?	Yes
Global end of trial date	12 July 2021
Was the trial ended prematurely?	No

Notes:

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## General information about the trial

Main objective of the trial:

To compare the efficacy of the combination STZ-5FU chemotherapy followed by Everolimus 10 mg/day upon progression versus the reverse sequence in the treatment of advanced pancreatic neuroendocrine tumours (pNET), in terms of rate of patients with second progression free survival at 84 weeks of treatment, assessed by local investigator using RECIST criteria 1.0.

Protection of trial subjects:

This assignment will designate the user as the primary user for the listed clinical trial in regards to result related information. It will enable them to prepare and post result related information for this trials on behalf of the sponsor in accordance with Commission Guideline 2012/C 302/03 and its technical guidance on the format of the data fields of result-related information on clinical trials submitted in accordance with article 57(2) of Regulation (EC) No 726/2004 and article 41(2) of Regulation (EC) No 1901/2006.

Background therapy:

STZ based chemotherapy, STZ-5FU, is the actual standard of care for advanced pancreatic Neuroendocrine tumours (pNETS) in the European Union. Everolimus has been recently approved for its use in advanced pNETs by the Food and Drug Administration (FDA) and in Europe by the European Medical Agency (EMA).

A randomized study is needed to have a clear knowledge about the best sequence for its administration; this is, before or after palliative chemotherapy.

There may or may not be any benefits from giving first each other treatment of the study. The information obtained from this study will help the physician improve the treatment and management of patients with advanced pNET.

This study was planned to compare STZ-5FU chemotherapy followed by everolimus upon progression versus the reverse sequence. However sequential studies with pNETs are hard to be managed in terms of time and costs. Therefore the protocol was amended to have PFS1 (progression free survival after course 1) as primary endpoint and PFS2 (i.e. progression free survival after both STZ based chemotherapy and Everolimus or the reverse order) as secondary endpoint. This information will be extremely valuable for the day to day clinical practice of NET oncologists

Evidence for comparator:

The first randomized phase III trial in pancreatic neuroendocrine tumours (pNETs) was performed by Moertel in 1980. 84 patients with pNETs were randomized to receive the combination of streptozocin (STZ) and 5-fluorouracil (5FU) or STZ as a single agent. The combination arm demonstrated superior results to those of the monotherapy arm in terms of overall response rate (ORR) (63% vs 36% respectively) and median overall survival (mOS) (26 versus 16.5 months), although the difference in mOS was not statistically significant.

STZ based chemotherapy, STZ-5FU, is the actual standard of care for advanced pNETS in the European Union (ENETS guidelines; Neuroendocrinology 2012)<sup>14</sup>. Everolimus has been recently approved for its use in advanced pNETs by the FDA and in Europe by the EMA . A randomized study is needed to have a clear knowledge about the best sequence for its administration; this is, before or after palliative chemotherapy. There may or may not be any benefits from giving first each other treatment of the study. The information obtained from this study will help the physician improve the treatment and management of patients with pNET.

Variation of treatment choices will still depend on physician expertise, the complexity of the treatment center and, access to novel treatments (ENETS guidelines, Neuroendocrinology 2016)<sup>26</sup>. There are not randomized trials comparing Progression Free Survival (PFS) of STZ based chemotherapy versus

Everolimus.

This study was planned to compare STZ-5FU chemotherapy followed by everolimus 10 mg/day upon progression versus the reverse sequence. However sequential studies with pNETs are hard to be managed in terms of time and costs. Therefore we propose to have PFS1 (progression free survival after course 1) as primary endpoint and PFS2 (i.e. progression free survival after both STZ based chemotherapy and Everolimus or the reverse order) as secondary endpoint. This information will be extremely valuable for the day to day clinica

Actual start date of recruitment	01 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Spain: 50
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Denmark: 20
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Italy: 19
Worldwide total number of subjects	141
EEA total number of subjects	136

Notes:

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### 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)	71
From 65 to 84 years	70
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This was a randomised phase III open label and cross-over treatment study to compare the efficacy and safety of everolimus followed by chemotherapy upon progression or the reverse sequence, in advanced progressive pNETs. The SEQTOR study design was based on clinical practice.

