A Phase Ib/II study evaluating the safety, tolerability and anti-tumor activity of polatuzumab vedotin in combination with rituximab (R) or obinutuzumab (G) plus bendamustine (B) in relapsed or refractory follicular or diffuse large B-cell lymphoma

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The primary objectives of the Phase Ib portion of the study are as follows:* To assess the safety and tolerability of the combination of polatuzumab vedotin with bendamustine and rituximab (BR) or bendamustine and obinutuzumab (BG) when administered...

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

Summary

ID

NL-OMON47634

Source
ToetsingOnline

Brief title
GO29365

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
disease of white bloodcells, Non-Hodgkin Lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Effficacy, Polatuzumab Vedotin, R / R diffuse large B-cell lymphoma, R / R follicualr lymphoma

Outcome measures

Primary outcome

Efficacy Outcome Measures:

Response assessment will be determined according to Modified Lugano Response Criteria for Malignant Lymphoma (Lugano Classification; Cheson et al. 2014; see Appendix 4 in the protocol).

* CR at primary response assessment (6*8 weeks after Cycle 6, Day 1, or last dose of study drug) based on PET/CT, as determined by the investigator and IRC

* OR (CR or PR) at primary response assessment based on PET/CT, as determined by the investigator and IRC

* CR at primary response assessment based on CT only, as determined by the investigator and IRC

* OR (CR or PR) at primary response assessment based on CT only, as determined by the investigator and IRC

* BOR (CR or PR) while on study based on PET/CT or CT only, as determined by the investigator

* NF cohort only: OS and EFS based on PET-CT or CT only, as determined by the investigator

Secondary outcome

PK outcome measures:

* Serum and plasma concentrations of polatuzumab vedotin, bendamustine and rituximab versus time

* PK parameters based on concentration*time data for polatuzumab vedotin, bendamustine and rituximab when these drugs are given in combination

Patient reported outcome measures:

* PROs of peripheral neuropathy symptom severity and symptom interference, as measured by the TINAS (Thomas et al. 2012; see Appendix 8)

Exploratory biomarker outcome measures:

* Biomarkers related to tumor biology and the mechanisms of action of polatuzumab vedotin and rituximab. These include but are not limited to the assessment of CD79b expression levels, apoptotic regulators (e.g., Bcl-2), markers of immune infiltration and immune regulation (e.g., CD3, CD8, PD-L1), and identification of other potential prognostic factors.

* Biomarkers will be assessed retrospectively using a tissue block (preferred) or 15 serial freshly cut, unstained slides plus punch biopsy of the tissue block from the time of initial diagnosis and, if possible, at the time of disease progression.

* For quantitative assessment of MRD levels of the lymphoma clone in

circulation, blood will be collected at baseline, between Cycle 3 Day 15 and

Cycle 4 Day 1, and at end of treatment corresponding to tumor assessments

Study description

Background summary

Non-Hodgkin*s lymphoma (NHL) is the most common hematologic malignancy in adults.
NHL can be divided into indolent and aggressive lymphomas. Follicular lymphoma (FL) is the most common subtype of indolent NHL in the Western hemisphere. Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive NHL.
B-cell NHL, including FL and DLBCL, express the CD20 antigen, and anti-CD20 therapy (rituximab) has been demonstrated to provide enhanced anti-tumor activity in combination with other agents targeting the disease leading to increased response rates, PFS and OS, which led to acceptance of rituximab as a standard component in initial therapy. Progress has been made in the treatment of FL and DLBCL; however, a significant number of patients will not be cured of the disease. There is a need for the continued development of safe and effective therapies for patients with disease that relapses or for those who develop refractory disease during or after first-line therapy.
Bendamustine with and without rituximab has demonstrated efficacy in patients with R/R iNHL.
BR is recommended as a second-line therapy for patients with FL who either received alternative therapy in first line or who previously received bendamustine-based therapy and had a DOR of * 1 year. Commonly used regimens used to treat transplant eligible patients with R/R DLBCL are also used to treat transplant-ineligible patients.
Polatuzumab vedotin is an ADC designed for the targeted delivery of MMAE, a potent microtubule inhibitor to lymphoma cells expressing CD79b.
To date, Phase I data suggest that polatuzumab vedotin in combination with rituximab has activity in R/R FL and DLBCL with a generally acceptable safety and tolerability profile. Nonclinical data from murine xenograft models support the combination of bendamustine, rituximab, and polatuzumab vedotin and demonstrate significantly improved anti-lymphoma activity of the combination over BR alone. Obinutuzumab ([G] also known as RO5072759, GA101, and GazyvaTM), a novel Type II and glycoengineered anti-CD20 antibody, has shown superiority over rituximab in a Phase III trial in first-line CLL.
The combination of obinutuzumab with bendamustine is being evaluated in several ongoing studies. Clinical trials with BR and BG have demonstrated efficacy but have been associated with neutropenia.
The goals of this Phase Ib/II study are to assess the safety, tolerability, and potential biologic and clinical activity of escalating doses of polatuzumab

