# Safety and Tolerability of Everolimus as Second-line Treatment in Poorly Differentiated Neuroendocrine Carcinoma / Neuroendocrine Carcinoma G3 (WHO 2010) and Neuroendocrine Tumor G3 - an Investigator Initiated Phase II Study (EVINEC)

**This study is currently recruiting participants.** (see Contacts and Locations)

*Verified August 2015 by AIO-Studien-gGmbH*

**Sponsor:**
AIO-Studien-gGmbH

**Collaborators:**
Assign Data Management and Biostatistics GmbH
Novartis Pharmaceuticals

**Information provided by (Responsible Party):**
AIO-Studien-gGmbH

**ClinicalTrials.gov Identifier:**
NCT02113800

First received: April 8, 2014
Last updated: August 31, 2015
Last verified: August 2015
History of Changes



## Purpose

The study is designed as an open-label, prospective, single arm, multicenter study of everolimus in histologically confirmed, neuroendocrine carcinoma G3 /neuroendocrine tumor G3 after failure of first-line platin-based chemotherapy (open-label pilot study).

The aim of this study is to provide a second line therapy to patients with any type of platinum based first line chemotherapy, to gather data on disease control rate and progression free survival.

| Condition | Intervention | Phas |
|---|---|---|
| Poorly Differentiated Neuroendocrine Carcinoma,<br>Neuroendocrine Carcinoma, Grade 3<br>Neuroendocrine Carcinoma, Grade 1 [Well-differentiated Neuroendocrine Carcinoma] That Switched to G3<br>Neuroendocrine Carcinoma, Grade 2 [Moderately Differentiated Neuroendocrine Carcinoma] That Switched to G3<br>Neuroendocrine Tumor, Grade 3 and Disease Progression as Measured by Response Evaluation Criteria in Solid Tumors (RECIST 1.1.) | Drug: Everolimus (Afinitor®) | Phas |

Study Type: Interventional
Study Design: Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Safety and Tolerability of Everolimus as Second-line Treatment in Poorly Differentiated Neuroendocrine Carcinoma / Neuroendocrine Carcinoma G3 (WHO 2010) and Neuroendocrine Tumor G3 - an Investigator Initiated Phase II Study

**Resource links provided by NLM:**

MedlinePlus related topics: Cancer Carcinoid Tumors

Drug Information available for: Sirolimus Everolimus Temsirolimus

Genetic and Rare Diseases Information Center resources: APUDoma Carcinoid Tumor Goblet Cell Carcinoid Neuroepithelioma

U.S. FDA Resources

**Further study details as provided by AIO-Studien-gGmbH:**

Primary Outcome Measures:

- Incidence of adverse events (AEs) [ Time Frame: approx. 18 month ] [ Designated as safety issue: Yes ]

  Incidence of adverse events (AEs) overall and by severity, and serious adverse events (SAEs). Severity will be assessed using the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) for Adverse Events, version 4.03 (CTCAEv4.03). To evaluate tolerability and safety of everolimus in second-line treatment of poorly differentiated neuroendocrine carcinoma / neuroendocrine carcinoma G3 according to WHO 2010 and neuroendocrine tumors G3.

Secondary Outcome Measures:

- Progression free survival (PFS) [ Time Frame: approx. 18 month ] [ Designated as safety issue: No ]

  Progression free survival (PFS) as the length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse as per local radiology assessment using Response Evaluation Criteria in Solid Tumors (RECIST 1.1.)

- Objective response rate (ORR) [ Time Frame: approx. 18 month ] [ Designated as safety issue: No ]

  Objective response rate defined as the rate of best overall response (CR+PR), determined by RECIST V 1.1.

- Disease control rate (DCR) [ Time Frame: approx. 18 month ] [ Designated as safety issue: No ]

  Disease control rate defined as the rate of best overall response and stable disease (CR+PR+SD), determined by RECIST V 1.1.

- Duration of response (DR) [ Time Frame: approx. 18 month ] [ Designated as safety issue: No ]

  Duration of response is defined as the time from onset of the first objective tumor response (CR/PR) to objective tumor progression or death from any cause.

- Overall Survival (OS) [ Time Frame: approx. 18 month ] [ Designated as safety issue: No ]

  OS is defined as the time from date of randomization to the date of death from any cause. If a patient is not know n to have died at the date of analysis cut-off, the OS w ill be censored at the last date of contact.

