CLINICAL TRIAL PROTOCOL

EudraCT number: 2013-000726-66

NCT02246127

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)

PROTOCOL CODE: GETNE1206

Version 4.0 25th of June 2018
Modified on the 7th of August 2018

Sponsor: GETNE

Collaborative Groups: ENETS

Study Coordinator: Dr Ramón Salazar

Protocol approval:

Title: 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).

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Relevant modification since version.0: , Change on main variable and sample size. Also, the text has been improved (corrections of typing errors, clarifications of the text).

Modified on the 7th of August to add a new sub-study as Annex VI.

Summary of changes:

	REVISION HISTORY		
Version	**Date**	**Section**	**Change**
1.0	12th Feb 2013		Initial version (EudraCTnumber)
2.0	30th Jan 2014 Amendment 1	II. Study coordination V. Institutions 3. Randomization 5.1 Everolimus & 6.1 Treatments allowed -All along the protocol	• Change on translational study coordinator (Section II • Blood sampling for future analysis (CTC) is deleted • Inclusion of detailed address for central CgA and CTScan determination • Confusing paragraph is deleted. • New information on everolimus (IB ed 12) • Correction of typing errors, and text clarification.
2.01	1st Sept 2014 Working version	Sections 2.1, 3, 7.4.1, 7.4.2 and 8	Clarification of study procedures suggested by Health Authorities.
3.0	26th Nov 2014 Amendment 2	V. Institutions VI. Timeliness 2. Study objectives 3. Study design 4. Study population 5. Investigational drugs 7.4.1 Safety Assessment 8. Statistics	• New Instututions are included. • Enlargement of study timing based on new information available from ENETS 2014. • Enlargement on the timing for the primary endpoint. Clarification suggested by Health Authorities • Enlargement on the timing for the primary endpoint and clarifications suggested by Health Authorities • Timing allowed between randomization and the start of treatment • Clarification suggested by Health Authorities • Information updated with Investigator's Brochure Ed 13 • Clarification of study procedures suggested by Health Authorities. • Enlargement on the timing for the primary endpoint & clarifications suggested by Health Authorities.

4.0		General Information 1.0 Background 2. Study objective and purposes 3. Study design 4.2.Withdrawal of sub-jects and study end 7.2.6. Laboratory 8. Statistics 8.1 Primary endpoint 8.4.3 Main analysis of efficacy Annex VI	● Update of timelines ● The study rational is updated ● New definition according to feasible sample size. ● The primary objective has been changed and the old one has been moved to secondary ● Secondary objective were revised ● Period between treatments is adjusted to clinical practice ● Follow-up of patients is detailed ● Clarification about laboratory determinations (standard analytical protocol at site is used). ● CTC sampling is deleted (not started) ● Updated as per changes on point 2 of this modification (Main analysis and sample size) ● Definition of event is included ● Inclusion of sensitivity analysis ● Deletion of an Ancillary trial (CTC, optional) that never started ● Inclusion of a new sub-study on tumor blocks

Sponsor / Coordinating investigator:

Signed: [redacted] Date

Biostatistician:

Signed: [redacted] Date

Coordinating Investigator's Signature (if applicable):

Study Title: **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)**

Study Number: **GETNE1206**

Protocol Version: **4.0**

Protocol/Date: **07 Aug 2018**

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in all sections of the protocol.

Signed: Date:

Name:

Address:

Investigator's Signature:

Study Title: **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)**

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Signed: Date:

Name:

Address:

GENERAL INFORMATION

I. SPONSOR AND MONITOR

Sponsor

Grupo Español de Tumores Neuroendocrinos (GETNE)

[redacted]

CRO:

Kantar Health GmbH

[redacted]

Statistics:

[redacted]

II. COORDINATING INVESTIGATOR AND ADDRESS

Dr. Ramón Salazar (chairman of GETNE & study coordinator)

[redacted]

Dr. Barbro Ericksson (coordinator of translational studies)

[redacted]

III. COORDINATING GROUPS

Grupo Español de Tumores Neuroendocrinos (GETNE) [redacted]	**Sponsor**
European Neuroendocrine Tumours Society (ENETS) [redacted]	**Collaborative group**

V. OTHER INSTITUTIONS INVOLVED

Centre for Applied Research on Cancer University of Verona - Policlinico G.B. Rossi [redacted]	**Translational Research** Detection of Predictive markers (paraffin blocks)
UCL Cancer Institute and Royal Free Hospital Neuroendocrine Tumour Unit [redacted]	**Translational Research** Detection of Predictive markers (Blood/serum)
Service de Radiologie Hôpital Beaujon [redacted]	**Translational Research** Central review & Analysis of ENETS Score
Institut Gustave-Roussy [redacted]	**Translational Research** CgA central analysis
Wren Laboratories [redacted]	**Translational Research** Biomarker of NET response

VI TIMELINES

The estimated timeliness for the study are:

First patient in (FPI): Third Q 2014

Last Patient in (LPI): Fourth Q 2018

Data matured for primary endpoint analysis: First Q 2020

Data base lock for primary endpoint analysis: Third Q 2020

Primary endpoint publication: First Q 2021 (assuming ENETS 2021)

Last Patient out (LPO): Fourth Q 2021

Final Clinical Study Report: Second Q 2022

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ABBREVIATIONS

AE	Adverse Event
AEMPS	Spanish Agency for Medicinal Products and Medical Devices
ALT	Alanine aminotransferase/Glutamic-pyruvic transaminase/GPT
ANC	Absolute neutrophil count
AR	Adverse Reaction
AST	Aspartate aminotransferase/Glutamic-oxalacetic transaminase/GOT
BAL	Bronchoalveolar Lavage
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CPK	Creatine kinase
CR	Complete response
CRF	Case Report Form
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DLCO	Diffusing capacity of the lung for carbon monoxide
DNA	Deoxyribonucleic acid
ECG	Electro-cardiogram
ECOG	Eastern Cooperative Oncology Group
ENETS	European Neuro Endocrine Tumor Society
EMA	European Medicines Agency
5FU	5-fluorouracil
FSH	Follicle-stimulating hormone
HB	Hepatitis B
HBcAb	Hepatitis B Virus Core Antigen Antibody
HBs Ag	Hepatitis B Virus Surface Antigen
HBV	Hepatitis B virus
HC	Hepatitis C
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDL	High-Density Lipoprotein

HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HT	Hormonal therapy
i.m.	intramuscular
ICH	International Conference of Harmonisation
ICER	Incremental Cost-effectiveness Ratio
IDTF	Image Data Transmittal Form
INN	International Non-Proprietary Name
INR	International Normalized Ratio
ITT	Intention to treat
IUD	Intrauterine Device
LAR	Long Acting Release
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
mOS	Median overall survival
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTOR	Mammalian Target of Rapamycin
NCI	National Cancer Institute
NET	Neuroendocrine tumour
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PFS1	First Progression-free survival
PFS2	Second Progression-free survival
PNET	Pancreatic neuroendocrine tumour
PP	Per-Protocol
PR	Partial response
PT	Prothrombin Time
RECIST	Response Evaluation Criteria in Solid Tumours
RT	Radiation therapy
RR	Response Rate
SAE	Serious Adverse Event

SD	Stable Disease
SS	Sandostatin analogue
STZ	Streptozotocin
SUSAR	Suspected Unexpected Serious Adverse Reaction
TTP	Time To Progression
ULN	Upper limit of normal
WHO	World Health Organisation

1. BACKGROUND INFORMATION AND RATIONALE

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[1].

A Swedish study[2] tested STZ in combination with 5FU or doxorubicin as first-line treatment and produced overall objective responses in 20 out of 44 (45%) patients with a median duration of response of 27.5 months.

In 1992, Moertel et al, published the results of another randomized phase III trial sponsored by the Eastern Cooperative Oncology Group (ECOG), where 105 patients with pNETs received STZ plus doxorubicin or STZ plus 5FU, or with chlorozotocin as a single agent. The STZ plus doxorubicin arm was superior to STZ plus 5FU in terms of ORR (69% versus 45%; p 0.05), in time to tumour progression (median 20 versus 6.9 months, p 0.001), and in median overall survival (26.4 versus 16.8 months, p 0.004). However, the combination arm with doxorubicin was associated with more noteworthy drug-related toxicity, mainly leukopenia and nephrotoxicity. Chlorozotocin alone produced a 30 % regression rate, with the length of time to tumor progression and the survival time equivalent to those observed with streptozocin plus fluorouracil[3].

Also in 1992, Bukowski et al reported that chlorozotocin plus 5FU tested by the Southwest Oncology Group (SWOG)[4] in 44 patients with pNETs showing 36% partial responses; side effects were moderate to severe and 13 patients developed renal toxicity, which was severe or life-threatening in 5 patients. This important toxicity has limited the use of chlorozotocin in subsequent trials.

In 1993, Eriksson and Oberg[5] reported their experience with 31 patients treated with STZ plus 5FU. STZ plus 5FU produced objective responses in 17 (54%) patients with a median duration of response of 23 months.

Retrospective reports of the use of STZ and doxorubicin have been published. In 2004, a retrospective review of 84 patients treated with combinations of 5FU, doxorubicin and STZ at the MD Anderson Cancer Centre has reported an overall response rate of 39%, and disease stabilization in 50% of the patients. The median response duration was 9.3 months. The 2-year progression free survival (PFS) rate was 41%, and the 2-year overall survival rate was 74%. Multivariate analysis showed that replacement of more than 75% of the liver was independently associated with inferior PFS[6]. In 1999 and 2004, the Memorial Sloan Kettering Cancer Center[7] and the Dana Farber Cancer Institute[8] respectively, reported their experience, with 16 patients each, with the use of this combination, obtaining response rates of 6%, which is much lower than previous reports.

The disparity of these results could be explained by the fact that the methodology used to assess response in older studies was not standardized. It could also be explained by tumour heterogeneity in terms of biological behaviour and responsiveness to chemotherapy. Another fact to be taken into account which could also influence these results is the introduction of biological therapies as first- or second-line treatment, starting chemotherapy only after the progression to those therapies[9].

Temozolomide has also been tried in combination with capecitabine with encouraging results. In vitro data indicate that the combination of capecitabine and temozolomide is synergistic for induction of apoptosis in neuroendocrine tumor cell lines. A retrospective study in 17 patients with pNETs showed 1 complete response (6%) and 9 partial responses (54%) by RECIST criteria, with a median duration of partial response of 284 days. All of the patients had failed first-line treatment with escalating doses of sandostatin LAR and 11 patients had failed multiagent chemotherapy (range 1-5 regimens) [10].

In another recent trial reported by Strosberg et al in 2011, 30 patients with progressive metastatic pNETs who had not received prior systemic chemotherapy were treated with capecitabine (750 mg/m2 twice daily, days 1-14) and temozolomide (200 mg/m2 once daily, days 10-14) every 28 days. 70% patients achieved an objective radiographic response, the median progression-free survival was 18 months, the rate of survival at two years was 92% and only 4 patients (12%) experienced grade 3 or 4 adverse events[11]. Therefore, this combination has a promising activity that should be evaluated in further studies.

Other combinations with STZ were reported in 2008. Treatment with combined streptozotocin and liposomal doxorubicin in 30 patients achieved an objective radiological response of 40% with a median duration of 9 months. The efficacy seems comparable to that of combined streptozotocin and doxorubicin, avoiding cardiac toxicity[12] (2008). Chemotherapy regimens with triple combinations have also been administered in intent to improve efficacy, but none has demonstrated to be superior to doublets and there was an increase in toxicity.

Well differentiated nets (WDNETs) are a subset of tumors with slow growth and relatively indolent behaviour. Recently the mTOR inhibitor, everolimus, has shown to be efficacious in WD- NETS. Everolimus 10mg/day, as compared with placebo, significantly prolonged progression-free survival among patients with progressive advanced pancreatic neuroendocrine tumors and was associated with a low rate of severe adverse events (RADIANT-3 study). Results published from this study showed a median progression-free survival of 11.0 months[13]. This study included patients with advanced, low-grade or intermediate grade pNET with radiologic progression within the previous 12 months.

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 (see section 5.1). 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 clinical practice of NET oncologists.

2. STUDY OBJECTIVES AND PURPOSE

The purpose of this study is to compare STZ vs everolimus as first line treatment for advanced pNET and elucidate which sequence of STZ based chemotherapy and the mTOR inhibitor, everolimus, gives better results in terms of PFS in well differentiated and advanced pancreatic NETs assessed by local investigator using RECIST criteria 1.0.

2.1 PRIMARY OBJECTIVE

To compare the progression free survival rate at 12 months which is the proportion of patients who are alive without progression to Course 1 therapy at 12 months from the date of randomization in STZ based CT vs Everolimus arms.

PNET lesions are usually multiple and difficult and therefore a measurement of a lower number of lesions, as suggested in version 1.1 of the RECIST criteria, not validated for this disease, could be misleading.

Primary endpoint:

Proportion of patients who are alive without progression to Course 1 therapy at 12 months from the date of randomization in STZ based CT vs Everolimus arms.

2.2 SECONDARY OBJECTIVES

The following secondary objectives considered for this study are listed below:

- 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 140±8 weeks of treatment, assessed by local investigator using RECIST criteria 1.0.
- To describe the efficacy of the two sequences of treatment STZ-5FU and everolimus 10 mg/day, as a continuous variable Hazard Ratio (HR), in advanced pNETs at 12 months (main analysis time point) and 140+/-8 weeks**.**
- To determine whether the overall survival of patients with advanced pNETs could

be modified by the upfront administration of each other treatment, STZ-5FU and everolimus 10 mg/day, upon progression.

- To compare the clinical activity of STZ-5FU and everolimus 10 mg/day treatment given in 1st or 2nd place in advanced pNETS, in terms of time to first and second progression, response rate (RR), and early biochemical response (4 week CgA levels), Quality of Life and Cost-effectiveness of each sequence, and to investigate the criteria for measuring progression free survival (RECIST 1.0, RECIST 1.1, composite RECIST 1.0 and composite RECIST 1.1) that correlates better with overall survival.
- To compare the safety and tolerability of treatment with STZ-5FU and everolimus 10 mg/day, given upfront each other upon progression, in patients with advanced pNET.
- To compare the Cost-effectiveness of treatment with STZ-5FU and everolimus 10 mg/day, given upfront each other upon progression, in advanced pNET patients.

Secondary endpoints:

- Second progression free survival defined as PFS of Course 1 + interval between treatments + PFS of Course 2, where PFS1 represents progression free survival of Course 1 and PFS2 represents progression free survival of Course 2.

  It will be expressed as the rate of second progression free survival; this is the proportion of patients which are free of second progression at 140±8 weeks.
- Second progression free survival (PFS of Course 1 + interval between treatments + PFS of course 2) as a continuous time variable.
- Time to first progression of STZ-5FU and Everolimus 10 mg/day or the reverse sequence in advanced pNETs.
- Time to second progression of STZ-5FU and Everolimus 10 mg/day or the reverse sequence in advanced pNETs.
- Time from first progression to second progression of STZ-5FU and Everolimus 10 mg/day or the reverse sequence in advanced pNETs.
- Response rate of STZ-5FU and Everolimus 10 mg/day or the reverse sequence in advanced pNETs assessed every 12 weeks.
- Quality of life score at baseline, upon progression and 30 days after the last dose of study treatment (both sequences).
- CgA levels at baseline and at 4 weeks of treatment start.

- Correlation between the four criteria for second progression free survival (RECIST 1.0, RECIST 1.1, composite RECIST 1.0 and composite RECIST 1.1) and Kendall tau variables.
- Overall survival (OS) of patients on treatment with the combination STZ-5FU chemotherapy followed by Everolimus 10 mg/day upon progression or the reverse sequence, in the treatment of advanced pancreatic neuroendocrine tumours (pNET).
- Number of adverse events, dose reductions, and total dose administered on patients treated with STZ-5FU followed by everolimus 10 mg/day or the reverse sequence, in advanced pNETs.
- Cost per progression free survival gained: Incremental Cost-effectiveness ratio (ICER) of the differential of costs incurred on by each treatment arm (A and B): ICER= (Arm A costs – Arm B costs)/(Arm A 2nd PFS – Arm B 2nd PFS).

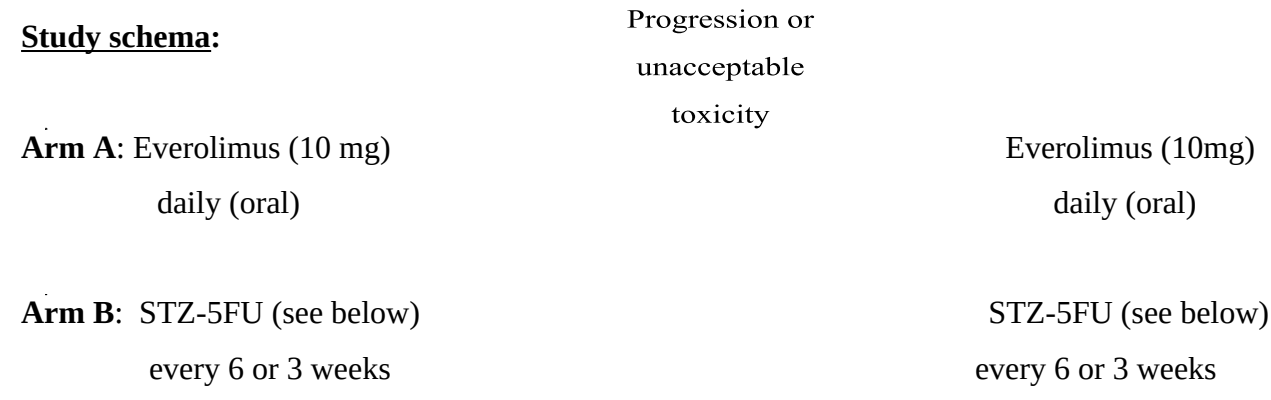
3. STUDY DESIGN

Randomized 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.

Study periods:

- Screening period: ≤ 28 days
- Treatment period: Estimated length, **up to** 140±8 weeks
  - *Arm A*: Everolimus+STZ-5FU.
  - An interval period of time between the end of first regime and the start of second regimen ≤ to 4 weeks approximately during which no active systemic treatment is given before the start of 2nd treatment.
  - *Arm B*: STZ-5FU+Everolimus.
- Safety Follow-up: 30 days after last dose intake (can be a face to face or telephone contact).
- Survival follow-up period: All patients will be followed-up for survival purposes, up to patient's death, up to 140±8 weeks + 30 days, or study end (this is, last visit of last patient included), whatever comes first.

Study schema:



Screening	Treatment visits	Resting period	Treatment visits	Visit at end of treatment
<28 days	(up to first progression or unacceptable toxicity or study end)	(approximately 4 weeks after end of first regime)	(up to second progression, unacceptable toxicity or at 140±8 weeks or study end)	(30 days after last study dose)

Treatment plan:

STZ-5FU (ENETS guidelines; Neuroendocrinology 2012):

- STZ 0.5 g/m2 days 1–5 and 5-FU 400 mg/m2 days 1–5 every 6 weeks (Moertel)

  or,
- 0.5 g/m2 STZ on days 1–5 and 400mg/m2 5-FU on days 1-3 and then,

  1-day treatment with 1g/m2 STZ and 1 day treatment with 400mg/m2 5-FU every 3 weeks (Uppsala).

Everolimus: 10mg per day (Prescription information on technical sheet).

This study includes a fixed-dose regime of treatment (see 5.1.1)

Randomization:

Assignment to treatment arms A and B is going to be done at random by an equal distribution algorithm automatically assigned by the EDC system. Study groups will be stratified according to ECOG Performance Status (PS): 0 versus 1 or 2. The size of randomization blocks will be reported on the Statistical Analysis Plan.

The analysis of the best option for radiological assessment (RECIST criteria and New Composite Score, and its versions 1.0 &1.1), will be done retrospectively. An ENETS Central Radiological Commission will be set up for a centralized evaluation of Computed Tomography (CTs).

Sites should have a copy of patient's CTs available for central radiological assessment. CTs will be collected and sent using electronic transfer/CD, to the Central Radiological Commission in Paris, France.

4. STUDY POPULATION

About 140 adult patients with a diagnosis of advanced pancreatic Neuroendocrine Tumour (pNET) will be recruited in approximately 8 countries all around Europe **(136 patients already included).**

4.1 SELECTION OF SUBJECTS

4.1.1 Inclusion criteria

1. Adult patients ≥ 18 years old.
2. Histologically proven diagnosis of unresectable or metastatic, advanced pancreatic NET.
3. Documented confirmation of pancreatic NET G1 or G2 as per ENETS classification system:

   G1: <2 mitoses per 2 mm^2 and/or Ki-67 index ≤ 2%

   G2: 2–20 mitoses per 2 mm^2 and/or Ki-67 index >2% and ≤ 20%
4. Patients from whom a paraffin-embedded primary tumour or metastasis block is available to be sent by courier (Section 7.2.10). Patient should give RECISThis/her consent for its use in future investigations.
5. Before study inclusion, patients must show progressive disease documented by radiology within 12 months prior to study inclusion. If patient received anti-tumour therapy during the past 12 months, he/she must have radiological documentation of progressive disease while on or after receiving that anti-tumour therapy. Treatment naive patients can be also included if, under investigator's judgment, the patient needs active treatment with either chemotherapy or everolimus.
6. Before starting with the second treatment in sequence, patients must show documented disease progression by RECIST 1.0 (local assessment) while on anti-tumour therapy or in case of toxicity caused by the first treatment period.
7. ECOG Performance status score 0 - 2.
8. Life expectancy > 12 months.

9. Presence of measurable disease as per RECIST criteria 1.0, documented by a Triphasic Computed Tomography (CT) scan or multiphase MRI radiological assessment.
10. Previous treatment with somatostatin (SS) analogues is allowed. Only those patients with active functioning syndrome at entry can continue with SS analogues during the study.
11. Adequate bone marrow function, documented by ANC > 1.5 x 10^9/L, platelets > 100 x 10^9/L, haemoglobin > 9 g/dL.
12. Adequate liver function documented by: serum bilirubin ≤ 2.0 mg/dL, INR ≤ 2, ALT and AST ≤ 2.5 x ULN (≤ 5 x ULN in patients with liver metastasis).
13. Adequate renal function documented by: serum creatinine < 1.5 x ULN.
14. Fasting serum cholesterol < 300 mg/dL or < 7.75 mmol/L and fasting triglycerides < 2.5 x ULN. If one or both thresholds are exceeded, the patient may only be included after starting treatment with an adequate lipid-lowering agent.
15. Women with child-bearing potential must have a negative serum pregnancy test within 14 days prior to enrollment and/or a urine pregnancy test 48 hours before the administration of the first study treatment.
16. Written Informed Consent obtained according to local regulations.

4.1.2 Exclusion criteria

1. Patients with poorly differentiated pancreatic neuroendocrine tumor; this is, pNET G3 as per ENETS classification system:

   G3: 21 or more mitoses per 2 mm^2 and/or Ki-67 index >20%

2. Previous treatment with chemotherapy and/or mTOR inhibitors (sirolimus, temsirolimus, everolimus, deforolimus) or tirosyne kinase inhibitors (sunitinib, sorafenib, axitinib, pazopanib, regerafenib).
3. Immune therapy or radiation therapy within 4 weeks prior to the patient entering the study.
4. Hepatic artery embolization within the last 6 months (1 month if there are other sites of measurable disease), or cryoablation/radiofrequency ablation of hepatic metastasis within 2 months of enrolment.
5. Previous treatment with Peptide-Receptor Radionuclide Therapy (PRRT) within the last 6 months and/or without progression following PRRT.
6. Uncontrolled diabetes mellitus defined as: fasting serum glucose > 1.5 x ULN.

7. Patients with any severe and/or uncontrolled medical conditions such as:
    a. unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to randomization, serious uncontrolled cardiac arrhythmia,
    b. active or uncontrolled severe infection,
    c. severe hepatic impairment (Child Pugh C) is not allowed; moderate hepatic impairment (Child Pugh B and A) requires a reduced dose of everolimus (5mg and 7.5 mg daily respectively). Positive HBV-DNA and or HBsAg patients at screening should receive prophylaxis treatment.
    d. severely impaired lung function (spirometry and DLCO 50% or less of normal and O_2 saturation 88% or less at rest on room air),
    e. active, bleeding diathesis
8. Treatment with potent inhibitors or inducers of CYP3A isoenzyme (rifabutin, rifampicin, clarithromycin, ketoconazole, itraconazole, voriconazole, ritonavir, telithromycin) within 5 days immediately before the start of treatment (a list of clinically significant drug interactions is shown in section 6. Concomitant Medication).
9. Patients on chronic treatment with corticosteroids or any other immunosuppressive agent.
10. Patients known to be HIV seropositive.
11. Known intolerance or hypersensitivity to everolimus or its excipients or other rapamycin analogues. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
12. Known intolerance or hypersensitivity to 5FU or STZ or its excipients (notice that this criterion includes patients with known deficit of dihydropyrimidine dehydrogenase deficiency –DPD-).
13. Participation in any other clinical trial or concomitant treatment with any other investigational drug.
14. No other prior or concurrent malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, or other adequately treated in situ cancer, or any other cancer from which the patient has been disease free for ≥ 3 years.

15. Pregnant, lactating women or fertile adults not using effective birth control methods. If barrier contraceptives are used, these must be continued to be used throughout the trial by both sexes and for up to 8 weeks after the end of treatment.

16. For administrative matters (insurance) patients ≥ 95 are not allowed during the trial.

Only those patients coming from the hospital pool will be included in SEQTOR trial (e.g. persons detained in an institution as a result of an official or court order are excluded).

4.2 WITHDRAWAL OF SUBJECTS AND STUDY END

All patients receiving treatment will be followed at least until 14 months (60 weeks which is the first radiological evaluation from 12 months) of the start of course 1 of last patient in (LPI). .

Patients will be taken off treatment if any of the following situations occurs:

- Disease progression of pNET
- Unacceptable toxicity (see next section) even with optimal supportive care, following investigator's judgement.
- Patient withdraws her/his consent to continue with study treatment.
- Patient dies.

In case of treatment discontinuation, the patient will continue in the study for survival follow-up, up to last visit of last patient.

Patients will be considered off study if any of the following occurs:

- Patient is lost to follow-up.
- Patient withdraws his/her consent for survival data collection.
- Patient dies.
- Study ends (up to last visit of last patient as defined above).

The study can be finished for administrative reasons.

5. INVESTIGATIONAL DRUGS

Interventional treatment consists on the administration of everolimus and a streptozotocin based therapy given upfront each other upon progression.

Physicians will prescribe the Study Drug in accordance with medical guidelines and in accordance with licensed indications of the Study Drug.

Drug substance 1

INN: Everolimus

Therapeutic group: L01X E10.

Trade name: Afinitor

Name used in the study: Everolimus

Pharmaceutical form: Elongated white to off-white tablets.

Route of Administration: Oral

Dose and method of administration: 10 mg/day

Storage temperature: Room temperature (up to 25ºC). Protect from light and moisture.

Drug substance 2

INN: Streptozotocin

Trade name: Zanosar

Therapeutic group: L01AD04

Name used in the study: Streptozotocin

Pharmaceutical form: Powder for solution

Route of Administration: inyectable

Dose and method of administration: 0,5g/m² days 1-5 in combination with 5FU (according to Moertel or Uppsala). STZ is administered as a short (30–60 min) infusion or rapid intravenous push.

Storage temperature: 2-8 ºC. **P**rotect from light (preferably stored in carton).

Drug substance 3

INN: Fluorouracil

Therapeutic group: L01BC02

Name used in the study: 5-Fluorouracil (5FU)

Pharmaceutical form: Vial

Route of Administration: intravenous infusion or injection

Dose and method of administration: 400 mg/m² 5FU (according to Moertel or Uppsala). 5FU is given as intravenous bolus injection.

Administration should be completed before 24 hours of preparation.

Storage temperature: 8 ºC to 25ºC (Do not refrigerate). Protect from light.

All the patients enrolled in the study will follow two treatments in sequence:

Treatment 1: Everolimus

Treatment 2: STZ-5FU

Or the reverse sequence.

Supply and storage of study drugs

Commercial drugs will be used in this study. No drug will be supplied by the sponsor since this is just a comparative study of the effect of sequencial order of two accepted therapies used in clinical practice from which there is no clinical evidence about its efficacy when given upfront each other.

Labelling

Commercial drug is going to be used in this trial. There is no labelling but commercial packaging. Pharmacy Service should annotate patient numbers and patient visit on the box. This information should be tracked separately per patient.

For documentation of everolimus intake patients will receive a patient diary

5.1 EVEROLIMUS

Everolimus obtained approval from the US and EU for the treatment of patients with advanced pNETs in 2011. In Europe, everolimus has been approved , on the following dates: Germany: Q3 2011, Sweden: Q3 2011, UK: Q3 2011, Denmark: Q3 2011, The Netherlands: Q3 2011, Scotland: Q2 2012, France: Q4 2012, Italy: Q4 2012, and Spain: Q2 2013.

5.1.1 Dose and administration

The recommended dose for everolimus is 10 mg once a day while a clinical benefit is observed or until unacceptable toxicity occurs. Everolimus length of cycles is 4 weeks (28 days).

Recommended dose for patients with mild hepatic impairment Child-Pugh A is 7,5 mg daily. Child-Pugh B patients (moderate impairment) should start at a reduced dose (5 mg daily) and the dose may be decreased to 2.5 if not well tolerated Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment.

Everolimus must be administered every day at the same time and under the same conditions, immediately after meals. The tablets must not be chewed or crushed, but taken whole with a glass of water. The blisters will only be opened when at the time of administration, since they are hygroscopic and sensitive to light.
If a dose is missed, an extra dose must not be taken; patient must wait until the next dose.
Recommendations stated on the Summary of Product Characteristics (Technical Sheet) and its updates is going to be followed in case of everolimus toxicity and should be consulted in case of AE. Summary of Product Characteristics of everolimus, STZ and 5-FU will be part of the Investigator's file as recommended on ICH guidelines.
Patient should document regularly the administration of everolimus on a patient diary.

