A randomized, double-blind, multicenter, Phase III study of everolimus (RAD001) plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced NET of GI or lung origin -

Published: 26-03-2012
Last updated: 26-04-2024

To determine whether treatment with everolimus 10 mg daily plus best supportive care prolongs PFS compared with placebo plus best supportive care in patients with advanced NET of GI or lung origin without a history of carcinoid symptoms

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

Summary

ID

NL-OMON37366

Source
ToetsingOnline

Brief title
RADIANT-4

Condition

- Endocrine neoplasms malignant and unspecified

Synonym
neuroendocrine tumor

Research involving

Human

Sponsors and support

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

Intervention

Keyword: GI, lung, NET, RAD001

Outcome measures

Primary outcome

PFS per modified RECIST 1.0 as defined in Appendix 1 and modified as per Section 7.2.1.1.1, assessed by central radiological assessment. 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.

PFS based on local radiology assessments will be used for supportive analysis of the primary endpoint.

Secondary outcome

OS is defined as the time from the date of randomization to date of death due to any cause.

The assessment of safety will be based mainly on the frequency and type of treatment emergent adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. vital signs) will be considered as appropriate.

Time to definitive deterioration in FACT-G total score, where deterioration is

defined as a decrease by at least 7 points compared to baseline

ORR and DCR per modified RECIST 1.0 as defined in Appendix 1 and modified as

per Section 7.2.1.1.1, according to central evaluation

CgA and NSE levels

Time to definitive deterioration in WHO Performance Status, where deterioration

is defined as an increase of at least one category compared to baseline

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. In patients with metastatic gastrointestinal NET, the secretion of serotonin and other vasoactive substances typically causes the so-called carcinoid syndrome that is characterized by flushing, diarrhea, teleangiectasia, bronchospasm, and valvular heart disease.

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). For tumors of thoracic (lung/thymus) origin, the WHO tumor grading relies on the mitotic rate

or the presence and extent of necrosis.

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 everolimus 10 mg daily plus best supportive care prolongs PFS compared with placebo plus best supportive care in patients with advanced NET of GI or lung origin without a history of carcinoid symptoms

Study design

After assessment of eligibility, patients qualifying for the study will be randomized in a 2:1 ratio, with two patients being randomly assigned to everolimus treatment for every one patient randomly assigned to matching placebo. This trial will be supported by Interactive Response Technology (IRT) for randomization and medication management.

Randomization will be stratified by:
1. prior SSA treatment
2. tumor origin
3. WHO performance status (0 vs. 1).

This study will enroll approximately 279 patients globally. Patients will receive daily oral doses of 10 mg everolimus (two 5mg tablets) or matching placebo as study drug. In both arms, the study drug will be combined with best supportive care.
Tumor response and progression will be assessed locally and centrally.

Intervention

The dose RAD001 is 10 mg orally qd. continues. The dose will be reduced to 5 mg qd in case of clinical relevant toxicities.
Patients randomized on placebo will take their medication likewise, ie 2 tablets qd, orally.

Study burden and risks

Study assessments will be performed at screening, baseline, week 1, week 5, week 9 et cetera until discontinuation, whereupon the patients will complete

the End of Treatment visit.

Risks:
* Toxicity due to the use of RAD001 / Placebo
* Reaction to the use of contrast fluid (used for CT scans)
* Side effects of bloodsampling

Contacts

Public
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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. Pathologically confirmed, well-differentiated (G1 or G2), advanced (unresectable or metastatic), neuroendocrine tumor of GI or lung origin;
2. No history of and no active symptoms related to carcinoid syndrome;
3. In addition to treatment-naïve patients, patients previously treated with SSA, interferon

(IFN), one prior line of chemotherapy, and/or PRRT are allowed into the study. Pretreated patients must have progressed on or after the last treatment.
4. Patients must have discontinued treatment prior to the day of randomization as follows:
a. Prior SSA for at least 4 weeks
b. Prior IFN for at least 4 weeks;
c. Prior chemotherapy for at least 4 weeks;
d. Prior PRRT for at least 6 months
5. Radiological documentation of disease progression within 3 months prior to randomization (i.e. 12 weeks from documentation of progression until randomization);
6. Measurable disease according to RECIST 1.0 (Appendix 1) determined by multiphasic Computer Tomography (CT) or Magnetic Resonance Imaging (MRI). Any lesions which have been subjected to percutaneous therapies, surgery, or radiotherapy should not be considered measurable, unless the lesion has clearly progressed since the procedure;
7. WHO performance status *1;
8. Adequate bone marrow function as shown by: ANC *1.5 x 109/L, Platelets *100 x 109/L, Hb >9 g/dL;
9. Adequate liver function as shown by:
a. Total serum bilirubin *2.0 mg/dL,
b. ALT and AST *2.5x ULN (*5x ULN in patients with liver metastases),
c. INR *2;
10. Adequate renal function: serum creatinin *1.5x ULN;
11. Fasting serum cholesterol *300 mg/dL OR *7.75 mmol/L AND fasting triglycerides *2.5x ULN.
12. Adult male or female patients *18 years of age;
13. Written informed consent obtained prior to any screening procedures.

Exclusion criteria

1. Patients with poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, pancreatic islet cell carcinoma, insulinoma, glucagonoma, gastrinoma, goblet cell carcinoid, large cell neuroendocrine carcinoma and small cell carcinoma;
2. Patients with NET origins other than GI and lung;
3. Patients with history of or active symptoms of carcinoid syndrome;
4. More than one prior line of chemotherapy
5. Prior targeted therapy
6. Hepatic intra-arterial embolization within the last 6 months. Cryoablation or radiofrequency ablation of hepatic metastases within 2 months of randomization;
7. Prior therapy with mTOR inhibitors (e.g. sirolimus, temsirolimus, deforolimus);
8. Known intolerance or hypersensitivity to everolimus or other rapamycin analogs (e.g. sirolimus, temsirolimus);
9. Known impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral everolimus;
10. 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;
11. 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 chronic hepatitis (i.e. quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV-RNA),
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;
12. Chronic treatment with corticosteroids or other immunosuppressive agents;
13. Known history of HIV seropositivity;
14. Patients who have received live attenuated vaccines within 1 week of start of study drug and during the study. Patient should also avoid close contact with others who have received live attenuated vaccines. Examples of live attenuated vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines;
15. Patients who have a history of another primary malignancy, with the exceptions of non-melanoma skin cancer, and carcinoma in situ of the cervix, uteri, or breast from which the patient has been disease free for *3 years;
16. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study;
17. Patients who are currently part of or have participated in any clinical investigation with an investigational drug within 1 month prior to dosing;
18. Pregnant or nursing (lactating) women;
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-03-2012
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	afinitor
Generic name:	everolimus
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	26-03-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	14-05-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	15-05-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	25-07-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	14-02-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-02-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	06-05-2013
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-002887-26-NL
ClinicalTrials.gov	NCT01524783
CCMO	NL39346.031.12