### Pre-assignment

Screening details:

Screening period : 28 days.

The screening assessments included: informed consent, demographics, inclusion/exclusion criteria, relevant clinical history, confirmation advanced NET, diagnosis and extension of cancer (disease metastasis sites), previous anticancer treatment, radiation therapy and surgery, physical examination, QoL question, CT scan

### Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Sequence A, Drug: Everolimus First

Arm description:

Sequence A, drug: everolimus first  
Everolimus (10mg/daily, oral) followed by STZ-5FU (injection/infusion; Moertel or Uppsala regime).

Arm type	Experimental
Investigational medicinal product name	Everolimus followed by STZ-5FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	powder for prolonged-release oral suspension, Solution for infusion
Routes of administration	Oral use, Solution for infusion

Dosage and administration details:

Drug: Drug: Everolimus

10mg/daily, oral. Number of Cycles: until progression or unacceptable toxicity develops.

Other Names:

Afinitor

Drug: STZ-5FU

0,5g/m<sup>2</sup> STZ on days 1-5 and 400mg/m<sup>2</sup> 5-FU on days 1-5 every 6 weeks (Moertel) or 0,5g/m<sup>2</sup> STZ on days 1-5 and 400mg/m<sup>2</sup> 5-FU on days 1-3, and then 1 day with 1g/m<sup>2</sup> and 1 day 400mg/m<sup>2</sup> 5-FU every 3 weeks (Uppsala).

Number of Cycles: until progression or unacceptable toxicity develops.

<b>Arm title</b>	Experimental: Sequence B, drug: STZ - 5FU first
Arm description:	
STZ-5FU (injection/infusion; Moertel or Uppsala regime) followed by Everolimus (10 mg/ daily, oral)	
Arm type	Experimental

Investigational medicinal product name	STZ - 5FU followed by Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Drug: STZ-5FU

0,5g/m<sup>2</sup> STZ on days 1-5 and 400mg/m<sup>2</sup> 5-FU on days 1-5 every 6 weeks (Moertel) or 0,5g/m<sup>2</sup> STZ on days 1-5 and 400mg/m<sup>2</sup> 5-FU on days 1-3, and then 1 day with 1g/m<sup>2</sup> and 1 day 400mg/m<sup>2</sup> 5-FU every 3 weeks (Uppsala).

Number of Cycles: until progression or unacceptable toxicity develops.

Drug: Drug: Everolimus

10mg/daily, oral. Number of Cycles: until progression or unacceptable toxicity develops.

Number of subjects in period 1	Sequence A, Drug: Everolimus First	Experimental: Sequence B, drug: STZ - 5FU first
Started	72	69
Completed	72	69

## Baseline characteristics

### Reporting groups

Reporting group title	Sequence A, Drug: Everolimus First
Reporting group description:	
Sequence A, drug: everolimus first Everolimus (10mg/daily, oral) followed by STZ-5FU (injection/infusion; Moertel or Uppsala regime).	
Reporting group title	Experimental: Sequence B, drug: STZ - 5FU first
Reporting group description:	
STZ-5FU (injection/infusion; Moertel or Uppsala regime) followed by Everolimus (10 mg/ daily, oral)	

Reporting group values	Sequence A, Drug: Everolimus First	Experimental: Sequence B, drug: STZ - 5FU first	Total
Number of subjects	72	69	141
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 randomization			
Units: years			
median	58	58	
full range (min-max)	33 to 83	33 to 80	-
Gender categorical			
Sex: Female, Male			
Measure Type: Count of Participants			
Units: Subjects			
Female	31	25	56
Male	41	44	85
ECOG-PS			
The ECOG Performance Status Scale is a widely used method to assess the functional status of a patient. The scale ranges from a score of 0 (Fully active, able to carry on all pre-disease performance without restriction) to 5 (death). Reported at randomization (Baseline)			
Units: Subjects			
score 0	50	47	97
score 1	20	22	42
score 2	2	0	2
M-distant metastasesat inclusion			
Presence of distant metastasis at the moment of randomization (baseline). Mx indicates that metastasis were assessed but the status of the patient regarding presence of metastasis could not be determined. M0 indicates no presence of distal metastasis. M1 indicates presence of distant metastasis and afectation of distant organs			

