A Phase 1/2 Study of FPA008, an anti-CSF1 Receptor Antibody, in Patients with Pigmented Villonodular Synovitis (PVNS)/ Diffuse Type Tenosynovial Giant Cell Tumor (dt-TGCT)

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Primary- Phase 1: To determine the recommended dose (RD) of cabiralizumab in patients with pigmented villonodular synovitis (PVNS)/diffuse type tenosynovial giant cell tumor (dt-TGCT)- Phase 2: To estimate the objective response rate (ORR = CR+PR)...

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

Summary

ID

NL-OMON47675

Source
ToetsingOnline

Brief title
Phase 1/2 of FPA008 in PVNS/dt-TGCT

Condition

- Synovial and bursal disorders
- Skeletal neoplasms benign

Synonym
Pigmented villonodular synovitis/Diffuse Type Tenosynovial Giant Cell Tumor; PVNS/dt-TGCT

Research involving
Human

Sponsors and support

Primary sponsor: Five Prime Therapeutics, Inc.
Source(s) of monetary or material Support: the study sponsor

Intervention

Keyword: dt-TGCT, FPA008, Phase 1/2, PVNS

Outcome measures

Primary outcome

- Phase 1: The incidence of Grade 3 and Grade 4 adverse events (AEs) and

clinical laboratory abnormalities defined as dose-limiting toxicities (DLTs)

- Phase 2: The incidence of confirmed objective responses per RECIST 1.1

Secondary outcome

Secondary Endpoints

- PK parameters

- The incidence of AEs, clinical laboratory abnormalities and ECG abnormalities

- Duration of response per RECIST 1.1

Study description

Background summary

Background of the study (in English):
Pigmented villonodular synovitis (PVNS) is a benign neoplasm of the synovium with features of both reactive inflammation and clonal neoplastic proliferation in which colony stimulating factor-1 (CSF1) is over expressed. A common translocation of the CSF1 gene (1p13) to the COL6A3 promoter (2q35) is present in approximately 60% of PVNS patients. The translocation is accompanied by CSF1 overexpression in the synovium. In addition, approximately 40% of PVNS patients have CSF1 overexpression in the absence of an identified CSF1 translocation. The consistent presence of CSF1 overexpression in all cases of PVNS and reactive synovitis suggests both an important role for CSF1 in the spectrum of synovial pathologies and the utility of targeting the CSF1/CSF1R interaction

therapeutically.

Surgery is the treatment of choice for patients with localized PVNS. Recurrences occur in 8 20% of patients and are easily managed by re-excision. PVNS/dt-TGCT tends to recur more often (33*50%) and has a much more aggressive clinical course. Patients are often symptomatic and require multiple surgical procedures during their lifetime. For patients with unresectable disease or multiple recurrences, systemic therapy using CSF1R inhibitors may help delay or avoid surgical procedures and improve functional outcomes.

Recently two studies of potent inhibitors of CSF1 signaling have shown preliminary but compelling clinical activity in patients with PVNS. PLX3397, a CSF1R kinase inhibitor, and RG7155, a monoclonal antibody targeting CSF1R have been evaluated in patients with PVNS. In both studies, a majority of patients with PVNS responded to treatment based on RECIST, FDG-PET, and/or total volume score, which is a measure of disease volume by MRI.

Cabiralizumab is a humanized IgG4 monoclonal antibody with a single amino acid substitution in the hinge region to prevent hemi-dimer exchange and has high affinity binding to human colony stimulating factor 1 receptor (CSF1R), a receptor tyrosine kinase.
In PVNS, overexpression of CSF1 by a minority of cells leads to recruitment of CSF1R-expressing cells that make up the bulk of the tumor mass. Cabiralizumab antagonizes CSF1R activation and should result in the reduction of CSF1R-expressing cells in the tumor thereby providing clinical benefit.