5.1.1.1 Summary of Adverse Drug Reactions

The most common ADRs (incidence ≥1/10 and suspected to be related to treatment by the investigator) from the pooled safety data were (in decreasing order): stomatitis, rash, fatigue, diarrhea, infections, nausea, decreased appetite, anemia, dysgeusia, pneumonitis, hyperglycemia, weight decreased, pruritus, asthenia, peripheral edema, hypercholesterolemia, epistaxis, and headache.
The most common grade 3/4 ADRs (incidence ≥1/100 to <1/10 and suspected to be related to treatment by the investigator) were stomatitis, anemia, hyperglycemia, fatigue, infections, pneumonitis, diarrhea, asthenia, thrombocytopenia, neutropenia, dyspnea, lymphopenia, proteinuria, hemorrhage, hypophosphatemia, rash, hypertension, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased and pneumonia.

5.1.2 Modification of dose in case of toxicity

This study includes a fixed-dose regime of treatment. For adverse reactions of Grade 1, dose adjustment is usually not required. However, if the patient experiences any treatment-related adverse event, Everolimus therapy may require temporary dose interruption (with or without dose reduction) or discontinuation.

The following dose reductions (also shown in Table I) are recommended:

If dose reduction is required, the suggested dose is aproximately 50% lower than the daily dose previously administrated. For dose reductions below the lowest dose available, alternate day dosing should be considered.

- Dose reduction to 5 mg a day.
- Dose reduction to 5 mg every other day.

Clinical judgement of the treating clinician should guide the management plan of each patient based on individual benefit/risk assessment.

Hepatic impairement

Dose adjustements should be made if a patient's hepatic status changes during treatment. The recommended dose for patients with moderate hepatic impairement (Child-Pugh B) is 5 mg daily; the dose may be decreased to 2.5mg daily if not well tolerated. Treatment with everolimus on a patient with severe hepatic impairement (Child-Pugh C) is not recommended.

Table I.- Guidelines for dose modification in case of suspected toxicity to everolimus and restart of treatment with everolimus

TOXICITY	ACTIONS
Stomatitis	
Grade 1 Minimal symptoms, normal diet	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouthwash several times a day.
Grade 2 Symptomatic but can eat and swallow modified diet	Temporary dose interruption until recovery to Grade ≤1. Re-initiate Everolimus at the same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate Everolimus at a lower dose (see section 6.1).
Grade 3 Symptomatic and unable to adequately eat or hydrate orally	Temporary dose interruption until recovery to Grade ≤1. Re-initiate Everolimus at a lower dose (see section 6.1) .
Grade 4 Symptoms associated with life-threatening consequences	Discontinue everolimus and treat with appropriate medical therapy.
Other non haematologic toxicities (excluding metabolic events)	
Grade 1 Asymptomatic, radiographic findings only	If toxicity is tolerable, no dose adjustemnt required. Initiate appropriate medical therapy and monitor.
Grade 2 Symptomatic, not interfering with ADL	If toxicity is tolerable, maintain the same dose. Initiate appropriate medical therapy and monitor. If toxicity becomes intolerable for the patient, discontinue everolimus until recovery to grade ≤1. Then restart everolimus at the same dose. If the event returns to grade 2, discontinue everolimus until it recovers to grade ≤1. Then restart everolimus at a lower dose.
Grade 3	Discontinue everolimus until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Consider restart everolimus at a lower dose. If toxicity recurs to grade 3, consider discontinuation.
Grade 4	Remove everolimus, and treat with appropriate medical therapy

Metabolic events (e.g. hyperglycemia, dyslipemia)	
Grade 1 and grade 2	No dose adjustment is required. . Initiate appropriate medical therapy and monitor.
Grade 3	Interrupt everolimus temporary. Re-initiate at a lower dose. Mange with appropriate medical therapy and monitor.
Grade 4	Remove everolimus, and treat with appropriate medical therapy
Haematologic toxicity	
Grade 2 thrombocytopoenia (platelets <75, ≥50x10^9/L)	Discontinue everolimus until recovery to grade ≤1 (>75 x10^9/L). Then restart everolimus at the same dose. If thrombocytopoenia returns to grade 2, discontinue everolimus until it recovers to grade ≤1. Then restart everolimus at the next lower dose.
Grade 3 and 4 thrombocytopoenia (platelets <50x10^9/L)	Discontinue everolimus until recovery to grade ≤1 (platelets ≥75 x10^9/L). Then restart everolimus at a lower dose. If grade 3 thrombocytopoenia recurs, remove everolimus.
Grade 2 neutropoenia (neutrophils (≥1 x10^9/L)	No dose adjustment is required.
Grade 3 neutropoenia (neutrophils (<1, ≥0.5 x10^9/L)	Discontinue everolimus until recovery to grade ≤2 (neutrophils ≥1 x10^9/L). Then restart everolimus at the same dose.
Grade 4 neutropoenia (neutrophils (< 0.5 x10^9/L)	Discontinue everolimus until recovery to grade ≤2 (neutrophils ≥1 x10^9/L). Then restart everolimus at the next lower dose level.
Grade 3 febrile neutropoenia (not life-threatening)	Discontinue everolimus until fever and neutropoenia subside to grade ≤2 (neutrophils ≥1,25 x10^9/L) and no fever. Then restart everolimus at a lower dose.
Grade 4 febrile neutropoenia (life-threatening)	Discontinue everolimus.

For the treatment of other toxicities such as stomatitis/mucositis, diarrhoea, hyperlipidaemia and hyperglycaemia, see *Allowed and Prohibited concomitant medications* Section 6 in the protocol.

Stomatitis or oral mucositis will be adequately classified using the functional classification for adverse events provided in the NCI-CTCAE scale, version 4.0.

Cases of hyperglycaemia have been reported in patients taking Everolimus. It is recommended to measure fasting glucose serum levels before starting treatment with everolimus and then monitor them regularly. More frequent monitoring is recommended when everolimus is co-administrated with other drugs that may induce hyperglycemia.
Dyslipemia (including hypercholesterolemia and hyprtriglyceridemia) has been reported. Monitoring of cholesterol and triglycerides prior to start and periodically thereafter is recommended.

Cases of non-infectious neumonitis (including interstitial lung disease) have been described in patients taking Everolimus. Some of these have been severe and on rare occasions, fatal

outcome was observed. In case of non-infectious pneumonitis with moderate symptoms (this is, grade 2), treatment interruption should be considered until the symptoms improve.

If the patient experiences grade 3 pneumonitis the treatment should be interrupted and the patient treated clinically following the standard procedures. A pulmonary function test and bronchoscopy with biopsy (and BAL) will be performed if considered clinically necessary. The use of corticosteroids may be indicated until symptoms subside. The treatment may be restarted at a reduced dose .

A diagnosis of non-infectious pneumonitis should be considered in patients with unspecific respiratory signs or symptoms, such as hypoxia, pleural effusion, cough, or dyspnoea. Therefore, **assessment by a pneumologist should be considered** if non-infectious pneumonitis is diagnosed, as well as in cases where the causes of infectious, neoplastic and non-pharmacological origin have been ruled out after performing the relevant investigations. Opportunistic infections such as PJP should be ruled out in the differential diagnosis of non-infectious pneumonitis.
For patients who required corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for pneumocystis jirovecii pneumonia (PJP) may be considered.

The patients must be instructed to notify immediately any new or worsening respiratory symptom. Patients participating in this study will be asked regularly for the presence or changes in pulmonary symptoms indicating pulmonary toxicity.

Table II. Schedule of the management of non-infectious pneumonitis

Worst grade	**Assessments needed**	**Treatment**	**Dose adjustment of everolimus**
Grade 1 asymptomatic radiographic findings only	Initiate appropiate monitoring CT with pulmonary window. Repeat at least every three cycles until return to normal limits.	No specific treatment is required.	Administer 100% of the everolimus dose.
Grade 2, symptomatic; does not interfere with activities of daily life.	CT with pulmonary window and pulmonary function tests, including: spirometry, DLCO and O2 saturation at rest with ambient air; Repeat in each cycle until return to baseline values. Consider the possibility of performing a bronchoscopy.	Only symptomatic treatment. Consider corticosteroids if coughing that is uncomfortable for the patient is observed.	Consider interruption of therapy, rule out infection and consider treatment with corticoesteroids until symptoms improve to grade ≤ 1. Reinitiate at a lower dose. Patients will be removed from treatment if they do not recover to ≤ grade 1 within 4 weeks.
Grade 3, symptomatic; does not interfere with activities of daily life. Oxygen therapy is indicated.	Rule out infection. CT with pulmonary window and pulmonary function tests, including: spirometry, DLCO and O2 saturation at rest with ambient air; Repeat in each cycle until return to baseline values. Bronchoscopy recommended.	Consider treatment with corticosteroids if an infectious origin is ruled out. Titrate the dose according to medical indication.	Interrupt treatment until resolution to grade ≤ 1. Rule out infection and consider treatment with corticoesteroids .The treatment may be restarted s at a reduced dose (by one level). If toxicity recurse at grade 3, consider discontinutaion.
Life-threatening, grade 4; assisted ventilation indicated.	Rule out infection. CT with pulmonary window and pulmonary function tests, including: spirometry, DLCO and O2 saturation at rest with ambient air. Repeat at least every two cycles until return to normal limits. If possible, bronchoscopy with biopsy and BAL are recommended.*	Consider the possibility of using corticosteroids if an infectious origin is ruled out. Titrate the dose according to medical indication.	Discontinue treatment. Rule out infection and consider treatment with corticoesteroids .
*** When a bronchoscopy is performed, a biopsy or bronchoalveolar lavage (BAL) should be also done.**			

In the event of localised or systemic infections (everolimus has immunosuppressive properties), including pneumonia, other bacterial, fungal, viral or protozoan infections including infections with opportunistic pathogens (PJP), including reactivation of the hepatitis B virus (some of these infections have been severe leeding to sepsis, respiratory or hepatic failure) and occasionally had a fatal outcome. **Both physicians and patients must be aware that everolimus is associated with an increased risk of infection**. Therefore, any existing infections must be treated appropriately and should have been resolved fully before starting treatment with everolimus. During treatment with everolimus, special

attention will be paid to symptoms and signs of infection; if any infections are diagnosed, the site should immediately provide the appropriate treatment and **consider temporary or definitive discontinuation of everolimus**. Should the patient require erythromycin, verapamil or oral cyclosporine, reducing the dose to 5 mg should be considered (see Section 6 Treatments Allowed).

In case of fungal invasive systemic infection, **treatment** with everolimus should be **discontinued immediately and permanently**.

Pneumocystis jirovecii pneumonia (PJP) cases, some with fatal outcome, have been reported in patients who received everolimus. PJP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

No dose adjustment is required for renal impairment. Everolimus has been associated with renal failure events (including fatal ones) and proteinuria. Renal function should be monitored particularly where patients have additional risk factors that may further impair renal function.

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Angioedema (rare adverse drug reaction): Patients taking concomitant angiotensin-converting enzyme (ACE) inhibitor therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment).

Based on non-clinical findings, male and female fertility may be compromised by treatment with everolimus. Everolimus may have an impact on female fertility and may affect male fertility

For the full list of all side effects reported with everolimus, see the Summary of Product Characteristics leaflet in the Investigator's file.

5.1.3 Monitoring patients with hepatitis B and prophylactic treatment for its reactivation

In patients with cancer and hepatitis B, whether carriers of virus or if they have developed chronic hepatitis, it has been shown that the use of antivirals during cancer treatment reduces the risk of reactivation of the hepatitis B virus (HBV) as well as the morbidity and mortality associated with this virus[15,16].

Everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infections is an expected event during periods of immunosuppression.

Lab Samples for detection of Hepatitis Viremia have to be taken at screening + at each examination during everolimus therapy whether carriers of hepatitis B (see tables below).

A/ Screening period: If hepatitis tests are performed before including the patient in the study, the following measures should be adopted based on the outcome obtained:

Table III. Detection of HBV

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ o -	-	-	-
HBs Ag	+ o -	+	-	-	-
Anti-HBs Ab	+ o -	+ o -	+ and no previous vaccination for HBV	+ o -	o + with previous vaccination for HBV
Anti-HBc Ab	+ o -	+ o -	+ o -	+	-
Recommendation	Administered prophylactic treatment between 1 and 2 weeks before administration of the first dose of the study drug;* monitor HBV-DNA approximately every 6 months.		No prophylaxis is required; monitor HBV-DNA approximately every 3 months.		No specific action is required.
* **Administration of the prophylactic antiviral treatment will be continued until at least 4 weeks following the last administration of the study drug.**					

B/ On-treatment period:

In the event of reactivation of hepatitis B during the study treatment, the following should be performed:

Table IV. Treatment of HBV reactivation* (with or without clinical signs or symptoms)

Patients with baseline results: Positive HBV-DNA OR Positive HBsAg ---------- Reactivation is defined as: [increase of 1 log in HBV-DNA from the baseline value of new measurable HBV-DNA OR HBV-DNA] AND increase of ALT 5 x ULN	Start treatment with a second antiviral drug; AND discontinue administration of the study drug until it subsides: >ALT ≤ grade 1 (or baseline ALT, if > grade 1); and HBV-DNA ≤ baseline values If the episode subsides within ≤ 28 days, administration of the study drug should be restarted with a lower dose, if possible (see Table I. Guidelines for changing the dose of everolimus). If the patient already receives the lowest dose of the study drug established in this protocol, the treatment will be restarted at the same dosage after it subsides. Administration of both antiviral treatments should be continued until at least 4 weeks following the last administration of the study drug. If the episode subsides within > 28 days, administration of the study drug should be definitively discontinued and administration of both antiviral treatments will continue until at least 4 weeks after the last administration of the study drug.
Patients with baseline results: Negative HBV-DNA and HBsAg AND [Positive anti-HBs Ab (with no history of vaccination for HBV) or anti-HBc Ab] ---------- Reactivation is defined as new measurable HBV-DNA.	Start treatment with a first antiviral drug; AND discontinue administration of the study drug until it subsides: HBV-DNA ≤ baseline values If the episode subsides within ≤ 28 days, administration of the study drug will be restarted with a lower dose, if possible (see Table I. Guidelines for changing the dose of everolimus). If the patient already receives the lowest dose of the study drug established in this protocol, the treatment will be restarted at the same dosage after it subsides. Administration should be continued until at least 4 weeks after the last administration of the study drug. If the episode subsides within > 28 days, administration of the study drug should be definitively discontinued and administration of the antiviral treatment will continue until at least 4 weeks after the last administration of the study drug.
* **All hepatitis B reactivations will be noted as grade 3** (according to CTCAE, version 4.0, Metabolic/Laboratory/Other: viral reactivation), **unless they are considered potentially life-threatening** in the investigator's opinion, in which case they will be noted as grade 4 (according to CTCAE, version 4.0, Metabolic/Laboratory/Other: viral reactivation). The viral **reactivation date** will be considered as the date when both the **criteria** for DNA and the ALT value **are met** (for instance, if a patient had positive results in the HBV-DNA analysis on 1 January, 2010) and reached a value of ALT ≥ 5 x ULN on 1 April, 2010, this will be the last date of viral reactivation).	

5.1.4 Monitoring patients with hepatitis C

HCV reactivation should be monitored every 6 weeks in the following patients:

- Patients with known history of infection by HCV, despite having negative results in the viremia analysis at baseline (also in patients receiving treatment and considered "cured").

Guidelines for the treatment of hepatitis C are detailed below:

Table V. Treatment of HCV reactivation*

In patients with the following baseline results: Detectable HCV-RNA, Reactivation is defined as: increase of ALT 5 x ULN	Definitively discontinue the study drug.
In patients with the following baseline results: known history of infection by HCV with no detectable HCV-RNA, Reactivation is defined as: new detectable HCV-RNA	Definitively discontinue the study drug.
*** All hepatitis C reactivations will be noted as grade 3 (according to CTCAE, version 4.0, Metabolic/Laboratory/Other: viral reactivation), unless they are considered life-threatening in the investigator's opinion, in which case they will be noted as grade 4 (according to CTCAE, version 4.0, Metabolic/Laboratory/Other: viral reactivation).**	

5.2 STZ-5FU THERAPY

5.2.1 Dose and administration

Treatment recommendations on ENETS guidelines (Moertel's or Uppsala regimens) should be followed for STZ-5FU dosage/regime[14], this is:

Moertel:

- STZ 0.5 g/m^2 on days 1–5
- 5FU 400 mg/m^2 on days 1–5

every 6 weeks.

Uppsala:

- STZ 0.5 g/m^2 on days 1–5

  5FU 400 mg/m^2 on days 1-3

and then every 3 weeks,

- 1-day treatment with 1g/m^2 STZ
  1-day treatment with 400mg/m^2 5-FU

STZ is administered as a short (30–60 min) infusion or rapid intravenous push and 5FU is given as intravenous bolus injection.

5.2.2 Dose modifications in case of toxicity

Dosage adjustments or discontinuance of STZ may be indicated, depending upon the degree of toxicity noted:

- Renal impairment: dose reductions of STZ should be considered when creatinine clearance is <60 ml/min and should not be given below 30 ml/min.
- Liver impairment: reduction of doses should be considered.
- Oral ulceration/GI side effects: Treatment with 5-FU should be discontinued at the first sign such as stomatitis, diarrhoea or bleeding from the G.I. tract.

Fluorouracil has a narrow margin of safety and is a highly toxic drug. Fluorouracil therapy should be discontinued promptly whenever one of the following signs of toxicity appears: leucopenia, thrombocytopenia, stomatitis, oesophagopharyngitis, intractable vomiting, diarrhoea, melena haemorrhage, oral ulceration, evidence of gastrointestinal ulceration or bleeding. The ratio between effective and toxic dose is small and therapeutic response is unlikely without some degree of toxicity. Care must be taken, therefore, in the selection of patients and adjustment of dosage.

Cytotoxic agents, including fluorouracil, may produce myelosuppression (including, but not limited to, leucopenia, granulocytopenia, pancytopenia and thrombocytopenia). Leucopenia and thrombocytopenia commonly follow treatment with fluorouracil. Clinical consequences of sever myelosuppression include infections. Viral, bacterial, fungal and/or parasitic infections, either localized or systemic, may be associated with the use of fluorouracil alone or in combination with other immunosuppressive agents. These infections may be mild, but can be severe and at times fatal.

Rarely, severe toxicity (e.g., stomatitis, diarrhoea, neutropenia, and neurotoxicity) associated with fluorouracil has been attributed to deficiency of dihydropyrimidine dehydrogenase (DPD) activity. Fatal outcome has been reported in some cases. Absence of

this catabolic enzyme appears to result in prolonged clearance of fluorouracil. Special attention should be given to DPD status when evaluating patients experiencing fluorouracil-related toxicities.

Recommendations stated on the Summary of Product Characteristics (Technical Sheet) is going to be followed in case of CT toxicity.

5.2.3 Monitoring of Adverse Events

- Check for extravasation.
- Before each course it is recommended checking: creatinine clearance, blood counts, transaminases, bilirubin, albumin, blood glucose, serial urinalysis, blood urea nitrogen, plasma creatinine, serum electrolytes.

Fluorouracil should be used with caution in elderly patients. Age 70 years or older and the female gender are reported independent risk factors for severe toxicity from fluorouracil based chemotherapy. Close monitoring for multiple organ toxicities and vigorous supportive care of those with toxicity are necessary.

Renal function must be monitored before and after each course of therapy with STZ. Serial urinalysis, blood urea nitrogen, plasma creatinine, serum electrolytes and creatinine clearance should be obtained prior to, at least weekly during, and for four weeks after drug administration. Serial urinalysis is particularly important for the early detection of proteinuria and should be quantitated with a 24 hour collection when proteinuria is detected. Mild proteinuria is one of the first signs of renal toxicity and may herald further deterioration of renal function. Reduction of the dose of STZ or discontinuation of treatment is suggested in the presence of significant renal toxicity. Adequate hydration may help reduce the risk of nephrotoxicity to renal tubular epithelium by decreasing renal and urinary concentration of the drug and its metabolites.

Fluorouracil is contraindicated in patients who are debilitated, who are suffering from bone marrow depression following radiotherapy or therapy with other antineoplastic agents, and in patients who are pregnant. Fluorouracil should not be readministered after a documented cardiovascular reaction (arrhythmia, angina, ST segment changes) as there is a risk of sudden death. Any form of therapy which adds to the stress of the patient, interferes with nutritional uptake or depresses bone marrow function, will increase the

toxicity of fluorouracil. Fluorouracil should be used with caution in patients with reduced renal or liver function or jaundice.

5.2.4 Adverse Events

- Nausea – try another 5-HT 3 -receptor blocker or add a prepitant.
- Renal impairment – dose reductions of STZ should be considered when creatinine clearance is <60 ml/min and should not be given below 30 ml/min.
- Liver impairment – reduction of doses should be considered.
- Stomatitis – frequent mouth care.
- Photosensitivity – avoid direct sunlight.

Many patients treated with STZ have experienced renal toxicity, as evidenced by azotemia, anuria, hypophosphatemia, glycosuria and renal tubular acidosis. Such toxicity is dose-related and cumulative and may be severe or fatal. Use of STZ in patients with preexisting renal disease requires a judgment by the physician of potential benefit as opposed to the known risk of serious renal damage. This drug should not be used in combination with or concomitantly with other potential nephrotoxins.

Most patients treated with STZ have experienced severe nausea and vomiting, occasionally requiring discontinuation of drug therapy. Some patients experienced diarrhea. A number of patients have experienced hepatic toxicity, as characterized by elevated liver enzyme (SGOT and LDH) levels and hypoalbuminemia. Hematological toxicity has been rare, most often involving mild decreases in hematocrit values. However, fatal hematological toxicity with substantial reductions in leukocyte and platelet count has been observed.
Mild to moderate abnormalities of glucose tolerance have been noted in some patients treated with STZ. These have generally been reversible, but insulin shock with hypoglycemia has been observed. Two cases of nephrogenic diabetes insipidus following therapy with STZ have been reported. One had spontaneous recovery and the second responded to indomethacin. Spontaneous reports have been received of local inflammation (i.e., edema, erythema, burning, tenderness) following extravasation of the product. In most cases, these events resolved the same day or within a few days.

For the full list of all side effects reported with STZ-5FU based regime, see the respective Summary of Product Characteristics leaflet in the Investigator’s file.

5.3 TREATMENT WITHDRAWAL AND END OF TREATMENT PERIOD

5.3.1 Reasons for treatment discontinuation

Patients will discontinue treatment with STZ-5FU or everolimus if any of the following situations occurs:

- First or second disease progression of pNET respectively.
- Unacceptable toxicity even with optimal supportive care, following investigator's judgement.
- Patient withdraws her/his consent.
- Patient dies.

5.3.2 Discontinuation of treatment due to everolimus toxicity

Treatment with everolimus will be discontinued in the following cases:

- Any grade 4 non haematological toxicity (see Table I)
- Grade 3 thrombocytopenia after everolimus restart (see Table I)
- Grade 4 thrombocytopenia (see Table I)
- Recurrent grade 3 and 4 neutropenia, see Table I
- Grade 4 febrile neutropenia (life-threatening for the patient).
- Life-threatening, grade 4, non-infectious pneumonitis (see Table I).
- Reactivation of hepatitis C (see Table V)
- Any toxicity that can not be reversed with a maximum of 21 days of discontinuation with study treatment (28 days in case of prophylactic treatment with antivirals for HBV) without a justified reason (adverse event that allows restart after recovery, urgent surgery, or toxicity that can be resolved with a restart at a lower dose) as per investigator's judgement.

In the event of discontinuation due to AEs or abnormal laboratory values, the patient will be monitored weekly until the adverse event disappears or decreases to grade 1.

If the patient was receiving prophylactic antiviral treatment, this will be continued until at least 4 weeks following the last administration of study drug.

5.3.3 Discontinuation of treatment due to STZ-5FU toxicity

- Renal impairment: STZ should not be given below 30 ml/min creatinine clearance.

Treatment with STZ-5FU will be discontinued as per recommendations stated on the Summary of Product Characteristics (Technical Sheet) and section 5.2 in this protocol.

6. CONCOMITANT MEDICATION

6.1. TREATMENTS ALLOWED WITH EVEROLIMUS

In case of diarrhoea attributed to everolimus treatment, the patient can be treated with loperamide. When required, other drugs may be used for diarrhoea, such as pancrealipase for the treatment of steatorrhoea due to the use of somatostatin analogues, or cholestyramine for the management of diarrhoea associated with short bowel syndrome.

In case of stomatitis/oral mucositis of grade 1-2 according to the CTCAE version 4.0 due to everolimus (if the examination shows mouth ulcers and not a general inflammation of the mouth) local support care should be given with mouth washes or rinses with salt water (0.9%) several times a day until they subside; avoid those containing alcohol or peroxides, iodine or thyme derivatives, since they can worsen mouth ulcers. For more severe toxicities (grade 2 when the patients experience pain but can maintain adequate intake, or grade 3 when the patients cannot maintain adequate intake), the recommended treatment is topical analgaesics (i.e., local anaesthetics, such as benzocaine, butyl aminiobenzoate, tetracaine hydrochloride, menthol or phenol). The use of highly active topical steroids such as oral triamcinolone paste at 0.1% (Kenalog in Orabase) is permitted. **Use antifungal agents only after fungal infection has been diagnosed.**

In case of hyperlipidaemia the patient condition will be considered before starting treatment, as well as his dietary habits. Blood tests for monitoring hyperlipidaemia should be performed under fasting conditions. Grade 2 hypercholesterolaemia (>300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridaemia (>2.5 x upper limit of normal) should be treated with a statin (HMG-CoA reductase inhibitor) or with an appropriate lipid-lowering drug, in addition to taking care of diet. The patients should be monitored clinically and through serum biochemistry to monitor the development of rhabdomyolysis and other adverse events described in the package leaflet of the HMG-CoA reductase inhibitors.

Note: Concomitant therapy with fibrates and a HMG-CoA reductase inhibitor is associated with an increased risk of uncommon but severe musculoskeletal toxicity, evidenced as rhabdomyolysis, marked increase in the levels of creatine kinase (CPK) and myoglobinuria,

acute renal failure and sometimes death. The risk/benefit of using this therapy should be evaluated individually based on the risk of cardiovascular complications of hyperlipidaemia.

Patients taking concomitant angiotensin-converting enzyme (ACE) inhibitor therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment).

Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

6.2 TREATMENTS NOT ALLOWED WITH EVEROLIMUS

Patients should be warned to avoid bitter oranges, grapefruit and their juices, since they affect the activity of the P450 cytochrome and Pgp; preparations containing St. John's wort should not be used.
Use of live vaccines should be avoided during treatment with everolimus, since it may affect the response to vaccines and vaccination can be less effective. Examples of live vaccines are: intranasal influenza, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a thyphoid vaccines.

Agents that may increase everolimus blood concentrations
Concurrent treatment with strong CYP3A4 inhibitors should be avoided (including but not limited to clarithromycin and telythromycin; see table in next section 6.3). Antifungal agents should not be used without a diagnosis of fungal infection. In particular, systemic antimycotic agents based on imidazole (including but not limited to ketoconazole, fluconazole, itraconazole) should be avoided in all patients due to their strong inhibition of the everolimus metabolism, which involves a higher exposure to everolimus. Therefore, topical antimycotic agents are preferred if a fungal infection is diagnosed. Furthermore, antiviral agents, such as acyclovir, should be avoided, unless a viral infection is diagnosed.

Concomitant treatment with moderate inhibitors of CYP3A4 including but not limited to erythromycin, verapamil, cyclosporin, fluconazole, diltiazem, amprenavir, fosamprenavir, or aprepitant) and PgP inhibitors requires caution. Reduce the everolimus dose if

coadministered with moderate CYP3A4/PgP inhibitors. Everolimus can affect the bioavailability of drugs administered concomitantly and substrates of CYP34A and/or Pgp. Should the patient require moderate CYP3A4/PgP inhibitors (e.g. erythromycin, verapamil or oral cyclosporine etc.), reducing the dose to 5 mg should be considered.

In patients receiving a CYP3A inhibitor, a low starting dose of 5 mg/day of everolimus should be considered, and if it is well tolerated at two weeks, the dose of everolimus may be increased to 10 mg/day.

Agents that may decrease everolimus blood concentrations

Avoid the use of potent CYP3A4 inducers. Concomitant use of potent CYP3A4 or PgP inducers such as rifampicin and ririfabutin, carbamazepine, phenobarbital or phenytoin should be avoided, unless the use of the drug is essential and then, it may be necessary to adjuste the dose. If the patient requires co-administration of potent CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutine, phenobarbital, St. John's wort), a dose increase of everolimus should be considered of up to double the daily dose or a 5 mg increase of current dose.

No dose changes are required in patients receiving a CYP3A substrate. If everolimus is taken with orally administered drugs with a narrow therapeutic index which are CYP3A substrates however, then patients should be monitored accurately for toxicity.

6.3 DRUG INTERACTIONS CLINICALLY SIGNIFICANT: SUBSTRATES OF CYP3A ISOENZYME/PGP.

Investigator will instruct the patient to notify the intake of any new medicine he/she takes after the start with everolimus.

Avoid the use of potent CYP3A4 inducers. If the patient requires co-administration of potent CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutine, phenobarbital, St. John's wort), a dose increase of everolimus should be considered of up to double the daily dose or a 5 mg increase of current dose.

Enzyme induction usually occurs at 7-10 days, so the dose of everolimus should be increased by one dose level 7 days after starting treatment with inducers. If there are no safety concerns

in the next 7 days, before starting treatment with potent CYP3A4 inducers, the dose may be increased up to a maximum of a dose twice a day.

This dose adjustment of everolimus intends to reach an AUC similar to the range observed without inducers. However, no clinical data are available for this dose adjustment in patients receiving potent CYP3A4 inducers. If treatment with potent inducers is removed, the dose of everolimus used before starting treatment with potent CYP3A4/Pgp should be restored.