Units: Subjects			
Mx	1	1	2
M0	2	6	8
M1	69	62	131
Bone metastases at randomization			
Number of patients who have distant organs affected by metastasis at randomization (Baseline). A patient may have more than one organ affected.			
Units: Subjects			
Yes	7	10	17
No	65	59	124
Lung metastasis at randomization			
Number of patients who have distant organs affected by metastasis at randomization (Baseline). A patient may have more than one organ affected.			
Units: Subjects			
Yes	2	3	5
No	70	66	136
Liver metastasis at randomization			
Number of patients who have distant organs affected by metastasis at randomization (Baseline). A patient may have more than one organ affected.			
Units: Subjects			
Yes	61	56	117
No	11	13	24
Lymph nodes metastasis at randomization			
Number of patients who have distant organs affected by metastasis at randomization (Baseline). A patient may have more than one organ affected.			
Units: Subjects			
Yes	4	6	10
No	68	63	131
Ki-67 index			
Ki-67 is a protein found only in cells that are dividing. A high Ki-67 proliferation index means that many cells are dividing rapidly and that the cancer is likely to grow and spread. Here we used the categories used by the WHO classification for neuroendocrine tumors			
Units: Subjects			
≤ 2	9	14	23
3-20	62	51	113
Unknown	1	4	5
Tumor Grade			
Tumor grade at randomization (baseline) using the World health organization (WHO) grading system for neuroendocrine tumors: G1: < 2 mitoses per 2 mm2 and/or Ki-67 index ≤2%, G2: 2-20 mitoses per 2 mm2 and/or Ki-67index >2% and ≤ 20%			
Units: Subjects			
Grade 1	9	12	21
Grade 2	63	55	118
Unknown	0	2	2
Number of previous systemic treatment lines			
Units: Subjects			
0 prior treatment lines	36	43	79
1 prior treatment line	32	22	54
2 prior treatment lines	4	4	8
Previous treatment with somatostatin analogues			
Units: Subjects			

Yes	31	24	55
No	41	45	86
Previous treatment with radiopharmaceuticals Units: Subjects			
Yes	4	3	7
No	68	66	134
Previous treatments - others Units: Subjects			
Yes	1	1	2
No	71	68	139



## End points

### End points reporting groups

Reporting group title	Sequence A, Drug: Everolimus First
Reporting group description:	
Sequence A, drug: everolimus first Everolimus (10mg/daily, oral) followed by STZ-5FU (injection/infusion; Moertel or Uppsala regime).	
Reporting group title	Experimental: Sequence B, drug: STZ - 5FU first
Reporting group description:	
STZ-5FU (injection/infusion; Moertel or Uppsala regime) followed by Everolimus (10 mg/ daily, oral)	

### Primary: First Progression Free Survival (PFS1)

End point title	First Progression Free Survival (PFS1)
End point description:	
Proportion of patients who are alive without progression to Course 1 from the date of randomization in STZ based CT vs Everolimus arms	
Definitions for PFS rate for course 1 at 12 months:	
No: number (proportion) of patients who were not alive and progression free according to the respective definition (main, conservative, and optimistic);	
Yes: number (proportion) of patients who were alive and progression free according to the respective definition (main, conservative, and optimistic).	
End point type	Primary
End point timeframe:	
12 months	

End point values	Sequence A, Drug: Everolimus First	Experimental: Sequence B, drug: STZ - 5FU first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	69		
Units: Percentage of patients				
number (confidence interval 95%)	71.4 (59.4 to 81.6)	61.8 (49.2 to 73.3)		

### Statistical analyses

Statistical analysis title	Cox regression
Comparison groups	Sequence A, Drug: Everolimus First v Experimental: Sequence B, drug: STZ - 5FU first
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.229
Method	Regression, Cox
Parameter estimate	Odds ratio (OR)
Point estimate	0.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.32

## Secondary: Second Progression Free Survival (Second PFS)

End point title	Second Progression Free Survival (Second PFS)
End point description: PFS of Course 1 (PFS1) + interval between treatments + PFS of Course 2 (PFS2), where PFS1 represents progression free survival of Course 1 and PFS2 represents progression free survival of Course 2	
End point type	Secondary
End point timeframe: Until the end of study every 12 weeks, approximately up to 5 years	

