Randomized phase II study of BEZ235 or everolimus in advanced pancreatic neuroendocrine tumors

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To assess the treatment effect of BEZ235 relative to everolimus on progression free survival in patients with advanced pancreatic neuroendocrine tumors who have not been previously treated with an mTOR inhibitor.

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

Summary

ID

NL-OMON40098

Source
ToetsingOnline

Brief title
BEZ235 versus everolimus in pancreatic neuroendocrine tumors

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, everolimus, NET, pancreas

Outcome measures

Primary outcome

Progression free survival based on investigator assessment

Secondary outcome

Frequency and severity of adverse events; other safety data as considered

appropriate

Objective Response Rate (best overall response)

Overall survival

Time to treatment failure

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.

Up-regulation of the PI3K signaling pathway may be involved in the development of resistance to mTOR inhibition. Based on this hypothesis, and since BEZ235 inhibits both PI3K and mTORC1 and 2 complexes, there is rationale for exploring the activity of BEZ235 in patients with pNET.

Study objective

To assess the treatment effect of BEZ235 relative to everolimus on progression free survival in patients with advanced pancreatic neuroendocrine tumors who have not been previously treated with an mTOR inhibitor.

Study design

This is a 2-arm trial evaluating the efficacy and safety of BEZ235 or everolimus.

Patients will be stratified for 1) Prior long acting somatostatin analogue (SSA) therapy (yes/no) and, 2) elevated biomarker levels (yes/no), with elevated defined as CgA >2xULN or neuron specific enolase (NSE) >1xULN (or both).

Patients will be randomized 1:1 BEZ235:everolimus.
The main analysis for PFS will be performed when approximately 70 tumor progressions or deaths due to any cause have been observed.

Intervention

Patients will be randomized 1:1 for the treatment of oral BEZ235 400mg BID or oral everolimus 10mg QD

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 1,15 of the first 2 cycles of 28 days, and on day 1 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 / everolimus
* Reaction to the use of contrast fluid (used for CT scans)
* Side effects of bloodsampling

Contacts

Public
Novartis

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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 pancreatic neuroendocrine tumor (pNET)
2. Radiological documentation of progressive disease within the last 12 months prior to randomization.
3. Measurable disease per RECIST Version 1.0 determined by multiphase MRI or triphasic CT.
4. WHO performance status * 2
5. Patient is * 18 years of age on the day of consenting to the study
6. Patient has adequate bone marrow and organ function shown by:
* ANC * 1.5 x 109/L
* trombocyten * 100 x 109/L
* Hemoglobine * 9.0 g/dL
* INR < 1.3
* ALAT en ASAT * 2.5 x ULN. Patients with known liver metastases who have an AST and ALT * 5 x ULN
* Total serum bilirubin * 1.5 x ULN
* Serum creatinine * 1.5 x ULN
* Fasting plasma glucose (FPG) * 140 mg/dL [7.8 mmol/L]
* HbA1c * 8%
7. Fasting serum cholesterol * 300 mg/dL OR * 7.75 mmol/L AND fasting triglycerides * 2.5 x ULN.

Exclusion criteria

1. Patients with poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, goblet cell carcinoid and small cell carcinoma
2. Previous treatment with PI3K and/or mTOR pathway inhibitors
3. Patients with more than 2 prior systemic treatment regimens
4. Patient has a known hypersensitivity, intolerance and/or contraindications to any of the study medications
5. Patient is receiving (or is planned to receive) any concurrent anti-neoplastic agents except SSA during the study
6. Patient has a concurrent malignancy or has had a malignancy within the last 3 years before study enrollment (except adequately treated cervical cancer in situ or non-melanoma skin cancer)
7. Patient has a history or active severe and/or uncontrolled cardiac conditions that could affect the participation in the study including any of the following:
8. Patient with inadequately controlled hypertension (i.e., SBP > 180 mmHg or DBP > 100 mmHg)
9. Patient has uncontrolled diabetes mellitus
10. Patient has impairment of gastrointestinal (GI) function or GI disease that may

significantly alter the absorption of BEZ235 (e.g. ulcerative diseases, uncontrolled nausea, vomiting, malabsorption syndrome or small bowel resection)
11. Patient is receiving chronic treatment with systemic high dose steroids or other immuno-suppressive agent at start of study treatment
12. Patient is consuming Seville oranges, grapefruit, grapefruit hybrids, pomelo and exotic citrus fruits (as well as their juices) during the last 7 days prior to start of treatment. Regular orange juice is permitted.
13. Immunocompromised patients including known seropositivity for HIV (testing is not mandatory)
14. Patient with diarrhea * Grade 2
15. Patient has other concurrent severe and/or uncontrolled medical condition that would, in the investigator*s judgment, contraindicated participation in the clinical study such as:
16. Patient is not able to understand or comply with study instructions and requirements or has a history of non-compliance to medical regimen
17. Pregnant or nursing (lactating) women,
18. Patient is a woman of child-bearing potential, , UNLESS she is using highly effective methods of contraception during dosing and for 12 weeks after study treatment discontinuation.
19. Patient is a fertile male, defined as a male physiologically capable of offspring, UNLESS he uses condoms during treatment and for 12 weeks after stopping study treatment.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-04-2013
Enrollment:	7
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:	BEZ235
Generic name:	BEZ235

Ethics review

Approved WMO Date:	03-10-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-12-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	08-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2014
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	EUCTR2012-000769-19-NL
ClinicalTrials.gov	NCT01628913
CCMO	NL41625.018.12