vedotin in combination with a standard regimen of an anti-CD20 antibody plus chemotherapy (rituximab plus bendamustine [BR] or obinutuzumab plus bendamustine [BG]) in patients with R/R FL or DLBCL.

Study objective

The primary objectives of the Phase Ib portion of the study are as follows:
* To assess the safety and tolerability of the combination of polatuzumab vedotin with bendamustine and rituximab (BR) or bendamustine and obinutuzumab (BG) when administered to patients with R/R FL or DLBCL
* To identify the Recommended Phase II Dose (RP2D) for polatuzumab vedotin given in combination with BR or with BG in patients with R/R FL or DLBCL

The primary objective of the Phase II portion of the study is as follows:
* To evaluate the efficacy of the combination of polatuzumab vedotin plus BR compared with BR alone in patients with R/R FL or DLBCL as measured by positron emission tomography (PET)-defined CR rate using Modified Lugano Response Criteria ((PET-computed tomography [CT] criteria) at the time of primary response assessment (6*8 weeks after Cycle 6, Day 1 or last dose of study drug) and as defined by the Independent Review Committee (IRC)

Secondary objectives:

Safety Objectives:
* To assess the safety and tolerability of the combination of polatuzumab vedotin with BR or BG when administered to patients with R/R FL or DLBCL during the Phase II portion of the study
* To assess the immunogenicity of polatuzumab vedotin and obinutuzumab, as measured by the formation of anti-drug antibodies (ADAs)
* To assess the potential relationships of such ADAs (anti-polatuzumab vedotin and anti-obinutuzumab) formation with other outcome measures (e.g., PK, efficacy, safety)

Pharmacokinetic Objectives
* To characterize the pharmacokinetics of polatuzumab vedotin in combination with BR or BG in patients with R/R FL or DLBCL
* To assess potential PK interactions between polatuzumab vedotin and BR or BG
* To evaluate the PK exposure response (e.g., efficacy, safety) relationship

Secondary efficacy objectives (Main study):
To evaluate the efficacy of the combination of polatuzumab vedotin and BR compared with BR alone according to Modified Lugano 2014 response criteria as measured by:
* Complete response (CR) at the time of Primary Response Assessment based on PET-CT, as determined by the investigator

* Objective response (OR; CR or partial response [PR]) at the time of Primary Response Assessment, based on PET-CT, as determined by the investigator and IRC
* CR at the time of Primary Response Assessment based on CT only, as determined by the investigator and IRC
* OR at the time of Primary Response Assessment based on CT only, as determined by the investigator and IRC
* Best objective response (BOR; CR or PR) while on study either by PET-CT or CT only,as determined by the investigator
* DLBCL cohorts only: BOR, DOR and PFS based on PET-CT or CT, as determined by IRC
To evaluate the efficacy of the combination of polatuzumab vedotin plus BG according to Modified Lugano 2014 response criteria as measured by:
* CR at the time of Primary Response Assessment based on PET-CT, as determined by the investigator and IRC
* OR (CR or PR) at the time of Primary Response Assessment, based on PET-CT, as determined by the investigator and IRC
* CR at the time of Primary Response Assessment based on CT only, as determined by the investigator and IRC
* OR at the time of Primary Response Assessment based on CT only, as determined by the investigator and IRC
* BOR (BOR, CR, or PR) while on study either by PET-CT or CT only as determined by the investigator
* DLBCL cohorts only: BOR, DOR, and PFS while on study by either PET-CT or CT only,as determined by IRC

* Patient-reported outcome (PRO) objective:
To evaluate peripheral neuropathy symptom severity and interference on daily functioning and to better understand treatment impact, tolerability, and reversibility, as measured by the Therapy-Induced Neuropathy Assessment Scale (TINAS).