End point values	Sequence A, Drug: Everolimus First	Experimental: Sequence B, drug: STZ - 5FU first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	69		
Units: months				
median (confidence interval 95%)	37.5 (27.1 to 53.7)	32.6 (23.7 to 41.1)		

## Statistical analyses

Statistical analysis title	Cox regression
Comparison groups	Sequence A, Drug: Everolimus First v Experimental: Sequence B, drug: STZ - 5FU first
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.135 <sup>[1]</sup>
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2.19

Notes:

[1] - significant differences between both arms is assumed in case p-val <0.05

## Secondary: Progression-free Survival (PFS) to First Treatment

End point title	Progression-free Survival (PFS) to First Treatment
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End point description:

Time from the date of randomization to the date of first disease progression.

End point type	Secondary
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End point timeframe:

Throughout the study period every 12 weeks, approximately up to 5 years

End point values	Sequence A, Drug: Everolimus First	Experimental: Sequence B, drug: STZ - 5FU first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	69		
Units: Months				
median (confidence interval 95%)	19.4 (16.8 to 27.3)	22.7 (13.3 to 28.6)		

## Statistical analyses

Statistical analysis title	Cox regression
Comparison groups	Sequence A, Drug: Everolimus First v Experimental: Sequence B, drug: STZ - 5FU first
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.474 <sup>[2]</sup>
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.75

Notes:

[2] - significant differences between both arms is assumed in case p-val <0.05

## Secondary: Adverse Events (AEs) Rate

End point title	Adverse Events (AEs) Rate
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End point description:

Number of patients experiending serious adverse events (SAEs)

End point type	Secondary
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End point timeframe:

Throughout the study period in continous monitoring at every visit for approximately up to 5 years

End point values	Sequence A, Drug: Everolimus First	Experimental: Sequence B, drug: STZ - 5FU first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69 <sup>[3]</sup>	66 <sup>[4]</sup>		
Units: Patients				
Experienced SAEs	28	26		
Not experienced SAEs	41	40		

Notes:

[3] - Only patients who received study drug

[4] - Only patients who received study drug

## Statistical analyses

No statistical analyses for this end point

## Secondary: Frequency of Dose Modifications to First Treatment

End point title	Frequency of Dose Modifications to First Treatment
End point description:	Percentage of patients who require a dose reduction or interruption for management of adverse events during the study period
End point type	Secondary
End point timeframe:	Throughout the study period, approximately up to 5 years

End point values	Sequence A, Drug: Everolimus First	Experimental: Sequence B, drug: STZ - 5FU first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68 <sup>[5]</sup>	66 <sup>[6]</sup>		
Units: Patients				
Interrupted or reduced doses	41	9		
Not Interrupted or reduced doses	27	57		

Notes:

[5] - Only patients who received study drug

[6] - Only patients who received study drug

## Statistical analyses

Statistical analysis title	Fisher test
Comparison groups	Experimental: Sequence B, drug: STZ - 5FU first v Sequence A, Drug: Everolimus First

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[7]</sup>
Method	Fisher exact

Notes:

[7] - significant differences between both arms is assumed in case p-val <0.0

### Secondary: Best Overall Response (BOR) to First Study Treatment

End point title	Best Overall Response (BOR) to First Study Treatment
End point description: Best response achieved with the first study treatment according to RECIST V1.0	
End point type	Secondary
End point timeframe: Throughout the study period, every 12 weeks up to approximately 5 years	

End point values	Sequence A, Drug: Everolimus First	Experimental: Sequence B, drug: STZ - 5FU first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69 <sup>[8]</sup>	66 <sup>[9]</sup>		
Units: Patients				
Complete response (CR)	3	3		
Partial response (PR)	5	17		
Stable disease (SD)	58	35		
Progression of the disease (PD)	2	9		
Not evaluable (NE)	1	2		

Notes:

