A multicenter, two stage, phase II study, evaluating the efficacy of oral BEZ235 plus best supportive care (BSC) versus placebo plus BSC in the treatment of patients with advanced pancreatic neuroendocrine tumors (pNET) after failure of mTOR inhibitor therapy

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To determine whether treatment with BEZ235 plus best supportive care prolongs PFS compared with placebo plus best supportive care in patients with advanced pancreas NET, after failure of a mTOR inhibitor therapy

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

Summary

ID

NL-OMON37043

Source
ToetsingOnline

Brief title
phase 2 study to the efficacy of BEZ235 in patients with pancreas NET

Condition

- Endocrine neoplasms malignant and unspecified

Synonym
NET, pancreas neuroendocrine tumor

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: BEZ235, mTOR, pancreas NET, placebo

Outcome measures

Primary outcome

PFS rate at 16 weeks according to local radiological assessment per modified

RECIST v1.1

Secondary outcome

Frequency and severity of AEs

Other safety data as considered appropriate

ORR

DCR

DoR

Study description

Background summary

Neuroendocrine tumors (NETs) are a genetically diverse group of rare malignant tumors that arise from neuroendocrine cells throughout the body. NETs present a clinical challenge, not only because of the diversity of biological behavior different types of NETs may exhibit, but also because of the variety of symptoms they may cause. Around 40-50% of NETs are functional tumors Nonfunctional tumors, showing clinical symptoms due to hypersecretion of

hormones or bioactive amines, typically present with symptoms of advanced tumor growth.

NETs have been classified according to their embryonic origin as foregut, midgut, or hindgut NETs. The WHO staging system classifies gastroenteropancreatic NET (GEP-NET) based on primary tumor localization, size, mitotic activity, invasiveness, and functional status In addition, the European Neuroendocrine Tumor Society (ENETS) has established a TNM staging system. Tumor grading is based on the determination of mitotic activity of the tumor measured by Ki-67 staining or by counting mitotic figures. Low grade (G1) tumors show Ki-67 in *2%, intermediate grade tumors (G2) >3-20% and high grade tumors (G3) in >20% of tumor cells. Low and intermediate grade NETs are also referred to as well-differentiated NETs, and high grade tumors are referred to as poorly differentiated NETs (Hochwald 2002, Klöppel 2009).

The prognosis of patients with NETs depends primarily on the tumor grade and the extent of tumor spread. While patients with G1 or G2 NET have a relatively good prognosis, patients with G3 tumors have a very poor prognosis and short survival. Likewise, patients with local disease have a better outcome than patients with distant disease. Survival also varies depending on the location of the primary tumor site (Yao et al 2008a) with median survival ranging from 5 months in metastatic colon NET to 57 months in duodenal NET.

Study objective

To determine whether treatment with BEZ235 plus best supportive care prolongs PFS compared with placebo plus best supportive care in patients with advanced pancreas NET, after failure of a mTOR inhibitor therapy

Study design

The trial comprises 2 stages: 1 and 2

During the first stage approx. 30 patients will be included and treated with BEZ235 (no randomisation). After a futility interim analysis, it will we decided whether stage 2 will open or not

During stage 2 patients will be randomized in 2:1 (BEZ235 vs Placebo). This trial uses IVRS for randomisation and drug management

IN total approx. 130 patients will be treated. Patient take medication orally, bid. In both arms therapy will be supported by Best support of care

Cycles are 28 days. Treatment continues until progression of disease of unacceptable toxicity

Intervention

DUring the first stage (N=30) all patient receive oral BEZ235 400mg bid
During the second stage (N=100) patient are being randomized 2:1 (BEZ235:placebo). Dose is 400mg Bid.

The dose will be reduced in case of clinical relevant toxicities, in case no discontinuation of the trial is required. Criteria are described in the protocol.

