A phase II study exploring the safety and efficacy of nintedanib (BIBF1120) as second line therapy for patients with eitherc differentiated and medullary thyroid carcinoma progressing after first line therapy.

Published: 13-02-2014
Last updated: 24-04-2024

The primary objective is to explore the efficacy of nintedanib (as measured by progression free survival) as second line therapy for patients with either differentiated or medullary thyroid cancer progressing after first line therapy.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Thyroid gland disorders
Study type	Interventional

Summary

ID

NL-OMON47685

Source
ToetsingOnline

Brief title
EORTC protocol 1209-EnTF

Condition

- Thyroid gland disorders

Synonym
thyroid cancer, thyroid carcinoma

Research involving

Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: Boehringer Ingelheim,EORTC Belgium and Boehringer Ingelheim France

Intervention

Keyword: nintedanib, thyroid carcinoma

Outcome measures

Primary outcome

* Progression free survival (RECIST 1.1)

Secondary outcome

* Secondary end-points

* Response Rate (RECIST 1.1)

* Duration of response

* Exploration of the molecular mechanisms of action of drug

* PFS at second progression (PFS-2) for patients crossing over from placebo to

nintedanib.

Safety

* Toxicity profile (CTCAE version 4.0 will be used for adverse event reporting)

Study description

Background summary

Angiogenesis pathway represents a set of potential targets for targeted therapies in thyroid cancer. VEGF receptors (VEGFR) and especially VEGFR-2 is

considered to be the crucial receptor involved in initiation of the formation as well as the maintenance of tumor vasculature. VEGF and VEGF receptors (VEGFR-1, VEGFR-2) as well as receptors of the fibroblast growth factor (FGF) and for the platelet-derived growth factor (PDGF) are often overexpressed in thyroid cancer (Ref. 11). These receptors are also expressed on perivascular cells, such as pericytes and smooth muscle cells, that are also involved in tumor angiogenesis. Tyrosine kinase inhibitors of the VEGFR or PDGFR pathway have been tested in thyroid cancer with

positive results. Vandetanib is approved for MTC and it is expected soon that sorafenib will be approved for differentiated thyroid cancer.
The treatment options for patients with DTC and MTC who have progressed on one line of therapy are limited and there is no treatment that is generally considered as standard of care. No clinically meaningful benefit has yet been demonstrated with cytotoxic chemotherapy. On the other hand patients are still in good general condition and may still benefit from treatment and experience survival prolongation.
Nintedanib is a triple angiogenesis inhibitor which inhibits receptors of VEGF, FGF and PDGF, therefore acting potentially not only on endothelial cells but also on pericytes and smooth muscle cells. Nintedanib also interacts with other kinases such as RET. Because of its multi-kinase activity rationale exists to develop it in both MTC and DTC.
By targeting these three major angiogenesis signaling pathways it is believed that nintedanib can prevent further tumor growth and related tumor escape mechanisms. This also means that nintedanib may be active in patients who have progressed on agents that target only one pathway.

Study objective

The primary objective is to explore the efficacy of nintedanib (as measured by progression free survival) as second line therapy for patients with either differentiated or medullary thyroid cancer progressing after first line therapy.

Study design

This is a randomized blinded, placebo controlled phase II trial.

Intervention

Treatment cycles are defined as a four week period to facilitate scheduling of visits and assessments. Treatment should start within 2 days from randomization. Patients will receive drug in a blinded fashion. Nintedanib should be administered orally at a dose of 200 mg twice daily. It should be swallowed unchewed, preferably together with a glass of water of about 250 mL. The doses

should be taken with a dose interval of approximately 12 hours.
Treatment should be administered until documented disease progression, unacceptable toxicity, or patient refusal.
Comparator treatment in this study will be placebo capsules, matching those of nintedanib, but with no active drug. Treatment in the placebo arm should also be administered until documented disease progression, unacceptable toxicity, or patient refusal. After documented disease progression (according to RECIST 1.1) patients will be unblinded and will be offered the option of receiving nintedanib.

Study burden and risks

Risks:
Before the start of each treatment cycle, the subject will be evaluated for possible toxicities that may have occurred after the previous cycle(s).
Toxicities are to be assessed according to the CTCAE, Version 4.0.
The predominant adverse events of nintedanib were diarrhea, nausea and vomiting followed by fatigue, decreased appetite and abdominal pain. These adverse events were reversible, mostly of low to moderate severity of CTCAE grade I or II and manageable in most cases with symptomatic therapy.

Benefit:
The treatment options for patients with DTC and MTC who have progressed on one line of therapy are limited and there is no treatment that is generally considered as standard of care. No clinically meaningful benefit has yet been demonstrated with cytotoxic chemotherapy. On the other hand patients are still in good general condition and may still benefit from treatment and experience survival prolongation.
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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

* Histologically confirmed differentiated or medullary thyroid cancer by local pathologist.
* Available tumor tissue at the time of initial diagnosis for histology review.
* Locally advanced or metastatic disease deemed incurable by surgery, radiotherapy and/or radioactive iodine (RAI).
* Patients must have measurable lesion with documented progression during the 12 months prior to randomization.
* Patients must have received one or 2 prior line of treatment (but no more than two) and must be off treatment for at least 4 weeks prior to randomization. Patients with an MTC must have received one or 2 prior line of treatment (but no more than two) and must be off treatment for at least 4 weeks prior to randomization. If it is available and reimbursed in the respective country one of the prior lines of treatment needs to be with Vandetanib as long as there is no contraindication or the patient refuses the treatment with Vandetanib.
* Age *18 years.
* Performance status (PS) 0-1 (WHO, Appendix C).
* Life expectancy of more than 12 weeks.
* Adequate organ function, evidenced by the following laboratory

results within 3 weeks prior to randomization

Exclusion criteria

* Current symptomatic brain metastases or if previously present, must have been treated at least two months before randomization.
* History of other malignancy within the last 5 years, except for adequately treated carcinoma in situ of the cervix or basal cell or spinocellular carcinoma of the skin.
* Ongoing treatment related toxicity due to prior treatment > grade I (except alopecia).
* History of significant cardiac disease
* Current uncontrolled hypertension
* Evidence of active bleeding or bleeding diathesis.
* Cerebrovascular accident at any time in the past, transient ischemic attack, deep venous thrombosis (DVT) or pulmonary embolism in the past 6 months
* History of clinically significant gastrointestinal disorders .
* Current severe, uncontrolled systemic disease or any other systemic disease/symptom that can hamper compliance with the protocol.
* Major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery.
* History of receiving any investigational treatment within 28 days prior to randomization
* Women or patients of child bearing potential who do not use any contraceptive methods
* Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.
* No hypersensitivity to nintedanib, peanut or soya, or to any of the excipients of nintedanib.
* Patients of childbearing / reproductive potential should use adequate birth control measures, as defined by the investigator, during the study treatment period and for at least 3 months after the last dose of study treatment. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly.
* Female subjects who are breast feeding should discontinue nursing prior to the first dose of study treatment and until at least 3 months after the last 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):	17-06-2014
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nintedanib
Generic name:	nintedanib

Ethics review

Approved WMO Date:	13-02-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-05-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-06-2014
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-05-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-05-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2012-004295-19-NL
ClinicalTrials.gov	NCT01788982
CCMO	NL46582.091.13