A Phase Ib/II, open label study evaluating the safery and pharmacokinetics of GDC-0199 (ABT-199) in combination with Rituximab (R) or Obinutuzumab (G) plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in patients with B Cell non-hodgkin's lymphoma (NHL) and DLBCL

Published: 23-06-2014
Last updated: 20-04-2024

The primary objective of the Phase I portion of the study is the following:* To estimate the maximum tolerated dosing schedule for venetoclax given in combination with R-CHOP or G-CHOP to patients with B-cell NHL, either previously untreated or...

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

Summary

ID

NL-OMON45171

Source
ToetsingOnline

Brief title
GO27878 studie - for patients with Non-Hodgkin's Lymphoma

Condition

- Lymphomas non-Hodgkin's B-cell
- Lymphomas non-Hodgkin's B-cell

Synonym
Non-Hodgkin's Lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: Farmaceutical Industry

Intervention

Keyword: GDC-0199 (ABT-199), Phase Ib/II study, Venetoclax

Outcome measures

Primary outcome

Safety outcome measures:

* Incidence and nature of combination DLTs

Pharmacokinetic and Pharmacodynamic Outcome Measures

From the plasma concentration*time profile of venetoclax following

administration:

* Total exposure (area under the concentration*time curve [AUC])

* Time to maximum observed plasma concentration (Tmax)

* Cmax of plasma

* Minimum concentration under steady-state conditions with a dosing interval

(Cmin) of

plasma

From the concentration-time profiles of rituximab, obinutuzumab and CHOP

components:

* Cmax of serum

* Cmin of serum

Activity outcome measures:

* CR, as defined by PET/CT scan as well as bone marrow examination when applicable

* CR as defined by CT scan and bone marrow examination, when applicable

* OR, defined as a PR or CR

* Duration of response (DOR), defined as the first occurrence of a documented response until the time of relapse or death from any cause

* PFS, defined as the time from date of first dose of study drug to the first occurrence of progression, relapse, or death while in the study, where death while in the study is defined as death from any cause within 12 weeks of the last tumor assessment

* Progression-free survival at 12 months

* Relative dose intensity

* OS, defined as the time from date of first dose of study drug until the date of death from any cause. For patients who have not died, survival data will be censored at the date of last contact.

Secondary outcome

Safety outcome measures:

* Incidence, nature, and severity of adverse events and serious adverse events graded according to NCI CTCAE v 4.0. AEs of special interest include Grade 4

neutropenic fever, Grade * 3 IRRs to rituximab or obinutuzumab, and Grade * 4

TLS

* Change in clinical laboratory results (including hematology, chemistry, and

urinalysis) and vital signs

* Maintenance of relative dose intensity of CHOP chemotherapy

Pharmacokinetic and Pharmacodynamic Outcome Measures

PK parameters such as clearance (CL), volume of distribution (V), and half-life

(T1/2) may also be calculated as data allow

Exploratory Assessments

The following correlative biology measures will be assessed:

* Bcl-2 high (Bcl-2 positive) as defined by immunohistochemistry

* Bcl-2 copy number gain by FISH and translocation t(14;18) by FISH

* Expression of transcripts for Bcl-2 family members, other apoptotic genes and

genes associated with the ABC or GCB subtypes of DLBCL

* Subgroups relevant to DLBCL biology, including CD79b, Myd88, CARD11, and

TNFAIP3; epigenetic markers; and MYC/BCL2 double hit

Study description

Background summary

Non-Hodgkin*s lymphoma (NHL) is the most common hematologic malignancy in adults. The majority of NHL (also known as malignant lymphoma) are of B cell origin, and are characterized by the expression of a membrane antigen, CD20, that is important in cell cycle initiation and differentiation. NHL can be

divided into aggressive and indolent NHL. The clinical course of indolent NHL is characterized by remission and relapse. Although there is no agreed-upon standard therapy for indolent NHL, R-CHOP is a common regimen, with a high response rates and long remission duration in many patients, particularly those patients with follicular lymphoma (FL). Patients with advance stage disease are not considered curable with conventional treatment and ultimately die from recurrent disease or treatment-related toxicity. Therefore, there is a need for the development of new treatments, that could improve both response and survival rates of patients with indolent NHL.

