An Open-Label, Multi-Center Phase II Study of the BRAF Inhibitor Vemurafenib in Patients with Metastatic or Unresectable Papillary Thyroid Cancer (PTC) positive for the BRAF V600 Mutation and Resistant to Radioactive Iodine.

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Primary Objective• To evaluate best overall response rate (BORR; CR + PR) in Cohort 1 (TKI-naïve patients).* BORR will be based on investigator assessment, based on the findings on computed tomography (CT) or magnetic resonance imaging, using RECIST…

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

Summary

ID

NL-OMON39294

Source
ToetsingOnline

Brief title
NO25530 Papillary Thyroid Cancer

Condition

- Skin neoplasms malignant and unspecified

Synonym
Metastatic or unresectable papillary thyroid cancer

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: Pharmaceutic Industry

Intervention

Keyword: BRAF V600 Mutation, Papillary Thyroid Cancer, resistent to Radioactive Iodine, unresectable stage

Outcome measures

Primary outcome

The primary efficacy variable for this study is the rate of best overall

response (BORR) assessed by the investigators according to the RECIST criteria

(Version. 1.1).

Secondary outcome

The secondary efficacy variables are: Clinical benefit rate (CBR), PFS, OS, and

duration of response, in TKI-naïve patients (Cohort 1) TKI-exposed patients

(Cohort 2).

Study description

Background summary

Carcinoma of the thyroid gland is an uncommon cancer but is the most common malignancy of the endocrine system, with estimates of up to 33,500 cases of diagnosed thyroid cancers, and 1,690 deaths in the US in 2010.

Managing PTC can be challenging, due to the lack of prospective randomized trials of treatments. Most patients can be cured when properly treated by experienced physicians and surgeons. The treatment of choice is surgery whenever possible, followed by radioiodine (131I) and thyroxine therapy. External-beam radiation therapy (RT) and chemotherapy have less prominent roles

in the management of DTC

The BRAF V600 mutation is seen in 29%-83% of papillairy thyroid cancer patients. The mutated gene can instruct thyroid cells continue to divide and grow with cancer as a result. A mutation of the same gene have previously been shown in melanoma.

In early studies, positive results were achieved with Vemurafenib in melanoma and papillary thyroid cancer patients. Thus the expectation is that Vemurafenib can lead to an improvement in PFS (progression free survival) in OS (overall survival) and even the PR (partial response) and CR (complete response) in this patient population.

Study objective

Primary Objective
• To evaluate best overall response rate (BORR; CR + PR) in Cohort 1 (TKI-naïve patients).
* BORR will be based on investigator assessment, based on the findings on computed tomography (CT) or magnetic resonance imaging, using RECIST 1.1

Secondary Objectives
• To evaluate clinical benefit (ORR + SD) in TKI-naïve patients
• To further assess efficacy of Vemurafenib using the following secondary variables: duration of response, PFS, and OS in TKI-naïve patients
• To evaluate the efficacy (BORR, CB, duration of response, PFS, and OS) in TKI-treated patients
• To evaluate the tolerability and safety profile of Vemurafenib using the NCI CTCAE (version 4.0) in both TKI naïve and TKI-treated patients
• To characterize the PK profile of Vemurafenib in patients with thyroid cancer.

Study design

3.1 Overview of Study Design
This is a multi-center, multi-national, open-label, single agent, non-randomized Phase 2 trial of Vemurafenib in treatment of patients with histologically confirmed papillary thyroid cancer harboring the BRAF V600 mutation that is metastatic or unresectable, is radioactive iodine resistant, and for which standard curative or palliative measures do not exist or are no longer effective.
There will be two cohorts of patients enrolling concurrently:
• Cohort 1: 25 evaluable patients, naive to any prior systemic TKI therapy
• Cohort 2: approximately 15 patients previously treated with TKI therapy active against VEGFR2.