- Quality of life [ Time Frame: approx. 18 month ] [ Designated as safety issue: No ]

  Quality of life (HRQoL) w ill be evaluated using the European Organisation for Research and Treatment of Cancer (EORTC), to assess the quality of life of cancer patients questionnaire (QLQ-C30)

- chromogranin A & B [ Time Frame: approx. 12 month ] [ Designated as safety issue: No ]

  Percentage of patients show ing normalization or a decrease of chromogranin A & B

- Time to Progression (TTP) [ Time Frame: approx. 18 month ] [ Designated as safety issue: No ]

  Time to progression (TTP) is the time from date of start of treatment to the date of event defined as the first documented progression due to underlying cancer.

- neuron-specific enolase [ Time Frame: approx. 12 month ] [ Designated as safety issue: No ]

  Percentage of patients show ing normalization or a decrease of neuron-specific enolase

- progastrin releasing peptide [ Time Frame: approx. 12 month ] [ Designated as safety issue: No ]

  Percentage of patients show ing normalization or a decrease of progastrin releasing peptide.

- Correlation mTOR pathw ay components in tumor tissue to tumor response [ Time Frame: approx. 18 month ] [ Designated as safety issue: No ]

  To explore expression of mTOR pathw ay components in tumor tissue (archive) in correlation to tumor response

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| Estimated Enrollment: | 40 |
| Study Start Date: | August 2015 |
| Estimated Study Completion Date: | February 2017 |
| Estimated Primary Completion Date: | November 2016 (Final data collection date for primary outcome measure) |

| Arms | Assigned Interv entions |
|---|---|
| Experimental: Single Arm<br>Patients receive Everolimus orally, 10 mg/day.<br>The end of study w ill be performed w hen tumor progression has been observed for 28 patients. Patients w ho are still under treatment at that time may continue w ith chemotherapy at the discretion of the investigator, but w ill be excluded from the study. | Drug: Everolimus (Afinitor®)<br>Formulation: 10 mg/day<br>Route: oral (tablet) |

**Detailed Description:**

As more efficient drugs are urgently needed for the treatment of neuroendocrine tumors the investigator evaluated phosphorylated Mammalian target of rapamycin (mTOR) and effectors in a series of NEC G3 at the Charité Center. Everolimus show ed antiproliferative effects in bronchial NET.

In a second approach the data of this study should be the basis to generate another study to further explore everolimus as maintenance therapy in NEC G3/ NET G3.

## Eligibility

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|---|---|
| Ages Eligible for Study: | 18 Years and older |
| Genders Eligible for Study: | Both |
| Accepts Healthy Volunteers: | No |

**Criteria**

Inclusion Criteria:

1. Signed w ritten informed consent
2. Male or female ≥ 18 years of age
3. Patients w ith poorly differentiated neuroendocrine carcinoma, neuroendocrine carcinoma G3 (NEC - G3 according to WHO 2010) or w ell or moderately differentiated neuroendocrine carcinoma (NET - G1 / G2) that sw itched to G3 (confirmed by histology) or neuroendocrine tumor G3 (NET G3) and disease progression as measured by RECIST 1.1
4. Progression during or after treatment w ith first-line platinbased chemotherapy. In NET G3 that sw itched from NET G2 the line of therapy is determined from the time of revised histology (confirming a G3 NEN)
5. Measurable disease according to RECIST 1.1
6. Performance Status according to Eastern Cooperative Oncology Group (ECOG) status 0 - 2 (Karnofsky Performance status ≥ 80%)
7. Women of child-bearing potential must have a negative pregnancy test

8. Laboratory requirements:
    - Hematology
        - Absolute neutrophil count ≥ 1.5 x 109/L
        - Platelet count ≥ 100 x 10^9/L
        - Leukocyte count ≥ 3.0 x 10^9/L
        - Hemoglobin ≥ 9 g/dL or 5.59 mmol/L
    - Hepatic Function
        - Total bilirubin ≤ 1.5 time the upper limit normal (ULN)
        - Aspartate Aminotransferase (AST) ≤ 3 x ULN in absence of liver metastases, or ≤ 5 x ULN in presence of liver metastases
        - Alanine Aminotransferase (ALT) ≤ 3 x ULN in absence of liver metastases, or ≤ 5 x ULN in presence of liver metastases
    - Renal Function
        - Creatinine clearance ≥ 50 mL/min according to cockroft-Gault formula
    - Metabolic Function
        - Magnesium ≥ low er limit of normal
        - Calcium ≥ low er limit of normal
    - Others:
        - CRP (PCT if CRP is elevated to exclude infection)
        - negative urinary screening test for leukocytes and nitrite (U - stix) to exclude urinary tract infection

Exclusion Criteria:

