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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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Endocrine neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON55657

Source
ToetsingOnline

Brief title
Efficacy and safety of everolimus

Condition

- Endocrine neoplasms malignant and unspecified

Synonym
Islet Cell Carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Grupo Espanol de Tumores Neuroendocrinos (GETNE)
Source(s) of monetary or material Support: European Neuroendocrine Tumours Society (ENETS) Germany,Novartis verstrekt het budget voor deze studie. ,Spaanse Verenging: Grupo Espanol de Tumores Neuroendocrinos (GETNE)

Intervention

Keyword: everolimus, pancreatic neuroendocrine tumours, progression pNET, STZ-5FU chemotherapy

Outcome measures

Primary outcome

* 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.

* 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.

Secondary outcome

* 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).

Study description

Background summary

STZ 5-FU chemotherapy is the actual standard of care for advanced pNETS in the European Union (ENETS guidelines; Neuroendocrinology 2012). Everolimus has been recently approved for its use in advanced pNETs by the FDA and in Europe by the EMA. A randomized study is needed to have a clear knowledge about the best sequence for its administration; this is, before or after palliative chemotherapy.

Study objective

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.

Primary
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.

Secondary
* 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.

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.

Intervention

50% of the patients will recieve everolimus followed by chemotherapy with STZ-5FU upon progression and the other 50% of patients the reverse sequence, chemotherapy with STZ-5FU followed by everolimus upon progression, in advanced progressive pNETs.

Study burden and risks

Not applicable

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

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 mm2 and/or Ki-67 index * 2%
G2: 2*20 mitoses per 2 mm2 and/or Ki-67 index >2% and * 20%
4. Patients from whom a paraffin-embedded primary tumour or metastasis block is available and to be sent by courier. Patient should give his/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 judgement, 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 109/L, platelets > 100 x 109/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.

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 mm2 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 O2 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 durling the trial.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-03-2016
Enrollment:	22

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Afinitor
Generic name:	Everolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Fluorouracil
Generic name:	5-Fluorouracil (5FU)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Zonasar
Generic name:	Streptozotocin

Ethics review

Approved WMO Date:	17-12-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-03-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2015

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2021

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-000726-66-NL
CCMO	NL48886.018.14

Study results

Results posted: 01-08-2022

First publication
14-07-2022