A randomized, open-label phase II multicenter study evaluating the efficacy of oral Everolimus alone or in combination with Pasireotide LAR i.m. in advanced progressive pancreatic neuroendocrine tumors (PNET) * The COOPERATE-II study

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PrimaryTo estimate the treatment effect of everolimus in combination with pasireotide LAR relative to everolimus alone on progression-free survival (PFS) in patients with advanced PNET and to assess the predictive probability of success in a...

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

Summary

ID

NL-OMON38419

Source
ToetsingOnline

Brief title
COOPERATE 2 study

Condition

- Endocrine neoplasms malignant and unspecified

Synonym
advanced progressive pancreatic neuroendocrine tumors (PNET), Pancreascancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V.

Intervention

Keyword: advanced progressive pancreatic neuroendocrine tumors (PNET), Everolimus alone or in combination with Pasireotide LAR, Phase II

Outcome measures

Primary outcome

PFS per RECIST 1.0. PFS is defined as the time from randomization to the date

of the first documented tumor progression or death from any cause, whichever

comes first

Secondary outcome

-Incidence of AEs, serious adverse events (SAEs), changes from baseline in

laboratory results (hematology, biochemistry), using (CTCAE version 3.0)

-ORR and DCR per RECIST 1.0

-Duration of OR per RECIST 1.0

-OS, defined as the time from date of randomization to date of death due to any

cause

-PFS per RECIST 1.0

-Everolimus PK parameters (Cmin, Cmax, AUC0-24hr) and pasireotide LAR PK

parameters (Cmin, Cmax,p2)

-Everolimus PK parameters (Cmin, Cmax, AUC0-24hr) when everolimus was

administered alone or in combination with pasireotide LAR

-Pasireotide LAR PK parameters (Cmin, Cmax,p2) when administered in combination with everolimus

Exploratory

-CgA and NSE change from baseline level; PFS

-Everolimus PK parameter (Cmin, Cmax, AUC0-24hr) and efficacy and safety end-points

-Levels of baseline blood/tumor biomarkers, in relation to response to everolimus alone or in combination with pasireotide

-Changes from baseline and/or actual levels of potential response and/or secretion biomarkers over time

-Changes from baseline in levels of potential response and/or secretion biomarkers in relation to response to everolimus alone or in combination with pasireotide

Study description

Background summary

Pancreatic neuroendocrine tumors (PNETs) are rare neuroendocrine neoplasms that represent approximately 5-7% of all neuroendocrine tumors (NETs) and * 3% of all pancreatic tumors (Strosberg, Gardner and Kvols 2009),
The only curative treatment option is complete surgical resection in regional or localized disease. In distant disease palliative care encompasses medical treatment of hormonal syndromes through local and/or systemic cytoreductive therapies including surgery, systemic chemotherapy, and polypeptide radionuclide receptor therapy (PRRT).
No randomized trials have shown an improvement in progression free survival (PFS) or OS for any of these combinations.

Everolimus has recently been shown to have superior antitumor efficacy compared

to placebo in patients with advanced PNET [CRAD001C2324]/RADIANT-3.

The combination of pasireotide and everolimus is currently being evaluated in a dose escalation study at the Dana Faber Cancer Institute. In this investigator-sponsored study the dose level of 10 mg was identified as recommended dose for further clinical development (Chan et al 2010).

This trial will evaluate the safety and efficacy of combining Everolimus and Pasireotide LAR.verolimus and 60 mg pasireotide LAR

Study objective

Primary
To estimate the treatment effect of everolimus in combination with pasireotide LAR relative to everolimus alone on progression-free survival (PFS) in patients with advanced PNET and to assess the predictive probability of success in a possible subsequent phase III study once 80 PFS events have been observed

Secondairy
* To evaluate the safety and tolerability profile of everolimus alone or in combination with pasireotide LAR
* To evaluate the Objective Response Rate (ORR) and Disease Control Rate (DCR)
* To evaluate the duration of response (DoR)
* To evaluate overall survival (OS)
* To estimate the treatment effect on PFS and to assess the predictive probability of success in a possible subsequent phase III study once 105 PFS events have been observed
* To assess pharmacokinetic (PK) exposures of everolimus and pasireotide LAR
* To assess potential PK drug-drug interactions between everolimus and pasireotide LAR

Exploratory
* To evaluate biochemical response (changes in CgA and NSE levels) and its association with PFS
* To evaluate the relationship between efficacy and safety parameters and everolimus PK exposure alone or in combination with pasireotide LAR PK exposure
* To assess whether baseline tumor (for patients who have a tumor tissue sample available) and/or blood biomarkers may be predictive of response to everolimus alone or in combination with pasireotide LAR
* To assess whether there is any effect of everolimus alone or in combination with pasireotide LAR on potential response and/or secretion biomarkers over time
* To assess the correlation between potential response and/or secretion biomarkers and response to everolimus alone or in combination with pasireotide LAR
* To assess on remaining biomarker samples additional hypotheses related to everolimus, pasireotide, neuroendocrine tumors, other endocrine diseases and/or

cancer which may arise from internal or external research activities (optional)

Study design

This is a prospective, global, multi-center, randomized, open-label, phase II study evaluating the safety and efficacy of everolimus alone or in combination with pasireotide LAR in patients with advanced PNET. Patients will be randomized in a 1:1 ratio to receive everolimus or everolimus plus pasireotide LAR. Randomization will be stratified by 1) prior SSA treatment (yes/no) and 2) elevated biomarkers (yes/no) (defined as chromogranin A (CgA) > 2xULN and/or NSE > 1xULN). Approximately 150 patients will be randomized globally.

