A Randomized, Controlled, Open-Label, Multicenter Phase 3 Study of the Bruton*s Tyrosine Kinase (Btk) Inhibitor, Ibrutinib, Versus Temsirolimus in Subjects with Relapsed or Refractory Mantle Cell Lymphoma Who Have Received at Least One Prior Therapy

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The primary hypothesis of this study is that ibrutinib compared with temsirolimus significantly prolongs PFS in subjects with relapsed or refractory MCL who have received at least 1 prior rituximab-containing chemotherapy regimen.

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

Summary

ID

NL-OMON40109

Source
ToetsingOnline

Brief title
PCI32765MCL3001 or RAY trial

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
an aggressive cancer of a kind of white blood cells, Non-Hodgkin lymphoma, who are called

B-lymfocytes

Research involving
Human

Sponsors and support

Primary sponsor: Janssen Cilag International N.V.
Source(s) of monetary or material Support: Janssen B.V.

Intervention

Keyword: Ibrutinib, Mantle cell lymphoma, One prior therapy, Temsirolimus

Outcome measures

Primary outcome

The primary objective of the study is to evaluate whether treatment with ibrutinib compared with temsirolimus will result in prolongation of progression-free survival (PFS) in subjects with relapsed or refractory mantle cell lymphoma (MCL) who have received at least 1 prior rituximab-containing chemotherapy regimen.

EFFICACY EVALUATIONS/ENDPOINTS

Disease evaluations (computed tomography [CT]/magnetic resonance imaging [MRI], clinical evaluation) will be performed every 9 weeks for up to 15 months from the start of study drug, and every 24 weeks thereafter, until disease progression, death, or the clinical cutoff, whichever comes first. Subjects who discontinue treatment prior to disease progression must continue to have regularly scheduled disease evaluations until disease progression, or death, or the clinical cutoff, whichever occurs first. For all subjects, the following data will be collected after the clinical cutoff: survival data, EQ-5D-5L, and subsequent anti-MCL therapy.

During the Crossover Treatment Phase, radiological assessments should be performed according to the standard of care until disease progression, unacceptable toxicity, or study end. For subjects who have crossed over to ibrutinib, site visits will be every 9 weeks.

For subjects in the crossover group, questionnaire will be collected until discontinuation of ibrutinib.

Secondary outcome

Key secondary objectives include evaluations of response rate, overall survival, 1-year survival rate, duration of response, safety of ibrutinib compared with temsirolimus, and characterization of the pharmacokinetic profile of ibrutinib.

PHARMACOKINETIC EVALUATIONS

Model-derived plasma concentrations or metrics of exposure parameters (eg, minimum observed serum concentration [Cmin] or area under the curve [AUC]) may be subjected to further analyses to explore pharmacokinetic correlation between ibrutinib exposure and relevant clinical or biomarker information.

BIOMARKER EVALUATIONS

A tumor sample from lymph node or other organ biopsy collected during Screening, blood collected at multiple timepoints, and a bone marrow aspirate will be evaluated to identify markers predictive of response or resistance to ibrutinib. A lymph node biopsy and bone marrow aspirate should be collected at progression, if feasible.

SAFETY EVALUATIONS

The safety will be assessed by physical examinations, ECOG criteria for

performance status, laboratory tests, monitoring adverse events, and concomitant medication usage. Adverse events that occur between the signing of the informed consent through 30 days following the last dose of ibrutinib or temsirolimus, or until the start of subsequent anti-MCL therapy will be collected. The severity of adverse events will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03. Intracranial hemorrhage and major hemorrhage have been identified as adverse events of special interest and will require enhanced reporting and data collection.

Study description

Background summary

Ibrutinib (JNJ 54179060: PCI-32765) is a first-in-class, selective, irreversible small molecular inhibitor of Bruton*s tyrosine kinase (BTK) currently being co-developed by Janssen Research & Development, LLC (JRD) and Pharmacyclics, Inc for the treatment of B-cell malignancies. It has demonstrated single-agent activity in several B-cell lymphomas, including relapsed mantle cell lymphoma (MCL), with an acceptable safety profile.A response rate of approximately 70% was observed in a Phase 2 clinical study of ibrutinib to treat patients with relapsed/refractory MCL.
Mantle cell lymphoma is a rare and incurable subtype of non-Hodgkin Lymphoma (NHL).
Intensive therapy is not an option for most patients with MCL because of their age and comorbidities. Once the disease has progressed after first-line therapy, the prognosis is dismal. Many agents/regimens have been studied and are used. However, there is no globally accepted standard treatment for patients with MCL who progress after initial therapy.

Study objective

The primary hypothesis of this study is that ibrutinib compared with temsirolimus significantly prolongs PFS in subjects with relapsed or refractory MCL who have received at least 1 prior rituximab-containing chemotherapy

regimen.