Forty patients with BRAFV600-positive papillary thyroid cancer will be treated, with an option to increase to 50 patients, according to the Cohort 2 expansion considerations found in Section 8.3 of the protocol.
Patients will receive Vemurafenib 960 mg orally bid daily on a continuing basis until disease progression, death due to any cause, unacceptable toxicity, or discontinuation from the study/or study treatment. A cycle is defined as 4 weeks (28 days).

Intervention

Patients receive oral OR5185426 of 960mg b.i.d. daily.

Study burden and risks

see section E9

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. Male or female patients >= 18 years of age
2. Histologically confirmed papillary thyroid cancer that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective.Patients whose tumors exhibit areas of *other histology* may be enrolled, provided the tumor histology remains predominantly papillary. Patients whose tumors exhibit *mixed* histology may be discussed with the Medical Monitor if there are questions about eligibility.
3. BRAFV600-positive thyroid cancer tissue, as determined by the Roche-designated Central Reference Laboratory using the cobas® 4800 BRAF V600 Mutation Test. Testing requires a formalin-fixed paraffin-embedded (FFPE) tumor tissue block or unstained sections from such a block. Samples may be either archival or new. Fine needle and core needle biopsies will not be accepted.
4. Must have radioactive iodine resistant disease, defined by any one of the following:
o lack of RAI uptake on either a low-dose diagnostic or a post-therapy RAI scan in the measurable lesion (or lesions) demonstrated previously (without time limitation), or
o radiographic progression of disease within 18 months of last course of RAI therapy despite the presence of RAI uptake on the scans performed with that prior therapy, or
o Patient that has exceeded a cumulative activity of at least 600 mCi of radioiodine therapy
5. Thyroid carcinoma tissue, either archival or recent biopsy must be available for submission and review by a central pathology laboratory.
6. Allowed Prior therapy:
- Cohort 1: may have received surgery, RAI, and/or standard of care chemotherapy (e.g. doxorubicin) [Note: Acceptable prior chemotherapy can be discussed with the Sponsor.]
Cohort 2: may have received surgery, RAI, and standard of care chemotherapy (e.g. doxorubicin), and must also have received prior treatment with investigational or commercial tyrosine kinase inhibitor with activity against VEGFR2 provided the drug is not a specific/selective BRAF or MEK pathway inhibitor. [Note: Acceptable prior chemotherapy can be discussed with the Sponsor.]
7. Must have fully recovered from the effects of any previous therapies.
8. Radiologic (CT or MRI) evidence of clinically relevant disease progression (as per RECIST 1.1) within the preceding 14 months prior to planned first treatment.
9. Measurable disease (by RECIST Version 1.1 criteria)
10. ECOG performance status of 0 or 1
11. Life expectancy > 3 months
12. Be able to swallow pills
13. Must have a head CT/MRI to evaluate for CNS metastasis within 28 days prior to study drug treatment (Cycle 1 Day 1). Patients with radiographically stable,

