Phase II Study of cisplatin and everolimus in patients with metastatic or unresectable neuroendocrine carcinomas (NEC) of extrapulmonary origin

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Neuroendocrine carcinomas are distinguished clinically from neuroendocrine tumours by their rapid growth and early development of metastases. Both large and small cell neuroendocrine carcinomas are generally treated based upon chemotherapy regimens...

Ethical review	Approved WMO
Status	Completed
Health condition type	Endocrine neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON47011

Source
ToetsingOnline

Brief title
cisplatin and everolimus in NEC of extrapulmonary origin

Condition

- Endocrine neoplasms benign

Synonym
NEC, neuroendocrine carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut

Source(s) of monetary or material Support: investigator initiated study,Novartis,stichting Ammado (financiering van de biopten)

Intervention

Keyword: cisplatin, everolimus, neuroendocrine carcinomas

Outcome measures

Primary outcome

Primary endpoint of this study will be Disease Control Rate (DCR), defined as the sum of Overall Response Rate (ORR) consisting of Complete (CR), Partial Response Rate (PR) and stable disease (SD), all according to RECIST 1.1

Secondary outcome

Secondary endpoints will be Time to relapse; Progression-free survival (PFS); Disease-free survival (DFS); Overall survival (OS); Effect on the markers chromogranin A (CgA) and neuron-specific enolase (NSE); Safety of everolimus in combination with cisplatin.

Exploratory endpoints will be the discovery of biomarkers (including circulating neuroendocrine tumour transcripts: NETTest) for treatment response; identification of resistance mechanisms; elucidation of driver events in NEC pathogenesis; identification of potential new targets for treatment.

Study description

Background summary

Neuroendocrine carcinomas are distinguished clinically from neuroendocrine tumours by their rapid growth and early development of metastases. Both large and small cell neuroendocrine carcinomas are generally treated based upon

chemotherapy regimens used for small cell neuroendocrine lung cancer and in case of disseminated disease, treatment strategies have focused on cytotoxic systemic therapy. Although neuroendocrine carcinomas are highly responsive to cytotoxic systemic therapy and radiotherapy, recurrence usually rapidly occurs with often a poor prognosis and lack of treatment options. Therefore, new combination treatment option are urgently needed.

Study objective

Neuroendocrine carcinomas are distinguished clinically from neuroendocrine tumours by their rapid growth and early development of metastases. Both large and small cell neuroendocrine carcinomas are generally treated based upon chemotherapy regimens used for small cell neuroendocrine lung cancer and in case of disseminated disease, treatment strategies have focused on cytotoxic systemic therapy. Although neuroendocrine carcinomas are highly responsive to cytotoxic systemic therapy and radiotherapy, recurrence usually rapidly occurs with often a poor prognosis and lack of treatment options. Therefore, new combination treatment option are urgently needed.

Study design

Phase II, open-label, multicentre national study. Patients with metastatic neuroendocrine carcinomas of extrapulmonary origin will be eligible. Treatment will be performed as indicated in the section *Investigational drug and reference therapy*. Cisplatinum and everolimus dosing is based upon earlier phase 1 studies (Fury et al. 2012). CTs will be done at 9 weekly intervals (after 3 courses of chemotherapy;). Patients will be treated until documented progression according to RECIST 1.1. Enrolment is expected to take between 14 * 16 months. The total study duration is estimated to be 2 to 3 years until publication. Three NET centres in The Netherlands will participate, of which two ENETS centres of Excellence (Erasmus Medical Center in Rotterdam, Netherlands Cancer Institute in Amsterdam), while the University Medical Center of Groningen is a well-known NET centre, currently in the process of ENETS certification.

Intervention

Cisplatin : 75 mg/m2 days 1,iv
Everolimus : 7.5 mg daily: days 1-21 orally
Cycles to be repeated every 3 weeks

Study burden and risks

Extra biopsy with a potential minor risk of bleeding.
The normal risk of cisplatin induced site toxicity-as standard chemotherapie for NEC and written in protocol

The normal risk of side toxicity of everolimus-written in protocol not standard treatment for NEC

Benefit: when this investigational treatment is superior than standard chemotherapy treatment.