Study design

This is a randomized, controlled, open-label, multicenter, Phase 3 study of approximately 280 eligible subjects to evaluate the efficacy and safety of ibrutinib when compared with temsirolimus in subjects with relapsed or refractory MCL who have received at least 1 prior rituximab-containing chemotherapy regimen. Subjects will be randomized in a 1:1 ratio and stratified by the number of prior lines of therapy (1 or 2 vs. * 3); and simplified MCL international prognostic index (MIPI) (low risk [0-3]; vs. intermediate risk [4-5]; vs. high risk [6-11]). The efficacy evaluations will be performed by an IRC that is blinded to study treatment information.
Subjects randomized to Treatment Arm A will receive 560 mg ibrutinib by mouth once daily on a 21-day cycle. Subjects randomized to Treatment Arm B will receive intravenous (IV) temsirolimus 175 mg on Days 1, 8, 15 of the first cycle followed by 75 mg on Days 1, 8, 15 of each 21-day cycle. Treatment on both arms will continue until disease progression or unacceptable toxicity, whichever occurs first.
Subjects who received treatment with temsirolimus and have IRC-confirmed disease progression may be eligible to crossover and receive treatment with ibrutinib 560 mg orally, daily, on a 21-day cycle until disease progression, unacceptable toxicity, or study end.

Intervention

see study design

Study burden and risks

Side effects from Ibrutinib and Temsirolimus:
see informed consent and see protocol page 27-29
Side effects of study procedures
Blood Sampling:
The possible side effects of taking blood include pain, bleeding, bruising, light-headedness, fainting and, on rare occasions, local blood clot formation or infection with redness and irritation of the vein.
Bone Marrow Sampling:
The possible side effects associated with a bone marrow biopsy include pain, bleeding, bruising, and infection, as well as a reaction to the numbing agent.
CT scans:
CT scans expose to radiation; Too much radiation over time can lead to the development of second cancers or leukemia.

Subjects randomized to Treatment Arm A will receive 560 mg ibrutinib by mouth once daily on a 21-day cycle. Subjects randomized to Treatment Arm B will

receive intravenous (IV) temsirolimus 175 mg on Days 1, 8, 15 of the first cycle followed by 75 mg on Days 1, 8, 15 of each 21-day cycle. Treatment on both arms will continue until disease progression or unacceptable toxicity, whichever occurs first.

Subjects who received treatment with temsirolimus and have IRC-confirmed disease progression may be eligible to crossover and receive treatment with ibrutinib 560 mg orally, daily, on a 21-day cycle until disease progression, unacceptable toxicity, or study end.

The length of time the patient spend in this study will vary and depends on the response to the treatment. It is anticipated that the study will last approximately 3 years after the last patient has been randomized into the study. If the patient stays on the study for the whole duration the patient may need to visit the study doctor up to 40 times.
If the results of the blood tests are not normal or if the patient is having side effects, the doctor might reduce the dose of study medication or stop the treatment altogether.

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

- Confirmed diagnosis of mantle cell lymphoma (MCL);- Received at least 1 prior rituximab-containing chemotherapy regimen (separate lines of therapy are defined as single or combination therapies that are either separated by disease progression or by a > 6 month treatment-free interval);- Documented relapse or disease progression following the last anti-MCL treatment;- At least 1 measurable site of disease according to Revised Response Criteria for Malignant Lymphoma;- Eastern Cooperative Oncology Group performance status grade 0 or 1;- Protocol-defined hematology and biochemical laboratory values;Major Inclusion Criteria for Cross Over to Ibrutinib treatment:
- IRC-confirmed disease progression after treatment with temsirolimus, and medical monitor approval.
- Protocol-defined hematology and biochemical laboratory values

Exclusion criteria

- Prior nitrosoureas within 6 weeks, chemotherapy within 3 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin-immunoconjugates within 10 weeks, radiation therapy or other investigational agents within 3 weeks, or major surgery within 4 weeks of randomization;- Prior treatment with temsirolimus, other mTOR inhibitors, ibrutinib, or other Bruton*s tyrosine kinase (BTK) inhibitors;- Known central nervous system lymphoma ;- Received an allogeneic or autologous hematopoietic stem cell transplant <=6 months from the date of randomization and on immunosuppressive therapy or have evidence of active graft versus host disease;- Diagnosed or treated for malignancy other than MCL, except: malignancy treated with curative intent and with no known active disease present for >=3 years before randomization, adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease, adequately treated cervical carcinoma in situ without evidence of disease;-Criterion modified per amendment: Requires anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon).
- Criterion modified per amendment: Requires treatment with a strong CYP3A4/5 inhibitor.
- Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification;- Known history of human immunodeficiency virus (HIV) or active hepatitis C virus (HCV) or active hepatitis B virus (HBV) infection or any uncontrolled active systemic infection requiring intravenous antibiotics;- Woman who is pregnant or breast-feeding;- Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator*s opinion, could compromise the subject*s safety,

interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk;Major Exclusion Criteria for Cross Over to Ibrutinib treatment:
- prior history of stroke or intracranial hemorrhage within 6 months prior to crossover treatment.
- require anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon).
- require treatment with a strong CYP3A inhibitor
- clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of pre-crossover screening.
- life-threatening illness, medical condition, or organ system dysfunction which, in the investigator*s opinion, could compromise the subject*s safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk.
- women who are pregnant or breastfeeding

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-07-2013
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ibrutinib

Generic name:	Bruton□s Tyrosine Kinase (Btk) Inhibitor
Product type:	Medicine
Brand name:	Torisel
Generic name:	Temsirolimus
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-09-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-10-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-01-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-02-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-09-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-11-2013
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2015
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:	01-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-12-2016
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	EUCTR2012-000601-74-NL
ClinicalTrials.gov	NCT01646021
CCMO	NL41823.029.12