Summary of inhibitors and inducers of CYP3A4/PgP as of Summary of Product Characteristics January 2014

Table 2 Effects of other active substances on everolimus

ACTIVE SUBSTANCE BY INTERACTION	**RECOMMENDATIONS CONCERNING CO-ADMINISTRATION**
***Potent* CYP3A4/PgP inhibitors**	
Ketoconazole	Concomitant treatment of everolimus and potent inhibitors is not recommended.
Itraconazole, posaconazole, voriconazole	
Telithromycin, clarithromycin, troleandamycin, cobicistat, conivaptan,	
Nefazodone	
Ritonavir, , saquinavir, indinavir, nelfinavir, tripanavir, telaprevir, lopinavir, boceprevir, elvitegravir	
***Moderate* CYP3A4/PgP inhibitors**	
Erythromycin, aprepitant, casopitant, cimetidine, tofisopam	Use caution when co-administration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, dose reduction to 5 mg daily or 2.5 mg daily may be considered. However, there are no clinical data with this dose adjustment. Due to between subject variability the recommended dose adjustments may not be optimal in all individuals, therefore close monitoring of side effects is recommended. If the moderate inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average elimination time for most commonly used moderate inhibitors) before the everolimus dose is returned to the dose used prior to initiation of the co-administration.
Imatinib, Verapamil , Ciclosporin	
Fluconazole, Diltiazem, Dronedarone, Amprenavir, fosamprenavir, atazanavir, darunavir	
Grapefruit juice or other food affecting CYP3A4/PgP Schisandra sphenanthrea	Combination should be avoided.
***Potent* CYP3A4 inducers**	

Rifampicin Carbamazepine, Phenobarbital, Phenytoin, Avasimibe, Mitotane, Rifabutin	Avoid the use of concomitant potent CYP3A4 inducers. If patients require co-administration of a potent CYP3A4 inducer, an everolimus dose increase from 10 mg daily up to 20 mg daily should be considered using 5 mg increments or less applied on Day 4 and 8 following start of the inducer. This dose of everolimus is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment. If treatment with the inducer is discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before the everolimus dose is returned to the dose used prior to initiation of the co-administration.
St John's Wort (Hypericum perforatum)	Preparations containing St John's Wort should not be used during treatment with everolimus
***Moderate* CYP3A4 inducers**	
Bosentan, efavirenz, etravine, genistein, modafinil, nafcilin, ritonavir, [talviradine], thioridazine, tiprnavir	
Weak CYP3A4 inducers	
Amprenavir, aprepitant, amodafinil (R-amodafinil), bexarotene, clobazam, danshen, dexamethasone, Echinacea, garlic (allium sativum), gingko (gingko biloba), glycyrrhizin, methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, [pleconaril], primidone, raltegravir, rufinamide, sorafenib, telaprevir, terbinafine, topiramate, [troglitazone], vinblastine.	

Investigator will instruct the patient to notify the intake of any new medicine he/she takes after the start with <u>everolimus</u>.

All treatments, including non-drug therapies (i.e. herbal therapy and blood transfusions) administered after the patient starts with study treatment will be reported in the CRF in the relevant section.

7. TRIAL DEVELOPMENT

7.1 STUDY PERIODS

The study will have an approximate duration of **6** years, distributed as follows:

- A screening of up to **28 days**.
- Recruitment period estimated in 30 months.
- Treatment period finishes upon second progression unacceptable toxicity or the end of the study.
- Safety follow-up at least 30 days after the intake of the last dose of study treatment**.**

This information should be included in the first survival follow-up visit if any.

- Survival follow-up period: All patients will be followed-up for survival purposes, up to patient's death 140±8 weeks + 30 days, or study end (this is, last visit of last patient included), whatever comes first.

When treatment follow up period of 14 months (60 weeks) is completed for the last patient included there will be enough data to analyze the primary study variable, so the statistical analysis and publication of the first data will take place.

7.2 STUDY ASSESSMENTS

7.2.1 Physical examination and vital signs

Physical examination will include examination of the whole body (general appearance, skin, neck, thyroids, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system).

The following vital signs should be measured: pulse, respiratory rate, blood pressure and height only at the screening visit.

Other relevant vital signs should be measured at the investigator's discretion when an adverse event occurs.

7.2.2 ECOG Performance status

Initially at screening, and then repeatedly at every cycle before intake of first dose, performance status will be recorded according to ECOG scale (Annex I to the protocol).

7.2.3 Chest X-ray and pulmonary function tests

A **chest X-ray** (and/or if the disease is present in the chest, a chest CT) will be performed in all patients. During treatment period, chest X-ray will be performed every 12 weeks; if any lesion occurs, then a chest CT scan will be performed for tumour assessment (a radiography will be no longer necessary).

If non-infectious pneumonitis is suspected, chest X-ray will be repeated as considered appropriate by the investigator.

Pulmonary function tests (spirometry, DLCO and oxygen saturation at rest in a ventilated room (room air O_2 saturation at rest) will be performed **if clinically necessary** in case of evidence of non-infectious pneumonitis.

If non-infectious pneumonitis is diagnosed, pneumologist consultation should be considered. When necessary to ensure patient care, a bronchoscopy with biopsy and/or bronchoalveolar lavage (BAL) will be performed.

Information on Pulmonary function tests should be collected if clinically indicated when an AE or SAE occurs.

7.2.4 Electrocardiogram (ECG)

During the screening period, a 12-lead ECG will be performed. Records should be dated and signed by the investigator (or designee) and kept with the source documents of patient.

An ECG can be repeated at the investigator's discretion at any time of the study, as clinically indicated; clinically significant findings will be noted in the Adverse Event section of the CRF.

7.2.5 Radiological tumor assessment

Tumour lesions should be measured following RECIST criteria **version 1.0** at each site. Main study endpoint will be based on local assessment (section 7.2.5.1).

ENETS Score will be assessed retrospectively by an ENETS Central Radiological Commission in Paris (section 7.2.5.2). A copy of the radiological assessments must be sent/provided by the site to the ENETS Central Radiological Commission for a retrospective centralized assessment (see 7.2.5.2) every 3 months or as soon as the last patient at site has been discontinued or completed the study. Assessments will be sent electronically.

7.2.5.1 Local assessment following RECIST criteria version 1.0

Tumour lesions should be measured following RECIST criteria **version 1.0** before the start of each treatment and every 12 weeks, procedures

All assessments performed during the study (at baseline and **every 12 weeks**) should be done using the **same method and the same technique**.

Assessments and measurements should be performed by the **same radiologist** or physician throughout the study. Therefore, each site must designate a radiologist or other medical staff responsible for the interpretation of the radiographs and triphasic CT scans or multiple-phase MRI.

All patients discontinuing the treatment due to disease progression, should have a documented diagnosis. Date of progression must be recorded on the CRF.

7.2.5.2 Retrospective centralised assessment of ENETS Score

An **ENETS Central Radiological Commission** will be set up for a centralized evaluation of CTs. The radiological commission will assess second progression free survival according to the four radiology criteria for response evaluation (RECIST versions 1.0 and 1.1, and Composite Scores according to RECIST 1.0 and to RECIST 1.1) here described:

1. **RECIST version 1.0.** See protocol Annex III.

2. **RECIST version 1.1.** See protocol Annex III.

3&4. ENETS Score

Tumour response following Composite ENETS Score will be assessed following the modified criteria of ENETS (based on Haesun Choi criteria), as defined on the next table:

Response	Definition
CR*	- Disappearance of all lesions - No new lesions
PR*	- A decrease in **size of 30 %** or a decrease in tumour **density (HU) **** on CT - No new lesions - No obvious progression of non-measurable disease
SD*	- Does not meet the criteria for CR, PR, or PD
PD	- An increase in tumour **size of 20%** and does not meet criteria of PR by tumour density (HU) on CT - New lesions

* Without symptomatic deterioration of general condition according to WHO scale or ECOG (modified ENETS criteria).

** A percentage of density decrease will be defined for the analysis, based on the results of the on-going validation studies for the ENETS Score. The results of validation studies will be available for the Statistical Analysis Plan of SEQTOR study and for the central and retrospective analysis of images.

Abbreviations: CR, complete response; PR, partial response; HU, Hounsfield Unit; CT, computed tomography; SD, stable disease; PD, progression of disease; RECIST, Response Evaluation Criteria in Solid Tumours.

3.1 ENETS Score following RECIST criteria version 1.0

Definitions

Baseline lesions: All patients must have at least one measurable lesion by triphasic CT scan performed at three specific time points: before the contrast, during the arterial phase and in the venous phase. If contrast is contraindicated in the patient, it is accepted a multiple-phase MRI instead.

Measurable lesions can be accurately measured in at least the dimension containing the longest diameter; if the diameter is ≥ 20 mm the measurement should be performed by conventional techniques and in case the diameter is ≥ 10 mm assessment should be performed by a triphasic CT scan (with a minimum lesion size, not below two times the layer thickness).

Selection of target lesions:

Target lesions should be selected based on their size (lesions with the longest diameter) and the possibility that precise repeated measurements can be performed. All measurable lesions will be identified as target lesions up to 5 lesions per organ and 10 lesions in total, representative of all organs involved. A baseline measurement of all target lesions will be available.

The sum of the longest diameter of all lesions will be calculated at baseline. The sum of the longest diameter at baseline will be used as reference to define objective tumour response.

Response evaluation:

Criteria defined in the schema included in section 3 and describing assessment of Composite Score.

The sum of longest diameters of target lesions measured as defined in **RECIST 1.0**.

3.2. ENETS Score following RECIST criteria version 1.1

Definitions:

Baseline: the closer time point before the beginning of the treatment

Nadir: the time point of the lowest size of the lesion since treatment started, progression is compared to this size.

Selection of target lesions:

Five target lesions (2 per organ) (if present) should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements.
It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. Measurement is performed at the portal phase of injection, the more clearly delineated and easy to locate in the liver, on the slice where the lesion is the biggest.

Non target lesions:
All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout the follow-up. It is possible to record multiple non target lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

Response evaluation:
Criteria defined in the schema included in section 3 and describing assessment of Composite Score. The sum of longest diameters of target lesions measured as defined on **RECIST 1.1**.

7.2.6 Laboratory

7.2.6.1 During everolimus treatment

Throughout treatment period with everolimus, several laboratory measurements should be carried out for the evaluation of patient safety as per clinical protocol at site; recomendations are detailed below.

All blood samples will be obtained before the start of the next cycle treatment and in fasting conditions.

Haematology

Haematology measurements should be performed and results available at each visit before start of next cycle study treatment. The haematological analysis should include:

- Haemoglobin

- Haematocrit
- Platelets
- Red Blood Cell Count
- Total, absolute and differential white blood cell count, including neutrophils, lymphocytes, monocytes, eosinophils, and basophils. The laboratory should calculate the absolute neutrophil count (ANC).

Coagulation

The following parameter should be measured and its results should be available at the **screening period** or before second treatment as applicable; during the study it is recommended to have it determined **every 12 weeks**:

Prothrombin time (it should be noted as international normalised ratio of prothrombin or INR).

Biochemistry and hormones

At the **day 1 of every cycle**, the following parameters should be measured and the results available:

- Sodium, potassium, ion chloride, bicarbonate
- Creatinine, albumin, total protein
- AST (GOT) and ALT (GPT) in serum, total bilirubin, alkaline phosphatase
- Uric acid, BUN
- Calcium, magnesium, phosphate
- Fasting glucose
- Total LDH

Cases of hyperglycaemia have been reported. It is recommended to measure fasting glucose serum levels before starting treatment with everolimus and then monitor them regularly.

At **screening period** and every **12 weeks** all along treatment period, the following should be measured and results available:

- Total Cholesterol
- Triglycerides
- LDL and HDL

At **screening period, every 24 weeks** all along treatment period, and whenever the investigator considers appropriate, the following should be measured:

- Vitamin B12.

Urinalysis

A standard urinalysis (pH, proteins, glucose, blood, ketones and WBC) should be performed during the screening period. During routine clinical procedures, Dipstick is used; then if abnormal, quantitative analysis should be performed.

A measurement with dipstick should be performed routinely on Day 1 of every cycle.

The pregnancy test can be performed in urine (see next section).

Viremia

Those patients considered, at investigator's discretion, as pertaining to the risk group of hepatitis B and/or C (Section 6.2.1.3: tables III y IV; section 6.2.1.4: table V), an analysis of viremia and serological markers should be performed at screening and throughout the study, following the criteria set out in Sections 6.2.1.3 and 6.2.1.4.

Biomarkers

Circulating Cromogranin A (CgA) levels will be determined at **baseline** (time 0) and also at **4 weeks**. Blood samples should be sent to the Institut Gustave-Roussy, Rue Camille Desmoulins 39, 94805 Villejuif, France to be centrally analyzed.

Participation on Ancillary trials (included in protocol amendment 2) is optional for sites and patients.

7.2.6.2 During STZ-5FU treatment

Throughout treatment period, several laboratory measurements should be carried out for the evaluation of patient safety, as detailed below. All blood samples should be obtained in fasting conditions. Hematology and Biochemistry standard analysis as per clinical protocol at site should be followed.

At **baseline**, all patients will have an **Haematology and Biochemistry standard analysis** as per clinical protocol at site.

At **every cycle** during STZ-5FU treatment**, all patients should have at least:**

Haematology

At **every cycle** a routine haematology should be performed and results available (before the start of next cycle):

- Haemoglobin
- Haematocrit
- Platelets
- Red Blood Cell Count
- Total, absolute and differential red blood cell count, including neutrophils, lymphocytes, monocytes, eosinophils, and basophils. The laboratory will calculate the absolute neutrophil count (ANC).

Biochemistry and hormones

At the day 1 of every cycle, the following standard determinations should be done and results available:

- Sodium, potassium, ion chloride, bicarbonate
- Creatinine, clearance of albumin, total protein
- AST (GOT) and ALT (GPT) in serum, total bilirubin, alkaline phosphatase
- Uuric acid, BUN
- Calcium, magnesium, phosphate
- Fasting glucose

Urinalysis

A standard urinalysis (pH, proteins, glucose, blood, ketones and WBC) should be performed during the screening period. During routine clinical procedures, Dipstick is used; then if abnormal, quantitative analysis should be performed.

At least dipstick measurement should be performed routinely on Day 1 of every cycle.

The pregnancy test can be performed in urine (see next section).

Biomarkers

Circulating Cromogranin A (CgA) levels should be determined **at baseline** (time 0) and also at **4 weeks.**

Blood samples should be sent to the Institut Gustave-Roussy, Rue Camille Desmoulins 39, 94805 Villejuif, France to be analyzed.

7.2.7 Pregnancy test. Male contraception.

Pregnancy test will be performed at screening period. In case of an undesired and unexpected pregnancy, it will be notified immediately as a Serious Adverse Event.

All women with child-bearing potential must have a negative pregnancy test within **14 days prior** to the first dose of everolimus/chemotherapy and/or a negative **urine** test **48 hours before the first dose** of treatment. A pregnancy test in urine will be performed monthly (if necessary) and at the end of treatment visit (mandatory).

It is recommended that postmenopausal status is considered after **at least 12 months** of amenorrhoea or FSH levels >40 mIU/ml in order to consider women as “non-procreators”; it is recommended a 6 weeks elapse since a surgical bilateral oophorectomy, with or without hysterectomy.

Contraception will be acceptable for the study when in the following cases: surgical sterilisation (for instance, bilateral tubal ligation, vasectomy), hormonal contraception (implantable, patch, oral) and double barrier methods (any combination of: intrauterine device (IUD), intrauterine system (IUS), male condom or female condom with spermicide gel, diaphragm, contraceptive sponge, cervical capsule). **Acceptable and efficient contraception must be used throughout the study and up to eight weeks (as per clinical sheet) following the last dose of everolimus, and up to 6 months (at least in France as per clinical protocol) after the last dose of chemotherapy.**

Male fertility and Male contraception

During the course of a clinical trial, sexually active males must use a condom during intercourse while taking the drug and should not father a child in this period and for up to 8 weeks after stopping treatment. A condom is required to be used also by vasectomised men in order to prevent delivery of the drug via seminal fluid.

Female partners of male patients must also be advised to use one of the following contraception methods: Use of (1) oral, injected, implanted or other hormonal methods of contraception, or (2) intrauterine device (IUD) or intrauterine system (IUS), or (3) prior male/female sterilization.

In order to preserve patient's safety, any pregnancy of a patient receiving study drug must be notified to the Pharmacovigilance Unit within 24 hours after it is known. Any pregnancy must be monitored to record the outcome, including abortion or miscarriage, details of birth and presence or absence of birth defects, congenital anomalies or maternal or newborn complications. Pregnancies must be recorded on the pregnancy form and the site investigator must notify it to the clinical safety and epidemiology department. The follow-up of pregnancy must be recorded in the same form and must include the possible causal relationship of any outcome with the study drug. Any SAE occurring during pregnancy must be reported in the SAE form.

Furthermore, any pregnancy of a partner from a patient taking the study drug should be communicated to the investigator/Pharmacology Unit and its outcome collected. In this situation, the mother should give her consent for the record of information about the pregnancy outcome.

7.2.8 Quality of Life assessments

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. Presently QLQ-C30 Version 3.0 is the most recent version and it is supplemented by disease specific modules for NET, the EORTC QLQ GINET21[20, 21,22]. Both the core questionnaire and its specific module will be used for the assessments of quality of life of patients under both treatments.

EORTC QLQ-C30 and the specific module for NET EORTC QLQ GINET21 Quality of Life Questionnaire will be administrated before the start of each treatment period, upon progression or unacceptable toxicity, or at the end of second treatment period if second period event (progression) is not reached.

7.2.9 Assessment of health resources used during study treatment

The following resources used for the care of all patients on each treatment will be recorded on the CRF at every visit:

- treatments: drugs, total dose and presentation.
- outpatient visits: number of visits including but not limited to the specialist, generalist, and emergency.
- hospitalizations: number of days
- AE related, diagnostic tests and treatment procedures performed.

To assess resource utilization and cost effectiveness of treatments during the study, information will be used from the clinical parts of the CRF (study treatments, concomitant medication, SAE treatment), as well as from the specific resource utilization pages.

7.2.10 Translational research

Translational research will be done in the next future as a sub-study of this. This translational research will include the detection of a panel of predictive markers. Predictive markers will be detected on paraffin embedded tumour blocks. The following panel of analysis has been planned:

(i) a selected set of mutational analysis using an amplicon next-generation-approach, based on the data published.

(ii) a genome expression profiling.

For these purposes, both paraffin embedded tumour block and blood samples should be available for each patient.

Blood/serum samples may be stored for future analysis not defined here.

The Patient must have accepted to donate samples for translational analysis at his/her enrolment; the Pathologist at each site should agree to deliver paraffin embedded tumour block from included patients including an anonymous copy of pathology report. All samples should be return back to hospital at the end of the analysis if so required.

For the validation of predictive markers by Immunochemistry[23, 24], tumour blocks will be sent to Verona, Italy, to the following address:

Professor Aldo Scarpa
Centre for Applied Research on Cancer
University of Verona - Policlinico G.B. Rossi
[redacted]

Blood/serum samples will be sent to London, to the following address:

Dr Tim Meyer
UCL Cancer Institute and Royal Free Hospital
Neuroendocrine Tumour Unit
Royal Free Hospital
[redacted]

Shipment material will be provided to the sites. The collection of samples will be coordinated by Kantar Health.

The protocol for both analyses will be developed as a sub-study of this clinical-trial and added as an Annex to the protocol.

7.3 ASSESSMENTS' SCHEDULE

The study is scheduled as follows:

- **Baseline visit (screening):** It will be better performed on day -28 to -0 before the start of first study treatment. Some procedures (laboratory tests) will be performed within 14 days before intake of first treatment dose.

Baseline visit includes:

- Tumour block will be separated for Translational research in Italy.
- Blood samples will be taken for future research, as described above in this protocol.
- CgA levels will be measured at baseline
- The CT scans will be used for the local assessment of tumour response and kept at

site; a copy will be sent electronically/on CD to the Radiology Service of Neuroendocrine Tumor (NET) Center, Hôpital Beaujon, Clichy, France, for the centralised retrospective assessment of ENETS Score.

- **Treatment visits:** A visit will be performed on the first day of every cycle until disease progression.
  -
  - CgA levels will be measured at 4 weeks of tretment.
  - Tumour evaluation following RECIST criteria 1.0 will be done every 12 weeks during both treatments. Radiological assessment can be done before the scheduled 12 weeks if disease progression is suspected. On those cases, the next CT scans should be done at 12 weeks of last assessment.

- **30 days Follow-up visit:** A follow-up visit will be performed (30 days after the last dose of last patient). This follow-up can be performed by phone or during a visit.
- **Survival follow-up after the end of treatment:** As per site clinical protocol, every 3 months until the patient dies or up to the end of the study (last patient out), whatever takes place first; survival information will be collected. This follow-up can be performed by phone or during a visit.

All potential patients screened for its enrolment in the study will be recorded in the CRF, including screening failures specifying the reason for its exclusion from the study. ***Screening failures*** are considered to be patients completing the information and informed consent procedures and finally not receiving everolimus after performing the tests for the evaluation of their eligibility because they do not meet some of the study screening criteria. This will be noted in the relevant CRF section.

7.3.1 Screening period/baseline visit: Baseline information and assessments

☞ <u>The following information will be collected at baseline:</u>

- EORTC QLQ-C30 and the specific module for NET EORTC QLQ GINET21 should be administrated **at randomization.**
- **A blood sample** should be taken prior to commencing long therapy with everolimus or chemotherapy, for future research and measurement of CgA levels at local or central

laboratory (Gustave Roussy, Villejuif, France) depending on funds available.

- **Tumour block** will be collected and stored properly for the study.
- Demographic data of the patient (age, sex, race, height and weight as allowed per local laws).
- Baseline characteristics and relevant clinical history of the study disease (history of cancer, diagnosis and extension of cancer, and anticancer therapies received before the patient enters the study).
- ECOG Performance status.
- Complete physical examination including an exam of the whole body (general appearance, skin, neck, thyroids, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system).
- Weight and height. Height will only be recorded at baseline.
- Vital signs: Pulse, respiratory rate and blood pressure, temperature. Blood pressure, pulse and respiratory rate will be measured for at least 3 minutes with the patient seated. These measurements will only be performed at the screening visit, unless the clinical condition of the patient requires so (for instance, in case of an adverse event).

☞ <u>The following criteria will be verified during the screening period:</u>

- Disease evaluation (progression) should be performed at any time within 12 months prior to the visit by the RECIST criteria, version 1.0.
- **Detection of hepatitis B:**

  An analysis of viremia and serological markers for hepatitis B (HBV-DNA, HbsAg, anti-HbsAb and anti-HbcAb) will be performed in all patients meeting any of the following risk factors:

  - confirmed or suspected infection by hepatitis B virus in the past;
  - blood transfusion receptors before 1990;
  - users of intravenous abuse drugs currently or in the past;
  - subject to dialysis currently or in the past;
  - regularly in contact with somebody infected by hepatitis B virus;
  - with high risk due to sexual activity currently or in the past;
  - with piercings or tattoos;
  - mother with presence of hepatitis B.
  - all patients with a history that indicates infection by hepatitis B virus, such as dark urine, jaundice or pain in the right hypochondrium**.**

See Tables III and IV (section 5.1.3) for the administration of prophylactic treatment between 1 and 2 weeks before the start of the study treatment.

- **Detection of hepatitis C** (under investigator's judgement)

  Patients with a known history of infection by HCV and those with detectable HCV-RNA will not be eligible for the study (section 5.1.4, Table V).

  It is recommended an RNA analysis by quantitative PCR in patients meeting any of the following risk factors:

  - confirmed or suspected infection by hepatitis C virus in the past (including patients treated with "intent-to-cure" interferon).
  - blood transfusion receptors before 1990.
  - users of intravenous abuse drugs currently or in the past.
  - subject to dialysis currently or in the past.
  - regularly in contact with somebody infected by the hepatitis C virus.
  - with high risk sexual activity currently or in the past.
  - with piercings or tattoos.

☞ <u>In the 28 days prior to the start with study drugs the following tests will be performed:</u>

- Chest X-ray and/or chest CT in case of chest disease.
- ECG
- Haematology and biochemistry tests; patients on everolimus will include hormonal, coagulation and lipid profile tests before treatment start (see Section 7.2.6).
- It is recommended to monitor <u>fasting glucose serum levels</u> before starting treatment with everolimus as well as regular monitoring. Optimum control of blood sugar levels should be obtained before starting administration with everolimus.
- Standard urinalysis (pH, proteins, glucose, blood, ketones, and WBC).
- Concomitant medication (including non-drug therapies) taken within the last 30 days of enrollment (see concomitant and allowed treatments sections in the protocol).

☞ <u>If no recent test and evaluation is available within 28 days before the start of treatment, the following assessments</u> will be done at baseline:

- Abdominal and pelvic three-phase CT scan or multiple-phase MRI.
- ***Baseline evaluation of tumour and its metastasis***, following RECIST criteria 1.0 (Section 7.2.5.1 Radiological tests for the diagnosis of the disease). All patients should

have at least one measurable lesion by three-phase CT scan or multiple-phase MRI.

☞ In the 14 days prior to the first dose of study drug women with child-bearing potential:
Should have a negative result in a pregnancy test or ***a pregnancy test in* urine *48 hours before*** the first dose of the study drug at first and second treatment.

☞ Within 7 days after randomization date, the patient should start with study treatment allocated by randomization.

7.3.2 Treatment visits

☞ The following procedures will be completed during treatment period:

- EORTC QLQ-C30 and the specific module for NET EORTC QLQ GINET21 Quality of Life Questionnaire will be administered **at randomization**, **at disease progression**, and **at the end of treatment**.
- **A blood sample** should be taken for the determination of CgA levels at **4 weeks after the start** of study treatment.
- A pregnancy test in urine will be performed monthly, when considered necessary under investigator's judgement and at the end of treatment (mandatory).
- In case of toxicity related to everolimus, the guidelines for dose adjustment specified in Tables I and II (protocol, section 5) will be applied.
- In case of toxicity related to STZ-5FU, the recommendations specified in the Technical Sheet of products will be applied.

☞ The following procedures will be completed at every cycle before the intake of first dose:

- Physical examination.
- Measurement of vital signs.
- Performance status according to ECOG scale.
- Haematology and biochemistry as per Section 7.2.6 Laboratory measurements. Results of laboratory test done before start of cycle x treatment, will be recorde in cycle x-1.
- Urinalysis (Section 7.2.6).
- Changes on concomitant medication (including non-drug therapies).
- **Adverse events** occurring during the screening period.

- ***Health resources*** incurred on affecting direct costs, this is: treatments (drugs, doses and presentation), visits outside the study (number of visits to the hospital: specialist, generalist, and emergency), SAE treatment (drugs given and tests performed) and hospitalizations (number of nihgts, number and kind of diagnostic tests performed).

In those patients with hepatitis B or C at baseline (screening), the results of HBV-DNA and HCV-RNA by PCR should be available and prophylactic treatment should have been given for hepatitis B before the start of treatment with everolimus if applicable (section 5.1.3 and 5.1.4, Table III, IV, and V).

☞ First visit at the start of second treatment will also include:

- Administration of EORTC QLQ-C30 and the specific module for NET EORTC QLQ-C30 and QLQ GINET21 Quality of Life Questionnaire (whenever possible, before the visit; strongly recommended).
- **Health resources** incurred on as specified on section 7.2.9.
- ***A blood sample*** for the determination of CgA levels.

☞ The following tests will be performed during treatment with everolimus:

Every 12 weeks (3 cycles):

- HCV reactivation should be monitored in patients with known history of infection by HCV, despite having negative results in the viremia analysis at baseline (also in patients receiving treatment and considered as "cured").
- **All** the tests specified for day 1 of every cycle.
- Haematology and biochemistry including:
  - Serum lipid profile (cholesterol, triglycerides, and LDL and HDL)
  - Coagulation tests (PT/INR).
  - Monitoring of glucose levels is recommended
- An analysis of HBV-DNA will be performed in patients receiving antiviral prophylactic treatment or with antibodies against HBV, according to Table III in section 5.1.3. Patients with history of previous HCV infection, even if they received treatment or considered as cured, should undergo the analysis of HCV-RNA by PCR according to section 5.1.4.

Every 24 weeks (6 cycles):

- Haematology and biochemistry should also include:
  - Vitamin B_{12}

☞ <u>The following tests should be performed during treatment with STZ-5FU</u>

- Standard Haematology
- Recommended Biochemistry

☞ <u>The following will be performed for tumour evaluation (every 12 weeks):</u>

- Chest X-ray and, if applicable, pulmonary capacity test.
- Triphasic CT scan or multiple-phase MRI.
- Response assessment following RECIST criteria version 1.0.

7.3.3 Visit at the end of treatment

The information about the end of first treatment (chemotherapy or everolimus) can be collected <u>on the first visit of the second treatment</u> (everolimus or chemotherapy), see section 7.3.2.

☞ <u>Visit at the end of second treatment</u>:

- Documented second disease progression by RECIST criteria 1.0 will be recorded at this visit.
- Adverse Events since last visit.
- If the patient is receiving prophylactic treatment for HBV, this will be continued for at least 4 weeks after the last dose of everolimus is taken.
- EORTC QLQ-C30 and the specific module for NET EORTC QLQ-C30 and QLQ GINET21 Quality of Life Questionnaire (whenever possible, (previously to the assessment; it is strongly recommended).
- Physical examination.
- Measurement of vital signs.
- Haematology and biochemistry (Section 7.2.6 Laboratory measurements).
- Urinalysis (Section 7.2.6).
- Changes on concomitant medication (including non-drug therapies). Anticancer treatment given after second disease progression will be recorded in the CRF in the corresponding Concomitant Treatments section.
- Pregnancy test.

