Phase II study of nilotinib efficacy in pigmented villo-nodular synovitis/tenosynovial giant cell tumor (PVNS/TGCT)

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PRIMARY OBJECTIVEThe primary objective of the study will be to determine the efficacy of 12 weeks of nilotinib treatment as measured by the non progression rate (Complete response + Partial Response + Stable disease according to Response Evaluation…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Synovial and bursal disorders
Study type	Interventional

Summary

ID

NL-OMON36562

Source
ToetsingOnline

Brief title
Phase II of nilotinib in PVNS

Condition

- Synovial and bursal disorders

Synonym
Pigmented Villonodulair Synovitis (PVNS) Giant Cell Tumor of Tendon

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Patient fee per patiënt vanuit het hoofdcentrum in Lyon;Centre Leon Berard;Prof. Blay

Intervention

Keyword: Nilotinib, PVNS

Outcome measures

Primary outcome

The primary objective of the study will be to determine the efficacy of 12 weeks of nilotinib treatment as measured by the non progression rate (Complete response + Partial Response + Stable disease according to Response Evaluation Criteria In Solid Tumors - RECIST) in patients with progressive or relapsing PVNS/TGCT who cannot be treated by surgery.

Secondary outcome

The secondary objectives will be:

• To evaluate the efficacy of nilotinib according to:

- The objective tumor response rate (Complete response + Partial Response according to RECIST) after 12 weeks of treatment

- The duration of treatment response

- The best overall reponse obtained during the study

- The progression-free survival (PFS)

- The time to progression

- The time to treatment failure

- The non-progression rate

- The proportion of patients with an operable tumor after nilotinib exposure according to investigator evaluation

- The description of concomitant treatments use

- The correlation between trough levels of nilotinib and PFS

• To explore the relationship between the objective tumor response and the following tumour characteristics (tissues collected in a prior surgery, or by biopsy, upon specific acceptance by the patient):

- presence of COL6A3/CSF1 fusion gene

- presence of M-CSF, CSF1R, KIT, PDGFRA and B on immunohistochemistry

- presence of phosphorylated c-fms on tumor samples

- Activation of the PI3K/Akt/mTor pathway (Akt, P-Akt, Pp70S6K,..), presence of activating mutations of ras, erk1/2 expression and P-erk1/2

• To assess the safety of nilotinib for PVNS/TGCT patients

Study description

Background summary

Pigmented villonodular synovitis (PVNS), also known as tenosynovial giant cell tumor (TGCT), is a rare pathological entity affecting the synovium in young adults. Initially considered as an inflammatory reactive process, recent observations have shown that this disease may actually be a benign neoplastic process with specific genetic alterations. Indeed, a specific t (1;2) translocation, involving the collagen 6A3 gene (on 2q35) and the M-CSF (also known as CSF1) gene (on 1p13), is present in a fraction of tumor cells in PVNS/TGCT. This fusion gene expressed by a fraction of the cells encodes for a fusion protein which attracts non-neoplastic cells expressing M-CSF receptor (macrophages and monocytes), through a paracrine - *landscape*- effect (1-4). Imatinib is a treatment indicated for chronic myeloid leukaemia (CML) and gastrointestinal stromal tumor which block M-CSF receptor activation at therapeutic concentration (5). PVNS/TGCT is usually treated by surgery alone (1). However, relapses may occur, and re-excision may be needed, sometimes with possible important functional impairment. Blay et al. recently reported the case of a patient with recurrent and symptomatic PVNS/TGCT following surgery, in whom surgical re-excision would have had important functional consequences (6). In the case report, the patient was treated with imatinib, providing rapid

tumor response. A relapse was observed at discontinuation of imatinib, and a secondary response was obtained at imatinib reintroduction. This is the first report of the activity of imatinib in a M-CSF/M-CSF receptor dependent solid tumor.
Although a potential contribution of the blockade of other tyrosine kinases by imatinib can not be ruled out, the frequency at which the col6A3/CSF1 fusion gene is observed in PVNS/TGCT (4) as compared to other pathological synovial process strongly suggests that imatinib activity involves M-CSF receptor blockade in this disease, despite recent observation showing limited biological activity of the product of the fusion gene.
As a consequence, imatinib is a good candidate to induce complete responses in relapsing PVNS/TGCT and may offer an option in patients in whom surgery is not feasible or implies to much risks. In the first 4 patients treated with imatinib in Lyon, 2 patients interrupted treatment because of poor tolerance (1 interruption at patient request, 1 interruption because of grade 4 liver toxicity).
Another phenylaminopyrimidine commercialized by Novartis called nilotinib (Tasigna®) has inhibitory properties similar to imatinib on M-CSF receptor pathway (7). Nilotinib is indicated for the treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.
The reason for selecting nilotinib as compared to imatinib came out from different considerations
1) In the limited experience with imatinib in PVNS reported so far the toxicity experienced by some patients was substantial.
2) Nilotinib has a more favourable toxicity profile in particular regarding soft tissue and facial oedema. This may favour a better compliance to the treatment.
In this context, it is interesting to set up a clinical study designed to explore the efficacy of nilotinib as a treatment of patients with inoperable PVNS/TGCT. This disease being rare, this clinical trial is a non-randomised open-label and international study. Nilotinib will be administered to patients with progressive or relapsing PVNS/TGCT who cannot be treated by surgery. Patients will receive the medication according to the posology recommended by the summary of product characteristics and used in the treatment of CML (400 mg twice a day).
The main benefit anticipated for the patients included in the protocol will be the tumor reduction and the consequent functional improvements. The main risk will be the non-response to the treatment and the known adverse effects of nilotinib. In case of secondary effects, doses of nilotinib will be adjusted according to the system showing the greatest degree of toxicity.
Also, upon specific acceptance of the patients, a biological analysis of the tumor will be conducted by a centralised laboratory to explore the relationship between the tumor response to the treatment and some characteristics of tumors (presence of COL6A3/CSF1 fusion gene, M-CSF and M-CSF receptor and phosphorylated c-fms/M-CSFR).