Study objective

Primary
- Phase 1: To determine the recommended dose (RD) of cabiralizumab in patients with pigmented villonodular synovitis (PVNS)/diffuse type tenosynovial giant cell tumor (dt-TGCT)
- Phase 2: To estimate the objective response rate (ORR = CR+PR) of FPA008 in patients with PVNS/dt-TGCT

Secondary
- To characterize the safety and tolerability of cabiralizumab in patients with PVNS/dt-TGCT
- To determine the duration of response in responding patients
- To assess the pharmacokinetics of cabiralizumab in patients with PVNS/dt-TGCT

Exploratory
- To assess the pharmacodynamics of cabiralizumab as measured by changes in serum levels of CSF1, IL34, TRAP5b, CTx, selected serum markers, and whole blood CD14+/CD16+ monocyte subsets
- To evaluate synovial biopsies by immunohistochemistry (IHC) or in situ hybridization (ISH) for CSF1, CSF1R, and CD68 markers in selected patients

- To evaluate synovial fluid for cabiralizumab concentration and changes in cellularity in selected patients.
- To assess the use of analgesic medications prior to, and during the study
- To assess functional outcomes as measured by:
* Ogilvie-Harris score developed specifically for PVNS
* Brief Pain Inventory
* Joint Stifness Numeric Rating Scale
* EQ-5D-5L
* Global Impression Scales
* Patient Global Impression of Symptom Severity (PGIS)
* Patient Global Impression of Treatment Satisfaction (PGITS)
* Patient Global Impression of Treatment Side Effects (PGITSE)
* Clinician Global Impression of Severity * PVNS/dt-TGCT
* Pigmented villonodular synovitis signs and symptoms assessment form (PVNS-SSAF)
* Patient Reported Outcomes Measurement Information System-Physical Function (PROMIS-PF) 10b

Study design

This is a Phase 1/2 study. Phase 1 is a dose escalation, open-label, safety, tolerability, PK and PD study of cabiralizumab.

Phase 2 is a dose expansion, open-label, efficacy study of cabiralizumab. Phase 2 consists of two parts: Cohort 2A * 4 mg/kg Q2W & Cohort 2B * 4 mg/kg on day 1 and 15, then Q4W thereafter.

Patients enrolled in Phase 1 and Cohort 2A will be treated with cabiralizumab in 28-day cycles.
Patients enrolled in Cohort 2B will receive 4 mg/kg cabiralizumab on Cycle 1 Day 1 and Cycle 1 Day 15, then every four weeks thereafter.

Intervention

Phase 1: FPA008 every 2 weeks in 28-day cycles at dose levels of 1 mg/kg, 2mg/kg and 4 mg/kg
Phase 2: FPA008 every 2 weeks in 28-day cycles at the recommended dose determined in phase 1
Cohort 2b: 4 mg/kg cabiralizumab on Cycle 1 Day 1 and Cycle 1 Day 15, then every four weeks thereafter.

Study burden and risks

See section E9

Contacts

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Understand and sign an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to any study-specific evaluation
2. Age *18 years
3. Histologically confirmed diagnosis of inoperable, progressive, or relapsing PVNS/ dt-TGCT or potentially resectable tumor that would result in unacceptable functional loss
4. Measurable PVNS/dt-TGCT by RECIST v1.1 on MRI
5. ECOG performance status * 1
6. Willing and able to comply with all study procedures
7. In sexually-active patients (i.e., females of childbearing potential, who have not undergone menopause as defined by 12 consecutive months of amenorrhea or had a permanent sterilization procedure and males, who have not had a permanent sterilization procedure), willingness to use 2 effective methods of contraception, of which one must be a physical

barrier method (condom, diaphragm, or cervical/vault cap) during the study and until 6 months after the last dose of cabiralizumab. Other effective forms of contraception are permanent sterilization (hysterectomy and/or bilateral oophorectomy, or bilateral tubal ligation with surgery, or vasectomy) at least 6 months prior to Screening. Females < 55 years of age should have FSH > 40. Female patients of childbearing potential must be on stable oral contraceptive therapy or intrauterine or implant device for at least 90 days prior to the study, or abstain from sexual intercourse as a way of living.
8. Patients being retreated with cabiralizumab must have completed 6 Cycles of initial treatment at the 1 mg/kg or 2 mg/kg dose levels and the End-of- Treatment Follow-Up Period. Note: Prior to re-treatment, patients will be re-assessed to ensure they meet the same eligibility requirements as untreated patients.
9. Patients must have a minimum average Brief Pain Inventory (BPI) score of two points during screening (based on the average of questions 3-6 of the BPI, assessed for at least 5 of 14 days prior to C1D1; see Appendix 7).
10. Patients must be on a stable analgesic regimen for two weeks prior o first dose.;No waivers of these inclusion criteria will be granted.