7.3.4 Follow-up visits

30 days follow-up (visit at the end of treatment)

A follow-up should be performed 30 days after the last dose intake. This follow-up can be performed by phone or face to face (this is, included in the first survival follow-up visit).

The following information will be collected in the CRF:

- Anticancer treatment given after second disease progression will be recorded in the CRF in the corresponding Concomitant Treatments section.
- AE since last visit.
- Life status.
- Last available date

When applicable: main cause of death (disease progression, toxicity, chronic disease not related to an AE or to progression, other cause not previously defined).

Survival follow-up after the end of treatment

Every 3 months, the patient will be treated as per usual clinical practice and the following information will be collected in the CRF:

- Anticancer treatments received after discontinuation of study treatment.
- Life status.
- Last date available on their condition.
- When applicable: main cause of death (disease progression, toxicity, chronic disease not related to an AE or to progression, other cause not previously defined).

This information can be collected at a visit or by phone.

Schema of study assessments

The table below shows a list with the assessments to be completed during the study, specifying the visits to be completed (ticked with an X in the appropriate box). All assessment's should be part of the source documents of the study filed in medical records at site.

Tests, procedures and visits should be completed as close as possible to study visits.

Assessment	Screening	FIRST TREATMENT				SECOND TREATMENT				FOLLOW-UP*	
		Cycle 1	Cycle 2	Cycle x	End of Course 1	Cycle 1	Cycle 2	Cycle 3	End of Course 2	30 days safety follow-up	Every 3 months
Visit Number	1	2	3	4	**n-1**	**n**[#]	n+1	n+2	m		
Time point (days)	-28 - 0[a]	1	1	1		n-1 plus (approximately 4weeks)				m+30d	
Demography and Medical History	X									Anticancer Treatment received after discontinuation of study treatment . AE since last visit; Life Status; Last available Date; if applicable: main cause of death	Anticancer Treatment received after discontinuation of study treatment; Life Status; Last available date; if applicable: main cause of death
Vital signs (height only at baseline)	X	X	X	X	X	(X)	X	X	X		
Physical examination [b]	X	X	X	X	X	(X)	X	X	X		
ECOG Performance status	X	X	X	X	X	(X)	X	X	X		
ECG [c]	X				X						
Haematology [d]	X	X(if done >14 days ago)	X	X	X	(X)	X	X	X		
Coagulation tests (PT/INR)	X	Every 12 weeks			X	(X)	Every 12 weeks		X		
Serum biochemistry [e]	X	X***((if done >14 days ago)	X***	X***	X***	(X***)	X***	X***	X***		
Serum lipid profile [f]	X	Every 12 weeks when on everolimus			X	(X)	Every 12 weeks when on everolimus		X		
Vitamin B12 test	X	Every 24 weeks when on everolimus			X	(X)	Every 24 weeks when on everolimus		X		
Biomarkers: CgA levels	X	At 4 weeks			X	(X)	At 4 weeks				
Urinalysis [g]	X	X	X	X	X[f]	(X[f])	X	X	X		
Serum or urine pregnancy test [h]	X	X	X	X		(X)	X	X	X		
Concomitant Medication	X	Continuous									
Adverse Events	X	Continuous									
**Radiological tumour assessment[o]	X	Every 12 weeks			X		Every 12 weeks				
ENETS Score CT copy	X	Every 12 weeks				(X)	Every 12 weeks				
HE Resources	x	x	x	x		(X)	X	x	x		
QoL questionnaire	X					(X)			X		
Chest X-ray, pulmonary function test [p]	X	Every 12 weeks									
Viremia: HBsAg, anti-HBsAb, anti-HBcAb [q]	X										
Viremia: HBV-DNA, HCV-RNA by PCR [r]	X	X	X	X		X	X	X	X		
Collection of serum sample [s]	X										
Paraffin embedded tumour block [s]	X										

Assessment between brackets should not be repeated whenever timeframe between visits *n-1* and *n* does not exceed the 4 weeks.
* Follow-up visits will include survival information (see section before in this protocol)** Tumour assessment by both, RR and ENETS Score is scheduled at 12 weeks unless progression is suspected.*** Biochemistry will be performed at baseline, and during study treatment.

EXPLANATORY NOTES ON THE ABOVE CHART

[a] The screening assessments include: administration of informed consent, demographics, inclusion/exclusion criteria, relevant clinical history/present medical condition, confirmation of advanced NET, diagnosis and extension of cancer (disease metastasis sites), previous anticancer treatment, radiation therapy and/or surgery, complete physical examination, and vital signs. QoL questionnaire and blood sample for future research and determination of CgA levels.

[b] Significant findings during the physical examination will be recorded in the adverse event pages, as appropriate.

[c] The baseline ECG may be repeated at the investigator's discretion if signs and symptoms of cardiotoxicity occur. Significant findings will be recorded in the corresponding adverse event pages.

[d] Haematology should include: haemoglobin, haematocrit, platelets, WBC, total and differential WBC.

[e] Serum biochemistry measurement should include determination of: sodium, potassium, ion chloride, bicarbonate, creatinine, albumin, total protein, AST (SGOT), ALT (SGPT), total bilirubin, alkaline phosphatase, uric acid, BUN, calcium, magnesium, phosphate, total LDH and fasting glucose when appropriate (see protocol relevant section).

[f] Serum lipid profile will be repeated every 12 weeks when patient on everolimus treatment and will include total cholesterol, triglycerides, LDL, and HDL determinations

[g] Standard urinalysis will include: pH, proteins, glucose, blood, ketones and WBC should be performed during the screening. In the next visits a dipstick should be used for routine assessment. In the event of any relevant anomaly, a quantitative assessment will be performed..

[h] All women with child-bearing potential will have a negative serum pregnancy test in the 14 days prior to the first dose of study drug, and an urine test 48 hours before the first administration of study treatment. Whenever necessary throughout the study, pregnancy test may be performed in urine.

[o] The scanner (triphasic CT) will be performed using the same technique at baseline and at any assessment during the study.

[P] At screening and every 12 weeks, an X-ray (or chest CT) will be performed. A pulmonary function test and bronchoscopy with biopsy (and BAL) will be performed if considered clinically necessary.

[q] Viremia: Presence of risk factors and history of hepatitis B or C will be determined in all patients. It is recommended a prophylactic treatment for those patients with positive results in the HBV-DNA or HBsAg tests 1 to 2 weeks before starting with everolimus. Antiviral prophylactic treatment will continue to be administered throughout the study and for at least 4 weeks after the last dose of everolimus. Patients with risk factors for infection by hepatitis C virus should undergo an analysis of HCV-RNA by PCR.

[r] Viremia: An analysis of HBV-DNA will be performed in patientsreceiving antiviral prophylactic treatment or with antibodies against HBV, according to Table III in section 5.1.3 Patients with history of previous HCV infection, even if they received treatment or considered as cured, should undergo the analysis of HCV-RNA by PCR according to section 5.1.4.

[s] Paraffin blocks of tumour (primary or methastasis) will be sent to Centre for Applied Research on Cancer (arc-net) in Italy; blood samples will be sent to Free Hospital in London. Those biological samples will be used for future translational sub-study purposes on prediction factors.

7.4 SAFETY ASSESSMENTS

Safety assessments will include:

- adverse events recording and monitoring (serious as well as non-serious adverse events).
- regular monitoring of laboratory determinations
- regular monitoring of vital signs and physical exam

Any degree of clinical adverse event will be evaluated as compared to normal reference values and according to CTCAE version 4.0.

Dose reduction will be performed according to recommendations followed in former studies of everolimus in pNET/recommended on the Investigator's Brochure.

7.4.1 Adverse events

Those patients included in the study who experience disease progression will be treated following the standard clinical protocols at site.

Bi-annual cumulative listings of all serious and non-serious events will be generated throughout the study.

Definitions

An **adverse event** (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the investigational medicinal product.

An **adverse reaction (AR)**

A response to a medicinal product which is noxious and unintended.

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

An **unexpected adverse reaction** is any adverse reaction, the nature or severity of which is not consistent with the applicable product information (for instance, investigator's brochure for an unauthorised investigational product or summary of product characteristics when authorised).

A **Serious Adverse Event** (SAE) is defined as any undesirable experience occurring to a patient whether or not considered related to the protocol treatment. A SAE considered to be related to the protocol treatment, is defined as a Serious Adverse Reaction.

Any AE or AR ocurred at any dose should be classified as an SAE if any of the following occurs:

- results in death (this is an outcome, not an event),
- is life-threatening (i.e., an event where the subject was at risk of death at the time of the event; it does not refer to an event which might have caused death had it were more severe).
- requires hospitalization or extension of existing inpatients hospitalization,
- results in persistent or significant disability or incapacity,
- is a congenital abnormality or birth defect,
- results in any other medically important condition (i.e., important adverse reactions that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardize the patient or require an intervention to prevent any of the other outcomes listed above).

7.4.2 Adverse event reporting

Monitoring and safety of the investigational treatment will be performed in accordance with the Detailed Guidance 2011/C 172/01 based on Article 18 of Directive 2001/20/EC of

the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm; "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use").

Reporting criteria

Any SAE occurring from the time the patient signs Informed Consent for the study until 30 days after the intake of the last dose of treatment must be reported to the Pharmacovigilance Unit within 24 hours.

Death for any cause different from disease progression must be reported within 24 hours.

Any death considered to be related to study drugs, regardless of the time since treatment was interrupted/finished must be reported immediately.

An experience will not be considered as an SAEs for reporting purposes if any of the following occurs:

- signs and symptoms of study disease, unless they are more severe than expected for the patient's condition.
- disease progression, unless more severe than expected for patient's condition.
- hospitalisation planned before patient gives consent to participate in the study not lasting more than expected.

SAE reporting procedures

SAEs will be reported to the Pharmacovigilance (PV) Unit of Kanthar-Health, for the follow-up, documentation and reporting of the event:

Pharmacovigilance Department
Kantar Health
[redacted]
[redacted]

Initial report

The SAE form will be sent automatically via the EDC system (eCRF) or by fax within **24 hours** after the event is first known.

The investigator will document any SAE in the EDC system within **24 hours** after the event is first known. After completion of the SAE form, the investigator will send a pdf of the report via the EDC system (eCRF) to Kantar Health. In case of technical issues, the SAE can be documented on the paper SAE form included in the investigator's file and faxed to Kantar Health.

This first report should contain at least the following information:

- Name of the SAE
- No. of patient in the study
- Date of event onset
- Severity
- Resolution/Outcome

Severity of the event: The greatest severity shown by the patient throughout the event will be reported. The severity of the AE will be assessed according to version 4.0 of the CTCAE (Common Terminology Criteria for Adverse Events): http://ctep.cancer.gov/reporting/ctc.html.

AEs for which the CTCAE does not define a severity rating scale will be assessed as follows: Grade 1= mild, Grade 2= moderate, Grade 3= severe, Grade 4= life-threatening, and Grade 5 = death.

Causal relationship: The investigator must evaluate the relationship between each investigational product and the onset of each SAE. The investigator will use clinical criteria to establish the relationship; this information will be recorded on the relevant CRF section. The principal investigator and the co-investigator will eventually decide whether or not these events are related to the study treatment (i.e., unrelated, probably related and non-evaluable) and the decision will be recorded in the serious adverse event form.

The following definitions will be used for the assessment of causal relationship:

Relationship with study drug	Description
UNRELATED	There is no evidence of a causal relationship with study treatment.
PROBABLY RELATED	There is (some) evidence suggesting a causal relationship with study treatment and the influence of other factors is improbable or nonexistent.
NON-EVALUABLE	There is insufficient or incomplete evidence to establish a clinical criterion of the causal relationship with study treatment.

The

The reference document for streptozotocin-5FU chemotherapy and everolimus is the Summary of product characteristics (http://www.emea.eu.int/htms/human/epar/epar.htm#) or Technical Sheet.

Reporting to Health Authorities

The Pharmacovigilance Unit delegated on by GETNE (Kanthar Health), will notify to the local Health Authorities, including the European Medicine Agency (EMA) via Eudravigilance, of all suspected unexpected serious adverse reaction (SUSARs), occurring during the study (expedite reporting); Kantar Health unit will also be responsible for the generation of the annual safety report of the study.

Follow-up reporting

Follow-up reports of on going SAEs should be made **every 15 days** by the reporting site, until its resolution or stabilisation or when there is an alternative explanation for the event, using the adverse event form of the eCRF or study forms available in the Investigator's File.

7.4.3 Pregnancies

Each pregnancy occurring in a patient taking study drug should be notified to the Pharmacovigilance Unit within 24 hours since it is first known. Pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and

the presence or absence of any birth defect, congenital abnormalities or maternal and newborn complications. The follow-up of pregnancies should include an assessment of possible relationship of study drugs with any pregnancy outcome. Any SAE experienced during pregnancy should be recorded in the SAE form.

8. STATISTICS

8.1 PRIMARY ENDPOINT

PFS is used as the primary endpoint for the evaluation of metastatic disease treatment for the control of the disease (not curative intention), where patients follow diferent treatments at relapse. PFS is particularly useful to evaluate slow-growing diseases difficult to cure, such as low-grade lymphoma, renal carcinoma, CHC or NET. PFS rates represents an early marker of treatment efficacy over time.

Proportion of patients who are alive without progression to Course 1 therapy at 12 months from the date of randomization in STZ based CT vs Everolimus arms.

Main analysis definition of an Event:

Patient will be considered as an Event in the following cases:

- If first progression occurs before or in 48th week radiological evaluation.
- If first progression occurs in 60th week radiological evaluation and patient did not received trial treatment from week 52.
- If death occurs before week 52.
- If death occurs between week 52 and theoretical date for 60th week for radiological evaluation, and death cause is disease under study or toxicity due to trial treatment

Patient will be considered as Event free in the following cases:

- If patient is alive and free of progression on 60th week radiological evaluation.
- If patient was free of progression on 48 the week radiological evaluation, suffers progression on 60th week radiological evaluation but receives at minimum one cycle of treatment posterior to 52th week.

- If death occurs between 52th week plus one day and the theoretical date for 60th week for radiological evaluation, and cause of death was not related to nor disease under study neither toxicity due to trial treatments

8.1.2 Sensitivity analysis and optimistic and conservative event definitions

Since 12 months has been chosen as the time point (52 weeks) for the main analysis and radiological evaluations were planned for 48 and 60 weeks, it is necessary to establish a well defined criteria for considering patients as event or event free, especially when the event happens between these two radiological evaluations.

In order to measure the robustness of the result, a sensitivity analysis will be performed adding two scenarios. Therefore they will be three scenarios: Main analysis (already defined), conservative and optimistic.

Conservative event scenario:

Event:

- If first progression occurs before or in 48th week radiological evaluation.
- If first progression occurs in 60th week radiological evaluation regardless patient had received study treatment between week 48 and 60.
- If death occurs before week 52.
- If death occurs between week 52 and theoretical date for 60th week for radiological evaluation, whichever had been the cause of death.

Event free:

- If patient is alive and free of progression on 60th week radiological evaluation.

Optimistic event scenario:

Event:

- If first progression occurs before or in 48th week radiological evaluation.
- If death occurs before week 52.

Event free:

- If patient is alive and free of progression on 60th week radiological evaluation.

- If patient was free of progression on 48 th week radiological evaluation, suffers progression on 60th week radiological evaluation regardless patient had received or not study treatment
- If death occurs between 52th week plus one day and the theoretical date for 60th week for radiological evaluation, whichever had been the cause of death

8.2 SECONDARY ENDPOINTS

The following definitions will be used for the secondary endpoints:
Second progression free survival is defined as the time from the date of randomization to the date of second disease progression.

Progression free survival Course 1 (PFS1) is defined as the time from the date of start of the first treatment to the first disease progression or death for any cause, whichever comes first.

Progression free survival Course 2 (PFS2) is defined as the time from the date of start of the second treatment to the second disease progression or death for any cause, whichever comes first.

Overall survival (OS) is defined as the time from the date of patient randomization to the date of death for any cause. OS will be evaluated at the end of study. It is estimated that all study patients will be on disease progression at this point.
The interest of performing an OS assessment with mature data (i.e., when death of all study patients has occurred), will be evaluated before study clossure.

Time to first progression is defined as the time from the date of randomization to the date of first disease progression (this happens during the first treatment administrated in sequence).

Time to second progression is defined as the time from the date of randomization to the date of second disease progression (this happens during the second treatment administrated in sequence).

Time from first progression to second progression is defined as the time between the date of first disease progression to the date of second disease progression.

Response Rate is defined as the rate of objective response (CR+PR+SD) measured by RECIST criteria version 1.0.

Biochemical reasponse: reduction on CgA levels at four weeks of the start with study treatment.

Cost per progression free survival gain will be estimated using the Incremental Cost-effectiveness ratio (ICER) defined as the ratio between the difference of costs incurred on by each treatment arm and the difference of first and/or second progression free survival at each arm. Directs costs include the use of the following health resources: treatments, visits and hospitalizations.

8.3 ANALYSIS POPULATIONS

The main analysis of efficacy will be based on ITT population.
Intention to treat (ITT) population will comprise all randomized patients**.** Those patients died during the first study treatment will be also considered for the ITT analysis as a "failure". Patients who will not receive second treatment due to different reasons (toxicity, patients' will of not receive more treatment,…etc) will be classified for intention to treat population as "failure"..

Per protocol (PP) population will comprise all patients of the ITT population meeting all screening criteria (no major protocol violation) and population completing study treatment according to the protocol or been withdrawn from treatment due to an early disease progression (i.e., within the first 12 weeks of each treatment).

Efficacy population (per protocol)

Patients must be dosed with the first therapy (everolimus or chemotherapy),

Patients being dead before first progression will not be included into the group *from first to second progression free survival analysis*.

Patients with no documented first progression won't be included into the analysis *from first to second progression analysis*.

Patients dead because of disease progression will be censored at date of death for *time to first progression analysis*.

At the end of the study as scheduled before in this protocol, and before locking the data base, the relevance of performing an assessment of overall survival with mature data will be evaluated, i.e., continuing the follow-up of all patients to death**.**

Safety population

Safety population will comprise all patients included in the study, having taken at least one dose of either of the two study drugs and undergoing at least one safety analysis after the baseline assessment. Patients receiving at least one dose of the study drug, but with no safety data of any type after the start of treatment will be excluded from the safety population.

8.4 Statistical Methods

All calculations will be made with the statistical package SAS version 9 or SPSS version 16, respectively, or a subsequent version. The use of bilateral tests will be applied, with a significance level of 0.05.

8.4.1 Randomization procedure

Arms assignment will be performed by randomization blocks. The stratifying factor to be considered for randomization is Performance Status (PS): 0 vs 1 or 2. The length of blocks will be defined in the Statistical Analysis Plan.

8.4.2 Main Analysis

The main analysis of efficacy is going to be performed using Contrast Hypothesis testing.

The null hypothesis assumes that everolimus achieves a first progression free survival of 50 % at 52 weeks (arm A: everolimus followed by STZ-5-FU upon progression) and arm B, the reverse sequence, achieves a first progression free survival of 75 % at 52 weeks. (data based on RADIANT-3 results of 11 months or 48 weeks; Yao et al, NEJM 2011[13],).

Therefore H_0: P_B-P_A=0, having P_A=P_B=0.5 at 52 weeks (12 months).

The alternative hypothesis assumes that the best treatment will achieve a first progression free survival of 75 %.

8.4.3 Main analysis of efficacy

The main hypothesis test to fix the trial result is a two-proportion binomial test with normal asymptotical approximation. If Z statistic (see appendix) is over the value 1.96 then the best treatment will be considered as superior significantly. This test has to be performed when all patients had been followed-up during 52 weeks (12 months) or when event had been observed (first progression).

This main hypothesis test will be performed using the main analysis definition of an event. A sensitivity analysis will be performed using the same test but considering the two definitions of event /event free (optimistic and conservative).

8.4.4 Other analysis

All time based endpoints (PFSI, PFS2, time to first progression, time to second progression, time from first to second progression) will be analyzed as follows: a Kaplan-Meier estimation (Kaplan-Meier 1958) will be performed, and also a log-rank test (Mantel N.1966) to detect possible differences between arms. Although sample size has not been calculated for these comparisons, it is planned to perform a Cox regression (Cox 1972) for detecting possible influencing factors.

A recurrent event analysis will be performed in order to estimate the confidence interval of the effect of the treatment in first progression and second progression (Juan R. Gonzalez & Edsel A.

Peña 2004). Recurrent event analysis will follow a cross-over design; the other secondary endpoints will be analyzed following a parallel design.

Response Rate is defined as the rate of objective response (CR+PR+SD) measured by RECIST criteria version 1.0. A confidence interval at level 95 % will be estimated and with an exploratory aim a logistic regression will be performed in order to detect factors that influence this rate.

CgA levels will be analysed using a paired Wilcoxon test comparing baseline and four weeks values.

Correlation and Kendall's tau values will be calculated between overall survival and the four proposed surrogate endpoints: progression free survival (RECIST 1.0, RECIST 1.1, composite RECIST 1.0 and composite RECIST 1.1). The endpoint in terms of correlation and Kendall tau values could be suggested for future studies.

Recurrent event analysis will follow a cross-over design; the other secondary endpoints will be analyzed following a parallel design.

Estimation of cost-efficiency and descriptive analysis of safety is described in sections 8.4.5 and 8.4.6.

Minimal level of patient compliance regarding intake of Afinitor

Adherence to "Afinitor" has been for large studied in previous trials; no patient will be excluded from efficacy analysis because of treatment adherence. This is a phase III trial with the purpose of having a scenario as close as possible to clinical practice.

Estimation of Cost-effectiveness and descriptive analysis of safety is described in sections 8.4.5 and 8.4.6.

8.4.5 Pharmacoeconomic analysis

The Cost-effectiveness analysis will be estimated using the incremental Cost-effectiveness ratio ratio (ICER) of the differential of costs incurred on by each treatment arm (A and B):

$$\text{ICER} = \frac{\text{(Arm A costs – Arm B costs)}}{\text{Arm A 1st/2nd progression free survival – Arm B 1st/2nd progression free survival}}$$

The perspective of the cost analysis will be direct medical costs from an overall health care provider. It is planned to perform a cost analysis per country. Cost –efficiency results will be expressed as cost per progression free survival gained (PFS1 and/or PFS2).

Quality of Life score will be presented descriptively at each study time (at baseline and at the end of each treatment).

8.4.6 Safety analysis

A table of AE and dose reductions specifying both, absolute and relative frequencies, will be generated. This table will contain information for different arms, including treatment relationship. A cross-over analysis will be done.

All grade 3 and 4 toxicities, the number and/or frequency of dose reduction and treatment discontinuations will be also assessed separately, and grade 2 toxicities of abnormal laboratory values for lymphocytes and neutrophils, haemoglobin and platelets, high levels of glucose, phosphate, cholesterol and triglycerides, creatinine and liver enzymes, will be also collected.

8.5. PLANNED INTERIM ANALYSES

No interim analyses have been planned.

8.6 SAMPLE SIZE AND NUMBER OF SUBJECTS PLANNED

This study has been designed assuming that Chemotherapy administered as first line achieves a higher progression free survival rate at 52 weeks (12 months) than everolimus.

Sample size is based on the ability to detect a clinically meaningful improvement on the main endpoint. The hypothesis considered under this study assumes the treatment everolimus followed by STZ-5-FU upon progression (arm A) achieves a first progression free survival of 50 % at 52 weeks (12 months) (data based on RADIANT-3 results; Yao et al, NEJM 2011). To demonstrate that STZ-5-FU followed by everolimus 10mg/day (arm B) achieves a first progression free survival of 75 % (alternative hypothesis, H1) a two-sided binomial test of proportion differences has been run. In order to ensure that type I error (alpha) is 0.05 and with a type II error (beta) of 0.20, a minimum sample size of 132 patients is required (Fleiss 1980). Assuming that a 5% of patients could be lost by several reasons, the proposed sample size is 140 patients (70 patients per study arm).

8.7 PROCEDURE FOR REPORTING ANY DEVIATION FROM THE ORIGINAL STATISTICAL PLAN

A statistical analysis plan will be prepared in detail prior to the closure of clinical database detailing all the analyses to be performed, procedures and techniques to be used for the final drafting of final clinical study report. Any change and/or modification in the originally planned analyses will be recorded in the SAP.

In the case that changes should be made in the analyses planned in the SAP in order to draft the report, this will be recorded in the final report.

9. STUDY RECORDS AND DATA HANDLING

9.1 STUDY RECORDS

A log of all patients evaluated for this protocol must be maintained at each site; the screening log will be completed with a clear explanation of the reasons why potential patients have been excluded from its participation in the study.

The trial master file will contain the essential documents which enable both the conduct of the study and the quality of the data produced to be evaluated as recommended by International Harmonized Conference (ICH) guidelines. The media used to store essential documents will be such that those documents remain complete and legible throughout the required period of retention and can be made available to the competent authorities upon request.

The investigator should retain the essential documents relating to a clinical trial for at least five years after its completion. They shall retain the documents for a longer period, where so required by other applicable requirements. Essential documents will be archived in a way that ensures that they are readily available, upon request, to the competent authorities.

Medical records of patients included in the study will be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

If the investigator withdraws from the study for whatever reason, study records should be transferred to a designee before leaving. Any transfer of responsibilities over the data or documents will be documented in study files. The new investigator shall assume responsibility for data retention and archiving in accordance with procedures detailed above.

The investigator's/institution's will retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed.

9.2 CASE REPORT FORM

All data from each patient will be recorded in a Case Report Form (CRF) provided by the sponsor or its designee. The CRF will be completed on a continuous basis at the site by the investigator or his/her designee.

The investigator or his/her designee is responsible for recording all data as specified in this protocol. Study CRF must be legibly, completed from the information gathered in the source

documents filed at the site. The study investigator at each site will confirm that the data recorded in the CRF are accurate and correct.

Traceability of any change on the CRF will be assured. Specific guidelines for data management will be generated for a correct data management at sites and for data entry purposes.

9.3 PUBLICATION POLICY

Trial results will be written on basis of the analysis performed with mature data at **52 weeks** of treatment and/or at the end of survival follow-up. The manuscript should be approved by all co-authors prior to its submission to the appropriate journal.

Any formal presentation or publication of data gathered as a direct or indirect result of this study will be considered as a joint publication by the investigator(s) and GETNE. Study results will be published once the main analysis and/or the study has been completed and statistical analysis has been performed. Papers will be written considering the revised CONSORT statement for reporting randomized trials (the CONSORT group- 2001).

For the purpose of enabling Novartis, the Authorized Marketing Holder of everolimus, to provide peer input regarding the scientific content and conclusions of such publications and presentations, to provide the Study Principal Investigator with information which may not have been previously provided, a copy of each proposed publication and presentation will be submitted to Novartis for review at least forty-five business days (or fifteen business days in the case of abstracts and full papers, posters presentations and oral presentations not exceeding two double spaced pages in length) prior to such submission.

10. ETHICS

10.1 STUDY IMPLEMENTATION

This study will be performed in compliance with the Protocol and with all applicable laws and guidelines, including without limitation any European Union and appropriate national regulations, the ICH Guideline for Good Clinical Practice or appropriate national good clinical practice ("GCP") guidelines which are consistent with the principles of the ICH Guideline for Good Clinical Practice and applicable laws, as well as, where applicable, generally accepted conventions such as the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. The ICH Guidelines (Harmonized Tripartite Guideline) on Good Clinical Practice can be found on the web page address: http://www.ich.org/products/guidelines.html

All necessary approvals of the appropriate ethics committee and competent health authorities must be obtained prior to commencement of the Study. All necessary approvals of the appropriate ethics committee and competent health authorities must be sent to the sponsor prior to commencement of the Study. The Sponsor will give his approval before the initiation of any site involved in the study.

10.2 PROTOCOL MODIFICATIONS

Any changes to this protocol will be documented in a memorandum and filed on the study master file. Any relevant changes (this is, affecting study objectives, study design, study procedures, patient population or any significant administrative procedures) will be registered as a formal Amendment to the protocol.

Any Amendment must be presented to the applicable institutional review boards (IRB) and should be approved by them and any applicable Health Authorities before its implementation following local laws.

The investigator will not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the

IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol. As soon as possible, the implemented deviation or change, the reasons for it, should be submitted to the sponsor for agreement and, if required, to be sent to the regulatory authority (ies).

10.3 PATIENT INFORMED CONSENT

The Informed Consent must meet the requirements of the latest version of the Declaration of Helsinki when applicable and any other applicable and current local regulations and guidelines at the time of study development. It will be approved by the corresponding IRB, together with the protocol. Any changes on the Patient Informed Consent will be also approved by the IRB before its implementation.

Prior to entry into the trial and before any procedure specific for this study are performed, investigators must explain the nature of the study, its objectives, and the implications of participation to any potential patient. They will also inform that patients' participation is voluntary and they may withdraw consent at any time. Potential patients will be given the opportunity to ask questions about the protocol. They will be also informed of local procedures followed to preserve confidentiality of patients' records as well as any personal information recorded for the study.

The entire trial can be finished for administrative reasons (section 4.2). Patient's rights will be fully respected: This is a comparative study of the effect of sequential order of two accepted therapies used in clinical practice; study discontinuation will not affect patient's treatment which is prescribed in accordance with medical guidelines and licensed indication (section 5).

Patient informed consent will be obtained in written. Consent will be signed and dated by each patient before any procedure specific for the study and before patient randomization into the study.

10.4 CONFIDENTIALITY

Patients will receive a unique number assigned at entry. Patients will be registered with this number in the study database.

The privacy of the patients will be protected at all times. The investigator at each site is responsible for assuring that all information collected from the study will be handled for the protection of personal data according to local laws.

The staff at site as well as any other representative of the sponsor will keep strict confidentiality about the information they may have access for the development of their tasks (source data verification at site during field monitoring and/or quality assurance audits/visits). The site will provide access to source documents to study monitors and other sponsor representatives to fulfill their tasks. Regulatory authorities should have also access to this information in case of audits.