asymptomatic previously treated lesions are eligible provided:
o Patient has received prior treatment (including radiation), stereotactic radiosurgery, surgical resection) to the
site(s) of CNS metastatic disease >= 28 days prior to starting study treatment
o Patient has no requirement for glucocorticoids, and discontinued >= 21 days prior to starting study treatment)
o Patient is not taking anticonvulsants (discontinued at least 3 weeks prior to treatment)
o Patient has no overt evidence of neurological deficit
14. Prior Surgery (excluding tumor biopsy at baseline for biomarker analysis) must have occurred at least 14 days prior to first dose of study treatment, and patients must have recovered from any effects from surgery and have adequate wound healing prior to first dose of study treatment.
15. External beam radiotherapy for the treatment of a symptomatic (e.g. bone) metastasis as clinically indicated must be at least 14 days prior to first dose of study treatment
16. Completed baseline skin exam by a dermatologist or other qualified physician for cutaneous squamous cell
carcinoma. Exam must be negative or if, suspected cuSCC, basal cell carcinoma (BCC), or other suspicious lesions are identified they must be excised, and there must be adequate wound healing prior to study treatment.
17. Thyroid stimulating hormone (TSH) level <0.5 mIU/L
18. Adequate hematologic, renal and liver function
o Absolute neutrophil count (ANC) >= 1.5 x 10^9/L
o Platelet count >= 100 x 10^9/L
o Hemoglobin >= 9 g/dL
o Serum creatinine <=1.5 X ULN or CrCl > 40 ml/hr by Cockcroft-Gault formula
o AST and ALT <= 2.5 times upper limit of normal (ULN) (<= 5 times ULN for patients with concurrent liver metastases)
o Bilirubin <= 1.5 times ULN
o Alkaline phosphatase <= 2.5 times ULN (<= 5 times ULN for patients with concurrent liver metastases)
19. Negative serum pregnancy test within 7 days prior to commencement of dosing in pre-menopausal women. Women of non-childbearing (see Appendix 6) potential may be included if they are either surgically sterile or have been postmenopausal for >= 1 year
20. Fertile men and women must use an effective method of contraception during treatment and for at least 6 months after completion of treatment as directed by their physician (in accordance with local requirements)
21. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before trial entry
22. Before study entry, signed informed consent must be obtained from patient prior to performing any study-related procedures

Exclusion criteria

1. Histological diagnosis other than papillary thyroid carcinoma (PTC), including squamous cell variants of PTC or PTC with areas of squamous metaplasia.Patients with anaplastic tumors are not eligible. However, patients whose tumors contain areas of *un-differentiated* or *de-differentiated* histology may enroll provided the original diagnosis was clearly PTC, and the tumor histology remains predominantly papillary at enrollment. Patients whose tumors exhibit mixed histology may be discussed with the Medical Monitor.
2. Active or untreated CNS metastases 3. History of or known carcinomatous meningitis
4. Anticipated or ongoing administration of any anti-cancer therapies other than those administered in this study
5. Active squamous cell skin cancer that has not been excised or has not yet adequately healed post excision
6. Pregnant or lactating women
7. Previous treatments with any commercial or investigational targeted agents that specifically and selectively targets the MEK or BRAF pathway
8. Received any investigational treatment within 28 days prior to start of study treatment
9. Prior radioactive iodine therapy within 28 days prior to start of study treatment
10. Chemotherapy or targeted therapy (in case of cohort 2) within 28 days prior to start of study treatment
11. Prior radiotherapy to the only measurable lesion
12. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate absorption
13. QTc >450 msec on screening ECG or history of congenital long QT syndrome or uncorrectable electrolytes abnormalities.At least one QTc measurement using Fridericia*s correction (QTcF)
must be <= 450 msec. Additionally, cases of patients with stable asymptomatic conduction delays (e.g., right bundle branch block) with QTc >450 msec may be discussed with the Medical Monitor for potential inclusion.
14. NCI CTCAE Version 4.0 grade 3 hemorrhage within 28 days of starting the study treatment
15. Any of the following within the 6 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, or active pulmonary embolism
16. Known clinically significant active infection at the time of study treatment start
17. History of allogeneic bone marrow transplantation or organ transplantation
18. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, which in the judgment of the investigator would make the patient inappropriate for entry into this study
19. Patients with a previous malignancy are excluded except for patients with adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer and/or curatively treated cancer, from which the patient is currently disease-free, or any malignancy from which the patient has been continuously disease-free for at least 5

years. Also, isolated elevation in PSA in the absence of prostate cancer is allowed
20. Known HIV positivity or AIDS-related illness, HBV, and active HCV

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-10-2011
Enrollment:	8
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	12-05-2011
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	31-10-2011

Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-11-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	23-01-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	09-02-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-02-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-02-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-02-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	07-03-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-09-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-09-2012

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	19-11-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	29-11-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-02-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-02-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-10-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-09-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2010-024133-23-NL
ClinicalTrials.gov	NCT01286753
CCMO	NL36157.058.11