Intervention

The pasireotide LAR im injections will be given every first day of a cycle (28 dagen)
The everolimus tablets(2x5 mg) will be administered daily

Study burden and risks

Toxicity of therapy and everolimis pasireotide LAR
Radiation exposure, CT scan / MRI
Frequent visits and blood sampling

An overview of all procedures during the visits are given in Appendix B of the patient information
The side effects can be found in Appendix C of the patient information
it is not certain that participation in the research directly benefit, the data can be useful for the future.
The burden on the patients is as expected from a phase II trial.

Contacts

Public
Novartis

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Scientific
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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. Advanced (unresectable or metastatic), histologically confirmed well differentiated (low to intermediate grade) pancreatic neuroendocrine tumor (PNET).
2. Radiological documentation of progressive disease within the last 12 months prior to randomization.
3. WHO performance status * 2
4. Adequate bone marrow function:
* WBC * 2.5 x 109/L,
* ANC * 1.5 x 109/L,
* Platelets * 100 x 109/L,
* Hb * 9 g/dL
5. No evidence of significant liver/pancreas disease:
* Serum total bilirubin * 1.5 x ULN,
* INR < 1.3,
* ALT or AST * 3 x ULN
* Serum lipase * 2 x ULN
6. Serum creatinine * 2.0 mg/dl and estimated glomerular filtration rate (eGFR) > 30 ml/min/m2 (calculated with MDRD formula).

Exclusion criteria

1. Patients currently requiring SSA treatment.
2. Patients who received prior therapy with mTOR inhibitors (e.g. sirolimus, temsirolimus, everolimus), or pasireotide.
3. Patients who received any cytotoxic chemotherapy, targeted therapy, SSAs, or biotherapy within the last 4 weeks.

4. Patients with more than 2 prior systemic treatment regimens
7. Prior treatment with radiolabeled SSAs within the last 12 months.
8. Patients with hepatic artery embolization, cryoablation or radiofrequency ablation of hepatic metastasis within the last 3 months prior to randomization.
9. Patients who have received radiotherapy of target lesions. Patients who have received local radiotherapy of non-target lesions for local symptom control within the last 4 weeks must have recovered from any adverse effects of radiotherapy prior to randomization.
10. Patients who have undergone major surgery/surgical therapy for any cause within 1 month or surgical therapy of loco-regional metastases within the last 3 months prior to randomization. Patients should have recovered from the treatment and have a good clinical condition before entering this study.
11. Patients receiving chronic treatment with corticosteroids or another immunosuppressive agent.
12. Patients with symptomatic cholelithiasis.
13. Patients who are not clinically euthyroid. Patients with history hypothyroidism are eligible if they are on adequate and stable replacement thyroid hormone therapy for at least 3 months.
14. Patients with abnormal coagulation (PT [INR] or aPTT elevated by 30% above normal limits).
15. QT-related exclusion criteria:
* Patients with a QTcF > 470 ms,
* History of syncope or family history of idiopathic sudden death, Long QT syndrome,
* Sustained or clinically significant cardiac arrhythmias,
* Patients with risk factors for torsades de pointes: Potassium < 3.0 mmol/L, magnesium < 0.4 mmol/L or, calcium < 1.75 mmol/L at baseline. If the electrolyte abnormalities are corrected prior to start of study drug, the patient may become eligible for the trial. Cardiac failure, clinically significant/symptomatic bradycardia or high-grade AV block,
* Concomitant medications known to prolong the QT interval (see Appendix 2).
* Concomitant disease(s) that could prolong QT such as autonomic neuropathy (caused by diabetes mellitus or Parkinson*s disease), HIV, liver cirrhosis, uncontrolled hypothyroidism or cardiac failure.
16. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
* Uncontrolled diabetes as defined by HbA1c * 8% despite adequate therapy,
* Fasting serum cholesterol > 300 mg/dL (7.75 mmol/L) OR fasting triglycerides > 2.5 x ULN despite appropriate lipid lowering medication.
* Severely impaired lung function defined as spirometry and DLCO that is 50% of the normal predicted value and/or O2 saturation that is 88% or less at rest on room air. DLCO should be adjusted to hemoglobin value and patient lung volumes.
* Patients with the presence of active or suspected acute or chronic uncontrolled infection or with a history of immunodeficiency, including a positive HIV test result (ELISA and Western blot). A HIV test will not be required; however, previous medical history will be reviewed.
* Non-malignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with this study treatment.
* History or active liver disease such as cirrhosis, decompensated liver disease, chronic active hepatitis or chronic persistent hepatitis.
* Quantifiable HBV-DNA or positive hepatitis B surface antigen (HbsAg).

* Quantifiable HCV-RNA.
* History of, or current alcohol misuse/abuse within the past 12 months.
* Known gallbladder or bile duct disease, acute or chronic pancreatitis.
* Life-threatening autoimmune and ischemic disorders.
* Patients who have a history of another primary malignancy within the last 3 years, with the exception of locally excised non-melanoma skin cancer and carcinoma in situ of uterine cervix.
* Symptomatic CNS metastases requiring corticosteroid therapy.
* Patients who have any current or prior medical condition that may interfere with the conduct of the study or the evaluation of its results in the opinion of the Investigator or the Sponsor*s Medical Monitor.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-09-2012
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Afinitor
Generic name:	Everolimus
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	N/A

Generic name:	Pasireotide LAR

Ethics review

Approved WMO Date:	16-08-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-03-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-04-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-07-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-10-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-10-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-11-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-12-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	02-01-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-01-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-03-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-04-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-10-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-10-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-07-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-08-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2010-023183-40-NL
CCMO	NL36097.042.11