10.5 ADMINISTRATIVE RESPONSIBILITIES

10.5.1 The Coordinating Investigator and the Coordinator of Translational Studies

The coordinating investigator will be responsible for direction of the study (reviewing all clinical data, discussing the contents of the report and for publishing the study results).

Principal investigator:

Dr Ramón Salazar

Catalan Institute of Oncology

[redacted]

Coordinator of translational studies:

Dr Barbro Ericksson

Uppsala University Hospital

[redacted]

10.5.2 The Sponsor

The sponsor transfers all of the sponsor's trial-related tasks and functions to a Contract Research Organisation (CRO; Kantar Health). The CRO will be in charge of the study implementation and development at closure in all countries, in full compliance with all the European and local laws in force.

10.5.3 The site principal investigator

The site principal investigator is responsible of the study is been conducted at his/her site in compliance with the Protocol. If a trial is conducted by a team of individuals at the trial site, the site principal investigator is the leader responsible for the team.

The site principal investigator is responsible to ensure that the local law and regulations currently in force, including any European Union, appropriate national regulations, the ICH Guideline for Good Clinical Practice or appropriate national good clinical practice (“GCP”), and is responsible for adherence to local data protection laws.

All centres will have to declare to the sponsor of details of other satellite institutions which may be responsible for providing protocol treatment to the patients. Details on these satellite institutions including CV for the local investigator, laboratory normal ranges and the Ethical approval, will have to be transmitted to the sponsor. Correspondence on study issues and data collection will however only performed with the primary institution which will assume all responsibilities and liabilities issues with the principal investigator.

10.5.4 The CRO

The CRO is responsible of overseeing the initiation, progress and the end of the clinical trial. The CRO will ensure that the study is conducted, in compliance with the protocol, and with all Applicable Laws and guidelines, including without limitation any European Union, the ICH Guideline for Good Clinical Practice or appropriate national good clinical practice guidelines which are consistent with the principles of the ICH Guideline for Good Clinical Practice and applicable laws.

The CRO is responsible for adherence to all data protection laws applicable to the countries involved in this study. The CRO shall in any case comply with the Organic Data Protection Law 15/1999, dated 13th December.

The CRO will maintain records of the receipt, storage, and administration or dispensing of Study Drug, identifying (but not necessarily by name) each patient to whom the drug is administered or dispensed at each site, and will make these records available to the sponsor at any time with the patient details redacted so as to preserve the patients' anonymity and Organic Data Protection Law 15/1999, dated 13th December.

The CRO shall submit all necessary reports for the Study/ies (e.g., EU Annual Safety Report/Development Safety Update Report (DSUR)) to applicable health authorities according to local national and international regulations.

10.5.5 Trial Financing

Novartis Pharma AG [redacted] will provide financial support for the Study.

European Neuroendocrine Tumour Society (ENETS) [redacted] may help the sponsor with financial support for the prolongation of the Study.

11. TRIAL INSURANCE

A clinical insurance has been taken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

Clinical trial insurance is only valid if the treatment is given in a centre authorized by the sponsor and which has obtained Ethical Committee approval (individually or centrally depending on the national regulations applicable).

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ANNEX I: ECOG PERFORMANCE STATUS SCALE

The ECOG scale can be found on the Eastern Cooperative Oncology Group web site at the following address:

http://www.ecog.org/general/perf_stat.html

ANNEX II: CTCAE VERSION 4.0

The Common Terminology Criteria for Adverse Events (CTCAE) will be used for recording of AEs all along the study. The CTCAE criteria could be found at the following web address: http://evs.nci.nih.gov/ftp1/CTCAE/About.html, by clicking with the mouse on the CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf document.

ANNEX III: RECIST CRITERIA VERSION 1.0 AND VERSION 1.1

The article of the published RECIST criteria version 1.0 can be found on the bottom of the following web page address:

http://www.eortc.be/Services/Doc/Recist.pdf

The RECIST criteria version 1.1 for Composite Score measurement can be found in the following website:
http://www.recist.com/

ANNEX IV: TUMOUR BLOCK ANALYSIS SUB-STUDY

ANNEX V: EVALUATION OF A BLOOD-BASED TRANSCRIPTIONAL ASSAY – THE NETEST – AS A BIOMARKER OF NEUROENDOCRINE TUMOUR RESPONSE

ANNEX VI: PanNETASSIGNER MOLECULAR SUBTYPES ASSAY

Kantar
Clinical & Real World Research, Germany
Health Division

Statistical Analysis Plan (SAP)

Study Title:	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)
Sponsor's Name:	Grupo Español de Tumores Neuroendocrinos (GETNE)
Protocol code:	GETNE1206
EudraCT number:	2013-000726-66
Study Drug:	Treatment sequence A: Everolimus + STZ-5FU Treatment sequence B: STZ-5FU + Everolimus
Study Type:	Phase III
Coordinating investigator at Sponsor:	Dr. Ramón Salazar, Grupo Español de Tumores Neuroendocrinos (GETNE), Catalan Institute of Oncology
Study Statistician at Sponsor:	[redacted]
Trial Lead Coordinator at Sponsor:	[redacted]
Project Manager at CRO Kantar Health:	[redacted]
Study Statistician at CRO Kantar Health:	[redacted]

Document History

Status and Version	Version Date	Change Reference (page / chapter)	Reason for Change / Description of Change
Draft 0.1	27 May 2019	-	-
Draft 0.2	25 Oct 2019	multiple changes	Split analyses in main and final analysis, referring protocol version 3.0 and 4.0
Draft 0.3	29 Nov 2019	minor changes	Review of draft 0.2 with clarifications of comments
Final 1.0	17 Dec 2019	no changes	

Abbreviations

5FU	5-fluorouracil
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT (SGPT)	Alanine Transaminase (Serum Glutamate-Pyruvate Transaminase)
AST (SGOT)	Aspartate Transaminase (Serum Glutamic Oxaloacetic Transaminase)
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CgA	Circulating Cromogranin A
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMP	Data Management Plan
eCRF	Electronic Case Report Form
ECG	Electro-Cardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENETS	European Neuro Endocrine Tumor Society
EoT	End of Treatment
EU	European Union
FPFV	First Patient First Visit
FDA	Food and Drug Administration
HR	Hazard Ratio
ICF	Informed Consent Form
ITT	Intention to treat
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mOS	Median Overall Survival
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression-free Survival
PFS1	First Progression-free Survival (equal to progression-free survival course 1)
PFS2	Progression-free Survival course 2
PFS2nd	Second progression-free Survival
PFS1R12m	Progression-free Survival rate for course 1 at 12 months
PNET	Pancreatic Neuroendocrine Tumor
PP	Per-Protocol
PR	Partial Response

PT	Preferred Term
PTT	Partial Thromboplastin Time
QoL	Quality of Life
QLQ	Quality of Life Questionnaire
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response Rate
SADR	Serious Adverse Drug Reaction
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Stable Disease
SI	International System of Units (Système international (d'unités))
SOC	System Organ Class
STD	Standard Deviation
STZ	Streptozotocin
TEAE	Treatment Emergent Adverse Events
TFL	Tables, Figures and Listings
TTP	Time to Progression
TTP1	Time to First Progression
TTP2nd	Time to Second Progression
ULN	Upper Limit of Normal
VRR	Validity Review Report
WHO DD	World Health Organization Drug Dictionary

Table of Contents

1 Introduction

Streptozotocin (STZ) based chemotherapy, i.e. Streptozotocin-5-fluorouracil (STZ-5FU), is the current standard of care for advanced pancreatic neuroendocrine tumors (pNETs) in the European Union (ENETS guidelines; Neuroendocrinology 2012, Salazar et al., 2011). 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, i.e. before or after the palliative chemotherapy. The information obtained from this study will help the physician to improve the treatment and the management of patients with pNET. Variations of treatment choices are still dependent on physician expertise, the complexity of the treatment center and access to novel treatments (ENETS guidelines, Neuroendocrinology 2016, Pavel et al., 2016). There are no randomized trials comparing Progression Free Survival (PFS) of STZ based chemotherapy versus Everolimus.

2 Study Design

This is a randomized, phase III, 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, in advanced progressive pNETs.

Treatment and dosage plan:

Arm A: First Everolimus, followed by STZ-5FU
Arm B: First STZ-5FU, followed by Everolimus

Treatment STZ-5FU:

- Moertel: STZ 0.5 g/m² and 5-FU 400 mg/m² on days 1 to 5 every 6 weeks or
- Uppsala: STZ 0.5 g/m² on days 1 to 5 and 5-FU 400 mg/m² on days 1 to 3 and afterwards, every 3 weeks 1-day treatment with STZ 1 g/m² and with 5-FU 400 mg/m²

Treatment Everolimus: 10 mg per day

Block randomization was performed, stratified according to ECOG Performance Status (PS): 0 versus 1 or 2. A block size of 4 patients per block was chosen.

It is planned to recruit 140 adult patients with a diagnosis of advanced pNET in approximately 8 countries all around Europe. Assignment to treatment arm A and B is done at random by an equal distribution algorithm automatically assigned by the EDC system. Study groups are stratified according to ECOG Performance Status (PS): 0 versus 1 or 2.

Study schedule:

Screening period / Baseline: day -28 to 0
Treatment period: estimated length 140 +/- 8 weeks
Safety follow-up: 30 days after last dose
Survival follow-up: up to patient's death or study end (last visit of last patient), whatever comes first

3 Study Objectives and Endpoints

The purpose of this study is to compare therapy STZ-5FU versus Everolimus as first line treatment for advanced pNET and elucidate which sequence of STZ-5FU based chemotherapy and the mTOR inhibitor, Everolimus, gives better results in terms of progression free survival (PFS) in well differentiated and advanced pNETs assessed by local investigator using RECIST criteria 1.0.

pNET lesions are usually multiple and difficult, therefore, a measurement of a lower number of lesions, as suggested in version 1.1 of the RECIST criteria, not validated for this disease, could be misleading.

Due to sponsor's decision, data analysis will be split in two parts, the main analysis and the final analysis. Main analysis will be scheduled at first quarter of 2020 and final analysis at third quarter of 2020.

Main analysis will comprise:

- The analysis of screening data.
- The analysis of tumor evaluations as per local assessments up to 60 weeks for ITT population. With it, the primary endpoint regarding Protocol version 4.0 will be calculated.

Final analysis will comprise:

- The main analysis repeated for SAF and PP populations.
- All other analyses defined within this SAP but not yet performed in the main analysis.

3.1 Primary study objective and endpoint

Based on study protocol, version 4.0, the primary objective of this study is to compare STZ-5FU versus Everolimus as first line treatment at 12 months.

Based on study protocol, version 4.0, the primary endpoint is the first progression-free survival rate at 12 months (PFS1R12m) of STZ-5FU versus Everolimus, based on assessments by local investigator using RECIST criteria 1.0.

Based on study protocol, version 3.0, the primary objective of this study is to compare STZ-5FU followed by Everolimus (arm B) versus the reverse sequence (arm A) at 140±8weeks.

Based on study protocol, version 3.0, the primary endpoint is the second progression-free survival (PFS2nd) rate at 140±8 weeks of arm B versus arm A, based on assessments by local investigator using RECIST criteria 1.0.

3.2 Secondary study objectives and endpoints

The secondary objectives of the study are:

- to compare the efficacy of the combination STZ-5FU chemotherapy followed by Everolimus upon progression, versus the reverse sequence, in terms of second progression free survival (PFS2nd) rate at 140+/-8 weeks of treatment, based on assessments by local investigator using RECIST criteria 1.0 (secondary objective regarding protocol version V4.0, primary objective regarding protocol version V3.0)
- to describe the efficacy of the two treatment arms as a continuous variable Hazard Ratio and obtaining the survival estimation of PFS1 for the two arms at 12 months (main analysis time point regarding protocol version V4.0) and at 140 weeks (main analysis time point regarding protocol version V3.0)
- to determine, whether the overall survival (OS) could be modified by the upfront administration of each other treatment, STZ-5FU and Everolimus, respectively, upon progression
- to compare the clinical activity of STZ-5FU and Everolimus given in 1st or 2nd place in terms of time to first (TTP1) and to second progression (TTP2nd), response rate (RR), and early biochemical response (4 week CgA levels), Quality of Life and Cost-effectiveness of each sequence and to investigate the criteria for measuring PFS (RECIST 1.0, RECIST 1.1, composite RECIST 1.0 and composite RECIST 1.1) that correlates better with OS
- to compare the safety and tolerability of upfront administration of each of the treatments, STZ-5FU and Everolimus, respectively, upon progression
- to compare the cost-effectiveness of upfront administration of each of the treatments, STZ-5FU and Everolimus, respectively, upon progression

The <u>secondary endpoints</u> of the study are:

- PFS2nd rates at 140 +/- 8 weeks of the combination STZ-5FU chemotherapy followed by Everolimus upon progression, versus the reverse sequence, based on assessments by local investigator using RECIST criteria 1.0 (secondary endpoint regarding protocol version V4.0, primary endpoint regarding protocol version V3.0)
- PFS2nd as a continuous time variable of the two treatment arms
- PFS1 as a continuous time variable (secondary endpoint regarding protocol version V3.0)
- Progression free survival course 2 (PFS2) (secondary endpoint regarding protocol version V3.0)
- TTP1 of the two treatment arms
- TTP2nd of the two treatment arms
- Time from first progression to second progression of the two treatment arms RR of the two treatment arms assessed every 12 weeks
- Quality of life score at baseline, upon progression and 30 days after the last dose of study treatment (both treatment arms)
- CgA levels at baseline and at 4 weeks of treatment start
- Correlation between the four criteria for PFS*2* (RECIST 1.0, RECIST 1.1, composite RECIST 1.0 and composite RECIST 1.1) and Kendall tau variables
- OS of patients on treatment with the two treatment arms
- Number of adverse events (AEs), dose reductions and total dose administered on patients treated with the two treatment arms. Cost per PFS gained: Incremental cost-effectiveness ratio (ICER) of the difference of costs incurred on by the two treatment arms Relevant Documents

Following documents have been used for the creation of the SAP:

- Study protocol GETNE1206, version 3.0, 26 November 2014
- Study protocol GETNE1206, version 4.0, 07 August 2018
- Study protocol GETNE1206, working protocol version 4.02, 30th of July 2019
- Electronic Case Report Form, version 3.3, 21 February 2018
- Data Management Plan, version 2.0, 16 January 2018
- Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, 14 June 2010
- EORTC QLQ-C30 Scoring Manual, Third edition, 2001
- EORTC QLQ-GINET21 Module Scoring Manual

4 Study Evaluations

4.1 Population Characteristics

At the Screening/Baseline visit following data will be collected:

- Demographic data, i.e. age, gender, childbearing potential for females, Race (except for France)
- Relevant medical or surgical history and current medical conditions
- Detailed disease diagnosis data, i.e. diagnosis and extension of advanced (unresectable or metastatic) progressive pNET including date of first diagnosis and tumor location and ENETS TNM classification and diagnosis details at inclusion in SEQTOR trial including diagnosis confirmation date and tumor ENETS TNM classification and location
- Prior antineoplastic therapies with details of medications, radiotherapies and surgeries
- Physical examination per body system, vital signs including systolic and diastolic blood pressure, heart rate, body temperature, respiration rate, body height and weight
- Local and centralized radiological tumor assessment including specification of target and non-target lesions

4.2 Study Medication

Patient will be treated with either Streptozotocin (STZ) in combination with 5-Fluorouracil (5_FU), i.e. STZ-5FU or with Everolimus as 1st line treatment and switch to the 2nd line treatment (STZ-5FU or Everolimus, respectively) upon disease progression. Everolimus consists of elongated white to off-white tablets for oral administration. STZ is administered as a short (30–60 min) infusion or rapid intravenous push and 5-FU is given as intravenous bolus injection. See section 2 for dosage details. Drug administration for STZ-5FU will be documented separately for the two components including the dosage recommendation mode, i.e. according to Uppsala or Moertel. For both study treatments Everolimus and STZ-5FU, the administered dosage will be recorded including reason for changes or discontinuation. Treatment interruptions will have to be recorded with 0 mg.

4.3 Efficacy

Efficacy evaluation will be based on radiological tumor assessments. Tumor lesions should be measured following RECIST criteria version 1.0 at each site. Main study endpoint will be based on local assessment. ENETS Score will be assessed retrospectively by an ENETS Central Radiological Commission in Paris.

- Local assessment following RECIST criteria version 1.0

Tumor lesions should be measured following RECIST criteria version 1.0 before the start of each treatment and every 12 weeks. All assessments performed during the study (at baseline and every 12 weeks) should be done using the same method and the same technique. Assessments and measurements should be performed by the same radiologist or physician throughout the study. Therefore, each site must designate a radiologist or other medical staff responsible for the interpretation of the radiographs and triphasic CT scans or multiple-phase MRI.

- Retrospective centralized assessment of ENETS Score

An ENETS Central Radiological Commission will be set up for a centralized evaluation of CTs. The radiological commission will perform tumor assessment according to the four radiology criteria for response evaluation (RECIST versions 1.0 and 1.1, and composite Scores according to RECIST 1.0 and to RECIST 1.1)

Tumor response following Composite ENETS Score will be assessed following the modified criteria of ENETS (based on Haesun Choi criteria), as defined on the table 1:

Table 1: ENETS Score

Response	Definition
CR*	- Disappearance of all lesions - No new lesions
PR*	- A decrease in size of 30 % or a decrease in tumor density (HU) of 15% on CT - No new lesions - No obvious progression of non-measurable disease
SD*	- Does not meet the criteria for CR, PR, or PD
PD	- An increase in tumor size of 20% and does not meet criteria of PR by tumor density (HU) on CT - New lesions

* Without symptomatic deterioration of general condition according to WHO scale or ECOG (modified ENETS criteria).

4.4 Safety

Safety assessments will be based on recording of Adverse Events, laboratory parameters determined at screening/baseline and at the treatment cycles, physical examination, vital signs and 12-lead ECG, ECOG performance status. Furthermore, a 30 days follow-up scheduled for 30 days after the last dose intake and survival follow ups scheduled at every 3 months after the end of the treatment will be performed with details about anticancer treatment given, adverse events and life status.

4.5 Other Variables

Chest X-ray (and/or if the disease is present in the chest, a chest CT) will be performed for all patients. During the treatment period, chest X-ray will be performed every 12 weeks. Pulmonary function tests will be performed if clinically necessary in case of evidence of non-infectious pneumonitis. If non-infectious pneumonitis is diagnosed, pneumologist consultation should be considered. When necessary to ensure patient care, a bronchoscopy with biopsy and/or bronchoalveolar lavage (BAL) will be performed.

Quality of life will be assessed based on the EORTC QLQ-C30 questionnaire. QLQ-C30 Version 3.0 is the most recent version and it is supplemented by disease specific modules for NET, the EORTC QLQ GINET21. EORTC QLQ-C30 and the specific module for NET EORTC QLQ GINET21 will be administrated before the start of each treatment period, upon progression or unacceptable toxicity, or at the end of second treatment period if second period event (progression) is not reached.

Documentation of resource utilization will be based on recordings of hospitalizations, outpatient visits and diagnostics and procedures performed related to adverse events.

5 Type of Analysis

6 General Statistical Considerations

6.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.4 (SAS Institute Inc., Cary, NC, USA).

Any statistical testing will be applied two-sided with a significance level of α=0.05. No interim analyses are planned. The analysis will be performed splitted into two parts: the main analysis first and the final analysis second. All data included in the main analysis will be cleaned and locked at the timepoint of main analysis. Final analysis comprises all analyses not yet performed within the main analysis. With this approach, inconsistencies of data between main and final analysis and multiple testing of the same parameter caused by splitted analyses will be avoided.

Sample size justification

As per protocol version 4.0 it is assumed that Everolimus achieves first progression free survival of 50 % at 52 weeks (arm A: Everolimus followed by STZ-5-FU upon progression) and arm B, the reverse sequence, achieves first progression free survival of 75 % at 52 weeks. As per protocol version 3.0 it is assumed that treatment arm A (Everolimus followed by STZ-5-FU upon progression) achieves a second progression free survival of 50 % at 140 weeks and arm B, the reverse sequence, achieves first progression free survival of 75 % at 140 weeks(data based on RADIANT-3 results of 11 months or 48 weeks; Yao et al, NEJM 201113).

The null hypothesis in this study is defined as H_0: P_B-P_A = 0 and the alternative hypothesis is defined as H_1: P_B-$P_A \neq 0$.

A two-sided binomial test of proportion differences has been run to determine the sample size.

According to protocol version 4.0, setting type I error (alpha) level to 0.05 and type II

error (beta) to 0.20, a minimum sample size of 132 patients is required (Fleiss 1980). Assuming that 5% of patients could be lost by several reasons, the proposed sample size is 140 patients (70 patients per study arm).

According to protocol version 3.0, setting type I error (alpha) level to 0.05 and type II error (beta) to 0.10, a minimum sample size of 170 patients is required (Fleiss 1980). Assuming that 5% of patients could be lost by several reasons, the proposed sample size is 180 patients (90 patients per study arm).

With 141 currently included patients, with at least 70 patients per treatment arm, the actual power amounts 83% at alpha-level of 5% and 75% at alpha-level of 2.5%.

6.2 Handling of Loss to Follow-up and Premature Discontinuation

Patients can be discontinued from study treatments (i.e. Everolimus and/or STZ-5FU) and/or withdraw completely from the study. In case of treatment discontinuation, “End of Course 1” and /or “End of Course 2” forms are to be completed and containing, amongst others, laboratory data and physical examination. Reasons for drug discontinuation will be documented at the drug administration sections, reason for withdrawal from the study will be documented at the End of Study/Final Status Form.

Sample size and disposition information at each analysis time point, as well as the final status of patients including reasons for withdrawal from the study or treatment, respectively, will be displayed in frequency tables. Relative frequency calculation will be based in general on the total population of patients (total population of stratum for subgroup-analysis, respectively) at any analysis time point, who have not dropped out until this time.

6.3 Data Rules

6.3.1 General Definitions

- Baseline: measurements documented at the screening visit will be considered as baseline values
- 1st line treatment: study treatment administered as the first treatment of the randomized sequence
- 2nd line treatment: study treatment administered as the second treatment of the randomized sequence after discontinuation of the 1st line treatment

6.3.2 Definition of Derived Variables

a) Following algorithms will be used to calculate derived variables

Table 2: Derived variables

Variable	Derivation
Duration - of first dose of prior antineoplastic therapies, medications	End date (of last dose) – start date (of first dose) + 1 In case only month and year are documented, the 1st of month will be imputed for the start date and the last of month will be imputed for the end date. No duration will be calculated in case only the year is documented.

- of antineoplastic therapies, radiotherapies	
Time from - date of first diagnosis of advanced pNET to date of ICF signature - date of confirmation of diagnosis to date of ICF signature	Date of ICF signature - date of first / confirmation of diagnosis In case only month and year are documented for the date of diagnosis, imputation with 1st of the month will be performed. No calculation will be done in case only the year is documented.
Time from date of ICF to collection date of paraffin embedded tumor block	Date of ICF signature - date of collection date of paraffin embedded tumor block
Duration of observation period	Date of last documented visit / date of end of study / date of last contact (whichever occurred last) – date of screening visit + 1
Duration of treatment before discontinuation	Date of last intake of study drug / date of final status (end of treatment) – date of first intake + 1
Time between visits [days]	● Duration of 1st (2nd) line treatment: Date of end of course 1 (end of course 2) visit – date of cycle 1 visit of 1st (2nd) line treatment + 1 ● Duration of resting period [days] Date of cycle 1 of 2nd line treatment / date of first intake of 2nd line treatment – date of last documented cycle of 1st line treatment / date of last intake of 1st line treatment -1 ● Days between Screening and Cycle 1 of 1st line treatment: Date of cycle 1 of 1st line treatment – date of screening visit ● Days between end of treatment and 30-days FU Date of 30 days FU – date of end of treatment
BMI [kg/m²]	Weight in kg / (height in m)²
12 lead-ECG worst diagnosis	In case several 12 lead-ECG assessments are documented for one analysis time point, only the one with the worst diagnosis will be taken, with *abnormal, clinically significant* defined as the worst, followed by *abnormal, not clinically significant,* followed by *normal*, followed by *non-evaluable*
Change from baseline	Measurement value at any post baseline visit - measurement value at baseline
Average actual daily dose [mg/kg]	Sum of all dosages multiplied with exposure duration in days of that dosage / total exposure duration, excluding off-days (days on interruption documented as 0 mg)
Dosing interruption	Dosages with a daily dose documented as 0 mg/kg
Dosing increase	Dosage increase compared to previously prescribed dose of same treatment, excluding doses documented as 0 mg/kg (interruption)
Dosing decrease	Dosage decrease compared to previously prescribed dose of same treatment, excluding doses documented as 0 mg/kg (interruption)
Duration of interruptions [days]	Sum of (End date of interruption – start date of interruption + 1)
Duration of exposure [days]	Sum of (date of last intake - date of first intake +1 - days with interruptions) by treatment arm
Treatment emergent adverse events (TEAE)	AEs with onset on or after the date of first exposure to study drug are considered as treatment emergent. AEs with onset date on or after the date of first exposure to the 1st line treatment or occurred during the treatment resting period are considered as treatment emergent for the 1st line treatment. For patients receiving the 2nd line treatment and AEs with onset on or after the date of first exposure to the 2nd line treatment will be allocated treatment emergent to the 2nd line treatment. Assignment of treatment emergent status in case of AE start and end date are completely or partially missing: ● If the start date of event is completely or partially missing and the event end date is before first exposure to 1st line treatment the AE will be assigned as not treatment

	emergent. In case end dates are partially provided, the respective month and year parts will be compared to the first exposure to 1st line treatment and if before, AE will be assigned as not treatment emergent. ● If end dates are equal to or after the first exposure to 1st line treatment or missing: o If the start date is completely missing, the AE will be considered as treatment emergent for the 1st line treatment o If the only the start year of the event is documented being equal or after the first exposure to 1st line treatment, the AE will be assigned as treatment emergent to the 1st line treatment. o If only the start day of the event is missing but start month and year of the event are equal or after first exposure to 1st line treatment, the AE will be assigned as treatment emergent for the 1st line treatment. For patients receiving the 2nd line treatment: in case the month and year are equal or after the first exposure of the 2nd line treatment the AE will be assigned as treatment emergent to the 2nd line treatment, unless the end date is indicating that the event stopped before the first exposure of the 2nd line treatment. In case of any other possible unclarity regarding assignment to either the first or 2nd line treatment, the event will be assigned as treatment emergent for the 1st line treatment.
Related adverse event	An AE with relationship documented by the reporter as missing, unknown, yes, not assessable, or not applicable will be analyzed as a related AE. AEs with relationship documented as no by the reporter are defined as not related AEs.
Duration of AE [days]	End Date of AE - Start Date of AE + 1 Duration will only be calculated, if complete event start and end dates are documented, no imputation will be performed.
Time between onset of AE and first treatment administration	Start Date of AE – date of first administration of study drug In case patient received 2nd line treatment and AE is treatment emergent to the 2nd line treatment, difference will be related to the 2nd line treatment. Duration will only be calculated, if complete event start and end dates are documented, no imputation will be performed.
Prior and concomitant medication or significant non-drug therapies	Therapies with onset before the first exposure to 1st line treatment will be classified as prior (also records with missing/unknown start date). Therapies which did not stop before the first exposure to 1st line treatment (stop date on or later than date of first exposure to 1st line treatment, stop date missing/unknown or 'ongoing') will be classified as concomitant.
Relevant prior and concomitant medical / surgical history / medical conditions	Conditions which are documented as ongoing will be derived as concomitant, conditions documented as not ongoing will be derived as prior. In case of missing ongoing status, condition will be derived as concomitant.
First progression free survival (PFS1R12m) rate at 12 months	PFS1R12m rate will be based on the overall response assessments by local investigators using RECIST criteria version 1.0. Those assessments are to take place every 12 weeks. The derivation of evaluation weeks is described in section 9.1, table 6. Week 52 will correspond to 1 year after randomization, e.g. if randomization took place on 05Mar2016, as per below mentioned definitions the 52nd week timepoint (TP52w) will correspond to 05Mar2017. PFS1 rate is the proportion of patients who are alive and progression free according to the below: **Main definition of PFS1R12m** Definition of progression free: - Patient is alive and progression free (i.e. CR, PR or SD documented) at the week 60 evaluation and no disease progression is documented up to the week 60 evaluation. - First disease progression is documented at the week 60 evaluation, but the patient was progression free (i.e. CR, PR or SD documented) at week 48 evaluation and patient is receiving at least one cycle of 1st line treatment posterior week 52 - Patient died between week 52 and the theoretical date of the week 60 evaluation with main cause of death NOT documented as toxicity or primary disease. Furthermore, no disease progression was documented up to the date of death

	Disease progression is defined as - First disease progression is documented before or at the week 48 evaluations - First disease progression is documented at the week 60 evaluations, but patient is not receiving 1st line treatment posterior week 52 - Patient died before week 52 - Patient died between week 52 and the theoretical date of the week 60 evaluations with main cause of death documented as toxicity or primary disease. In case of week 48 evaluation is not available or not unique, the last available tumor evaluation between week 46 and TP52w will be taken into account. In case of week 60 tumor evaluation is not available or not unique, the first available evaluation at or after TP52w will be taken into account. **Conservative definition of PFS1R12m** Patient is to be considered progression free, if patient is alive and progression free (i.e. CR, PR or SD documented) at the week 60 evaluations and no disease progression is documented up to the week 60 evaluations. Death of any cause or first disease progression until including the week 60 evaluation will be considered as disease progression. In case of week 60 tumor evaluation is not available or not unique, the first available evaluation at or after TP52w will be taken into account. **Optimistic definition of PFS1R12m** Patient is to be considered progression free, if - Patient is alive and progression free (i.e. CR, PR or SD documented) at the week 60 evaluations. No disease progression is documented up to the week 60 evaluation. - First disease progression is documented at the week 60 evaluations, but the patient was progression free (i.e. CR, PR or SD documented) at week 48 evaluations. - Patient died due to any cause between week 52 and the theoretical date of the week 60 evaluation. Furthermore, no disease progression was documented up to the date of death Disease progression is defined as - First disease progression is documented before or at the week 48 evaluations - First disease progression is documented at the week 60 evaluation and the week 48 evaluations is not CR, PR or SD or not available. - Patient died before week 52 In case of week 48 evaluation is not available or not unique, the last available tumor evaluation between week 46 and TP52w will be taken into account. In case of week 60 tumor evaluation is not available or not unique, the first available evaluation at or after TP52w will be taken into account.
Second progression free survival (PFS2nd) rate at 140 weeks +/- 8 weeks	PFS2nd rate will be based in analogy of PFS1R12m on the overall response assessments by local investigators using RECIST criteria version 1.0. It refers to the timepoint 140 weeks (=980days) after randomization (TP140w). PFS2nd rate is the proportion of patients who are alive and had at least one progression according to the below mentioned definitions: **Main definition of PFS2nd** Definition of progression free: - Patient is alive and progression free (at least) at cycle 2 of the 2nd line treatment (i.e. CR, PR or SD documented) at the week 144 evaluation and no 2nd disease progression is documented up to the week 144 evaluation.