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, comprising approximately 30% of all NHL cases. Approximately 75% of patients with DLBCL who are treated with current standard therapy (R-CHOP) achieve a complete remission, and 50%*60% of patients is cured of their disease with this treatment. DLBCL is a molecularly heterogeneous disease, with different molecular subtypes having been identified through gene expression profiling. Bcl-2 is an anti-apoptotic molecule over expressed in many hematologic malignancies, including many DLBCLs. Bcl-2 protein inhibits death of lymphoma cells in response to chemotherapy and other anti-neoplastic agents, including rituximab (R). Overexpression of Bcl-2 has been shown to be associated with inferior outcomes in DLBCL with standard treatment. The frequent overexpression of Bcl-2 combined with its contribution to therapy resistance makes Bcl-2 inhibition an attractive therapeutic target in DLBCL.

venetoclax is a highly selective, orally available small molecule Bcl-2 family protein inhibitor that
binds with high affinity to Bcl-2 and with lower affinity to other Bcl-2 family proteins.

Obinutuzumab is a humanized and glycoengineered monoclonal antibody, derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics
* High-affinity binding to CD20
* Type II binding to the CD20 epitope
* Compared with rituximab, increased antibody-dependent cell-mediated cytotoxicity (ADCC)
* Compared with rituximab, increased direct cell death induction

Obinutuzumab is currently being compared with rituximab in combination with CHOP chemotherapy in a randomized trial in DLBCL (Study BO21005). If obinutuzumab proves to be superior to rituximab, standard of care would change to G-CHOP.
Therefore, the combination of venetoclax with both R-CHOP and G-CHOP will be examined in this study.

This study will explore the safety of the combination of venetoclax and R-CHOP or G-CHOP in patients with B cell NHL who are felt to be appropriate candidates

for R-CHOP therapy during initial dose-finding cohorts and will further explore safety and efficacy in Phase II cohorts of previously untreated DLBCL in order to identify appropriate populations for evaluation in a Phase III setting.

Study objective

The primary objective of the Phase I portion of the study is the following:
* To estimate the maximum tolerated dosing schedule for venetoclax given in combination with R-CHOP or G-CHOP to patients with B-cell NHL, either previously untreated or relapsed/refractory after a maximum of one prior therapy

The primary objectives of the Phase II portion of the study are the following:
* To assess the safety and tolerability of the combination of venetoclax and R-CHOP or G-CHOP administered to patients with previously untreated DLBCL
* To make a preliminary assessment of efficacy as measured by CR rate determined by PET/CT scan, of the combination of venetoclax and R-CHOP administered to patients with previously untreated DLBCL, co expressing both Bcl-2 and c-Myc proteins

Study design

This is a Phase Ib/II, multicenter, open-label, dose-finding study of venetoclax administered orally in combination with rituximab or obinutuzumab and standard doses of CHOP in patients with NHL. Two parallel treatment arms will explore doses of venetoclax ranging from 200 to 800 mg in combination with R-CHOP and G-CHOP. Patients will be treated for a total of eight cycles (6 cycles of CHOP and 8 cycles of venetoclax and rituximab or obinutuzumab). Each cycle will consist of 21 days.

Intervention

Phase Ib: Dose finding
Each study arm (R-CHOP or G-CHOP) will have up to 4 dose-finding cohorts exploring venetoclax doses ranging from 200 to 800 mg. Patients will be allocated to a study arm in an alternating fashion, starting with Arm A, Cohort 1, followed by Arm B, Cohort 1, Arm A, Cohort 2, etc.
TLS is a known risk following initiation of chemotherapy and anti-CD20 therapy in DLBCL. It is possible that, with the combination of venetoclax and chemoimmunotherapy, an increased rate and severity of TLS could occur. In order to mitigate the risk for TLS, venetoclax will be initiated on Day 4 of Cycle 1.

Cycle 1
Patients in the R-CHOP arm will receive the first rituximab infusion (375 mg/m2), administered per package insert (along with standard premedications) on Day 1 (Cycle 1 Day 1)

Patients in the G-CHOP arm will receive their first obinutuzumab infusion (1000 mg) on Day 1 (Cycle 1 Day 1) along with standard premedication. During Cycle 1, obinutuzumab will also be administered on Days 8 and 15.

Following rituximab or obinutuzumab infusion, patients will receive CHOP chemotherapy as per standard administration procedures, along with standard premedications.

Oral dosing of venetoclax will start on Day 4 of the first cycle (Cycle 1 Day 4). Patients will be monitored for signs of acute TLS for at least 8 hours after the first venetoclax dose. Oral dosing of venetoclax will continue on a daily basis through Cycle 8 Day 21.