Contacts

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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. Pathologically confirmed unresectable locally advanced NEC where no curative (chemoradiation) treatment options are available, and/or metastatic NECs of extrapulmonary origin as first line therapy NEC of extrapulmonary origin (WHO 2010 classification; Ki67 >20 %) including merkel cell carcinoma.
2. Measurable disease according to RECIST 1.1, on CT-scan or MRI

3. ECOG Performance status 0-2 (see Appendix 2)
4. Adequate bone marrow function as shown by: ANC*1.5 x 109/L, Platelets *100 x 109/L, Hb >6 mmol/L
5. Adequate liver function as shown by:
Total serum bilirubin *1.5 ULN
ALT and AST *2.5x ULN (*5x ULN in patients with liver metastases)
6. Adequate renal function: calculated creatinin clearance > 60ml/min. (Cockcroft-Gault formula)
7. Life expectancy of at least 3 months.
8. Male or female age * 18 years.
9. Signed informed consent.
10. Able to swallow and retain oral medication.
11. Locally advanced or metastatic lesion(s) of which a histological biopsy can safely be obtained:
a. Patients with safely accessible locally advanced or metastatic lesion(s) including bone lesions.
b. Patients not known with bleeding disorders (such as hemophilia) or bleeding complications from biopsies, dental procedures or surgeries.
c. Patients not using any anti-coagulant medication at the time of biopsy: all aspirin derivatives, NSAID*s, coumarines, platelet function inhibitors, heparins (including LMWHs) and oral factor Xa inhibitors are not allowed, unless medication can either be safely stopped or counteracted.
d. Adequate coagulation status as measured by:
i. PT < 1.5 x ULN or PT-INR < 1.5
ii. APTT < 1.5 x ULN
iii. On the day of biopsy in patients using coumarines: PT-INR < 1.5
e. Patients not known with contraindications for lidocaine (or its derivatives)

Exclusion criteria

1. Previous chemotherapy for metastatic or unresectable NEC of extrapulmonary origin. (prior peri-operative chemotherapy or chemoradiation for curative intention is allowed if at least 6 months have elapsed between completion of this therapy and enrolment into the study).
2. Prior therapy with mTOR inhibitors (e.g. sirolimus, temsirolimus, deforolimus, everolimus)
3. Other malignancy within the last 5 years, except for carcinoma in situ of the cervix, or basal cell carcinoma.
4. Known intolerance or hypersensitivity to everolimus or other rapamycin analogs (e.g. sirolimus, temsirolimus) or cisplatin
5. Known impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral everolimus
6. Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy. Patients with a known history of impaired fasting glucose or diabetes mellitus (DM) may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary
7. Patients who have 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. liver disease such as cirrhosis, decompensated liver disease, and known history chronic hepatitis d. known 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. Chronic treatment with corticosteroids or other immunosuppressive agents
9. Known history of HIV seropositivity
10. Pregnant or nursing (lactating) women
11. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 6 months after stopping study treatment.
12. Sexually active males, unless they use a condom during intercourse while taking study medication and for 6 months after stopping study medication.
13. History of documented congestive heart failure; angina pectoris requiring medication; evidence of transmural myocardial infarction on ECG; poorly controlled hypertension (systolic BP >180 mmHg or diastolic BP >100 mmHg); clinically significant valvular heart disease; or high risk uncontrollable arrhythmias.
14. Patients with dyspnoea at rest due to complications of advanced malignancy or other disease, or who require supportive oxygen therapy.
15. History or clinical evidence of brain metastases.
16. Any investigational drug treatment within 4 weeks of start of study treatment.
17. Radiotherapy within 4 weeks of start of study treatment (2 week interval allowed if palliative radiotherapy given to bone metastastic site peripherally and patient recovered from any acute toxicity).

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	30-03-2016
Enrollment:	39

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:	Cisplatine
Generic name:	Cisplatinum
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-10-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-11-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-01-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-05-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-12-2018

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-12-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 24870
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2014-004735-39-NL
CCMO	NL50842.031.15
OMON	NL-OMON24870