Study burden and risks

Study assessments will be performed at screening, day 1,8,15,22 of the first cycle of 28 days, day 1 and 15 of the following cycles until discontinuation, whereupon the patients will complete the End of Treatment visit and if applicable, follow up

Risks:
* Toxicity due to the use of BEZ235 / Placebo
* Reaction to the use of contrast fluid (used for CT scans)
* Side effects of bloodsampling

Contacts

Public
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL
Scientific
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patient must have advanced, histologically confirmed low or intermediate grade pancreatic pNET according to the WHO 2010 classification and show radiological evidence of disease progression since last treatment.
NOTE: Tissue (archival or fresh) must be provided if available in order to identify molecular profiles relevant to PI3K pathway signaling.
2. Patients* disease is refractory to treatment with mTOR inhibitor. Patients must not have taken another treatment between mTOR inhibitor and BEZ235.
NOTE: Refractory is defined as progression while on treatment or within 3 months of treatment discontinuation.
3. Measurable disease per RECIST Version 1.1 using Computed Tomography (CT) or Magnetic Resonance Imaging (MRI).
4. Prior or concurrent therapy with SSA is permitted; however, for concurrent therapy with SSA while on study, patients must be on a stable dose at least 2 months prior to study start and must continue on the stable dose while receiving study treatment.
5. Adequate bone marrow function or organ function as shown by:
* Absolute Neutrophil Count (ANC) * 1.5 x 109/L,
* Platelets * 100 x 109/L
* Hemoglobin > 9 g/dL
* INR < 2.0,
* Serum creatinine * 1.5 x ULN,
* Total serum bilirubin * 1.5 x ULN
* ALT and AST * 3 x ULN (or * 5x ULN in patients with liver metastases),
* Fasting plasma glucose (FPG) * 140 mg/dL or * 7.8 mmol/L,
* HbA1c * 8%.
6. WHO PS * 1.
7. Adult male or female patients * 18 years of age.
8. Written informed consent obtained before any trial related activities and according to local guidelines.

Exclusion criteria

1. Patient has received previous treatment with any PI3K inhibitor or AKT inhibitor for the treatment of pNET.
2. Patient has discontinued prior mTOR inhibitor therapy due to toxicity
3. Patient has poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, goblet cell carcinoid and small cell carcinoma.
4. Patient has received cytotoxic chemotherapy, targeted therapy, immunotherapy, radiotherapy, or major surgery within 4 weeks prior to enrolment in the study.
5. Patient has been treated with hepatic artery embolization within the last 6 months or cryoablation/ radiofrequency ablation of hepatic metastasis within 2 months of enrollment.
6. Patients with more than 3 prior systemic treatment regimens.
7. Patient is being treated at start of study treatment with any of the following drugs:
* Drugs known to be moderate and strong inhibitors or inducers of isoenzyme CYP3A4
* Drugs with a known risk to induce Torsades de Pointes
* Warfarin and coumarin analogues
8. Patient is consuming Seville oranges, grapefruit, pummelos and exotic citrus fruits (during the last 7 days prior to start of treatment.
9. Patient who has any severe and/or uncontrolled medical conditions, for example:
* active or uncontrolled severe infection,
* cirrhosis, chronic active hepatitis or chronic persistent hepatitis,
* severely impaired lung function inadequately controlled hypertension (i.e., SBP>180 mmHg or DBP>100mmHg),
* active bleeding diathesis.
10. Patient has any of the following cardiac abnormalities:
* symptomatic congestive heart failure, myocardial infarction * 6 months prior to enrolment,
* unstable angina pectoris,
* serious uncontrolled cardiac arrhythmia,
* symptomatic pericarditis,
* history of documented congestive heart failure; documented cardiomyopathy,
* abnormal Left Ventricular Ejection Fraction (LVEF) as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO),
* QTcF > 480 msec on the screening ECG
* currently receiving treatment with medication that has a known risk to prolong the QT interval or inducing Torsades de Pointes,
11. Patient has impairment of GI function or GI disease that may significantly alter the absorption of study drug (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
12. Patient is receiving chronic high dose treatment with corticosteroids or another immunosuppressive agent that would cause the patient to be immunocompromised.
13. Patient is immunocompromised, including known seropositivity for HIV.
14. Patient has other prior or concurrent malignancy
15. Patient has a history of non-compliance to medical regimen or is considered potentially unreliable or is unable to grant consent.
16. Patient is a pregnant or nursing (lactating) woman,
17. Patient who does not apply highly effective contraception during the study and through

the duration, as defined below, after the final dose of study treatment.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-10-2012
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BEZ235
Generic name:	BEZ235

Ethics review

Approved WMO

Date:	10-08-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	13-09-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-02-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-06-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-06-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2012-000675-16-NL
ClinicalTrials.gov	NCT01658436
CCMO	NL41370.056.12