A Phase 1/3, Randomised, Parallel-Group, Active-Controlled, Double-Blind Study to Demonstrate Equivalence of Pharmacokinetics and Noninferiority of Efficacy for CT-P10 in Comparison With Rituxan, Each Administered in Combination With Cyclophosphamide, Vincristine, and Prednisone (CVP) in Patients With Advanced Follicular Lymphoma

Published: 22-01-2014
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The primary objective:To demonstrate that CT-P10 is similar to Rituxan in terms of pharmacokinetics as determined by AUCtau and CmaxSS at Cycle 4 and maximum serum concentration at steady state The secondary objective:Efficacy: the primary endpoints...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON47777

Source
ToetsingOnline

Brief title
Celltrion CT-P10 3.3 AFL

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Advanced Follicular Lumphoma, Cancer

Research involving
Human

Sponsors and support

Primary sponsor: CELLTRION, Inc
Source(s) of monetary or material Support: Sponsor/Farmaceut

Intervention

Keyword: Advanced Follicular Lymphoma, CT-P10 3.3, CVP, Rituximab

Outcome measures

Primary outcome

Primary PK Endpoints:

* AUCtau

* CmaxSS

Primary efficacy endpoint:

* Overall response rate (CR + CRu + PR) during the Core Study Period, according

to the 1999 IWG

criteria

Secondary outcome

Secondary PK Endpoints:

* Cmax at each dose

* Ctrough at each dose

* Cav

* Vd

* CL

* T1/2

* Tmax

* MRT

* PTF

* *z

Secondary Efficacy Endpoints:

* Overall response rate (CR + PR) during the Core Study Period, according to

the 2007 IWG criteria

for patients who underwent PET-CT

* Progression-free survival

* Time to progression

* Time to treatment failure

* Response duration

* Disease-free survival

* Overall survival

Additional efficacy parameters:

pharmacokinetics, pharmacodynamics and overall safety

Study description

Background summary

CT-P10 is developped as a biosimilar of Rituxan (rituximab). At this point the standard of care treatment for advance follicular lymphoma (FL) is to use rituximab in combination with chemotherapy , followed by a maintenance therapy with rituximab. This Study contains a maintenance period with rituximab at patients with FL stage III IV. The proposed dosing adheres to the approved labels of Rituxan.
Maintenance therapy with Rituxan showed improved progression-free survival in patients with FL in clinical phase 3 research studies. It is expected that the general safety profile of CT-P10 (rituximab) equivalents that of Rituxan. The most unwanted observed medication reactions with patients who received Rituxan were infusion related reactions that occurred during the first infusion at most patients.
The proposed safety monitoring is expected to be sufficient to monitor possible risks of CT-P10 administration. This research is set up to show that CT-P10 is equivalent to Rituxan in pharmacokinetics and non-inferior towards efficacy, if coprimairely endpoints at simultaniously administration of CVP in patients with advanced FL.

Study objective

The primary objective:
To demonstrate that CT-P10 is similar to Rituxan in terms of pharmacokinetics as determined by AUCtau and CmaxSS at Cycle 4 and maximum serum concentration at steady state

The secondary objective:
Efficacy: the primary endpoints will be overall response rate (CR + CRu + PR) according to the 1999 International Working Group (IWG) criteria.
To demonstrate overall response rate (CR + PR) over 8 cycles (Core Study Period) according to the 2007 IWG criteria.
To evaluate additional efficacy parameters (progression free survival, time to progression, time to treatment failure, response duration, disease-free survival, and overall survival) according to the 1999 IWG criteria and 2007 IWG criteria for patients who underwent positron emission tomography (PET) or PET-computed tomography (PET CT).

To evaluate pharmacodynamics (B-lymphocyte [B-cell] kinetics, including depletion and recovery), overall safety, efficacy and biomarkers of CT-P10 in comparison with Rituxan.

Study design

A Phase 1/3, Randomised, Parallel-Group, Active-Controlled, Double-Blind Study to Demonstrate Equivalence of Pharmacokinetics and Noninferiority of Efficacy for CT-P10 in Comparison With Rituxan, Each Administered in Combination With Cyclophosphamide, Vincristine, and Prednisone (CVP) in Patients With Advanced Follicular Lymphoma

Intervention

Patients will receive either CT-P10 or Rituxan administered (375 mg/m2 IV) in combination with CVP: cyclofosfamide (750 mg/m2 IV), vincristine (1,4 mg/m2 [to maximum 2 mg] IV) and prednison (40 mg/m2 oral) during each dosinh cycle.

Study burden and risks

1x medical history
24-27x physical examination
23x vital signs
7x ECG
1x biopsy for pathology (optional)
1x bone marrow biopsy (or 3 is physician deems it necessary)
20x urine sampling
23x pregnancy test (3x blood, 20x urine)
7x X-ray
8-11x CT Scan
23x TBC symptoms
Max 8 cycles administration of study medication during core period
Max 12 cycles administration of study medication during maintenance period
Max 8 cycles chemo during core period
24-27x blood sampling, in total 421 mL per patient plus 168 mL for PK (only first 120 patients)

The most frequent side effects and discomforts that have been reported for CT-P10/Rituxan are infusion related reactions, infections, and disorders such as angina, heart failure, myocardial infarction, depression, anxiety, dizziness, diarrhoea, abdominal pain. In addition, subjects might experience some discomforts from the administration of the concomitant chemotherapy (CVP) and from study procedures.