[8] - Only patients having tumor assessments

[9] - Only patients having tumor assessments

### Statistical analyses

No statistical analyses for this end point

### Secondary: Objective Response Rate (ORR) to First Study Treatment

End point title	Objective Response Rate (ORR) to First Study Treatment
End point description: The ORR is defined as the number of patients having as their BOR to first treatment either Complete response (CR) or Partial Response (PR) measured by RECIST criteria version 1.0.	
End point type	Secondary
End point timeframe: Throughout the study period every 12 weeks, up to approximately 5 years	

End point values	Sequence A, Drug: Everolimus First	Experimental: Sequence B, drug: STZ - 5FU first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69 <sup>[10]</sup>	66 <sup>[11]</sup>		
Units: Patients				
CR / PR	8	20		
SD / PD / NE	61	46		

Notes:

[10] - Only patients having tumor assessments

[11] - Only patients having tumor assessments

### Statistical analyses

Statistical analysis title	Fisher test
Comparison groups	Sequence A, Drug: Everolimus First v Experimental: Sequence B, drug: STZ - 5FU first
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 <sup>[12]</sup>
Method	Fisher exact

Notes:

[12] - significant differences between both arms is assumed in case p-val <0.05

### Secondary: Frequency of Dose Modifications to Second Treatment

End point title	Frequency of Dose Modifications to Second Treatment
End point description:	Percentage of patients who require a dose reduction or interruption for management of adverse events during the study period
End point type	Secondary
End point timeframe:	Throughout the study period, approximately up to 5 years

End point values	Sequence A, Drug: Everolimus First	Experimental: Sequence B, drug: STZ - 5FU first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36 <sup>[13]</sup>	33 <sup>[14]</sup>		
Units: Patients				
Interrupt or reduced doses	5	18		
Not interrupt or reduced doses	31	15		

Notes:

[13] - Patients starting second line treatment

[14] - Patients starting second line treatment

### Statistical analyses

<b>Statistical analysis title</b>	Fisher test
Comparison groups	Sequence A, Drug: Everolimus First v Experimental: Sequence B, drug: STZ - 5FU first
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 <sup>[15]</sup>
Method	Fisher exact

Notes:

[15] - significant differences between both arms is assumed in case p-val <0.05

## Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description: The median OS defined as the time from the date of randomization until death from any cause. This is estimated by kaplan meier method.	
End point type	Secondary
End point timeframe: Throughout the study period, up to approximately 5 years	

End point values	Sequence A, Drug: Everolimus First	Experimental: Sequence B, drug: STZ - 5FU first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	69		
Units: months				
median (confidence interval 95%)	61.7 (49.1 to 100)	50.6 (40.9 to 64.5)		

## Statistical analyses

<b>Statistical analysis title</b>	Cox regression
Comparison groups	Sequence A, Drug: Everolimus First v Experimental: Sequence B, drug: STZ - 5FU first
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.168 <sup>[16]</sup>
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	2.37

Notes:

[16] - significant differences between both arms is assumed in case p-val <0.05

### Secondary: Best Overall Response (BOR) to Second Study Treatment

End point title	Best Overall Response (BOR) to Second Study Treatment
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End point description:

Best response achieved with the second study treatment according to RECIST V1.0

End point type	Secondary
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End point timeframe:

Throughout the study period, every 12 weeks up to approximately 5 years

End point values	Sequence A, Drug: Everolimus First	Experimental: Sequence B, drug: STZ - 5FU first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36 <sup>[17]</sup>	33 <sup>[18]</sup>		
Units: Patients				
Complete response (CR)	1	0		
Partial response (PR)	10	3		
Stable disease (SD)	15	20		
Progression of the disease (PD)	8	8		
Not evaluable (NE)	2	2		

Notes:

[17] - Patients starting second line treatment

[18] - Patients starting second line treatment

### Statistical analyses

No statistical analyses for this end point

### Secondary: Objective Response Rate (ORR) to Second Study Treatment

End point title	Objective Response Rate (ORR) to Second Study Treatment
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End point description:

The ORR is defined as the number of patients having as their BOR to second treatment either Complete response (CR) or Partial Response (PR) measured by RECIST criteria version 1.0.