1. Know n or suspected allergy or hypersensitivity reaction to any of the components of study treatment or their excipients.
2. Previous therapy w ith mTOR inhibitor
3. Radiotherapy :
    - Concurrent radiotherapy involving target lesions used for this study.
    - Concurrent palliative radiation (but radiation for non-target lesions is allow ed if other target lesions are available outside the involved field)
    - previous pre-operative or post-operative radiotherapy w ithin 3 months before study treatment
4. History of other malignant tumors w ithin the last 5 years, except basal cell carcinoma or curatively excised cervical carcinoma in situ
5. Know n brain metastases unless adequately treated (surgery or radiotherapy) w ith no evidence of progression and neurologically stable off anticonvulsants and steroids
6. Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤ 1 year before enrolment
7. Inadequate pulmonary function according to the Investigator's judgment, history of interstitial lung disease e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline chest CT scan
8. Know n active Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) or HIV infection
9. Serious concomitant disease or medical condition that in the judgment of the investigator renders the patient at high risk from treatment complication
10. Any systemic disease requiring oral intake of corticosteroids (except for replacement therapy of corticosteroids - hydrocortisone in case of adrenal or pituitary insufficiency)
11. Hearing loss ≥ Grade 3 (CTCAE v4.03)
12. Patient pregnant or breast feeding, or planning to become pregnant w ithin 8 w eeks after the end of treatment
13. Patient (male or female) is not w illing to use highly effective methods of contraception (per institutional standard) during treatment and for 8 w eeks (male or female) after the end of treatment.
14. Concurrent treatment w ith other experimental drugs or participation in another clinical trial w ith any investigational drug w ithin 28 days prior to treatment start
15. Concurrent treatment w ith inhibitors (e.g. itraconazole, ketoconazole) and inducers (e.g. phenytoin, rifampicin) of Cytochrome P450 3A4 (CYP3A4) and / or the multidrug efflux pump P-glycoprotein (PgP).
16. Know n drug abuse/alcohol abuse
17. Peripheral polyneuropathy ≥ Grade 2 (CTCAE v4.03)
18. Active chronic inflammatory bow el disease
19. Any condition w hich might interfere w ith study objectives (e.g. infections) or w ould limit the patient's ability to complete the study in the opinion of the investigator
20. Patient w ho has been incarcerated or involuntarily institutionalized by court order or by the authorities. (AMG §40, Abs. 1 No. 4)
21. Affected persons w ho might be dependent on the sponsor or the investigator

## Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk w ith your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below . For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02113800

### Contacts

Contact: Katrin Krause, B.Sc. +49 30 8145 344 ext 32 Katrin.Krause@aio-studien-ggmbh.de

### Locations

**Germany**

Charité-Universitätsmedizin, Medizinische Klinik m. S. Hepatologie und Gastroenterologie, Campus Virchow -Klinikum **Recruiting**

Berlin, Germany, 13353
Contact: Marianne Pavel, Prof. Dr. marianne.pavel@charite.de
Principal Investigator: Marianne Pavel, Prof. Dr.

**Sponsors and Collaborators**

AIO-Studien-gGmbH

Assign Data Management and Biostatistics GmbH

Novartis Pharmaceuticals

**Investigators**

Principal Investigator: Marianne Pavel, Prof. Dr. Charité-Universitätsmedizin

## More Information

Additional Information:

Working Group for Medical Oncology (AIO) from the German Cancer Society (DKG)

No publications provided

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|---|---|
| Responsible Party: | AIO-Studien-gGmbH |
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| Other Study ID Numbers: | **AIO-NET-0112** CRAD001KDE55T 2012-004550-28 |
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| Health Authority: | Germany: Federal Institute for Drugs and Medical Devices |

Additional relevant MeSH terms:

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|---|---|
| Apudoma | Neuroectodermal Tumors |
| Carcinoid Tumor | Pathologic Processes |
| Carcinoma | Everolimus |
| Carcinoma, Neuroendocrine | Sirolimus |
| Disease Progression | Anti-Bacterial Agents |
| Neuroendocrine Tumors | Anti-Infective Agents |
| Adenocarcinoma | Antibiotics, Antineoplastic |
| Adenoma | Antifungal Agents |
| Disease Attributes | Antineoplastic Agents |
| Neoplasms | Immunologic Factors |
| Neoplasms by Histologic Type | Immunosuppressive Agents |
| Neoplasms, Germ Cell and Embryonal | Pharmacologic Actions |
| Neoplasms, Glandular and Epithelial | Physiological Effects of Drugs |
| Neoplasms, Nerve Tissue | Therapeutic Uses |

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