# 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 |

**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:

## 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:

## 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)14. 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)26. 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:

## 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:

### 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 |
| **Arm title** | 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/m2 STZ on days 1-5 and 400mg/m2 5-FU on days 1-5 every 6 weeks (Moertel) or 0,5g/m2 STZ on days 1-5 and 400mg/m2 5-FU on days 1-3, and then 1 day with 1g/m2 and 1 day 400mg/m2 5-FU every 3 weeks (Uppsala).

Number of Cycles: until progression or unacceptable toxicity develops.

| | |
|---|---|
| **Arm title** | 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/m2 STZ on days 1-5 and 400mg/m2 5-FU on days 1-5 every 6 weeks (Moertel) or 0,5g/m2 STZ on days 1-5 and 400mg/m2 5-FU on days 1-3, and then 1 day with 1g/m2 and 1 day 400mg/m2 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<br>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<br>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<br>Measure Type: Count of Participants | | | |
| Units: Subjects | | | |
| Female | 31 | 25 | 56 |
| Male | 41 | 44 | 85 |
| ECOG-PS | | | |
| he 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).<br>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).<br>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.<br>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:<br>G1: < 2 mitoses per 2 mm2 and/or Ki-67 index ≤2%,<br>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<br>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<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Yes | 31 | 24 | 55 |
| No | 41 | 45 | 86 |
| Previous treatment with radiopharmaceuticals<br>Units: Subjects | | | |
| Yes | 4 | 3 | 7 |
| No | 68 | 66 | 134 |
| Previous treatments - others<br>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<br>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<br>Definitions for PFS rate for course 1 at 12 months:<br>No: number (proportion) of patients who were not alive andprogression free according to the respective definition (main,conservative, and optimistic);<br>Yes: number (proportion) of patients who were alive andprogression 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 [1] |
| 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 |
| End point description: | |
| Time from the date of randomization to the date of first disease progression. | |
| End point type | Secondary |
| 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 [2] |
| 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 |
| End point description: | |
| Number of patients experiending serious adverse events (SAEs) | |
| End point type | Secondary |
| 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[3] | 66[4] | | |
| 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[5] | 66[6] | | |
| 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 [7] |
| 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[8] | 66[9] | | |
| 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 tofirst 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[10] | 66[11] | | |
| 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 [12] |
| 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[13] | 33[14] | | |
| 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

| 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 | 69 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 [15] |
| 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

| 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 | = 0.168 [16] |
| 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 |
|---|---|

End point description:

Best response achieved with the second 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 | 36[17] | 33[18] | | |
| 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 |
|---|---|

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 |
|---|---|

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[19] | 33[20] | | |
| Units: Patients | | | | |
| CR / PR | 11 | 3 | | |

| | | | | |
|---|---|---|---|---|
| SD / PD / NE | 25 | 30 | | |

Notes:

[19] - Patients starting the second line treatment

[20] - Patients starting the second line treatment

### 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 | 69 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.072 [21] |
| 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 |
|---|---|

End point description:

Patient self-reported quality of life (QoL) was assessed using the European Organisation for Research and Treatment of Cance r(EORTC) QLQ-C30 questionnaire and the specific module for NETs, QLQ-GINET21.
These questionnaires have a puntuation that ranges from 100 (best patient performance) to 0 (worse patient performance).
Here we report the total QLQ-C30 score.

| End point type | Secondary |
|---|---|

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[22] | 49[23] | | |
| 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

No statistical analyses for this end point

## 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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 22 |

### 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)

| Serious adverse events | 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 | 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 | |
| Bacteremia | | | |
| 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 | |
| Biliary tract infection | | | |
| 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 | |
| Infection | | | |
| 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 | |
| Infection without focus | | | |
| subjects affected / exposed | 2 / 69 (2.90%) | 0 / 66 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 69 (4.35%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | 2 / 66 (3.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 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 %

| **Non-serious adverse events** | 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 | | | |

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

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

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported