Dipeptidylpeptidase IV (CD26) on Philadelphia-positive leukemic stem cells (LSC) as marker and novel therapeutic target in chronic myeloid leukemia (CML).

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Ethical review	Approved WMO
Status	Completed
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON55403

Source
ToetsingOnline

Brief title
Dolphin-STAR

Condition

- Leukaemias

Synonym
Chronic myeloid leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Albert Schweitzer Ziekenhuis
Source(s) of monetary or material Support: Novartis,Novartis Pharma

Intervention

Keyword: Dipeptidylpetidase IV (CD26), Ph+ CML, Second attempt treatment free remission

Outcome measures

Primary outcome

For the Phase 1 section of the study:

Presence of research medication related adverse events resulting in

dose-limited toxicity to vildagliptin when combined with nilotinib in the

treatment of CML patients.

For the Phase 2 part of the study:

Reduction of Ph + CD34 + CD38-CD26 + cell frequency in the bone marrow in CML

patients before and after adding vildaglitpine to nilitonib in the treatment of

CML patients.

Secondary outcome

For the Phase 1 section of the study:

Number of adverse events for combination treatment of vildagliptin and

nilotinib in CML patients.

For the Phase 2 part of the study:

1. The percentage of patients receiving a reduction of at least 1 log BCR-ABL

level in the bone marrow or peripheral blood during the combination treatment

of nilotinib and vildagliptin

2. Percentage of patients with Ph + CD34 + CD38-CD26 + cells in the bone marrow

after stopping nilotinib (TKI) and discontinuation of vildagliptin.

3. The percentage of patients who are in a treatment-free remission 6 months

after stopping nilotinib (TKI), but still being treated with vildagliptin.

4. The percentage of patients who are in treatment-free remission, 12 months

after stopping nilotinib (TKI) and 6 months after discontinuation of

vildagliptin treatment.

5. The incidence of infectious adverse events during the combination treatment

of nilotinib and vildagliptin.

Study description

Background summary

Until recently, it was believed that treatment with a BCR-ABL TKI had to be continued for lifelong time. Recent studies have demonstrated the feasibility of stopping treatment with a TKI in Ph + CML patients after reaching a prolonged deep molecular response. However, there is a risk of relapse after stopping a TKI. Only a minority of CML patients remain in treatment free remission (TFR) after discontinuation of treatment with a TKI.

At present, little research has been carried out on a second attempt at treatment free remission after stopping a two-line TKI (including Nilotinib) and its success.

Recently, Philadelphia chromosome positive stem cells have been shown to exhibit selective expression of dipeptidylpeptidase IV (DPP-4). DPP-4 inhibitors are registered for the treatment of diabetes mellitus type 2 (DM2) in adults and belong to the group of medication: gliptines. Vildagliptin (DPP-4 inhibitor) is not registered for the treatment of CML and thus subjected to this study.
Low blood sugar (hypoglycemia) due to gliptin treatment rarely occurs in both diabetic and non-diabetic patients. This means that a combination treatment of DPP-4 inhibitor (Vildagliptin) with a TKI inhibitor (Nilotinib) is a viable

combination for both diabetic and non-diabetic Ph + CML patients.
Because after mono treatment with a TKI in Ph + CML patients, only a minority remains in a treatment free remission and further improvement of the results is desired, this study will be conducted.

Study objective

The purpose of this study is to determine the safety and efficacy of Nilotinib and Vildagliptin as combination therapy in optimal dosage. In addition, it is investigated whether the addition of Vildagliptin to Nilotinib treatment causes the prolonged deep molecular response (when the disease is almost completely disappeared) to be maintained longer after stopping the TKI after this result was not achieved at mono treatment with a primary tyrosine kinase inhibitor (the disease had returned).
Both drugs are widely known, but the use of the drugs together needs to be further investigated.

Study design

All patients participating in this study will receive the same treatment. Only the research has been divided into two seperate phases:

Phase 1 part:
the combination treatment of Vildagliptin and Nilotinib has not been studied previously in humans. Therefore, in phase 1 part of this study, it is investigated what is the best dose of Vildagliptin and how the combination of these two drugs is tolerated.
The first 3 patients in the study receive a certain dose of Vildagliptin. Depending on how this dose is tolerated, the dose of Vildagliptin in the following 3 patients will be increased up to 1 time the recommended maximum dose for treatment for patients with diabetes. If this dose is not tolerated properly, the dose of Vildagliptin is reduced again.
For Nilotinib, the standard dose is used twice daily 300 mg. The first 1-6 patients are treated in the phase I part of this study.

After selecting the final Vildagliptin dose, the study continues with this dose in phase 2 part of this study.

However, patients who benefit from the treatment will be treated with this combination of medicines as long as the disease responds positively.

Phase 2 part:
Patients participating in the second part (Phase 2) of the study are treated according to the dose that appeared to be the most optimal in the Phase 1 part.

Intervention

2nd generation TKI (Nilotinib) for the duration of 12 months
After 6 months of Nilotinib use, DPP-IV inhibitor (Vildagliptin) use starts for 12 months

Study burden and risks

This examination does not guarantee a treatment free remission, at any time, the disease can return.

Disadvantages of participating in the research can
- possible side effects of Nilotinib and Vildagliptin and the combination treatment Nilotinib / Vildagliptin
- possible adverse effects of the measurements as performed during this study.

Participation in research also means:
- the subject has to spent extra time in the hospital
- (extra) testing;
- there are pre-arranged agreements to which the subject must keep

Contacts

Public
Albert Schweitzer Ziekenhuis

Albert Schweitzerplaats 25
Dordrecht 3318AT
NL
Scientific
Albert Schweitzer Ziekenhuis

Albert Schweitzerplaats 25
Dordrecht 3318AT
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patients >=18 years of age.
2. At diagnosis chronic myeloid leukemia in chronic phase.
3. Previous relapse during attempt at TFR (Treatment Free Remission)
4. Documented regain of deep molecular remission at the level of at least MR4.0, defined as a measurable BCR-ABL level <=0.01% IS or an undetectable BCR-ABL with a minimal total control gene copy number of ABL1 *10*000 or GUSB *24*000 in two replicates. A sample showing MR4.0 or better needs to have been taken within 31 days of study inclusion.
5. Continuous treatment with any TKI for a minimum of 12 months prior to entering the study
6. No other current or planned anti-leukemia therapy.
7. ECOG Performance status 0,1, or 2.
8. Adequate organ function as defined by:
a) Total bilirubin <1.5 x ULN (ULN = local lab upper limit of normal). Does not apply to patients with isolated hyperbilirubinemia (e.g. Gilbert*s disease) grade <3.
b) ASAT and ALAT <2.5 x ULN.
c) Serum amylase and lipase <=1.5 x ULN.
d) Alkaline phosphatase <=2.5 x ULN.
e) Creatinine clearance >30 ml/min.
f) Mg++, K+ >=LLN.
9. Life expectancy of more than 12 months in the absence of any intervention
10. Written informed consent to participate in the study

Exclusion criteria

1. Prior accelerated phase or blast crisis.
2. Patient has received another investigational agent within last 6 months.
3. Prior stem cell transplantation.
4. History of occlusive cardiovascular disease, including peripheral occlusive arterial disease, cerebrovascular disease and coronary artery disease.
5. Other clinically significant uncontrolled heart disease (e.g. unstable angina, congestive heart failure or uncontrolled hypertension)
6. Increased risk of cardiac arrhythmia, defined as:
a) Inability to monitor the QT/QTc interval on ECG.
b) Long QT syndrome or a known family history of long QT syndrome.

c) Clinically significant resting brachycardia (<50 beats per minute).
d) QTc >450 msec on baseline ECG (using the QTcF formula). If QTcF >450 msec and electrolytes are not within normal ranges, electrolytes should be corrected and then the patient re-screened for QTc.
e) History of or presence of clinically significant ventricular or atrial tachyarrhythmias
6. Known atypical BCR-ABL transcript not quantifiable by standard RQ-PCR
7. History of active malignancy during the past 2 years with the exception of basal carcinoma of the skin or carcinoma in situ of cervix uteri or breast.
8. Acute liver disease or cirrhosis.
9. Previous or active acute or chronic pancreatic disease.
10. Another severe and/or life-threatening medical disease.
11. History of significant congenital or acquired bleeding disorder unrelated to cancer.
12. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug.
13. Patients actively receiving therapy with strong CYP3A4 inhibitors where the treatment cannot be either discontinued or switched to a different medication prior to starting study drug.
14. Patients who are currently receiving treatment with any medication that has the potential to prolong the QT interval and the treatment cannot be either discontinued or switched to a different medication prior to starting study drug.
15. Patients who are:
a) pregnant.
b) breast feeding.
c) of childbearing potential without a negative pregnancy test prior to baseline.
d) male or female of childbearing potential unwilling to use contraceptive precautions throughout the trial (post-menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential).
16. Interruption of TKI therapy for a cumulative period in excess of 21 days in the preceding 3 months.
17. Known intolerance to nilotinib
18. Known intolerance to vildagliptin
19. History of non-compliance, or other inability to grant informed consent.
20. Past or present history of alcohol abuse, use of illicit drugs, or severe psychiatric disorders, including depression.
21. Autoimmune hepatitis or a history of autoimmune disease.
22. Pre-existing thyroid disease unless it can be controlled with conventional treatment.
23. Epilepsy and/or compromised central nervous system (CNS) function.
24. HCV/HIV patients.
25. Poorly controlled diabetes mellitus(i.e. HbA1c >9.0) or clinically relevant diabetic complications such as neuropathy, retinopathy, nephropathy, coronary or peripheral vascular disease.

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):	28-09-2018
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Galvus
Generic name:	Vildagliptin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tasigna
Generic name:	Nilotinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	15-11-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	04-09-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2017-000899-28-NL
CCMO	NL61068.029.17