	- 2nd disease progression is documented at the week 144 evaluation, but the patient was progression free (i.e. CR, PR or SD documented) at week 132 evaluation and patient is receiving at least one cycle of 2nd line treatment posterior week 140 - Patient died between week 140 and the theoretical date of the week 144 evaluation with main cause of death NOT documented as toxicity or primary disease. Furthermore, no disease progression was documented up to the date of death Disease progression is defined as - 2nd disease progression is documented before or at the week 132 evaluations - 2nd disease progression is documented at the week 144 evaluations, but patient is not receiving 2nd line treatment posterior week 140 - Patient died before week 140 - Patient died between week 140 and the theoretical date of the week 144 evaluations with main cause of death documented as toxicity or primary disease. In case of week 132 evaluation is not available or not unique, the last available tumor evaluation between week 132 and TP140w will be taken into account. In case of week 144 tumor evaluation is not available or not unique, the first available evaluation at or after TP140w will be taken into account. **Conservative definition of PFS2nd** Patient is to be considered progression free, if patient is alive and progression free (i.e. CR, PR or SD documented) at the week 144 evaluations and no disease progression is documented up to the week 144 evaluations. Death of any cause or first disease progression until including the week 144 evaluation will be considered as disease progression. In case of week 144 tumor evaluation is not available or not unique, the first available evaluation at or after TP140w will be taken into account. **Optimistic definition of PFS2nd** Patient is to be considered progression free, if - Patient is alive and progression free (at least) at cycle 2 of the 2nd line treatment (i.e. CR, PR or SD documented) at the week 144 evaluations. No 2nd disease progression is documented up to the week 144 evaluation. - 2nd disease progression is documented at the week 144 evaluations, but the patient was progression free (at least) at cycle 2 (i.e. CR, PR or SD documented) at week 132 evaluations. - Patient died due to any cause between week 140 and the theoretical date of the week 60 evaluation. Furthermore, no disease progression was documented up to the date of death Disease progression is defined as - 2nd disease progression is documented before or at the week 132 evaluations - 2nd disease progression is documented at the week 144 evaluation and the week 132 evaluations is not CR, PR or SD or not available. - Patient died before week 140 - In case of week 132 evaluation is not available or not unique, the last available tumor evaluation between week 132 and TP140w will be taken into account. In case of week 144 tumor evaluation is not available or not unique, the first available evaluation at or after TP140w will be taken into account.
Second progression free survival (PFS2nd) according to local assessment using RECIST 1.0	Date of second disease progression based on assessment by local investigator using RECIST criteria version 1.0 or date of death from any cause (whichever occurred earlier) - date of randomization +1 Patients without second progression will be censored at the date of last tumor evaluation. Patients without tumor evaluations will be censored at day 1.

First Progression free survival (PFS1) according to local assessment using RECIST 1.0	Date of first disease progression based on assessment by local investigator using RECIST criteria version 1.0 or date of death from any cause (whichever occurred earlier) - date of randomization +1 Patients without progression will be censored at the date of last tumor evaluation. Patients without tumor evaluations will be censored at day 1.
First Progression free survival (PFS1) according to central assessment using RECIST 1.0	Date of first disease progression based on central assessment using RECIST criteria version 1.0 or date of death from any cause (whichever occurred earlier) - date of randomization +1 Patients without progression will be censored at the date of last tumor evaluation. Patients without tumor evaluations will be censored at day 1.
First Progression free survival (PFS1) according to central assessment using RECIST 1.1	Date of first disease progression based on central assessment using RECIST criteria version 1.1 or date of death from any cause (whichever occurred earlier) - date of randomization +1 Patients without progression will be censored at the date of last tumor evaluation. Patients without tumor evaluations will be censored at day 1.
First Progression free survival (PFS1) according to central assessment using ENETS SCORE RECIST 1.0	Date of first disease progression based on central assessment using ENETS SCORE RECIST criteria version 1.0 or date of death from any cause (whichever occurred earlier) - date of randomization +1 Patients without progression will be censored at the date of last tumor evaluation. Patients without tumor evaluations will be censored at day 1.
First Progression free survival (PFS1) according to central assessment using ENETS SCORE RECIST 1.1	Date of first disease progression based on central assessment using ENETS SCORE RECIST criteria version 1.1 or date of death from any cause (whichever occurred earlier) - date of randomization +1 Patients without progression will be censored at the date of last tumor evaluation. Patients without tumor evaluations will be censored at day 1.
Progression free survival course 2 (PFS2) according to local assessment using RECIST 1.0	Date of second disease progression based on assessment by local investigator using RECIST criteria version 1.0 or date of death from any cause (whichever occurred earlier) - date of first intake of 2nd line treatment Patients without second progression will be censored at the date of last tumor evaluation. Patients without tumor evaluations will be censored at day 1.
Time to first progression (TTP1) according to local assessment using RECIST 1.0	Date of first disease progression based on assessment by local investigator using RECIST criteria version 1.0 - date of randomization +1 Patients without progression will be censored at the date of last tumor evaluation. Patients without tumor evaluations will be censored at day 1.
Time to first progression (TTP1) according to central assessment using RECIST 1.0	Date of first disease progression based on central assessment using RECIST criteria version 1.0 - date of randomization +1 Patients without progression will be censored at the date of last tumor evaluation. Patients without tumor evaluations will be censored at day 1.
Time to first progression (TTP1) according to local assessment using RECIST 1.1	Date of first disease progression based on central assessment using RECIST criteria version 1.1 - date of randomization +1 Patients without progression will be censored at the date of last tumor evaluation. Patients without tumor evaluations will be censored at day 1.
Time to first progression (TTP1) according to local assessment using ENETS SCORE RECIST 1.0	Date of first disease progression based on central assessment using ENETS SCORE RECIST criteria version 1.0 - date of randomization +1 Patients without progression will be censored at the date of last tumor evaluation. Patients without tumor evaluations will be censored at day 1.
Time to first progression (TTP1) according to local assessment using ENETS SCORE RECIST 1.1	Date of first disease progression based on central assessment using ENETS SCORE RECIST criteria version 1.1 - date of randomization +1 Patients without progression will be censored at the date of last tumor evaluation. Patients without tumor evaluations will be censored at day 1.
Time to second progression (TTP2nd) according to local assessment using RECIST 1.0	Date of second disease progression based on assessment by local investigator using RECIST criteria version 1.0 - date of randomization +1 Patients without second progression will be censored at the date of last tumor evaluation. Patients without tumor evaluations will be censored at day 1.

Time from first progression to second progression	Date of second disease progression based on assessment by local investigator using RECIST criteria version 1.0 - date of first disease progression based on assessment by local investigator using RECIST criteria version 1.0 Patients without second progression will be censored at the date of last tumor evaluation. Patients without tumor evaluations will be censored at day 1
Objective response rate (ORR) according to local assessment	Rate of objective response (CR+PR+SD) according to local assessment measured by RECIST criteria version 1.0 Calculation will be performed by evaluation following the regular 12-week basis. The derivation of evaluation weeks is described in section 9.1, table 6
Objective response rate (ORR) according to central assessment	Rate of objective response (CR+PR+SD) according to central assessment measured by RECIST criteria version 1.0 Calculation will be performed by evaluation following the regular 12-week basis. The derivation of evaluation weeks is described in section 9.1, table 6
Overall response rate	Rate of patients that have observed during all evaluations as a best response CR or PR or SD
Overall survival (OS)	Date of death – date of randomization +1 Patients alive or lost to follow up will be censored at the last date known to be alive. Patients without any documentation post randomization will be censored with day 1.
Incremental Cost-Effectiveness (ICER)	$\frac{Costs\ Everolimus\ as\ 1st\ line\ treatment - Costs\ STZ{-}5FU\ as\ 1st\ line\ treatment}{PFS1\ of\ Everolimus\ as\ 1st\ line\ treatment - PFS1\ of\ STZ{-}5FU as\ 1st\ line\ treatment}$ Details for calculation of cost effectiveness will be defined in a separate statistical analysis plan
CTCAE grades (if possible, grades will be derived based on original documented units and values and not on converted to SI units)	
Anemia	Grade 1: Hemoglobin <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L Grade 2: Hemoglobin <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L Grade 3: Hemoglobin <8.0 g/dL; <4.9 mmol/L; <80 g/L Grade 4: -
Hemoglobin increased	Grade 1: Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN Grade 2: Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN Grade 3: Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN Grade 4: -
Leukocytosis	Grade 1: - Grade 2: - Grade 3: WBC count >100,000/mm3 Grade 4: -
Alanine aminotransferase (ALT) increased	Grade 1: >ULN - 3.0 x ULN Grade 2: >3.0 - 5.0 x ULN Grade 3: >5.0 - 20.0 x ULN Grade 4: >20.0 x ULN
Alkaline phosphatase increased	Grade 1: >ULN - 2.5 x ULN Grade 2: >2.5 - 5.0 x ULN Grade 3: >5.0 - 20.0 x ULN Grade 4: >20.0 x ULN
Aspartate aminotransferase (AST) increased	Grade 1: >ULN - 3.0 x ULN Grade 2: >3.0 - 5.0 x ULN Grade 3: >5.0 - 20.0 x ULN Grade 4: >20.0 x ULN
Blood bilirubin increased	Grade 1: >ULN - 1.5 x ULN Grade 2: >1.5 - 3.0 x ULN Grade 3: >3.0 - 10.0 x ULN Grade 4: >10.0 x ULN

Cholesterol high	Grade 1: >ULN - 300 mg/dL; >ULN - 7.75 mmol/L Grade 2: >300 - 400 mg/dL; >7.75 - 10.34 mmol/L Grade 3: >400 - 500 mg/dL; >10.34 - 12.92 mmol/L Grade 4: >500 mg/dL; >12.92 mmol/L
Creatinine increased	Grade 1: >1 - 1.5 x baseline; >ULN - 1.5 x ULN Grade 2: >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN Grade 3: >3.0 baseline; >3.0 - 6.0 x ULN Grade 4: >6.0 x ULN
Lymphocyte count decreased	Grade 1: <LLN - 800/mm^3; <LLN - 0.8 x 10^9/L Grade 2: <800 - 500/mm^3; <0.8 - 0.5 x 10^9/L Grade 3: <500 - 200/mm^3; <0.5 - 0.2 x 10^9/L Grade 4: <200/mm^3; <0.2 x 10^9/L
Lymphocyte count increased	Grade 1: - Grade 2: >4000/mm3 - 20,000/mm3 Grade 3: >20,000/mm3 Grade 4: -
Neutrophil count decreased	Grade 1: <LLN - 1500/mm^3; <LLN - 1.5 x 10^9/L Grade 2: <1500 - 1000/mm^3; <1.5 - 1.0 x 10^9/L Grade 3: <1000 - 500/mm^3; <1.0 - 0.5 x 10^9/L Grade 4: <500/ mm^3; <0.5 x 10^9/L
Platelet count decreased	Grade 1: <LLN - 75,000/mm^3; <LLN - 75.0 x 10^9/L Grade 2: <75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9/L Grade 3: <50,000 - 25,000/mm^3; <50.0 - 25.0 x 10^9/L Grade 4: <25,000/mm^3; <25.0 x 10^9/L
White blood cell decreased	Grade 1: <LLN - 3000/mm^3; <LLN - 3.0 x 10^9/L Grade 2: <3000 - 2000/mm^3; <3.0 - 2.0 x 10^9/L Grade 3: <2000 - 1000/mm^3; <2.0 - 1.0 x 10^9/L Grade 4: <1000/mm^3; <1.0 x 10^9/L
Hyperglycemia	Grade 1: Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L Grade 2: Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L Grade 3: Fasting glucose value >250 - 500 mg/dL; >13.9 - 27.8 mmol/L Grade 4: Fasting glucose value >500 mg/dL; >27.8 mmol/L
Hypoglycemia	Grade 1: Fasting glucose value <LLN - 55 mg/dL; <LLN - 3.0 mmol/L Grade 2: Fasting glucose value <55 - 40 mg/dL; <3.0 - 2.2 mmol/L Grade 3: Fasting glucose value <40 - 30 mg/dL; <2.2 - 1.7 mmol/L Grade 4: Fasting glucose value
Hyperkalemia	Grade 1: Potassium >ULN - 5.5 mmol/L Grade 2: Potassium >5.5 - 6.0 mmol/L Grade 3: Potassium >6.0 - 7.0 mmol/L Grade 4: Potassium >7.0 mmol/L
Hypokalemia	Grade 1: Potassium <LLN - 3.0 mmol/L Grade 2: Potassium <LLN - 3.0 mmol/L Grade 3: Potassium <3.0 - 2.5 mmol/L Grade 4: Potassium <2.5 mmol/L
Hypermagnesemia	Grade 1: Magnesium >ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L Grade 2: - Grade 3: Magnesium >3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L Grade 4: Magnesium >8.0 mg/dL; >3.30 mmol/L
Hypomagnesemia	Grade 1: Magnesium <LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L Grade 2: Magnesium <1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L Grade 3: Magnesium <0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L Grade 4: Magnesium <0.7 mg/dL; <0.3 mmol/L;

Hypernatremia	Grade 1: Sodium >ULN - 150 mmol/L Grade 2: Sodium >150 - 155 mmol/L Grade 3: Sodium >155 - 160 mmol/L Grade 4: Sodium >160 mmol/L
Hyponatremia	Grade 1: Sodium <LLN - 130 mmol/L Grade 2: - Grade 3: <130 - 120 mmol/L Grade 4: <120 mmol/L;
Hypertriglyceridemia	Grade 1: 150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L Grade 2: >300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L Grade 3: >500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L Grade 4: >1000 mg/dL; >11.4 mmol/L
Hypoalbuminemia	Grade 1: <LLN - 3 g/dL; <LLN - 30 g/L Grade 2: <3 - 2 g/dL; <30 - 20 g/L Grade 3: <2 g/dL; <20 g/L Grade 4: -
Hypophosphatemia	Grade 1: <LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L Grade 2: <2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L Grade 3: <2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L Grade 4: <1.0 mg/dL; <0.3 mmol/L

b) Conversion factors for laboratory recordings:

For laboratory parameters different units can be documented in the eCRF. Following conversion factors will be used to obtain SI units for summarization of the results:

Table 3 Conversation factors for laboratory parameters

Parameter	SI Unit for analysis	Alternative eCRF Units	Conversion factors
Haemoglobin	g/L	mmol/L g/dL	1g/L = 1mmol/L / 16.1 1g/L = 0.1g/dL
Haematocrit	L/L	%	1L/L = 100%
Platelets	10^9/L	10^3/µL 1/µL (= 1/mm^3)	10^3/µL = 10^9/L 10^9/L = 1000/µL
Red Blood Cell Count, total	10^{12}/L	10^9/L 10^3/mm^3 10^3/µL	10^{12}/L = 1000*10^9/L 10^3/mm^3 = 10^3/µL = 10^9/L
White Blood Cell Count, total	10^9/L	10^3/mm^3 10^3/µL	10^9/L = 10^3/mm^3 = 10^3/µL
Absolute Neutrophil Count (ANC) Lymphocyte Count Monocyte Count Eosinophil Count Basophil Count	1/µL (= 1/mm^3)	10^9/L 10^3/µL	1/µL = 10^9/L / 1000 10^3/µL = 10^9/L
Sodium	mmol/L	mEq/L mval/L mg/dL	mmol/L = mEq/L = mval/L 1mmol/L= 1mg/dL / 0.435
Potassium	mmol/L	mEq/L mval/L mg/dL	mmol/L = mEq/L = mval/L 1mmol/L= 1mg/dL / 0.256

Ion Chloride	mmol/L	mEq/L mval/L mg/dL	1mmol/L= 1mg/dL / 0.2821
Bicarbonate	mmol/L	mEq/L mval/L mg/dL	mmol/L = mEq/L = mval/L mmol/L = mg/dL / 0.1639
Creatinine	µmol/L	mg/dL mg/L	1µmol/l = 1mg/dl × 88.4 1µmol/l = 1mg/l × 884
Albumin	g/L	mmol/L g/dL	1g/L = 1mmol/L × 66.46 1g/L = g/dL / 10
Protein, total	g/L	g/dL	1g/L = 1g/dL / 10
AST (SGOT) ALT (SGPT) Alkaline Phosphatase	U/L	µmol/Ls µkat/L	1U/L = 1µkat/L / 60 µkat/L = µmol/Ls
Bilirubin, total	µmol/L	mmol/L mg/dL mg/L	1µmol/l =1mmol/L / 1000 1µmol/l = 1mg/dl / 17.1 1µmol/l = 1mg/L / 1.71
Uric Acid	µmol/L	mmol/L mg/dL mg/L	1µmol/l = 1mmol/L / 1000 1µmol/l = 1mg/dL / 59.5 1µmol/l = 1mg/L / 5.95
Urea	mmol/L	mg/dL	1mmol/L = 1mg/dL / 0.166
Blood Urea Nitrogen (BUN)	mmol/L	mg/dL	1mmol/L = 1mg/dL/ 0.3561
Calcium	mmol/L	mEq/L mval/L mg/dL	1mmol/L = 1mEq/L / 0.50 1mmol/L = 1mval/L / 0.50 1mmol/L = 1mg/dL / 0.25
Magnesium	mmol/L	mg/dL	1mmol/L = 1mg/dL / 0.411
Phosphate	mmol/L	mg/dL	1mmol/L = 1mg/dL / 0.323
LDH, total	µkat/L	µmol/L U/L	1µkat/L = 1µmol/L × 60 1µkat/L = 1U/L / 0.0167
Glucose, fasting	mmol/L	mg/dL	1mmol/l = 1mg/dl / 0.0555
Urine – Proteins	mmol/L	mg/dL	1mmol/L = 1mg/dL × #
Urine – Glucose	mg/dL	mmol/L	1mg/dL = 1mmol/L / 18.02
Urine - Blood	Categories negative/1/2/3 or 4		
Urine – Ketones	mg/dL	mmol/L	1mg/dL = 1mmol/L / 10
Urine - White Blood Cell Count	/µL	1e+9/L 10^3/mm^3 10^3/µL	1/µL = 1e+9/L / 1000 1/µL = 103/µL /1000 103/mm3 = 103/µL
PTT	sec	1/1	(no conversion, separate analysis)
Total Cholesterol	mmol/L	mg/dL	1mmol/L = 1mg/dL / 0.0259
Triglycerides	mmol/L	mg/dL	1mmol/L = 1mg/dL / 0.0113
LDL	mmol/L	mg/dL	1mmol/L = 1mg/dL / 0.0259
HDL	mmol/L	mg/dL	1mmol/L = 1mg/dL / 0.0259
Vitamin B_{12}	pmol/L	pg/mL	1pmol/L = 1pg/mL / 0.7378

c) Scoring instructions for EORTC QLQ-C30 including GINET21 module:

Scoring of EORTC QLQ-C30:

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

The principle for scoring these scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the raw score. For each scale (see below for details) at least half of the items have to be answered.

2. Use a linear transformation to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

Technical summary of scoring:

In practical terms, if items I_1, I_2, ..., I_n are included in a scale, the procedure is as follows:

Raw score
Calculate the raw score (i.e. mean of the items answers) if at least half of the items of a scale are answered = $RS = (I_1 + I_2 + ... + I_n) / n$

Linear transformation
Apply the linear transformation to 0-100 to obtain the score S,

Functional scales: $S = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$

Symptom scales / items: $S = \left\{\frac{RS-1}{range}\right\} \times 100$

Global health status / QoL: $S = \left\{\frac{RS-1}{range}\right\} \times 100$

Range is the difference between the maximum possible value of *RS* and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of *RS* equals the range of the item values. Most items are scored 1 to 4, giving *range* = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have *range* = 1.

Table 4 Overview of scales:

Scale	Scale abbreviation	Number of items	Item range*	Item numbers
Global health status / QoL				
Global health status/QoL (revised)†	QL2	2	6	29, 30
Functional scales				

Physical functioning (revised)†	PF2	5	3	1 to 5
Role functioning (revised)†	RF2	2	3	6, 7
Emotional functioning	EF	4	3	21 to 24
Cognitive functioning	CF	2	3	20, 25
Social functioning	SF	2	3	26, 27
Symptom scales / items				
Fatigue	FA	3	3	10, 12, 18
Nausea and vomiting	NV	2	3	14, 15
Pain	PA	2	3	9, 19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhoea	DI	1	3	17
Financial difficulties	FI	1	3	28

* *Item range* is the difference between the possible maximum and the minimum response to individual items;
most items take values from 1 to 4, giving *range* = 3.
† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

Dealing with missing data:

No imputation will be applied for unanswered questionnaire items. Instead, the following procedure will be applied. For each scale, at least half of the items must be answered and the unanswered item will be excluded (ignored) for the raw score calculation. That is, for calculation of the EF scale at least 2 items must be answered, for the PF2 scale at least 3 items must be answered. In case not at least half of the items are answered for a scale, scale score will be set to missing for a patient for the respective visit.

Examples:

Emotional functioning scale:

All 4 items answered:

Raw score= $(Q_{21} + Q_{22} + Q_{23} + Q_{24}) / 4$
EF score: (1 - (RS - 1) / 3) x 100

Item Q_{23} is missing:

Raw score= $(Q_{21} + Q_{22} + Q_{24}) / 3$
EF score: (1 - (RS - 1) / 3) x 100

Scoring of EORTC QLQ-GINET21

The GINET21 module for patients with G.I. related Neuroendocrine Tumors include 21 items, conceptualized as consisting of 5 scales and 4 single items. The following section is the scoring algorithm for the scales described in a similar fashion to the scoring for the EORTC QLQ-C30.

Following scales are defined:

1. **Endocrine scale (items 31, 32 and 33)**
2. **G.I. scale (items 34, 35, 36, 37 and 38)**

3. **Treatment scale (items 39, 40 and 46)**
4. **Social function scale (items 42, 44 and 49)**
5. **Disease related worries scale (items 41, 43 and 47)**

Technical summary of scoring:

Note for all scales a high score is equivalent to worse or more problems. For each scale, calculate the raw score by the addition of item responses divided by the number of items. Then a linear transformation is used to standardize the raw score, so that scores range from 0 to 100.

Score = (raw score - 1) / range x 100

Range is the difference between the maximum and minimum possible value of the raw score. All items are scored from 1 to 4, giving a range = 3.

Multi items

1. **Endocrine symptoms scale (items 31, 32 and 33)**
   a) Add questionnaire items 31, 32 and 33 and divide this sum by the number of items (3):
      Endo= $(Q_{31} + Q_{32} + Q_{33}) / 3$
   b) Carry out linear transformation to convert to a 1-100 scale:
      FinalEndo= (Endo - 1) / 3 x 100
2. **G.I. symptoms scale (items 34, 35, 36, 37 and 38)**
   a) Add questionnaire items 34, 35, 36, 37 and 38 and divide this sum by the number of items (5):
      GI= $(Q_{34} + Q_{35} + Q_{36} + Q_{37} + Q_{38}) / 5$
   b) Carry out linear transformation to convert to a 1-100 scale:
      FinalGI = (GI - 1) / 3 x 100
3. **Treatment related symptoms scale (items 39, 40 and 46)**
   a) Add questionnaire items 39, 40 and 46 and divide this sum by the number of items (3):
      Treat= $(Q_{39} + Q_{40} + Q_{46}) / 3$
   b) Carry out linear transformation to convert to a 1-100 scale:
      FinalTreat = (Treat - 1) / 3 x 100

4. **Social function scale (items 42, 44 and 49)**
   a) Add questionnaire items 42, 44 and 49 and divide this sum by the number of items (3):
      Soc= (Q_{42} + Q_{44} + Q_{49}) / 3
   b) Carry out linear transformation to convert to a 1-100 scale:
      FinalSoc = (Soc - 1) / 3 x 100
5. **Disease related worries (items 41, 43 and 47)**
   a) Add questionnaire items 41, 43 and 47 and divide this sum by the number of items (3):
      Dis= (Q_{41} + Q_{43} + Q_{47}) / 3
   b) Carry out linear transformation to convert to a 1-100 scale:
      FinalDis = (Dis - 1) / 3 x 100

Single items

These items are treated individually. They should be linearly transformed to a 0-100 scale.

1. **Muscle /bone pain symptom (item 48)**
   Pain= (Q_{48} - 1) / 3 x 100
2. **Sexual function (item 51)**
   Sx = (Q_{51} - 1) / 3 x 100
3. **Information/communication function (item 50)**
   Inf= (Q_{50} - 1) / 3 x 100
4. **Body Image (item 45)**
   BI= (Q_{45} - 1) / 3 x 100

Dealing with missing data:

It is possible to estimate the missing score. A simple method for imputing items from multi-item scales, which has been used by many QoL instruments, is the following:

- If at least half of the items from the scale have been answered then use all the items that were completed and apply the standard equation for calculating the raw score. Ignore the missing values when making the calculations.
- It is not possible to estimate missing answers for single items or for scales where less then ½ items have been completed. Result invalid for scale on that patient.

Not applicable box (items 39, 40, 47 and 51)

For descriptive purposes it is important to distinguish between missing data and items which are not applicable. For calculations, N/A data should be managed as for missing data.

6.3.3 Handling of Data Inconsistencies

To ensure integrity and quality of data, multiple validation checks are implemented in the electronic data capture (EDC) system. Data directly entered into the EDC system are checked automatically during data entry. The process of data validation as well as the specifications for the electronic and manual review of data are defined in the Data Validation/Edit Check catalogue please refer to the DMP for further details.

6.3.4 Handling of Missing Data

Missing data in the eCRF will be detected during data entry via automatic edit checks by the EDC system to assess whether the information is available at the study sites. For data that remain missing, no imputation of missing information will be applied. Number of patients with missing data will be presented as separate category. Relative frequencies will be calculated based on all values of the patient set including patients with missing data. In special cases, where the basis differs from total population, this will be mentioned in the table titles.

6.3.5 Decisions of the Data Review Meeting

Pending, to be included when available, i.e. after the Data Review Meeting (DRM).

6.4 Coding

The most recent Medical Dictionary of Regulatory Activities (MedDRA) version will be used for coding of medical history, adverse events and the specification of the physical examination.

Coding of prior and concomitant medications will be performed by the most recent World Health Organization (WHO) Drug Dictionary.

7 Patient Enrolment and Analysis Sets

It is planned to recruit 140 adult patients with a diagnosis of advanced pNET in 8 European countries. Patients will be assigned to the following analysis sets for statistical analysis with the following criteria:

The Safety Analysis Set (SAF) will consist of patients who fulfil the following criteria:

- Patient has been randomized
- At least one dose of the two study treatments has been documented, i.e. STZ-5FU or Everolimus
- Availability of post-baseline safety data of any kind (i.e. documentation of post-baseline physical examination, post-baseline ECOG performance status, post-baseline laboratory data of any kind, post-baseline 12-lead ECG, post-baseline vital signs or experience of AEs)

The Intention-To-Treat Analysis Set (ITT) will consist of patients who fulfil the following criteria:

- Patient has been randomized

Patients in the ITT set will be analyzed as randomized irrespective of their actual intake of study treatment.

The Per-Protocol Set (PP) will consist of patients who fulfil the following criteria:

- Included in the ITT set
- No major protocol deviation documented

The main analysis of efficacy will be based on the ITT population set.

Patients who have been included into the study despite of a violation of inclusion or exclusion criterion or who show other protocol deviations in the course of the study will be compiled in a list of protocol deviations. A classification of these protocol deviations into major/minor and decisions how to handle these subjects will take place in a Data Review Meeting (DRM). The DRM will take place after data collection is completed and the database is clean (soft lock), but prior to database lock (hard lock). Results of the DRM will be outlined in Data Review Meeting minutes to be created after the DRM.

Outcome of the selection process and for general study overview, following frequency tables will be prepared, for details see section 12.1:

- Number of participating sites
- Screening and randomization of patients
- Analysis sets

Furthermore, patients discontinued from the study, protocol deviations and patients excluded from the efficacy analyses will be displayed in a listing.

8 Statistical Analysis

8.1 Presentation of Analysis Results

Continuous data will be described by the total number of patients in the respective analysis set/subgroup, number of non-missing and missing values, mean, standard deviation, median, minimum, maximum as well as lower and upper quartiles. Unless otherwise noted, mean, median and percentiles of a set of values will be printed out to one more decimal than the original value, the standard deviation to two more decimals than the original value.

Categorical data including categories of continuous data will be presented in frequency tables containing absolute and relative frequencies. All table percentages will be reported with one decimal point unless otherwise noted. Frequency tables will include the total number of observations and the number of missing values as additional categories. Multiple response data will be presented as distribution of single entries

If applicable, 95% confidence intervals (CIs) will be displayed for the mean of continuous data or frequencies, respectively. Details on analyses including CIs and the calculated method will be specified in the respective in section 9.2.

Results will be summarized treatment arm, as applicable.