Contacts

Public
CELLTRION, Inc

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Scientific
CELLTRION, Inc

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KR

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patient is male or female 18 years and older.
2. Patient has histologically confirmed FL according to the World Health Organization 2008 classification (Jaffe 2009); grades 1 to 3a based on local laboratory review.
3. Patient has at least 1 measurable tumour mass that has not previously been irradiated, and the mass must be:
- Nodal lesion >15mm in the longest dimension; or
- Nodal lesion >10mm to *15mm in the longest dimension and >10mm in the shortest dimension; or
- Extranodal lesion with both long and short dimensions *10mm.
4. Patient has confirmed CD20+ lymphoma, as assessed by local laboratory review.
5. Patient has Ann Arbor stage III or IV disease.
6. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (Oken 1982).
7. For both male and female patients and their partners of childbearing potential, patient agrees to practice total abstinence or to use one of the following medically acceptable methods of contraception during the course of the study and for 12 months following discontinuation of study treatment (excluding women who are not of childbearing potential and

men who have been sterilised):
* Barrier contraceptives (male condom, female condom or diaphragm with a spermicidal gel)
* Hormonal contraceptives (implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings)
* Intrauterine devices
Male or female patients and their partners who have been surgically sterilised for less than 6 months prior to study entry must agree to use 1 medically acceptable method of contraception or practice total abstinence. Menopausal females must have experienced their last period more than 12 months prior to study entry (ie, when the informed consent form [ICF] is signed) to be classified as not of childbearing potential.
8. For both premenopausal women and women who are less than or equal to 12 months after the onset of menopause, patient has a negative serum pregnancy test during the Screening Period.
9. Patient has adequate bone marrow, hepatic, and renal function reserve as evidenced by:
* Haemoglobin level of *8 g/dL
* Absolute neutrophil count (ANC) of *1500/mm3
* Platelet count of *75 000/mm3
* Total bilirubin level of *2.0 mg/dL
* Aspartate aminotransferase and alanine aminotransferase levels of *3 times the upper limit of normal (ULN) for the reference laboratory (*5 × ULN for the reference laboratory with known hepatic involvement by lymphoma)
* A serum creatinine level of *1.5 × ULN for the reference laboratory, or a calculated creatinine clearance by the Cockcroft-Gault equation (Rostoker et al 2007) of *50 mL/min

Exclusion criteria

1. Patient has received rituximab (or a rituximab proposed biosimilar product), cyclophosphamide, or vincristine.
2. Patient has allergies or hypersensitivity to murine, chimeric, human or humanised proteins, cyclophosphamide, vincristine, or prednisone.
3. Patient has evidence of histological transformation to high-grade or diffuse large B-cell lymphoma.
4. Patient has known central nervous system involvement.
5. Previous treatment including chemotherapy, radiotherapy, immunotherapy, and/or surgery (except previous biopsy). However, patients who have received radiotherapy as part of the palliative therapy are eligible if the last fraction of radiotherapy was administered at least 4 weeks prior to Day 1 of Cycle 1 and patients must have recovered from all radiotherapy-related toxicities prior to randomisation.
- All doses of corticoid therapy for treatment of NHL.

- Corticoid therapy during the previous 4 weeks from Day 1 of Cycle 1 with prednisone >20mg per day for the treatment for any purpose
6. Patient has a current diagnosis of active tuberculosis (TB) defined by chest x-ray, CT, or proper image) or other severe infections, such as sepsis, abscesses, or opportunistic infections.
7. Patient has a known infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C. (Carriers of hepatitis B are not permitted to enrol into the study.)
8. Patient has New York Heart Association class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina, clinically significant electrocardiogram abnormalities), or myocardial infarction within the previous 6 months before the ICF is signed.
9. Patient has any malignancy other than NHL, except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ, within the previous 5 years before Day 1 of Cycle 1.
10. Patient has a current or recent (within 30 days before Day 1 of Cycle 1) treatment with any other investigational medicinal product or device.
11. Patient has uncontrolled diabetes mellitus, even after insulin treatment.
12. Patient is pregnant or lactating. Patients who are planning to be pregnant or to breastfeed before, during, or within 12 months after the last infusion of study treatment are not permitted to enrol into the study.
13. Patient is taking a live, live-attenuated, or nonlive vaccine within 4 weeks before Day 1 of Cycle 1 of study treatment.
14. Patient has evidence of any other coexisting disease or medical or psychological condition, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational product, or patient is a high risk for treatment complications.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-10-2014
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CT-P10
Generic name:	Rituximab
Product type:	Medicine
Brand name:	Rituxan
Generic name:	Rituximab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	22-01-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-03-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	28-04-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-05-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-03-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-04-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-04-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-02-2016
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-05-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-01-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-01-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2013-004493-96-NL
CCMO	NL47361.101.14

Study results

Results posted: 24-12-2019

First publication
30-07-2019