Phase 3 Randomized, Double-Blind, Placebo Controlled, Multicenter Study to Compare the Efficacy and Safety of Lenalidomide (CC-5013) Plus R-CHOP Chemotherapy (R2-CHOP) Versus Placebo Plus R-CHOP Chemotherapy in Subjects With Previously Untreated Activated B-Cell Type Diffuse Large B-Cell Lymphoma

Published: 08-12-2014
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To evaluate the efficacy and safety of lenalidomide, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R2-CHOP) chemotherapy versus placebo, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (placebo-R-CHOP)...

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

Summary

ID

NL-OMON45071

Source
ToetsingOnline

Brief title
ROBUST

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Previously Untreated Activated B-Cell Type Diffuse Large B-Cell Lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: Sponsor/farmaceut

Intervention

Keyword: ABC type, Diffuse B-cell lymphoma, Lenalidomide, R2-CHOP

Outcome measures

Primary outcome

Progression-free Survival (PFS)

Secondary outcome

Key secondary endpoint:

Event-free Survival (EFS)

Other secondary endpoints:

• Overall Survival (OS)

• Complete Response (CR) rate

• Duration of CR

• Time to next lymphoma therapy (TTNLT)

• Objective response rate (ORR)

• Health-related quality of life (HRQoL) as measured by the EuroQuol 5

Dimension Scale (EQ-5D) and the Functional Assessment of Cancer Therapy for

Patients with Lymphoma (FACT-Lym) standardized measures of health status

Exploratory Endpoints:

• Progression-free Survival 2 (PFS2)

• Correlation of MRD status to clinical outcome measures such as PFS and OS,

and sensitivity and specificity of the MRD NGS test

• Correlation of pretreatment levels of molecular markers with clinical outcome

Study description

Background summary

CHOP chemotherapy in combination with the anti-CD20 monoclonal antibody rituximab on a 21-day schedule is a standard of care in newly diagnosed cases in most countries worldwide. While approximately 50% to 60% of patients are cured, for those patients who are refractory or who progress following R-CHOP, treatment options are limited and outlook is poor; most die within the next two years. Since roughly 40% to 50% of patients are not cured on initial therapy, evaluating other front line treatment options is warranted. Other attempts to improve cure rate, including R-ACVBD, CHOEP, dose dense regimens (R-CHOP14), and high dose regimens (DA-EPOCH), have not replaced R-CHOP21 as a standard of care.

The R2-CHOP efficacy data from previous studies compare favorably to historical R-CHOP21 data with a better Complete Response (CR) rate at the end of induction therapy and better Progression Free Survival (PFS). Furthermore, promising efficacy results were also demonstrated in the non-GCB subtype, which generally has a poorer outcome when treated with R-CHOP alone. Clinically meaningful improvements as demonstrated by higher CR rate and longer PFS in non-GCB DLBCL subjects are considered significant in this difficult to treat sub-population.
The addition of lenalidomide could ameliorate the poor prognosis effect of the ABC phenotype and improve treatment outcome in this subgroup of subjects.
From a safety perspective, this combination is tolerable, without unexpected toxicities. The Grade 3 and 4 toxicities are primarily hematological in nature, and manageable with supportive care.

Study objective

To evaluate the efficacy and safety of lenalidomide, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R2-CHOP) chemotherapy versus placebo, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (placebo-R-CHOP) chemotherapy in subjects who have

previously untreated ABC type DLBCL.

Primary Objective
The primary objective of the study is to compare the efficacy of R2-CHOP versus placebo-RCHOP.

Secondary Objective
The secondary objective of this study is to compare the safety of R2-CHOP versus placebo-RCHOP.

Exploratory Objectives
The exploratory objectives of this study are to compare the progression free survival 2 and genetic mutations of subjects receiving R2-CHOP versus placebo-R-CHOP; to explore minimal residual disease and clonal heterogeneity/succession in subjects receiving R2-CHOP versus placebo R-CHOP who achieve a CR; and to explore molecular markers related to lenalidomide mechanism of action.

Study design

This randomized, placebo controlled study is designed to evaluate the efficacy and safety of R2-CHOP chemotherapy versus placebo-R-CHOP chemotherapy in previously untreated ABC type DLBCL. The study is divided into the Screening Period, Treatment Period, and Follow-up Period. Approximately 560 subjects will be randomized over approximately a 34-month accrual period.

The Screening Period for eligibility determination may begin after the subject signs the informed consent form. During the Screening Period subjects will undergo safety and other assessments, including central pathology confirmation of DLBCL diagnosis and determination of ABC type. Following confirmation of eligibility, subjects will undergo randomization to either the experimental or control arm in a 1:1 ratio.