Table 5 Assignment of treatment groups for TFL output

Detailed treatment description	Name for TFL output
STZ-5FU according to Moertel or Uppsala Code List	STZ-5FU
Everolimus 10 mg per day	Everolimus

Treatment arm: STZ-5FU – Everolimus 10 mg per day Everolimus 10 mg per day - STZ-5FU according to Moertel or Uppsala Code List	 STZ-5FU - Everolimus Everolimus - STZ-5FU

All variables documented at different analysis time points / cycles will be summarized by the available cycle, as defined in table below.

Table 6 Assignments of visits for TFL output

Visit in EDC	**Visit name for TFL output**
Screening (Day -28 to 0)	Baseline
Everolimus / STZ-5FU Cycle 1 to Cycle X with X corresponding to the maximum cycle number documented	Cycle 1 to Cycle X, 1st line / 2nd line with X corresponding to the maximum cycle number documented
End of Course 1 or End of Course 2	EoT assigning end of treatment for the respective treatment
Survival Follow-Ups: 30 days following end of treatment 3 months following end of treatment 6 months following end of treatment […] 30 months following end of treatment Interim-/additional follow-up	 FU 30 days FU 3 months FU 6 months […] FU 30 months FU Add. No. X *with X corresponding to the maximum FU number documented*
Biomarkers evaluation (CgA), CTC, NETest Screening At 4 weeks in course 1 Cycle 1 of 2nd treatment* / Before start of 2nd treatment** At 4 weeks at course 2* ** **only for Biomarkers* *** only for NETest*	 Baseline At 4 weeks Cycle 1 2nd line* / Before start of 2nd line** At 4 weeks 2nd line* ** **only for Biomarkers* *** only for NETest*
Presentation by evaluation week for assessments performed every 12 weeks and not documented during the treatment visits Evaluation will be assigned to respective week in relation to the baseline visit with a range of +/- 14 days	Baseline Week 12 Week 24 Week 36 Week 48 Week 60 … Week X *with X corresponding to the maximum week number documented*

8.2 Analysis variables

8.2.1 Population Characteristics

Demographic data including vital signs, physical examination, ECOG performance status, 12-lead-ECG, height in cm, weight in kg and BMI at the Screening/Baseline visit will be summarized in frequency tables or with descriptive statistics, as appropriate.

Relevant medical/surgical history and medical conditions will be summarized in frequency tables containing the number and percentage of patients with no and with any condition/disease and broken down by diagnosis displayed as MedDRA SOC/PT, separately for prior and for concomitant diseases. Records documented as not ongoing will be classified as prior, records documented as ongoing will be classified as concomitant. Records leading to same MedDRA PT for the same patient with same ongoing status will be counted only once.

Prior antineoplastic therapies (i.e. medications, radiotherapies, surgeries and non-drug therapies) will be summarized separately per therapy type as patient-based and event-based analyses. Patient based analyses will contain the total number and percentage of patients with any and with no prior antineoplastic therapies based on the total number of patients included in the analyzed population set. For medications, WHO DD ATC level 1 and 3 coding will be included. Further details, like setting, location, number of cycles, duration, reason for discontinuation, best response etc., will be tabulated event based with absolute and relative frequencies or descriptive statistics based on the total number of therapies documented.

Documented records for prior and concomitant medications and non-drug therapies will be classified as prior or concomitant as specified in section 7.3.2 and summarized separately for these two groups including the number and percentage of patients with any and no therapy, including WHO DD ATC level 1 and 3 coding of the specified therapies based on the total number of patients in the population under investigation.

Disease diagnosis data with details regarding the first diagnosis of pNET and diagnosis confirmation at study inclusion will be summarized with descriptive statistics and frequency tables as appropriate. Tumor assessments at baseline will be summarized separately for the central and the local radiological assessment including details for target and non-target lesions.

Demographic data and disease diagnosis data will also be displayed in a listing.

8.2.2 Study Medication

Details of documented study medication administration will be summarized with descriptive statistics or in frequency tables in terms of initial daily dose, average daily dose, number of documented dose adjustments per patient including a differentiation of dose increases, dose decreases and dose interruptions along with the documented reasons for the adaptation. Furthermore, duration of interruptions and duration of exposure will be analyzed. As for study treatment STZ-5FU details will be documented separately for the two components STZ and 5-FU, all analyses regarding study medication will be tabulated separately for these two components.
See section 7.3.2 for derivation and definitions of the above-mentioned variables.

8.2.3 Efficacy

The main efficacy endpoints are the primary endpoints as described in chapter 3.1. For derivation see section 7.3.2.. The primary endpoints will be analyzed in a frequency table displaying the number and percentage of patients who achieved and who did not achieve the criterions for progression free survival according to the main, conservative and optimist definition as stated in section 7.3.2. P-value from the two-sided Chi-square test will be displayed. If the expected cell count for any cell is less than 5, Fisher's exact test will be applied instead.

Time-to event analysis will be performed for the PFS1, PFS2nd, PFS2, TTP1, TTP2nd and OS (overall survival) and displayed with Kaplan-Meier summary statistics including p-value from the log-rank test. PFS1 and TTP1 will be derived based on the local and the central radiological assessments (see section 7.3.2).

Although sample size has not been calculated for these comparisons, it is planned to perform a Cox regression (Cox 1972) for detecting possible influencing factors.

Correlation analysis will be performed for the OS and the PFS1 and displayed in a scatterplot including Pearson's correlation coefficient.

Listings will be prepared with tumor assessments of central and local radiological assessments including details for target and non-target lesions.

Response Rate is defined as the rate of objective response (CR+PR+SD) measured by RECIST criteria version 1.0. It will be derived separately for local and central radiological assessments and by tumor evaluation following the regular 12-week basis with its confidence interval at level 95 %.

Overall response rate will be analyzed and a logistic regression will be performed with an exploratory aim in order to detect factors that influence this rate.

Regressions will be performed with the following factors included in the model: Age, Gender, Race, Location, Prior surgery (yes – curative – Non residual disease, Yes-curative-residual disease, Yes- other than curative, No surgery), Baseline ecog, CgA, Translational and biomarker parameters, TNM, Tumor histology, Mitotic Index, Ki67, Enets classification, histopathological grade.

A recurrent event analysis will be performed in order to estimate the confidence interval of the effect of the treatment in first progression and second progression (Juan R. Gonzalez & Edsel A. Peña 2004). Recurrent event analysis will follow a cross-over design; the other secondary endpoints will be analyzed following a parallel design.

8.2.4 Safety

Safety analysis will be based on the analysis of adverse events and on post baseline evaluations of laboratory assessments, physical examination, ECOG performance status, 12-Lead ECG and vital signs.

1.1.1.1 Adverse events

Only treatment emergent adverse events (TEAEs) will be analyzed in summary tables which are derived as stated in section 7.3.2. Non-treatment emergent AEs will be included in the adverse event listings.

An overview summary of TEAEs will be prepared on a patient based and event-based level. Event based summary of TEAE will contain the total number of TEAEs, number of related TEAEs (all, serious and non-serious), number of TEAEs leading to permanent discontinuation from treatment (all, serious and non-serious) and TEAEs with outcome death. The patient-based summary will contain the number of patients without any TEAE, with at least one TEAE (all, serious and non-serious), the number of patients with related TEAEs (all, serious and non-serious), number of patients with at least one TEAEs leading to permanent discontinuation from treatment (all, serious and non-serious) and the number of patients with TEAE with the outcome death.

TEAEs will also be summarized by MedDRA SOC and PT as patient-based and event-based. For the patient-based analyses, multiple occurrences of a specific event within one patient (i.e. leading to same SOC/PT), the event will be counted only once. Both, the patient-based and event based analyses will be performed for all TEAEs (all, serious and non-serious), related TEAEs (all, serious and non-serious), TEAEs by relationship (all, serious and non-serious), TEAEs by CTCAE grade (all, serious and non-serious), TEAEs by action taken (all, serious and non-serious), TEAEs resulting in permanent discontinuation from study drug (all, serious and non-serious) and TEAEs leading to death.

1.1.1.2 Laboratory data

Post baseline laboratory assessments will be summarized in the SI unit with descriptive summary statistics or in frequency tables, as appropriate, separately per laboratory parameter and evaluation time point. Furthermore, where applicable, change from baseline results will also be summarized. For each parameter, where applicable, it will be determined whether the value (original, not converted) is within, below or above the documented normal range for that parameter and the number of values within, below and above will be summarized per evaluation time point in a frequency table. In addition, CTCAE grades will be derived as stated in section 7.3.2 and the frequency and percentages of CTCAE grades will be summarized per CTCAE term and evaluation time point.

For the change from baseline in CgA values the p-value from Wilcoxon rank-sum test (Mann–Whitney U test) for the difference between the two study treatments will be presented.

1.1.1.3 Other safety data

Post baseline assessments of physical examination, ECOG performance status, 12 lead-ECG, weight, BMI and vital signs including change from baseline results will be summarized per evaluation timepoint with descriptive statistics or in frequency tables, as appropriate.

1.1.2 Other Variables

Scores from the EORTC QLQ-C30 and the disease specific EORTC QLQ-GINEt21 questionnaire will be derived as described in section 7.3.2 summarized with descriptive

statistics per score and evaluation time point. In addition, answers to the single items will be displayed in frequency tables.

Resource utilization data will be tabulated with descriptive statistics or frequency tables, as appropriate separately for hospitalizations, outpatient visits, diagnostics and procedures related to AEs. Further calculation of cost effectiveness will be described in a separate statistical analysis plan.

1.2 Subgroup Analysis and Stratifications

All data will be examined by treatment arm and if applicable in total for the respective analysis population as defined in column “Subgroup/Strata” in section 12.1. Apart from these subgroups/strata, no further stratifications or subgroup analyses will be performed.

2 Changes to Planned Analyses

This section is to be finalized and specified in more detail when above mentioned analyses are fixed and open comments are resolved. Following deviations are currently applicable/possible:

- CgA levels will be analyzed using a paired Wilcoxon test comparing baseline and four weeks values. -> no paired design
- No cross over design as stated at several parts of the protocol. Treatment switch only in case of progression and not mandatory like in a cross over design, patient does not serve as his own comparator, but parallel comparison of treatments
- Cut off of data collection time for analysis, but data collection not truncated.
- Correlation analysis of OS/PFS and display Kendall’s Tau (only for paired analyses), here parallel design

3 References

Not applicable.

4 Appendix

4.1 Tables, Figures and Listings (TFLs)

The structure and organization of the TFLs, variable names or categories might be changed, as deemed necessary, during programming, without requiring a separate SAP amendment or new SAP version.

Table Name	Statistics / Categories	Subgroup / Strata
14.1 Study Patients and Demographic Data		
Disposition of sites and patients, analysis sets, study and treatment discontinuation		
Number of participating sites	Number of participating sites Number of sites with at least one patient screened (ICF signed) Number of sites with at least one patient randomized Number of sites with at least one patient included in SAF Number of sites with at least one patient included in ITT Number of sites with at least one patient included in PP Number of sites with at least one patient treated with STZ-5FU Number of sites with at least one patient treated with Everolimus	In total and by country
Screening and randomization of patients	Number of patients screened (ICF signed) Number of not randomized patients Number of patients randomized Number of patients randomized to treatment sequence STZ-5FU – Everolimus Number of patients randomized to treatment sequence Everolimus – STZ-5FU	In total and by country and site
Reason for screening failure	Inclusion-/Exclusion criteria not fulfilled Patient rejects participation on the trial Patient decided to retract from participation before random allocation Patient did not come to screening visit Other	Subgroup of patients assigned as screening failure at end of study form
Final status at end of treatment	**Final status at end of treatment** Total Treatment/Study completion according to Protocol (incl Disease Progression) Withdrawal 1st treatment Withdrawal 2nd treatment **If withdrawal is ticked, primary reason:** Total Missing Adverse Event Death Protocol Violation Lost to Follow-Up Withdrawal of Consent Investigator Discretion Sponsor Discretion Other **If death, main cause of death:** Total Missing Primary Disease Toxicity Chronic disease not related to an AE or to progression	SAF, ITT, PP By treatment arm

	Other cause **Does the Subject agree to be followed for post treatment evaluations?** Total Missing Yes No **Does the Subject agree to be followed for survival?** Total Missing Yes No **If yes, reason for study end** Total Missing Death Lost to Follow-Up Withdrawal of Consent for survival data collection Investigator Discretion Sponsor Discretion Other	
Analysis sets	Number of patients screened (ICF signed) Number of patients in SAF Number of patients excluded from the SAF Reasons for exclusion from SAF Number of patients in ITT Number of patients excluded from the ITT Reasons for exclusion from ITT Number of patients in PP Number of patients excluded from the PP Reasons for exclusion from PP	In total and by treatment arm
Violation of eligibility criteria at randomization	Number of patients violated any eligibility criterion at randomization Number of patients per violated inclusion and exclusion criterion	Subgroup of patients who did not meet all eligibility criteria at randomization
Violation of eligibility criteria post randomization (end of first line treatment)	**Did the subject meet all eligibility criteria?** Total Yes No **If no:** Number of patients violated any eligibility criterion at post randomization Number of patients per violated inclusion and exclusion criterion	SAF, ITT, PP by treatment arm
Number of patients per treatment	Total number of patients in respective population Number of patients treated with STZ-5FU Number of patients treated according to Moertel Number of patients treated according to Uppsala Number of patients treated with STZ-5FU as 1st line Number of patients treated according to Moertel Number of patients treated according to Uppsala Number of patients treated with STZ-5FU as 2nd line Number of patients treated according to Moertel Number of patients treated according to Uppsala	SAF, ITT, PP

	Number of patients treated with Everolimus Number of patients treated with Everolimus as 1st line Number of patients treated with Everolimus as 2nd line	
Primary reason for permanent discontinuation of study treatment	**Primary reason for discontinuation of study treatment** Total Progressive disease Adverse Event Patient decision (retrieval of consent) Other **Duration of treatment before discontinuation [days]** Quantitative statistical parameters	Subgroup of patients who discontinued study treatment permanently SAF, ITT, PP By treatment, by treatment arm
Number of patients per cycle/follow up visit	Total Baseline Cycle 1 Cycle 2 … Cycle X EoT FU 30 days …	SAF, ITT, PP By treatment arm
Observation period [days]	Quantitative statistical parameters	SAF, ITT, PP by treatment arm
Time between visits [days]	**Days between Screening and Cycle 1 of 1st line treatment** **Duration of 1st line treatment** **Days between end of treatment and 30-days FU** *Only for patients receiving 2nd line treatment:* **Duration of resting period** **Duration of 2nd line treatment** Quantitative statistical parameters	SAF, ITT, PP By treatment arm
Demographic data and other baseline characteristics		
Gender	Total Missing Male Female	SAF, ITT, PP by treatment arm
Age	Quantitative statistical parameters	SAF, ITT, PP by treatment arm
Childbearing potential	Total Child bearing potential Surgically sterile Post menopausal	Subgroup of females SAF, ITT, PP by treatment arm
Race	Total Asian Black or African American White Other	Not for French patients SAF, ITT, PP by treatment arm
Physical examination at baseline	**Performance of physical examination at baseline** Total Missing Yes No If yes: *Separately by body system* **General Appearance** **Skin** **[…]**	SAF, ITT, PP by treatment arm

	Basic Nervous System **Other (MedDRA PT)** Total Missing Normal Abnormal, not clinically significant Abnormal, clinically significant Not done	
Height, weight and BMI at baseline	**Body height at baseline [cm]** **Body weight at baseline [kg]** **BMI [kg/m²] at baseline** Quantitative statistical parameters	SAF, ITT, PP by treatment arm
Vital signs at baseline	**Performance of vital signs assessment at baseline** Total Missing Yes No If yes: *Separately by measurement* **Systolic blood pressure [mmHg]** **Diastolic blood pressure [mmHg]** **Heart rate [beats per minute]** **Body temperature [°C]** **Respiration Rate [breaths per minute]** Quantitative statistical parameters	SAF, ITT, PP by treatment arm
ECOG performance status at baseline	Total Missing 0: Fully active […] 1: Restricted in physically strenuous activity […] 2: Ambulatory and capable of all selfcare […] 3: Capable of only limited selfcare […] 4: Completely disabled […] 5: Dead	SAF, ITT, PP by treatment arm
12 lead-ECG worst documented diagnosis at baseline	Total Missing Normal Abnormal, not clinically significant Abnormal, clinically significant Non-evaluable	SAF, ITT, PP by treatment arm
Medical history, prior or concomitant therapies		
Medical and surgical history and medical conditions		
Relevant prior medical / surgical history / medical conditions	Total Total number of patients with no prior medical condition or event Total number of patients with any prior medical condition or event MedDRA SOC and PT	SAF, ITT, PP by treatment arm
Relevant concomitant medical / surgical history / medical conditions	Total Total number of patients with no concomitant medical condition or event Total number of patients with any concomitant medical condition or event MedDRA SOC and PT	SAF, ITT, PP by treatment arm
Prior antineoplastic therapies		
Prior antineoplastic therapies, medications		

Incidences of prior antineoplastic therapies, medications	Total Total number of patients with no prior antineoplastic therapies, medications Total number of patients with any prior antineoplastic therapies, medications WHO DD ATC level 1 and 3	SAF, ITT, PP by treatment arm in total and by therapy type
Prior antineoplastic therapies, medications – details (event based)	Total number of prior antineoplastic therapies, medications **Setting** Missing Adjuvant Neoadjuvant Therapeutic Prevention Palliative Other **Number of cycles** Quantitative statistical parameters **Duration** Quantitative statistical parameters **Reason for discontinuation** Missing Adverse event(s) not related to toxicity Adverse event(s) Toxicity Completed prescribed regimen Disease Progression Patient's decision Lost to follow-up Unknown Other **Best response** Missing Complete response Partial response Stable disease Progressive disease Complete response/unconfirmed Unknown Not applicable	SAF, ITT, PP by treatment arm in total and by therapy type
Prior antineoplastic therapies, radiotherapies		
Incidences of prior antineoplastic therapies, radiotherapies	Total Total number of patients with no prior antineoplastic therapies, radiotherapies Total number of patients with any prior antineoplastic therapies, radiotherapies	SAF, ITT, PP by treatment arm in total and by type
Prior antineoplastic therapies, radiotherapies – details (event based)	Total number of prior antineoplastic therapies, radiotherapies **Location (multiple response)** Missing Pancreas Liver […] Breast	SAF, ITT, PP by treatment arm in total and by type

	Other **Duration** Quantitative statistical parameters **Setting** Missing Adjuvant Neoadjuvant Therapeutic Prevention Palliative Other **Reason for discontinuation** Missing Adverse event(s) not related to toxicity Adverse event(s) Toxicity Completed prescribed regimen Disease Progression Patient's decision Lost to follow-up Unknown Other **Best response** Missing Complete response Partial response Stable disease Progressive disease Complete response/unconfirmed Unknown Not applicable	
Prior antineoplastic therapies, surgeries		
Incidences of prior antineoplastic therapies, surgeries	Total Total number of patients with no prior antineoplastic therapies, surgeries Total number of patients with any prior antineoplastic therapies, surgeries	SAF, ITT, PP by treatment arm in total and by surgery type
Prior antineoplastic therapies, surgeries – details (event based)	Total number of prior antineoplastic therapies, surgeries **Reason for surgery** Missing Curative Palliative Biopsy Prophylaxis Unknown Other **Residual disease** Yes No Unknown Not applicable	SAF, ITT, PP by treatment arm in total and by surgery type
Prior and concomitant medication or significant non-drug therapies		

Prior medication or significant non-drug therapies	Total Number of patients with no prior medication or significant non-drug therapies Number of patients with any prior medication or significant non-drug therapies WHO DD level 1 and 3	SAF, ITT, PP by treatment arm
Concomitant medication or significant non-drug therapies	Total Number of patients with no concomitant medication or significant non-drug therapies Number of patients with any concomitant medication or significant non-drug therapies WHO DD level 1 and 3	SAF, ITT, PP by treatment arm
Disease diagnosis data		
Diagnosis and extension of advanced (unresectable or metastatic) progressive pNET	**Time from date of first diagnosis of advanced pNET to date of ICF signature** Quantitative statistical parameters **Primary site of tumor (multiple response)** Total Missing Pancreas Peritoneum Other (adhoc codes) **ENETS TNM Classification (Rindi, 2010):** **T – Primary tumor** Missing Tx Cannot be assessed T0 No evidence of primary tumor T1 Confined to pancreas and < 2 cm T2 Confined to pancreas and 2 -4 cm T3 Confined to pancreas and > 4 cm; or invasion of duodenum or bile duct T4 Invasion of adjacent organs or major vessels **N – Regional lymph nodes** Missing Nx Cannot be assessed N0 No regional lymph node metastases N1 Regional lymph node metastases **M – Distant metastases** Missing Mx Cannot be assessed M0 No distant metastases M1 Distant metastases If M1 Distant metastases is ticked: **Location of Tumor Metastasis (multiple response)** Missing Pancreas Liver Peritoneum Lung Bone Other (adhoc codes)	SAF, ITT, PP by treatment arm
Diagnosis at inclusion in SEQTOR trial	**Time from date of confirmation of diagnosis to date of ICF signature**	

	Quantitative statistical parameters **ENETS TNM Classification (Rindi, 2010):** **T – Primary tumor** Missing T1 Confined to pancreas and < 2 cm T2 Confined to pancreas and 2 -4 cm T3 Confined to pancreas and > 4 cm; or invasion of duodenum or bile duct T4 Invasion of adjacent organs or major vessels Tx Cannot be assessed **N – Regional lymph nodes** Missing Nx Cannot be assessed N0 No regional lymph node metastases N1 Regional lymph node metastases **M – Distant metastases** Missing Mx Cannot be assessed M0 No distant metastases M1 Distant metastases If M1 Distant metastases is ticked: **Location of Tumor Metastasis (multiple response)** Missing Pancreas Liver Peritoneum Lung Bone Other (adhoc coded) **Type of tissue** Missing Primary tumor Metastasis Other (adhoc codes) **Mitotic Index assessed?** Missing Yes No **If yes, Mitotic Index [%]** Quantitative statistical parameters **Ki67 assessed?** Missing Yes No **If yes, Ki67 [%]** Quantitative statistical parameters **ENETS / WHO Classification** Missing G1: <2 mitoses per 2 mm2 and/or Ki-67 index ≤ 2% G2: 2–20 mitoses per 2 mm2 and/or Ki-67 index >2% and ≤ 20%	

	Unknown	
Tumor assessments at baseline		
Type and location of tumor assessment at baseline, local radiological tumor assessment	Total number of tumor assessments **Type of tumor assessment** Missing Triphasic CT Multiple-phase MRI Other (adhoc codes) **Location of tumor assessment** Missing CNS supratentorial CNS infratentorial […] Gall bladder Other (adhoc codes) **Overall response following RECIST 1.0** Missing CR – Complete Response PR – Partial Response SD – Stable Disease PD – Progression of Disease Not applicable / Not assessable / Unknown	SAF, ITT, PP by treatment arm
Type and location of tumor assessment at baseline, centralized radiological tumor assessment	Total number of tumor assessments **Type of tumor assessment** Missing Triphasic CT Multiple-phase MRI Other (adhoc codes) **Location of tumor assessment** Missing CNS supratentorial CNS infratentorial […] Gall bladder Other (adhoc codes) **Tumor density** Quantitative statistical parameters **Overall response following RECIST 1.0** Missing CR – Complete Response PR – Partial Response SD – Stable Disease PD – Progression of Disease Not applicable / Not assessable / Unknown **Overall response following RECIST 1.1** Missing CR – Complete Response PR – Partial Response SD – Stable Disease PD – Progression of Disease Not applicable / Not assessable / Unknown **ENETS Score following RECIST 1.0**	SAF, ITT, PP by treatment arm

	Missing CR – Complete Response PR – Partial Response SD – Stable Disease PD – Progression of Disease Not applicable / Not assessable / Unknown **ENETS Score following RECIST 1.1** Missing CR – Complete Response PR – Partial Response SD – Stable Disease PD – Progression of Disease Not applicable / Not assessable / Unknown	
Target lesion definition at baseline, local radiological tumor assessment	**Total number of target lesions** **Location of target lesion** Missing CNS supratentorial […] Other (adhoc codes) **Status of lesion** Missing New Lesion / Baseline Lesion Splitted Lesion Merged Lesion	SAF, ITT, PP By treatment arm
Target lesion definition at baseline, local radiological tumor assessment, patient based analysis	**Number of target lesions per patient** Quantitative statistical parameters **Location of target lesion (multiple response)** Total CNS supratentorial […] Other (adhoc codes) **Status of lesion (multiple response)** Tota New Lesion / Baseline Lesion Splitted Lesion Merged Lesion	SAF, ITT, PP By treatment arm
Target lesion definition at baseline, centralized radiological tumor assessment	**Total number of target lesions** **Location of target lesion** Missing CNS supratentorial […] Other (adhoc codes) **Status of lesion** Missing New Lesion / Baseline Lesion Splitted Lesion Merged Lesion	SAF, ITT, PP By treatment arm
Target lesion definition at baseline, centralized radiological tumor assessment, patient based analysis	**Number of target lesions per patient** Quantitative statistical parameters **Location of target lesion (multiple response)** Total CNS supratentorial […]	SAF, ITT, PP By treatment arm

	Other (adhoc codes) **Status of lesion (multiple response)** Tota New Lesion / Baseline Lesion Splitted Lesion Merged Lesion	
Non-target lesion definition at baseline, local radiological tumor assessment	**Total number of non target lesions** **Location of non-target lesion** Missing CNS supratentorial […] Other (adhoc codes)	SAF, ITT, PP By treatment arm
Non-target lesion definition at baseline, local radiological tumor assessment, patient based analysis	**Number of non-target lesions per patient** Quantitative statistical parameters **Location of non-target lesion (multiple response)** Total CNS supratentorial […] Other (adhoc codes)	SAF, ITT, PP By treatment arm
Non-target lesion definition at baseline, centralized radiological tumor assessment	**Total number of non-target lesions** **Location of non-target lesion** Missing CNS supratentorial […] Other (adhoc codes)	SAF, ITT, PP By treatment arm
Non-target lesion definition at baseline, centralized radiological tumor assessment, patient based analysis	**Number of non-target lesions per patient** Quantitative statistical parameters **Location of non-target lesion (multiple response)** Total CNS supratentorial […] Other (adhoc codes)	SAF, ITT, PP By treatment arm
Extent of exposure and drug concentration data		
Initial daily dose administered [mg]	Quantitative statistical parameters *For STZ-5FU patient separately for the two components*	SAF, ITT, PP By treatment arm
Average actual daily dose [mg/kg] (excluding interruptions)	Quantitative statistical parameters *For STZ-5FU patient separately for the two components*	SAF, ITT, PP By treatment arm
Number of dose adjustment per patient (excluding interruptions)	Quantitative statistical parameters In categories: Missing No dose adjustments 1 dose adjustment 2 dose adjustments 3 dose adjustments More than 3 dose adjustment *For STZ-5FU patient separately for the two components*	SAF, ITT, PP By treatment arm
Number of dose increases per patient (excluding interruptions)	Quantitative statistical parameters In categories: Missing	SAF, ITT, PP By treatment arm

	No dose increases 1 dose increase 2 dose increases 3 dose increases More than 3 dose increases *For STZ-5FU patient separately for the two components*	
Reason for dose increase (excluding interruptions)	Total number of documented increases **Reason for dose increase** Missing Adverse Event/Toxicity Dosing error Other Not applicable/Initial dose *For STZ-5FU patient separately for the two components*	SAF, ITT, PP By treatment arm
Number of dose decreases per patient (excluding interruptions)	Quantitative statistical parameters In categories: Missing No dose decreases 1 dose decrease 2 dose decreases 3 dose decreases More than 3 dose decreases *For STZ-5FU patient separately for the two components*	SAF, ITT, PP By treatment arm
Reason for dose decrease (excluding interruptions)	Total number of documented decreases **Reason for dose** de**crease** Missing Adverse Event/Toxicity Dosing error Other Not applicable/Initial dose *For STZ-5FU patient separately for the two components*	SAF, ITT, PP By treatment arm
Number of dosage interruptions per patient	Quantitative statistical parameters In categories: Missing No dose interruptions 1 dose interruption 2 dose interruptions 3 dose interruptions More than 3 dose interruptions *For STZ-5FU patient separately for the two components*	SAF, ITT, PP By treatment arm
Reason for dose interruptions (excluding interruptions)	Total number of documented interruptions **Reason for dose** de**crease** Missing Adverse Event/Toxicity Dosing error Other Not applicable/Initial dose *For STZ-5FU patient separately for the two components*	Subgroup of patients with interruptions SAF, ITT, PP By treatment arm