End point type	Secondary
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End point timeframe:

Throughout the study period every 12 weeks, up to approximately 5 years

End point values	Sequence A, Drug: Everolimus First	Experimental: Sequence B, drug: STZ - 5FU first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36 <sup>[19]</sup>	33 <sup>[20]</sup>		
Units: Patients				
CR / PR	11	3		



SD / PD / NE	25	30		
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Notes:

[19] - Patients starting the second line treatment

[20] - Patients starting the second line treatment

## Statistical analyses

<b>Statistical analysis title</b>	Fisher test
Comparison groups	Sequence A, Drug: Everolimus First v Experimental: Sequence B, drug: STZ - 5FU first
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.072 <sup>[21]</sup>
Method	Fisher exact

Notes:

[21] - significant differences between both arms is assumed in case p-val <0.05

## Secondary: Quality of Life Questionnaire (QLQ). The EORTC QLQ-C30 GlobalHealth Status

End point title	Quality of Life Questionnaire (QLQ). The EORTC QLQ-C30 GlobalHealth Status
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End point description:

Patient self-reported quality of life (QoL) was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and the specific module for NETs, QLQ-GINET21.

These questionnaires have a punctuation that ranges from 100 (best patient performance) to 0 (worse patient performance).

Here we report the total QLQ-C30 score.

End point type	Secondary
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End point timeframe:

Before any dose of study treatment (basal), before the first dose of the second treatment at line 2 cycle 1 (L2C1) and after completion of both treatments (EOT)

End point values	Sequence A, Drug: Everolimus First	Experimental: Sequence B, drug: STZ - 5FU first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47 <sup>[22]</sup>	49 <sup>[23]</sup>		
Units: Score				
arithmetic mean (standard deviation)				
Basal	78.3 (± 17.6)	77.8 (± 12.1)		
L2C1	75.1 (± 16)	84.1 (± 9.5)		
EOT	68.4 (± 15.2)	75.4 (± 17.9)		

Notes:

[22] - Patients completing the QLQ questionnaires at any timepoint

[23] - Patients completing the QLQ questionnaires at any timepoint

## Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Throughout the study period, approximately up to 5 years of follow-up

Adverse event reporting additional description:

Reported during the first treatment assigned in each arm.

Reported in the safety population, comprising only patients who received at least one dose of the study treatment.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22
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### Reporting groups

Reporting group title	Sequence A, Drug: Everolimus First
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Reporting group description:

Sequence A, drug: everolimus first

Everolimus (10mg/daily, oral) followed by STZ-5FU (injection/infusion; Moertel or Uppsala regime).

Reporting group title	Experimental: Sequence B, drug: STZ - 5FU first
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Reporting group description:

STZ-5FU (injection/infusion; Moertel or Uppsala regime) followed by Everolimus (10 mg/ daily, oral)

<b>Serious adverse events</b>	Sequence A, Drug: Everolimus First	Experimental: Sequence B, drug: STZ - 5FU first	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 69 (40.58%)	26 / 66 (39.39%)	
number of deaths (all causes)	26	35	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Liver metastasis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloma			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urotelial carcinoma			

subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	4 / 69 (5.80%)	4 / 66 (6.06%)	
occurrences causally related to treatment / all	2 / 6	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 69 (2.90%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Creatinine increased			
subjects affected / exposed	1 / 69 (1.45%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Increased urea			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight loss			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Presyncope			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	0 / 69 (0.00%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 69 (4.35%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	2 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 69 (1.45%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental caries			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric hemorrhage			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	1 / 69 (1.45%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 69 (1.45%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomach pain			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute cholangitis			
subjects affected / exposed	1 / 69 (1.45%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localized edema			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash acneiform			

subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Cholecystitis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hematuria			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Calculi			
subjects affected / exposed	0 / 69 (0.00%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	