The Treatment Period begins with Cycle 1 Day 1 dosing. Subjects will receive protocol-specified treatments for 6 cycles. Treatment will continue to completion; or until the outcome of the computed tomography (CT) scan between Weeks 9 - 12 (after Cycle 3 but before Cycle 4) indicates a treatment change based on response assessment; disease progression; unacceptable toxicity; death; or withdrawal of consent, whichever occurs first.

The Follow-up Period begins upon study treatment completion or upon early discontinuation of study treatment. Subjects will be followed for first and second progressions, subsequent antilymphoma therapy, development of any second primary malignancies (SPMs), and overall survival according to the schedule described in Table 5 of the protocol.

Intervention

Study treatments in a 21-day cycle are: lenalidomide / placebo Days 1 - 14; rituximab, cyclophosphamide, doxorubicin, and vincristine Day 1; prednisone Days 1 - 5. Refer to Table 7 of the protocol for complete details.

Study burden and risks

The subjects will undergo the following procedures:
1x CNS lymphoma evaluation (is applicable)
1x Hepatitis B test
1x creatinine clearance
1x ECG
2x MUGA/echocardiogram
1 of 2x bone marrow biopsy
1x bone marrow aspirate (optional)
1x saliva sample
1x tumorbiopsy
25x physical exam
25x vital signs
25x blood sampling (not all parameters are assessed during each visit)
Max. 19x pregnancy test, depending on regularity of menstrual cycle
19x QoL questionnaire
18x CT
2x PET
18x B symptoms

Side effects which have been reported in more than 10% of the patients participating in studies sponsored by Celgene investigating Lenalidomide:
• Low number of white blood cells (with owithout fever)
• Anemia; Decrease in cells that help your blood clot
• Vision Blurred
• Diarrhea
• Pain (Upper abdominal pain, Abdominal pain, Toothache)
• Constipation
• Indigestion
• Nausea
• Vomiting
• Feeling weak and unwell
• Tired
• Swelling
• Fever
• Chills
• Pneumonia or other infections
• Sore throat
• Stuffy nose

• Weight loss
• Decreased appetite
• High blood sugar
• Chemical imbalance in blood
• Abnormal liver lab tests
• Pain including muscles, joints, and non-cardiac chest pain
• Dizziness
• Altered sense of taste
• Headache
• Eye lens cloudiness (cataract)
• Abnormal sense of touch
• Pain and decreased sensation in nerves
• Shaking
• Cough
• Shortness of breath
• Nosebleed
• Blood clot in lower extremities, lungs, heart, brain, and other organs
• Dry skin
• Itching
• Allergic reaction
• Feeling sad
• Not sleeping well

Furthermore, subjects will experience possible risks of study procedures: Tumor biopsy, Bone marrow aspirate and biopsy, CSF Sampling, Blood Tests / IV needle insertion, CT scans,
PET scans, MUGA, GEP typing test.

Contacts

Public
Celgene Corporation

Morris Avenue 86
Summit NJ 07901
US
Scientific
Celgene Corporation

Morris Avenue 86
Summit NJ 07901
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Histologically proven Diffuse Large B-Cell Lymphoma (DLBCL) of the ABC type.
- Newly diagnosed, previously untreated Diffuse Large B-Cell Lymphoma (DLBCL)
- Measurable Diffuse Large B-Cell Lymphoma (DLBCL) disease by Computed Tomography (CT)
- Eastern Cooperative Oncology Group (ECOG) performance status 0 - 2.
- Age 18 -80 years

Exclusion criteria

- Diagnosis of lymphoma histologies other than Diffuse Large B-Cell Lymphoma (DLBCL).
- History of malignancies, other than Diffuse Large B-Cell Lymphoma (DLBCL), unless the patient has been disease free for 5 years or more.
- Known seropositive for, or history of, active Human Immunodeficiency Virus (HIV) Hepatitis B Virus (HBV), Hepatitis C Virus (HCV)
- Contraindication to any drug in the chemotherapy regimen, and specifically: LVEF < 45% or peripheral neuropathy grade > =2.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-12-2015
Enrollment:	44
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	REVLIMID®
Generic name:	Lenalidomide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-12-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-05-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2015
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-05-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-03-2019
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2020
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	EUCTR2013-004054-21-NL
CCMO	NL50402.029.14

Study results

Results posted: 28-03-2023

First publication
01-01-1900