Exclusion criteria

1. Prior therapy with another anti-CSF1R antibody within three months of first study dose administration (Note: Patients that discontinued prior anti-CSF1R antibody due to a drug-related serious adverse events will not be permitted to enroll).
2. Prior therapy with pexidartinib (PLX3397), imatinib, or nilotinib within four weeks of first study dose administration.
3. Liver function tests (including ALT, AST, and total bilirubin), outside of the range of local laboratory normal at Screening
4. Inadequate organ or bone marrow function defined as: hemoglobin < 10 g/dL, absolute neutrophil count <1.5x 10^9/L, platelet count <100x 10^9/L, serum creatinine >1.5x ULN or calculated creatinine clearance <30 mL/min
5. Any surgical procedure of the involved joint within 12 weeks prior to first study dose administration (except baseline synovium biopsy, if performed)
6. Current or history of clinically significant muscle disorders (e.g., myositis), recent unresolved muscle injury, or any condition known to elevate serum CK levels
7. History of congestive heart failure or myocardial infarction <1 year prior to first study dose administration
8. Decreased cardiac function with NYHA > Class 2
9. Uncontrolled or significant heart disorder such as unstable angina
10. Significant abnormalities on ECG at Screening. QTcF > 450 msec for males or > 470 msec for females at Screening
11. Contraindications to MRI and use of intravenous gadolinium-based contrast agents
12. History of severe allergic, anaphylactic, or other infusion related reaction to a previous biologic agent
13. Treatment with any anticancer therapy or participation in another therapeutic clinical study with investigational drugs * 28 days prior to first dose of cabiralizumab
14. Known history of ADAs to previous biologic agents

15. Known history of sensitivity to any component of the study drug formulation
16. Consumption of non-pasteurized milk on a regular basis, or known significant risk of exposure to opportunistic intracellular infections such as listeria, or other such pathogens.
17. Receipt of any vaccine within 28 days prior to first day of treatment. The effect of cabiralizumab on mounting an immunologic vaccine response is not known. Flu or other vaccinations may be administered while on study but the impact of cabiralizumab on the safety and efficacy of the vaccination is unknown.
18. Current unresolved infection or history of chronic active clinically significant infection (viral [e.g., HBV, HCV], bacterial, fungal, or other), which in the opinion of the Investigator would place the patient at risk from exposure to a CSF1R inhibitor
19. Known positive test for human immunodeficiency virus (HIV)
20. Active TB
21. Positive test for latent TB at Screening (T-spot or Quantiferon test)
22. History of prior malignancy, except:
* Curatively treated non-melanoma skin malignancy
* Cervical cancer in situ
* Solid tumor treated curatively more than 2 years previously without evidence of recurrence
23. Lack of peripheral venous access or any condition that would interfere with drug administration or collection of study samples
24. Any uncontrolled medical condition or psychiatric disorder which in the opinion of the Investigator would pose a risk to patient safety or interfere with study participation or interpretation of individual patient results
25. Inability to perform and/or comply with study and follow-up procedures.
26. Known history of metastatic PVNS/dt-TGCT
27. Creatine kinase (CK) * 1.5x ULN
28. Patients with a Screening anti-nuclear antibody (ANA) titer of 1:160 or higher
29. Active, known, or suspected autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism requiring only hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.;No waivers of these exclusion criteria will be granted.

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):	20-11-2015
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cabiralizumab
Generic name:	N/A

Ethics review

Approved WMO

Date:	01-06-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	18-11-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	11-12-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	27-01-2016
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	14-10-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	03-07-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	11-09-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	24-10-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	18-12-2017
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	03-10-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	14-01-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	16-05-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	18-09-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2015-000547-17-NL
ClinicalTrials.gov	NCT02471716
CCMO	NL52824.058.15