Infections and infestations Appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 69 (1.45%) 1 / 1 0 / 0	0 / 66 (0.00%) 0 / 0 0 / 0	
Bacteremia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 69 (1.45%) 1 / 1 0 / 0	0 / 66 (0.00%) 0 / 0 0 / 0	
Biliary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 69 (1.45%) 0 / 2 0 / 0	0 / 66 (0.00%) 0 / 0 0 / 0	
Infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 69 (1.45%) 0 / 1 0 / 0	0 / 66 (0.00%) 0 / 0 0 / 0	
Infection without focus subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 69 (2.90%) 0 / 2 0 / 0	0 / 66 (0.00%) 0 / 0 0 / 0	
Lung infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 69 (1.45%) 0 / 1 0 / 0	1 / 66 (1.52%) 1 / 1 0 / 0	
Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 69 (4.35%) 0 / 3 0 / 0	1 / 66 (1.52%) 0 / 1 0 / 0	
Urinary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 69 (1.45%) 0 / 1 0 / 0	2 / 66 (3.03%) 1 / 3 0 / 0	
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycemia			
subjects affected / exposed	2 / 69 (2.90%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertriglyceridemia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Sequence A, Drug: Everolimus First	Experimental: Sequence B, drug: STZ - 5FU first	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 69 (98.55%)	62 / 66 (93.94%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 69 (11.59%)	1 / 66 (1.52%)	
occurrences (all)	9	1	
Thromboembolic event			
subjects affected / exposed	2 / 69 (2.90%)	4 / 66 (6.06%)	
occurrences (all)	2	6	
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	17 / 69 (24.64%)	5 / 66 (7.58%)	
occurrences (all)	33	8	
Fatigue			
subjects affected / exposed	39 / 69 (56.52%)	37 / 66 (56.06%)	
occurrences (all)	76	159	
Fever			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Flu like symptoms</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Non-cardiac chest pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>14 / 69 (20.29%)</p> <p>21</p> <p>10 / 69 (14.49%)</p> <p>17</p> <p>4 / 69 (5.80%)</p> <p>4</p> <p>3 / 69 (4.35%)</p> <p>3</p>	<p>5 / 66 (7.58%)</p> <p>8</p> <p>9 / 66 (13.64%)</p> <p>10</p> <p>4 / 66 (6.06%)</p> <p>4</p> <p>6 / 66 (9.09%)</p> <p>7</p>	
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pneumonitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>8 / 69 (11.59%)</p> <p>9</p> <p>6 / 69 (8.70%)</p> <p>7</p> <p>6 / 69 (8.70%)</p> <p>7</p> <p>6 / 69 (8.70%)</p> <p>10</p>	<p>5 / 66 (7.58%)</p> <p>6</p> <p>6 / 66 (9.09%)</p> <p>7</p> <p>0 / 66 (0.00%)</p> <p>0</p> <p>0 / 66 (0.00%)</p> <p>0</p>	
<p>Psychiatric disorders</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 69 (5.80%)</p> <p>4</p>	<p>8 / 66 (12.12%)</p> <p>8</p>	
<p>Investigations</p> <p>Alanine aminotransferase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Alkaline phosphatase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Aspartate aminotransferase increased</p>	<p>8 / 69 (11.59%)</p> <p>11</p> <p>3 / 69 (4.35%)</p> <p>4</p>	<p>2 / 66 (3.03%)</p> <p>2</p> <p>4 / 66 (6.06%)</p> <p>5</p>	