Patients will be treated by nilotinib for 1 year. In case of treatment efficacy as assessed by intermediary analyses, maintenance of the treatment upon patients* acceptance will be considered.
This study will be conducted following local legal requirements and according to Good Clinical Practices.

Study objective

PRIMARY OBJECTIVE
The primary objective of the study will be to determine the efficacy of 12 weeks of nilotinib treatment as measured by the non progression rate (Complete response + Partial Response + Stable disease according to Response Evaluation Criteria In Solid Tumors - RECIST) in patients with progressive or relapsing PVNS/TGCT who cannot be treated by surgery.

SECONDARY OBJECTIVES
The secondary objectives will be:
• To evaluate the efficacy of nilotinib according to:
- The objective tumor response rate (Complete response + Partial Response according to RECIST) after 12 weeks of treatment
- The duration of treatment response
- The best overall reponse obtained during the study
- The progression-free survival (PFS)
- The time to progression
- The time to treatment failure
- The non-progression rate
- The proportion of patients with an operable tumor after nilotinib exposure according to investigator evaluation
- The description of concomitant treatments use
- The correlation between trough levels of nilotinib and PFS
• To explore the relationship between the objective tumor response and the following tumour characteristics (tissues collected in a prior surgery, or by biopsy, upon specific acceptance by the patient):
- presence of COL6A3/CSF1 fusion gene
- presence of M-CSF, CSF1R, KIT, PDGFRA and B on immunohistochemistry
- presence of phosphorylated c-fms on tumor samples
- Activation of the PI3K/Akt/mTor pathway (Akt, P-Akt, Pp70S6K,..), presence of activating mutations of ras, erk1/2 expression and P-erk1/2
• To assess the safety of nilotinib for PVNS/TGCT patients

Study design

The efficacy of nilotinib will be assessed for most of the criteria using RECIST. Tumor will be evaluated at each visit of the study by Magnetic resonance imaging (MRI) or CT scan. All images will be read locally at the site and this interpretation will be used for all clinical decision making.

Assessments will be then validated by a central review committee. Centrally reviewed tumor assessments data will be used in all efficacy analysis.
Upon patient specific acceptance, tumor specimen obtained from a prior surgery or from a biopsy, as well as tumor samples collected after the initiation of the treatment, will be analysed by a central laboratory (one laboratory per continent: Europe, North America and Australia) for col6A3-M-CSF fusion gene expression, MCSFR, KIT, PDGFRs expression, phospho M-CSFR expression, Akt, P-Akt, P-p70S6K, ras mutation, erk

Intervention

Treatment with nilotinib 400 mg BID up to one year or untill disease progression

Study burden and risks

Limited side effects of venapuncture (5 times) limited risk of MRI contrast allergy

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

Patients will be included in the study if they meet all the following inclusion criteria:
1. Age >= 18 years
2. Histologically confirmed diagnosis of inoperable progressive or relapsing PVNS/TGCT OR resectable tumor requesting mutilating surgery
3. Demonstrated progressive disease in the last 12 months
4. At least one measurable site of disease on CT/MRI scan according to RECIST criteria based on investigator*s assessment
5. WHO Performance status of 0, 1 or 2
6. Adequate organ, electrolyte and marrow function, defined as the following: serum bilirubin <=1.5 x ULN, ALT and AST <=2.5 x ULN, serum creatinine <=1.5 x ULN or 24 hour creatinine clearance >=50 mL/min, absolute neutrophil count (ANC) >=1.5x109/L, platelets >=100x109/L
7. Prior physical examination adapted to the research
8. Signed written informed consent form
9. Covered by a medical insurance organism (in countries where applicable)

Exclusion criteria

Patients will not be included in the study if they meet any of the following non-inclusion criteria:
1. Pregnant or lactating female or female of child-bearing potential not employing adequate contraception during the study and for up to three months following termination of the study
2. Hypersensitivity to nilotinib or to any of the excipients
3. Acute or chronic uncontrolled liver disease, or severe renal disease
4. Impaired cardiac function, including: LVEF<45% or below the institutional lower limit of the normal range (whichever is higher) as determined by echocardiogram or MUGA scan; history or signs of prior myocardial infarction; history of unstable angina; other clinically significant heart disease (e.g. congestive heart failure or uncontrolled hypertension)
5. Patients with severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol e.g. uncontrolled diabetes, active or uncontrolled infection
6. History of non-compliance to medical regimens
7. Concomitant treatment with medicinal products that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St. John*s Wort), or that inhibit the CYP3A4 activity (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin)
8. Concomitant treatment with warfarin

9. Concomitant treatment with medication that prolong the QT interval

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):	25-03-2011
Enrollment:	15
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Tasigna
Generic name:	Nilotinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-03-2011
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-03-2011

Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-10-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-11-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	19-12-2011
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	EUCTR2010-023887-41-NL
ClinicalTrials.gov	NCT01207492
CCMO	NL34688.058.10

Study results

Date completed:	15-12-2016

Actual enrolment: 16

Summary results
Trial is onging in other countries