* The exploratory objectives for this study are as follows:
To make a preliminary assessment of biomarkers related to the drug targets and mechanism of action of polatuzumab vedotin and/or rituximab or obinutuzumab, and/or of biomarkers related to disease biology and/or assessments that inform the improvement of diagnostic tools, and that might predict disease response or resistance to treatment with polatuzumab vedotin in combination with BR or BG in R/R FL or DLBCL.

The exploratory efficacy objectives for this study are to evaluate longer-term outcomes for patients treated with using the Lugano 2014 response criteria

Study design

This design is a Phase Ib/II, multicenter, open-label study of polatuzumab vedotin administered by IV infusion in combination with standard doses of

bendamustine (B) and rituximab (R) in patients with relapsed or refractory FL or DLBCL.
The Netherlands will only participate in the Phase II stage: randomization and expansion phase.

Study treatment will be given in 28-day cycles for patients with FL and in 21-day cycles for patients with DLBCL. The first day of treatment will constitute Study Day 1. Patients will be treated up to a total of six cycles.

All patients will be evaluated for safety and efficacy according to the schedules of assessments (Appendix 1).
All patients will be assessed for response to treatment by the investigator with the use of standard criteria according to the Lugano Response Criteria (Cheson et al. 2014; see Appendix 4) at screening and at the following timepoints: Interim response assessment (between Cycle 3 Day 15 and Cycle 4 Day 1) Primary response assessment: 6*8 weeks after completion of study treatment (i.e., Day 1 of Cycle 6 or after last dose of study medication.

For more information, including a figure of the study design, see pages 67-69 of the protocol.

Intervention

The treatment consists of 6 cycli of infusions with one or a combination of more of the following treatments:
De cycle in the FL population is 28 days.
De cycle in the DLBCL population is 21 days.

The following tretaments are used in this trial:

Polatuzumab Vedotin (PV): 1,8 mg/kg IV infusion

Rituximab (MabThera®/Rituxan®) (R): 375 mg/m2 IV infusion

Bendamustine (Levact®) (B): 90 mg/m2 IV infusion

In one of the following combinations:

Bendamustine + Rituxumab
Schedule of Cycle 1 day 1: Rituxumab, day 2+3: Bendamustine
Cycle 2 - 6 day 1: Rituxumab + Bendamustine, day 2: Bendamustine

OR

Polatuzumab Vedotin + Bendamustine + Rituxumab
Schedule cycle 1 day 1: Rituxumab, day 2: Polatuzumab Vedotin + Bendamustine, day 3: Bendamustine

Schedule cycle 2 - 6 day 1: Rituxumab + Polatuzumab Vedotin + Bendamustine, day 2: Bendamustine

Study burden and risks

This information is stated in sections E4, E6 and E9.

The subject may get side effects from the drugs or procedures used in this study. Side effects can vary from mild to sever and can vary from person to person. In some cases, side effects can be severe, long persisting or never disappear. There is also a ery small risk of death.

Side effects associated with Polatuzumab Vedotin
-There is a risk that use of Polatuzumab Vedotin resulting in an inability to get full doses and cycles of Rituximab + Bendamustine.
-Neutropenia
-Peripheral sensory and / or motor neuropathy

Potential side effects of Polatuzumab:
-Possible side effects on reproduction and fertility.
-It is possible that it has effect on the control of blood sugar levels.
-Small possibility that the immune system produces special antibodies that will bind to the studied drugs. This may affect the response of the body to similar medicines.
-There may occur infusion-related reactions such as: fever, chills, rash, nausea, vomiting, head-ache, cold-like symptoms,difficulty with breathing, shortness of breath.
-An allergic reaction can occur.
-It can affect the liver: abnormal liverfunction tests or changes on scans. It is unclear whether this is temporary or permanent.
-Possibility of tumor lysis syndrome.
-Other side effects reported in studies, but which has not been known to be caused by Polatuzumab: fatigue, nausea, vomiting, diarhea, loss of appetite, weight loss, anemia, fever, rash, cold, diziness, upper-respiratory infection, shortness of breath, hair loss, joint pain, back pain, weakness, abdominal pain, changed liver function, higher blood levels, constipation, mild visual symptoms.