Duration of interruptions [days]	Quantitative statistical parameters *For STZ-5FU patient separately for the two components*	SAF, ITT, PP By treatment arm
Duration of exposure [days]	Quantitative statistical parameters *For STZ-5FU patient separately for the two components*	SAF, ITT, PP By treatment arm
14.2 Efficacy Data		
Progression free survival rate at 12 months (PFS1R12m) according to RECIST criteria 1.0	Missing Yes No Separately for **Main analysis** **Conservative analysis** **Optimistic analysis** Including p-value	ITT, PP by treatment arm
Progression free survival to 1st line treatment (PFS1) according to local assessment using RECIST criteria version 1.0	Time to events analysis Descriptive summaries of Kaplan-Meier estimates (Number of events, number of censored, 25%, 50% and 75% quartiles including 95% CI) Kaplan-Meier curve Including p-value from log rank test	ITT, PP by treatment arm
Progression free survival to 1st line treatment (PFS1) according to central assessment using RECIST criteria version 1.0	Time to events analysis Descriptive summaries of Kaplan-Meier estimates (Number of events, number of censored, 25%, 50% and 75% quartiles including 95% CI) Kaplan-Meier curve Including p-value from log rank test	ITT, PP by treatment arm
Progression free survival to 1st line treatment (PFS1) according to central assessment using RECIST criteria version 1.1	Time to events analysis Descriptive summaries of Kaplan-Meier estimates (Number of events, number of censored, 25%, 50% and 75% quartiles including 95% CI) Kaplan-Meier curve Including p-value from log rank test	ITT, PP by treatment arm
Progression free survival to 1st line treatment (PFS1) according to central assessment using ENETS SCORE RECIST criteria version 1.0	Time to events analysis Descriptive summaries of Kaplan-Meier estimates (Number of events, number of censored, 25%, 50% and 75% quartiles including 95% CI) Kaplan-Meier curve Including p-value from log rank test	ITT, PP by treatment arm
Progression free survival to 1st line treatment (PFS1) according to central assessment using ENETS SCORE RECIST criteria version 1.1	Time to events analysis Descriptive summaries of Kaplan-Meier estimates (Number of events, number of censored, 25%, 50% and 75% quartiles including 95% CI) Kaplan-Meier curve Including p-value from log rank test	ITT, PP by treatment arm
Time to first progression (TTP1) according to local assessment using RECIST criteria version 1.0	Time to events analysis Descriptive summaries of Kaplan-Meier estimates (Number of events, number of censored, 25%, 50% and 75% quartiles including 95% CI) Kaplan-Meier curve Including p-value from log rank test	ITT, PP by treatment arm
Time to first progression (TTP1) according to central assessment	Time to events analysis	ITT, PP by treatment arm

using RECIST criteria version 1.0	Descriptive summaries of Kaplan-Meier estimates (Number of events, number of censored, 25%, 50% and 75% quartiles including 95% CI) Kaplan-Meier curve Including p-value from log rank test	
Time to first progression (TTP1) according to central assessment using RECIST criteria version 1.1	Time to events analysis Descriptive summaries of Kaplan-Meier estimates (Number of events, number of censored, 25%, 50% and 75% quartiles including 95% CI) Kaplan-Meier curve Including p-value from log rank test	ITT, PP by treatment arm
Time to first progression (TTP1) according to central assessment using ENETS SCORE RECIST criteria version 1.0	Time to events analysis Descriptive summaries of Kaplan-Meier estimates (Number of events, number of censored, 25%, 50% and 75% quartiles including 95% CI) Kaplan-Meier curve Including p-value from log rank test	ITT, PP by treatment arm
Time to first progression (TTP1) according to central assessment using ENETS SCORE RECIST criteria version 1.1	Time to events analysis Descriptive summaries of Kaplan-Meier estimates (Number of events, number of censored, 25%, 50% and 75% quartiles including 95% CI) Kaplan-Meier curve Including p-value from log rank test	ITT, PP by treatment arm
Overall survival (OS)	Time to events analysis Descriptive summaries of Kaplan-Meier estimates (Number of events, number of censored, 25%, 50% and 75% quartiles including 95% CI) Kaplan-Meier curve Including p-value from log rank test	ITT, PP by treatment arm
Correlation of OS and PFS1 according to local assessment using RECIST criteria version 1.0	Scatterplot and correlation coefficient	ITT, PP by treatment arm
Correlation of OS and PFS1 according to central assessment using RECIST criteria version 1.0	Scatterplot and correlation coefficient	ITT, PP by treatment arm
Correlation of OS and PFS1 according to central assessment using RECIST criteria version 1.1	Scatterplot and correlation coefficient	ITT, PP by treatment arm
Correlation of OS and PFS1 according to central assessment using ENETS SCORE RECIST criteria version 1.0	Scatterplot and correlation coefficient	ITT, PP by treatment arm
Correlation of OS and PFS1 according to central assessment using ENETS SCORE RECIST criteria version 1.1	Scatterplot and correlation coefficient	ITT, PP by treatment arm
Objective response rate (ORR) according to local assessment	Missing Yes No	ITT, PP by treatment arm, by evaluation following the regular 12-week basis
Objective response rate (ORR) according to central assessment	Missing Yes No	ITT, PP by treatment arm, by evaluation following the regular 12-week basis

Overall response rate according to local assessment	Quantitative statistical parameters Results of the logistic regression	ITT, PP By treatment arm
Overall response rate according to central assessment	Quantitative statistical parameters Results of the logistic regression	ITT, PP By treatment arm
Type and location of tumor assessment post-baseline, local radiological tumor assessment	Total number of tumor assessments **Type of tumor assessment** Missing Triphasic CT Multiple-phase MRI Other (adhoc codes) **Location of tumor assessment** Missing CNS supratentorial CNS infratentorial […] Gall bladder Other (adhoc codes) **Overall response following RECIST 1.0** Missing CR – Complete Response PR – Partial Response SD – Stable Disease PD – Progression of Disease Not applicable / Not assessable / Unknown	ITT, PP by treatment arm by evaluation week
Type and location of tumor assessment post-baseline, centralized radiological tumor assessment	Total number of tumor assessments **Type of tumor assessment** Missing Triphasic CT Multiple-phase MRI Other (adhoc codes) **Location of tumor assessment** Missing CNS supratentorial CNS infratentorial […] Gall bladder Other (adhoc codes) **Tumor density** Quantitative statistical parameters **Overall response following RECIST 1.0** Missing CR – Complete Response PR – Partial Response SD – Stable Disease PD – Progression of Disease Not applicable / Not assessable / Unknown **Overall response following RECIST 1.1** Missing CR – Complete Response	ITT, PP by treatment arm by evaluation week

	PR – Partial Response SD – Stable Disease PD – Progression of Disease Not applicable / Not assessable / Unknown **ENETS Score following RECIST 1.0** Missing CR – Complete Response PR – Partial Response SD – Stable Disease PD – Progression of Disease Not applicable / Not assessable / Unknown **ENETS Score following RECIST 1.1** Missing CR – Complete Response PR – Partial Response SD – Stable Disease PD – Progression of Disease Not applicable / Not assessable / Unknown	
14.3 Safety Data		
14.3.1 Adverse Events		
Event based summary of TEAEs	Total number of TEAE Number of related TEAEs Number of TEAEs resulting in permanent discontinuation of study drug Number of non-serious TEAEs Number of non-serious related TEAEs Number of non-serious TEAEs resulting in permanent discontinuation of study drug Number of serious TEAEs Number of serious related TEAEs Number of serious TEAEs resulting in permanent discontinuation of study drug Number of TEAEs with outcome death	SAF In total and by treatment arm
Patient based summary of TEAEs	Total number of patients Number of patients without any TEAE Number of patients with at least one TEAE Number of patients with at least one related TEAE Number of patients with at least one TEAE resulting in permanent discontinuation of study drug Number of patients with at least one non-serious TEAEs Number of patients with at least one non-serious related TEAEs Number of patients with at least one non-serious TEAEs resulting in permanent discontinuation of study drug Number of patients with at least one serious TEAEs Number of patients with at least one serious related TEAEs Number of patients with at least one serious TEAEs resulting in permanent discontinuation of study drug Number of patients with TEAEs with outcome death	SAF In total and by treatment arm

Classification of TEAE	Total number of TEAEs **SAE** Yes No **If yes, serious criteria (multiple response)** Death Life-threatening Hospitalization or prolongation of existing hospitalization Persistent or significant disability or incapacity Congenital abnormality or birth defect Other medically important condition **CTCAE Grade/Severity** Missing CTCAE grade 1 CTCAE grade 2 CTCAE grade 3 CTCAE grade 4 CTCAE grade 5 CTCAE not defined** Mild* Moderate* Severe* Unknown* Not assessable* **: only to be documented if "CTCAE grade" documented as "not defined";* ***: only if severity is missing in case "CTCAE grade" is documented as "not defined"* **Relationship by reporter** Missing Yes No Unknown Not assessable Not applicable **Action taken with study drug** Missing None Discontinued Reduced/interrupted Dosage increased Unknown Not applicable **Outcome** Missing Ongoing Resolved Recovered with sequelae Fatal Unknown Not assessable	SAF In total and by treatment arm
Event based TEAEs by MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm

Event based related TEAEs by MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Event based TEAEs by relationship, MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Event based TEAEs by CTCAE grade, MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Event based TEAEs by MedDRA SOC and PT resulting in permanent discontinuation of study drug by MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Event based TEAEs by action taken, MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Event based non-serious TEAEs by MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Event based non-serious related TEAEs by MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Event based non-serious TEAEs by relationship, MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Event based non-serious TEAEs by CTCAE grade, MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Event based non-serious TEAEs resulting in permanent discontinuation of study drug by MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Event based non-serious TEAEs by action taken, MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Patient based TEAEs by MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm
Patient based TEAEs by relationship, MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm
Patient based TEAEs by CTCAE grade, MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm
Patient based TEAEs by MedDRA SOC and PT resulting in permanent discontinuation of study drug by MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm
Patient t based TEAEs by action taken, MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm
Patient based non-serious TEAEs by MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm

Patient based non-serious related TEAEs by MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm
Patient based non-serious TEAEs by relationship, MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm
Patient based non-serious TEAEs by CTCAE grade, MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm
Patient based non-serious TEAEs resulting in permanent discontinuation of study drug by MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm
Patient based non-serious TEAEs by action taken, MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm
14.3.2 Deaths, Other Serious and Significant Adverse Events		
Event based serious TEAEs by MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Event based serious related TEAEs by MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Event based serious TEAEs by relationship, MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Event based serious TEAEs by CTCAE grade, MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Event based serious TEAEs resulting in permanent discontinuation of study drug by MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Event based TEAEs leading to death by MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Event based serious TEAEs by action taken, MedDRA SOC and PT	Total number of TEAEs MedDRA SOC and PT	SAF In total and by treatment arm
Patient based serious TEAEs by MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm
Patient based serious related TEAEs by MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm
Patient based serious TEAEs by relationship, MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm
Patient based serious TEAEs by CTCAE grade, MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm
Patient based serious TEAEs resulting in permanent discontinuation of study drug by MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm
Patient based TEAEs leading to death by MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm

Patient based serious TEAEs by action taken, MedDRA SOC and PT	Total number of patients MedDRA SOC and PT	SAF In total and by treatment arm
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events		
No TFL output, only heading for report		
14.3.4 Laboratory Data and Other Safety Variables		
Laboratory data		
Laboratory – sampling and fasting condition	**Were any lab samples obtained?** Total Missing Yes No **Was Patient fasting?** Total Missing Yes No Unknown	SAF, ITT, PP by treatment arm by visit
Laboratory – pregnancy test	**Were any lab samples for pregnancy test obtained?** Total Missing Yes No **If yes:** **Sample** Total Serum Urine *(not at Baseline visit)* **Result of pregnancy test** Total Missing Negative Positive	Subgroup of females with child bearing potential SAF, ITT, PP by treatment arm by visit (only those visits where pregnancy test is mandatory or optional performed tests)
Laboratory – Hematology sample collection	Total Missing Yes No	SAF, ITT, PP by treatment arm by visit
Laboratory – Hematology results	**Per laboratory parameter in SI unit** Quantitative statistical parameters	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit
Laboratory – Hematology results, change from baseline	**Per laboratory parameter in SI unit** Quantitative statistical parameters	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit
Laboratory – Hematology results, categorical analysis	**Per laboratory parameter** Total LLN Normal ULN	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit

Laboratory – Serum Biochemistry sample collection	Total Missing Yes No	SAF, ITT, PP by treatment arm by visit
Laboratory – Serum Biochemistry results	**Per laboratory parameter in SI unit** Quantitative statistical parameters	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit
Laboratory – Serum Biochemistry results, change from baseline	**Per laboratory parameter in SI unit** Quantitative statistical parameters	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit
Laboratory – Serum Biochemistry results, categorical analysis	**Per laboratory parameter** Total LLN Normal ULN	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit
Laboratory – Urinalysis sample collection	Total Missing Yes No	SAF, ITT, PP by treatment arm by visit
Laboratory – Urinalysis results	**Per laboratory parameter in SI unit** Quantitative statistical parameters	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit
Laboratory – Urinalysis results, change from baseline	**Per laboratory parameter in SI unit** Quantitative statistical parameters	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit
Laboratory – Urinalysis results results, categorical analysis	**Per laboratory parameter** Total LLN Normal ULN	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit
Laboratory – Dipstick Urinalysis sample collection	Total Missing Yes No	SAF, ITT, PP by treatment arm by visit
Laboratory – Dipstick Urinalysis results	**pH** Total Missing <=4.5 5.0 5.5 6.0 6.5 7.0 7.5 >=8.0 **Proteins, Glucose, Blood, Ketones, WBC** Total Missing Negative	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit

	Trace 1+ 2+ 3+ 4+	
Laboratory – Coagulation sample collection	Total Missing Yes No	SAF, ITT, PP by treatment arm by visit
Laboratory – Coagulation results	**Per laboratory parameter in SI unit** Quantitative statistical parameters	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit
Laboratory – Coagulation results, change from baseline	**Per laboratory parameter in SI unit** Quantitative statistical parameters	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit
Laboratory – Coagulation results, categorical analysis	**Per laboratory parameter** Total LLN Normal ULN	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit
Laboratory – Serum Lipide profile sample collection	Total Missing Yes No	SAF, ITT, PP by treatment arm by visit
Laboratory – Serum Lipide profile results	**Per laboratory parameter in SI unit** Quantitative statistical parameters	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit
Laboratory – Serum Lipide profile results, change from baseline	**Per laboratory parameter in SI unit** Quantitative statistical parameters	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit
Laboratory – Serum Lipide profile results, categorical analysis	**Per laboratory parameter** Total LLN Normal ULN	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit
Laboratory – Vitamin B_{12} test sample collection	Total Missing Yes No	SAF, ITT, PP by treatment arm by visit
Laboratory – Vitamin B_{12} test results	Quantitative statistical parameters	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit
Laboratory – Vitamin B_{12} test, change from baseline	Quantitative statistical parameters	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit

Laboratory – Vitamin B_{12} test, categorical analysis	Total LLN Normal ULN	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit
Abnormal laboratory values CTCAE grades 1-4	**Per CTCAE Term (as specified in section 7.3.2)** Total Grade 1 Grade 2 Grade 3 Grade 4	SAF, ITT, PP by treatment arm by visit
Laboratory – CgA	Quantitative statistical parameters	ITT, PP by treatment arm by visit
Laboratory – CgA, change from baseline	Quantitative statistical parameters including p-value	ITT, PP by treatment arm by visit
Laboratory – Circulating tumor cells	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit by central assessor
Laboratory – Circulating tumor cells, change from baseline	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit by central assessor
Laboratory – NETest score	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit by central assessor
Laboratory – NETest score, change from baseline	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit by central assessor
Laboratory – Hepatitis viremia sample collection	Total Missing Yes No	SAF, ITT, PP by treatment arm by visit
Laboratory – Hepatitis viremia results	**Per laboratory parameter** Total Missing negative positive Only at Screening: **Is Patient being monitored routinely for HBV-DNA?** Total Missing Yes No Not applicable **Is Patient being monitored routinely for HCV-RNA?** Total Missing Yes	Subgroup of patients with collected sample SAF, ITT, PP by treatment arm by visit

	No Not applicable	
Collection of paraffin embedded tumor block at screening	**Was a Paraffin Embedded Tumour Block collected? (Inclusion criteria No.4)** Total Missing Yes No **Time from date of ICF to collection date of Paraffin Embedded Tumour Block** Quantitative statistical parameters	SAF, ITT, PP by treatment arm
Other safety data		
Physical examination post baseline	**Performance of physical examination post baseline** Total Missing Yes No **Any changes from the previous visit?** Total Missing Yes No **If yes:** *Separately by body system* **General Appearance** **Skin** **[…]** **Basic Nervous System** **Other (MedDRA PT)** Total Missing Normal Abnormal, not clinically significant Abnormal, clinically significant	SAF, ITT, PP by treatment arm by visit
ECOG performance status post baseline	Total Missing 0: Fully active […] 1: Restricted in physically strenuous activity […] 2: Ambulatory and capable of all selfcare […] 3: Capable of only limited selfcare […] 4: Completely disabled […] 5: Dead	SAF, ITT, PP by treatment arm by visit
12 lead-ECG worst documented diagnosis post baseline	Total Missing Normal Abnormal, not clinically significant Abnormal, clinically significant Non-evaluable	SAF, ITT, PP by treatment arm by visit
Weight and BMI post baseline and change from baseline	**Body weight [kg]** **Body weight [kg] – change from baseline** **BMI [kg/m²]** **BMI [kg/m²] – change from baseline** Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit

Vital signs post baseline and change from baseline	**Performance of vital signs assessment** Total Missing Yes No If yes: *Separately by measurement* **Systolic blood pressure [mmHg]** **Systolic blood pressure [mmHg] – change from baseline** **Diastolic blood pressure [mmHg]** **Diastolic blood pressure [mmHg] – change from baseline** **Heart rate [beats per minute]** **Heart rate [beats per minute] – change from baseline** **Body temperature [°C]** **Body temperature [°C] – change from baseline** **Respiration Rate [breaths per minute]** **Respiration Rate [breaths per minute] – change from baseline** Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
Follow up (30 days and survival)	**Kind of follow-up** Missing Visit Phone Contact Other **Is the Subject alive** Missing Yes No Unknown **If no, cause of death:** Total Missing Disease Progression Toxicity Chronic disease not related to an AE or to progression Other cause (adhoc codes) **If yes, did the subject receive any anticancer treatment after discontinuation of study treatment / since last visit?** Total Yes No Unknown **If yes, specify therapy type:** Total Biotherapy Chemotherapy Hormonal therapy Immunotherapy Targeted therapy Peptide Receptor Radionucleic Therapy (PRRT) Radiofrequency ablation (RFA) Radioembolization (SIRF) Selective Chemo embolization (TACE) Cryoablation Biopsy	SAF, ITT, PP by treatment arm by visit

	Other	
14.4 Other data		
Number of patients consented per protocol version	Total Missing Version 2.0, 30th of January 2014 Version 2.01, 1st of September 2014 Version 3.0, 26th of November 2014	SAF, ITT, PP by treatment arm
Did the Subject sign the Informed Consent for the optional CTC and NETest Sub Studies?	Total Missing Yes No Not applicable (starting only with Prot. Vers. 3.0)	SAF, ITT, PP by treatment arm
Chest X-Ray	Total Missing Normal Clinically insignificant abnormality Clinically significant abnormality	SAF, ITT, PP by treatment arm
Pulmonary function test	**Spirometry done?** Total Missing Yes No If, yes: **Findings** Total Missing Normal Clinically insignificant abnormality Clinically significant abnormality Other **Diffusion Capacity for CO (DLCO) done?** Total Missing Yes No If, yes: **Findings** Total Missing Normal Clinically insignificant abnormality Clinically significant abnormality Other **Pulse Oximetry done?** Total Missing Yes No If, yes: **Findings** Total Missing Normal Clinically insignificant abnormality	SAF, ITT, PP by treatment arm

	Clinically significant abnormality Other	
Bronchoscopy	**Was Infection Agent identified?** Total Missing Yes No **Was Broncho-Alveloar Lavage (BAL) done?** Total Missing Yes No **Was BAL Cell Count done?** Total Missing Yes No **Was Alveolar Hemorrhage seen?** Total Missing Yes No **Findings** Total Missing Normal Clinically insignificant abnormality Clinically significant abnormality Other **Was Transbronchial Biopsy done?** Total Missing Yes No If, yes: **Findings** Total Missing Malignancy Infection Non-infectious Pneumonitis Other If, non-infectious Pneumonitis: **Specification of non-infectious Pneumonitis** Total Missing Lymphoid interstitial pneumonia (LIP) Organizing Pneumonia Other	SAF, ITT, PP by treatment arm
Patient questionnaires		
Check for patient questionnaires	**Was the EORTC QLQ-C30 completed by the patient?** Total Missing Yes	SAF, ITT, PP by treatment arm by visit

	No **Was the EORTC QLQ GINET21 completed by the patient?** Total Missing Yes No	
EORTC QLQ-C30, global health status / QoL score	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-C30, physical functioning score	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-C30, role functioning score	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-C30, emotional functioning score	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-C30, cognitive functioning score	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-C30, social functioning score	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-C30, symptom score, fatigue	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-C30, symptom score, nausea and vomiting	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-C30, symptom score, pain	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-C30, symptom score, dyspnoea	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-C30, symptom score, insomnia	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-C30, symptom score, appetite loss	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-C30, symptom score, constipation	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-C30, symptom score, diarrhoea	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-C30, symptom score, financial difficulties	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-C30, global health status/ QoL frequency table	**29. How would you rate your overall health during the past week?** **30. How would you rate your overall quality of life during the past week?** Total Missing 1 (very poor)	

	2 3 4 5 6 7 (excellent)	
EORTC QLQ-C30, functional scales, physical functioning items frequency table	**1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?** **2. Do you have any trouble taking a long walk?** **3. Do you have any trouble taking a short walk outside of the house?** **4. Do you need to stay in bed or a chair during the day?** **5. Do you need help with eating, dressing, washing yourself or using the toilet?** Total Missing Not at all A little Quite a bit Very much	
EORTC QLQ-C30, functional scales, role functioning items frequency table	**6. Were you limited in doing either your work or other daily activities?** **7. Were you limited in pursuing your hobbies or other leisure time activities?** Total Missing Not at all A little Quite a bit Very much	
EORTC QLQ-C30, functional scales, emotional functioning items frequency table	**21. Did you feel tense?** **22. Did you worry?** **23. Did you feel irritable?** **24. Did you feel depressed?** Total Missing Not at all A little Quite a bit Very much	
EORTC QLQ-C30, functional scales, cognitive functioning items frequency table	**20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?** **25. Have you had difficulty remembering things?** Total Missing Not at all A little Quite a bit Very much	
EORTC QLQ-C30, functional scales, social functioning items frequency table	**26. Has your physical condition or medical treatment interfered with your family life?** **27. Has your physical condition or medical treatment interfered with your social activities?** Total Missing Not at all A little Quite a bit Very much	

EORTC QLQ-C30, symptoms scales, fatigue items frequency table	**10. Did you need to rest?** **12. Have you felt weak?** **18. Were you tired?** Total Missing Not at all A little Quite a bit Very much	
EORTC QLQ-C30, symptoms scales, nausea and vomiting items frequency table	**14. Have you felt nauseated?** **15. Have you vomited?** Total Missing Not at all A little Quite a bit Very much	
EORTC QLQ-C30, symptoms scales, pain items frequency table	**9. Have you had pain?** **19. Did pain interfere with your daily activities?** Total Missing Not at all A little Quite a bit Very much	
EORTC QLQ-C30, symptoms scales, dyspnoea frequency table	**8. Were you short of breath?** Total Missing Not at all A little Quite a bit Very much	
EORTC QLQ-C30, symptoms scales, insomnia frequency table	**11. Have you had trouble sleeping?** Total Missing Not at all A little Quite a bit Very much	
EORTC QLQ-C30, symptoms scales, appetite loss frequency table	**13. Have you lacked appetite?** Total Missing Not at all A little Quite a bit Very much	
EORTC QLQ-C30, symptoms scales, constipation frequency table	**16. Have you been constipated?** Total Missing Not at all A little Quite a bit Very much	
EORTC QLQ-C30, symptoms scales, diarrhoea frequency table	**17. Have you had diarrhea?** Total Missing Not at all A little Quite a bit Very much	

EORTC QLQ-C30, symptoms scales, financial difficulties frequency table	**28. Has your physical condition or medical treatment caused you financial difficulties?** Total Missing Not at all A little Quite a bit Very much	
EORTC QLQ-GINET21, endocrine symptoms score	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-GINET21, G.I. symptoms score	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-GINET21, treatment related symptoms score	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-GINET21, social function score	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-GINET21, disease related worries score	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-GINET21, muscle /bone pain symptom score	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-GINET21, sexual function score	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-GINET21, Information / communication function score	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-GINET21, body Image score	Quantitative statistical parameters	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-GINET21, endocrine symptoms items frequency table	**31. Did you have hot flushes?** **32. Have you noticed or been told by others that you looked flushed/red?** **33. Did you have night sweats?** Total Missing Not at all A little Quite a bit Very much	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-GINET21, G.I. symptoms items frequency table	**34. Did you have abdominal discomfort?** **35. Did you have a bloated feeling in your abdomen?** **36. Have you had a problem with passing wind/gas flatulence?** **37. Have you had a acid indigestion or heartburn?** **38. Have you had difficulties with eating?** Total Missing Not at all A little Quite a bit Very much	SAF, ITT, PP by treatment arm by visit

EORTC QLQ-GINET21, treatment related symptoms items frequency table	**39. Have you had side-effects from your treatment?** **40. Have you had a problem from repeated injections?** Total Missing N/A Not at all A little Quite a bit Very much **46. Has weight gain been a problem for you?** Total Missing Not at all A little Quite a bit Very much	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-GINET21, social function items frequency table	**42. Were you concerned about disruption of home life?** **44. How distressing has your illness or treatment been to those close to you?** **49. Did you have any limitations in your ability to travel?** Total Missing Not at all A little Quite a bit Very much	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-GINET21, disease related worries items frequency table	**41. Were you worried about the tumor recurring in other areas of the body?** **43. Have you worried about your health in the future?** Total Missing Not at all A little Quite a bit Very much **47. Did your worry about the results of your tests?** Total Missing N/A Not at all A little Quite a bit Very much	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-GINET21, muscle /bone pain symptom item frequency table	**48. Have you had aches or pains in your muscles or bones?** Total Missing Not at all A little Quite a bit Very much	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-GINET21, sexual function item frequency table	**51. Has the disease or treatment affected your sex life (for the worse)?** Total Missing N/A Not at all A little Quite a bit Very much	SAF, ITT, PP by treatment arm by visit

EORTC QLQ-GINET21, Information / communication function item frequency table	**50. Have you had problems receiving adequate information about your disease and treatment?** Total Missing Not at all A little Quite a bit Very much	SAF, ITT, PP by treatment arm by visit
EORTC QLQ-GINET21, body image item frequency table	**45. Has weight loss been a problem for you?** Total Missing Not at all A little Quite a bit Very much	SAF, ITT, PP by treatment arm by visit
Resource utilization		
Resource utilization - hospitalization	**Total number of documented hospital admissions** **Main reason for hospitalization** Missing Treatment AE Other **Hospital wards** Missing Oncology Internal Medicine Neurology Intensive Care Unit Step down ward Chemotherapy administration Pneumology Gastroenterology/Digestive Cardiology Other	SAF, ITT, PP by treatment arm
Resource utilization - hospitalization	**Number of nights** Quantitative statistical parameters	SAF, ITT, PP by treatment arm, by hospital ward
Resource utilization – outpatient visit	**Total number of documented outpatient visits** **Main reason for visit** Missing Treatment AE Other **Physician speciality** Missing Oncologist General medicine Pneumologist Hematologist Cardiologist Gastroenterologist Endocrinologist Nurse (Oncology, general medicine) Other	SAF, ITT, PP by treatment arm

Resource utilization – diagnostics related to AEs	**Total number of documented diagnostics related to AEs** **Diagnostics performed (multiple response)** Missing Broncoscopy Pulmonary function test Biopsy CT Scan RMN Chest X- ray Chest CT ECG Laboratory test Physical examination Other	SAF, ITT, PP by treatment arm
Resource utilization – procedures related to AEs	**Total number of documented procedures related to AEs** **Procedures performed (multiple response)** Missing Surgery Dialysis Drug prescription and treatment Study treatment interruption Other	SAF, ITT, PP by treatment arm
16.2 Patient Data Listings		
Listing of patients discontinued from study	Center, Patient number, randomized treatment sequence, treatment before discontinuation, sex, age, reason for discontinuation	
Listing of protocol deviations	Center, Patient number, randomized treatment sequence, sex, age, description of protocol deviation	
Listing of patients excluded from the efficacy analysis	Center, Patient number, randomized treatment sequence, sex, age, reason from exclusion from the analysis populations	
Listing of demographic and disease diagnosis data	Center, Patient number, randomized treatment sequence, age, sex, race, inclusion into analysis sets, first diagnosis data (date of first diagnosis, primary site of tumor, ENETS TMN classification), diagnosis data at study entry (date of confirmation, ENETS TNM classification, location of tumor)	
Listing of local radiological tumor assessments	Center, Patient number, randomized treatment sequence, age, sex, evaluation timepoint, date of assessment, type, location, overall response according to RECIST 1.0	
Listing of central radiological tumor assessments	Center, Patient number, randomized treatment sequence, age, sex, evaluation timepoint, date of assessment, type, location, tumor density, , overall response according to RECIST 1.0/1.1/ENETS score 1.0/1.1,	
Listing of target lesions of local radiological tumor assessments	Center, Patient number, randomized treatment sequence, age, sex, location, status, date, longest diameter, reappearance, disappearance	
Listing of target lesions of central radiological tumor assessments	Center, Patient number, randomized treatment sequence, age, sex, location, status, date, longest diameter, short axis, reappearance, disappearance	
Listing of non-target lesions of local radiological tumor assessments	Center, Patient number, randomized treatment sequence, age, sex, date, status	
Listing of non-target lesions of central radiological tumor assessments	Center, Patient number, randomized treatment sequence, age, sex, date, status	

Listing of adverse events	Center, Patient number, randomized treatment sequence, treatment age, sex, AE term including MedDRA PT, start date, end date, duration, TEAE, time since first intake of treatment to AE onset, SAE and details, CTCAE grade/severity, relationship, action taken, additional therapy, dechallenge, rechallenge, outcome	
Listing of serious adverse events	Center, Patient number, randomized treatment sequence, treatment age, sex, AE term including MedDRA PT, start date, end date, duration, TEAE, time since first intake of treatment to AE onset, SAE and details, CTCAE grade/severity, relationship, action taken, additional therapy, dechallenge, rechallenge, outcome	
Listing of deaths	Center, Patient number, randomized treatment sequence, treatment age, sex, AE term including MedDRA PT, start date, end date, duration, TEAE, time since first intake of treatment to AE onset, SAE and details, CTCAE grade/severity, relationship, action taken, additional therapy, dechallenge, rechallenge, outcome	