Cycle 2-6
Patients will continue to receive an oral daily dose of venetoclax. On Day 1 of each cycle, venetoclax will be administered prior to any infusions. Rituximab or obinutuzumab will be administered on Day 1 along with CHOP as per standard administration guidelines. venetoclax will continue on a daily basis for all cycles.

Cycles 7-8
Patients will continue receiving an oral daily dose of venetoclax. On Day 1 of Cycles 7 and 8, venetoclax will be administered prior to infusion of rituximab or obinutuzumab.

On days that predose PK sampling is required, venetoclax dosing will occur in the clinic to facilitate PK sampling.

Patients should be premedicated with antihistamines and acetaminophen (corticosteroids if necessary) and anti-emetics and IV hydration per institutional policy and standard of practice.

Phase II:
The Phase II portion of the study will consist of one cohort for each study arm using the established dosing schedule identified during the dose-finding stage. Patients will be assigned to Arm A (venetoclax + R-CHOP) or Arm B (venetoclax + G-CHOP) through randomization. The Phase II portion will only enroll patients with previously untreated DLBCL.

Study burden and risks

venetoclax
Treatment with venetoclax in cancer patients has been associated with nausea, decreases in lymphocytes and neutrophils (two different types of white blood cells), decreases in red blood cells (anemia), infections and tumor lysis syndrome (TLS).
Obinutuzumab

The side effects of obinutuzumab appear generally similar to those with rituximab. During or after treatment administration patients may develop fever, chills and shivering or other infusion-related effects. Preexisting heart conditions such as angina pectoris or congestive heart failure may get worse. The frequency of such reactions decreases with subsequent infusions. Because of the possibility of a reaction like this, patients will be monitored closely during each infusion and for a time afterward. Other side effects such as TLS, allergic reactions, infections or abnormal laboratory tests can occur.

Contacts

Public
Hoffmann-La Roche

Bldg. 74, Grenzacherstrasse 124
Basel 4071
CH
Scientific
Hoffmann-La Roche

Bldg. 74, Grenzacherstrasse 124
Basel 4071
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

General Inclusion Criteria:
- Patients, age ><= 18 years

- At least one bi-dimensionally measurable lesion defined as >1.5 cm in its longest dimension
- Ability and willingness to comply with the study protocol procedures
- Confirmed availability of archival or freshly biopsied tumor tissue prior to study enrollment
- ECOG performance status of 0, 1, or 2
- Adequate hematologic function
- For female patients of childbearing potential and male patients with female partners of childbearing potential, agreement to use highly effective forms of contraception ;Dose Escalation Portion of the Study:
- Patients must have histologically confirmed B-cell non-Hodgin's Lymphoma (NHL)
- Patients must have never received previous R-CHOP treatment
- Any relapsed/refractory patients that are enrolled during the dose escalation should have received only a single previous treatment regimen;Expansion Portion of the Study:
- Patients must have previously-untreated diffuse large, B-cell lymphoma
- International prognostic index (IPI) score must be 2-5

Exclusion criteria

General Exclusion Criteria:
- Contraindication to receive any of the individual components of CHOP, rituximab or obinutuzumab
- Primary CNS lymphoma
- Vaccination with live vaccines within 28 days prior to randomization
- History of other malignancy that could affect compliance with the protocol or interpretation of results
- Evidence of significant, concomitant disease or illness
- Use of CYP3A inhibitors or inducers within 7 days of the first dose of venetoclax
- Requires use of Warfarin
- Recent major surgery
- Women must not be pregnant or breastfeeding;Dose Escalation Portion of the Study:
- Prior anthracycline therapy
- Chemotherapy or other investigational therapy within 5 half-lives of a biologic agent with a minimum of 28 days prior to the start of Cycle 1
- histologically confirmed mantle cell lymphoma (MCL) or small lymphocytic lymphoma (SLL);Expansion Portion of the Study:
- Patients with transformed lymphoma
- Prior therapy for non-hodgkin's lymphoma (NHL)
- Current Grade > 1 peripheral neuropathy

Study design

Design

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):	15-09-2014
Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Gazyvaro
Generic name:	OBINUTUZUMAB
Product type:	Medicine
Brand name:	MabThera
Generic name:	Rituximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA
Generic name:	Venetoclax

Ethics review

Approved WMO

Date:	23-06-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	27-08-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-11-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-01-2015
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:	02-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	03-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-06-2019
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	EUCTR2013-003749-40-NL
ClinicalTrials.gov	NCT02055820
CCMO	NL48557.029.14