The adverse reactions of all treatment drugs in this trial are described in the protocol as well as the risks of all study procedures.

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

- Age * 18 years
- Histologically confirmed FL (Grade 1, 2, or 3a) or DLBCL
- Must have received at least one prior therapy for FL or DLBCL. Patients must have either relapsed or have become refractory to a prior regimen as defined in the protocol.
- If the patient has received prior bendamustine, response duration must have been > 1 year (for patients who have relapse disease after a prior regimen)
- At least one bi-dimensionally measurable lesion on imaging scan defined as > 1.5 cm in its longest dimension
- Confirmed availability of archival or freshly collected tumor tissue prior to study enrollment
- Life expectancy of at least 24 weeks
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
- Adequate hematologic function unless inadequate function is due to underlying disease.
- For women who are not postmenopausal (* 12 months of non*therapy*induced

amenorrhea and age > 45 years) or surgically sterile: agreement to remain abstinent or to use single highly effective or combined contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for * 12 months after the last dose of rituximab or for * 18 months after the last dose of obinutuzumab, and agreement to refrain from donating eggs.
- For women of childbearing potential, a negative serum pregnancy test result within 7 days prior to commencement of dosing.
- For men, agreement to remain abstinent or to use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 6 months after the last dose of study drug and agreement to refrain from donating sperm during this same period

Exclusion criteria

- History of severe allergic or anaphylactic reactions to humanized or murine MAbs (or recombinant antibody-related fusion proteins) or known sensitivity or allergy to murine products
- Contraindication to bendamustine, rituximab, or obinutuzumab
- History of sensitivity to mannitol (mannitol is an excipient in bendamustine)
- Prior use of any MAb, radioimmunoconjugate, or ADC within 5 half-lives or 4 weeks, whichever is longer before Cycle 1 Day 1
- Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational agent for the purposes of treating cancer within 2 weeks prior to Cycle 1 Day 1
- Ongoing corticosteroid use > 30 mg/day prednisone or equivalent, for purposes other than lymphoma symptom control
- Treatment with chimeric antigen receptor T-cell therapy within 100 days prior to Cycle 1 Day 1
- Completion of autologous stem cell transplant within 100 days prior to Cycle 1 Day 1
- Prior allogeneic stem cell transplant
- Eligibility for autologous SCT
- Grade 3b follicular lymphoma
- History of transformation of indolent disease to DLBCL
- Primary or secondary CNS lymphoma
- Current Grade > 1 peripheral neuropathy
- History of other malignancy that could affect compliance with the protocol or interpretation of results.
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease or significant pulmonary disease
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection at study enrollment or any major episode of infection requiring treatment with intravenous (IV) antibiotics or hospitalization within 4 weeks prior to Cycle 1 Day 1

- Patients with suspected or latent tuberculosis,
- Positive test results for chronic hepatitis B virus infection or for hepatitis C virus antibody
- Known history of HIV seropositive status
- Known infection of human T-cell leukemia virus 1 virus
- Vaccination with a live vaccine within 28 days prior to treatment
- Recent major surgery (within 6 weeks before the start of Cycle 1 Day 1) other than for diagnosis
- Women who are pregnant or lactating or who intend to become pregnant within a year of the last dose of study treatment in the rituximab cohorts or within 18 months of the last dose of study treatment in the obinutuzumab cohort
- Any abnormal laboratory values as defined in the protocol, unless abnormal laboratory values are due to underlying lymphoma per the investigator
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications

Study design

Design

Study phase:	2
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):	22-06-2016
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MabThera
Generic name:	Rituxumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Polatuzumab Vedotin
Generic name:	Polatuzumab Vedotin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Ribomustin
Generic name:	Bendamustine

Ethics review

Approved WMO Date:	29-10-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-03-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-04-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-05-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-11-2016
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-03-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-10-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-12-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-10-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-10-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-08-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2014-001361-28-NL
ClinicalTrials.gov	NCT02257567
CCMO	NL53976.091.15