subjects affected / exposed	7 / 69 (10.14%)	1 / 66 (1.52%)	
occurrences (all)	10	1	
Cholesterol high			
subjects affected / exposed	10 / 69 (14.49%)	2 / 66 (3.03%)	
occurrences (all)	16	2	
Creatinine increased			
subjects affected / exposed	4 / 69 (5.80%)	6 / 66 (9.09%)	
occurrences (all)	5	16	
GGT increased			
subjects affected / exposed	4 / 69 (5.80%)	0 / 66 (0.00%)	
occurrences (all)	5	0	
Weight loss			
subjects affected / exposed	9 / 69 (13.04%)	5 / 66 (7.58%)	
occurrences (all)	12	5	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 69 (1.45%)	4 / 66 (6.06%)	
occurrences (all)	1	6	
Dysgeusia			
subjects affected / exposed	8 / 69 (11.59%)	5 / 66 (7.58%)	
occurrences (all)	10	9	
Headache			
subjects affected / exposed	7 / 69 (10.14%)	3 / 66 (4.55%)	
occurrences (all)	11	5	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	10 / 69 (14.49%)	3 / 66 (4.55%)	
occurrences (all)	22	6	
Febrile neutropenia			
subjects affected / exposed	2 / 69 (2.90%)	5 / 66 (7.58%)	
occurrences (all)	2	7	
Platelet count decreased			
subjects affected / exposed	10 / 69 (14.49%)	7 / 66 (10.61%)	
occurrences (all)	23	12	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	14 / 69 (20.29%)	17 / 66 (25.76%)	
occurrences (all)	21	27	
Constipation			
subjects affected / exposed	10 / 69 (14.49%)	15 / 66 (22.73%)	
occurrences (all)	11	24	
Diarrhea			
subjects affected / exposed	26 / 69 (37.68%)	19 / 66 (28.79%)	
occurrences (all)	63	46	
Dry mouth			
subjects affected / exposed	3 / 69 (4.35%)	4 / 66 (6.06%)	
occurrences (all)	5	5	
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 69 (0.00%)	4 / 66 (6.06%)	
occurrences (all)	0	5	
Mouth ulcer			
subjects affected / exposed	4 / 69 (5.80%)	2 / 66 (3.03%)	
occurrences (all)	9	2	
Mucositis oral			
subjects affected / exposed	34 / 69 (49.28%)	16 / 66 (24.24%)	
occurrences (all)	87	26	
Nausea			
subjects affected / exposed	21 / 69 (30.43%)	26 / 66 (39.39%)	
occurrences (all)	33	50	
Stomach pain			
subjects affected / exposed	6 / 69 (8.70%)	3 / 66 (4.55%)	
occurrences (all)	7	3	
Vomiting			
subjects affected / exposed	12 / 69 (17.39%)	13 / 66 (19.70%)	
occurrences (all)	15	23	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	12 / 69 (17.39%)	3 / 66 (4.55%)	
occurrences (all)	14	5	
Nail changes			

subjects affected / exposed	4 / 69 (5.80%)	2 / 66 (3.03%)	
occurrences (all)	7	2	
Nail ridging			
subjects affected / exposed	4 / 69 (5.80%)	0 / 66 (0.00%)	
occurrences (all)	4	0	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	5 / 69 (7.25%)	4 / 66 (6.06%)	
occurrences (all)	7	5	
Pruritus			
subjects affected / exposed	7 / 69 (10.14%)	8 / 66 (12.12%)	
occurrences (all)	8	10	
Rash acneiform			
subjects affected / exposed	26 / 69 (37.68%)	4 / 66 (6.06%)	
occurrences (all)	39	4	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 69 (1.45%)	4 / 66 (6.06%)	
occurrences (all)	1	6	
Proteinuria			
subjects affected / exposed	6 / 69 (8.70%)	5 / 66 (7.58%)	
occurrences (all)	8	8	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 69 (7.25%)	7 / 66 (10.61%)	
occurrences (all)	8	8	
Cramps			
subjects affected / exposed	3 / 69 (4.35%)	4 / 66 (6.06%)	
occurrences (all)	3	6	
Infections and infestations			
Lung infection			
subjects affected / exposed	7 / 69 (10.14%)	0 / 66 (0.00%)	
occurrences (all)	8	0	
Pharyngitis			
subjects affected / exposed	4 / 69 (5.80%)	0 / 66 (0.00%)	
occurrences (all)	4	0	
Skin infection			

subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 4	0 / 66 (0.00%) 0	
Urinary tract infection subjects affected / exposed occurrences (all)	11 / 69 (15.94%) 19	3 / 66 (4.55%) 3	
Upper respiratory infection subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 5	0 / 66 (0.00%) 0	
Metabolism and nutrition disorders			
Anorexia subjects affected / exposed occurrences (all)	16 / 69 (23.19%) 23	12 / 66 (18.18%) 24	
Hyperglycemia subjects affected / exposed occurrences (all)	23 / 69 (33.33%) 36	9 / 66 (13.64%) 14	
Hypertriglyceridemia subjects affected / exposed occurrences (all)	8 / 69 (11.59%) 18	0 / 66 (0.00%) 0	
Hypokalemia subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 7	1 / 66 (1.52%) 1	
Hypomagnesemia subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 10	1 / 66 (1.52%) 1	
Hypophosphatemia subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 7	1 / 66 (1.52%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2014	Change on main variable and sample size.
26 November 2014	New Institutions are included. Enlargement of study timing

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported