An Open-Label, Randomized, Phase 3 Study Of Inotuzumab Ozogamicin Administered In Combination With Rituximab Compared To Defined Investigator*s Choice Therapy In Subjects With Relapsed Or Refractory CD22-Positive Aggressive Non-Hodgkin Lymphoma Who Are Not Candidates For Intensive High-Dose Chemotherapy.

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Objectives:Primary:- To evaluate efficacy as measured by overall survival (OS), with a goal of demonstrating the superiority of inotuzumab ozogamicin when administered in combination with rituximab, compared with an active comparator arm.Secondary…

Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39239

Source
ToetsingOnline

Brief title
B1931008 (9002/0060)- Non-Hodgkin Lymphoma Inotuzumab

Condition

- Other condition
- Lymphomas non-Hodgkin's unspecified histology

Synonym
cancer of the lymphoid tissue, malign lymphnodes

Health condition

Subject with a diagnosis of CD20 and CD22- positive agressive non-Hodgin lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Pfizer

Intervention

Keyword: Inotuzumab Ozogamicin, Non-Hodgkin Lymphoma, Phase 3

Outcome measures

Primary outcome

Overall survival (OS).

Secondary outcome

- Progression free survival (PFS);

- Overall (objective) response rate (ORR);

- Duration of response (DoR);

- Patient-reported health-related quality of life, lymphoma specific symptoms,

and health status for subjects in each treatment arm as measured by the

Functional Assessment of Cancer Therapy for Lymphoma (FACT-Lym) and EuroQol-5D

(EQ-5D) questionnaires

Study description

Background summary

Inotuzumab ozogamicin is an antibody targeting CD22, conjugated with a cytotoxic antitumor antibiotic (calicheamicin) in development for the treatment of Non-Hodgkin Lymphoma (NHL), the tenth most commonly diagnosed cancer worldwide. The majority (>90%) of NHL represents malignancies of B-lymphocyte lineage, expressing both CD20 and CD22.
Aggressive NHLs, including diffuse large B-cell lymphoma (DLBCL) which represents the largest sub-group of NHL patients, are potentially curable cancers. First line treatment options often include rituximab (an antibody targeting CD20) in combination with chemotherapy, and response rates are high (overall response rate, ORR = 75% to 90%). However, approximately half of all responding patients relapse and subsequent treatments, which typically include rituximab, tend to be less efficacious (ORR = 20% to 85%) and are not considered curative without further consolidation therapy (involving high-dose chemotherapy and autologous stem cell transplant [aSCT]). Consolidation therapy is limited to those patients with adequate medical status to tolerate additional myeloablative conditioning. Thus, a robust therapy for the majority of patients with relapsed aggressive NHLs (ie, including those who are not eligible for consolidation therapy) remains an unmet medical need. The current clinical experience of inotuzumab ozogamicin in combination with rituximab suggests this regimen has similar or greater activity compared to that observed with other commonly used 2nd line or later therapies for relapsed aggressive NHLs. To date, an ORR of 80% and median progression free survival (PFS) of 15.1 months has been achieved in 40 relapsed DLBCL patients participating in a nearly completed phase 1/2 study, with 79% of patients surviving 1 year after initiation of treatment with inotuzumab ozogamicin in combination with rituximab. Responses have also been observed in patients with other aggressive NHL subtypes, including mantle cell lymphoma. Based on these favorable findings, this study will further evaluate the clinical activity and safety of inotuzumab ozogamicin plus rituximab in subjects with relapsed/refractory aggressive NHLs who are not candidates for intensive high-dose chemotherapy compared to an investigators best choice between 2 rituximab (R)-containing chemotherapy regimens, R-bendamustine and R-gemcitabine. Each of these regimens has demonstrated activity for treatment of relapsed aggressive NHLs in phase 2, single-arm clinical trials.

Study objective

Objectives:
Primary:
- To evaluate efficacy as measured by overall survival (OS), with a goal of demonstrating the superiority of inotuzumab ozogamicin when administered in

combination with rituximab, compared with an active comparator arm.
Secondary:
- To evaluate the safety and tolerability of inotuzumab ozogamicin in combination with rituximab compared with an active comparator arm.
- To evaluate the efficacy of inotuzumab ozogamicin in combination with rituximab compared with an active comparator arm using the following endpoints:
- ORR;
- PFS;
- Duration of response (DoR).
- To compare patient-reported health-related quality of life (HRQOL), lymphoma specific symptoms, and health status between treatment arms.

Study design

This is a 2-arm, randomized, open-label, phase 3 trial designed to evaluate efficacy and safety of inotuzumab ozogamicin in combination with rituximab compared to the investigator*s choice of 1 of 2 defined chemotherapy regimens (R-bendamustine or R-gemcitabine

Intervention

Subjects will be randomly assigned to 1 of 2 treatment arms in a 1:1 ratio.
Subjects in Arm 1 will receive inotuzumab ozogamicin in combination with rituximab (R-inotuzumab ozogamicin).
Subjects in Arm 2 will receive the investigator*s choice regimen (rituximab + bendamustine orrituximab + gemcitabine).

Study burden and risks

Subject undergo the following during this research:

Questions about:
- medical history;
- cancer history and treatment;
- usual physical activity;
- regular care of assistance received because of you condition;
- Other anti-cancer treatment received;
Physical examination;
Urine collection;
Blood collection: the total volume of blood collected from each subject will be approximately up to 320 mL over 2 years;
CT, MRI or PET;
ECG and ECHO or MUGA;
2 questionnaires ((FACT-Lym and EQ-5D)
Bone marrow aspirate and/or biopsy (optional)

see also question E9 and E9a

Contacts

Public
Pfizer

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Scientific
Pfizer

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New York NY10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subjects with a diagnosis of CD20 and CD22-positive aggressive NHL (based on local immunophenotyping and histopathology) who have:
a. Refractory disease: defined as disease progression while receiving their most recent prior cytotoxic chemotherapy (single-agent immunotherapy as maintenance is not considered cytotoxic therapy);
b. Persistent disease: defined as stable disease or partial response at the completion of their most recent prior cytotoxic chemotherapy;
c. Relapsed/recurrent disease: defined as complete response at the end of their most recent prior cytotoxic chemotherapy with subsequent relapse or disease recurrence.

Eligible aggressive subtypes identified per the 2008 World Health Organization classification include: a) DLBCL (including DLBCL with follicular elements), b) transformed indolent lymphoma with DLBCL, and c) primary mediastinal large B-cell lymphomas.
2. Subjects must have received prior rituximab and may have received up to 3 prior regimens containing cytotoxic chemotherapies for aggressive NHL. In order to ensure consistency in the application of the inclusion criterion:
•Only count regimens that contain 1 or more cytotoxic drug. Do not count palliation with steroids alone, vaccines, non-systemic therapy such as radiation, or maintenance therapies such as rituximab.
•Only count INDUCTION regimens. Do not count maintenance or consolidation therapy.
•If a patient had progression of disease between 2 cytotoxic regimens, they always count as 2 separate regimens.
Note: If a regimen was changed (e.g. because the patient did not tolerate it or for financial reasons) and the patient did not progress before the regimen was changed, it is not counted as a separate regimen.
•If a patient has transformed indolent lymphoma with DLBCL, only count the regimens received for aggressive lymphoma.
3. Subjects must not be candidates for intensive high-dose chemotherapy, with or without an autologous stem cell transplant (aSCT), due to one or more of the following factors: age, comorbid disease, performance status, prior high-dose chemotherapy, or persisting toxicities from prior chemotherapy (*transplant preparatory regimen, eg, BEAM, BEAC).
4. Age 18 years or older (For Japan: Age 20 years or older).
5. Absolute neutrophil count (ANC) >=1.0 x 109/L (1000/µL) and platelets >= 75 x 109/L (75,000/µL), unless related to bone marrow infiltration.
6. Serum creatinine <=1.5 x the upper limit of normal (ULN) (or any serum creatinine level associated with a measured or calculated creatinine clearance of >=40 mL/min).
7. Total bilirubin <=1.5 mg/dL (25.65 µmol/L) unless Gilbert*s syndrome, aspartate and alanine aminotransferase (AST, ALT) <=2.5 x ULN.
8. At least 1 measurable disease lesion that is >=1.0 cm in 2 perpendicular dimensions, with the product diameter >=2.25 cm2 by computed tomography (CT) or magnetic resonance imaging (MRI).
Tumor lesions that are located in a previously irradiated area will be considered measurable only if progression is documented following completion of radiation therapy.

Exclusion criteria

1. Prior allogeneic hematopoietic stem cell transplant (HSCT).
2. Within <=6 months before first dose of investigational product:
a. Prior treatment with anti-CD22 antibodies;
b. Prior radioimmunotherapy.
3. Prior autologous stem cell transplant within <=4 months before first dose of investigational product.
4. Contraindication to rituximab.
5. Contraindication to both investigator*s choice immuno-chemotherapy regimens.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 4 and/or a life

expectancy <12 weeks.
7. Subjects with known systemic vasculitides (eg, Wegener's granulomatosis, polyarteritis nodosa, systemic lupus erythematosus), primary or secondary immunodeficiency (such as HIV infection or severe inflammatory disease).
8. Current or chronic hepatitis B or C infection as evidenced by hepatitis B surface antigen and anti-hepatitis C antibody positivity, respectively, or known seropositivity for human immunodeficiency virus (HIV). HIV testing may need to be performed in accordance with local regulations or local practice.
9. History of veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS).
10. Evidence of serious active infection (eg, requiring an intravenous [IV] antibiotic, antiviral, or antifungal agent), or subjects with a recent history of deep tissue infections such as fascitis or osteomyelitis.

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:	Will not start
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	gemzar
Generic name:	gemcitabine
Registration:	Yes - NL outside intended use
Product type:	Medicine

Brand name:	Levact
Generic name:	BENDAMUSTINE HYDROCHLORIDE
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Mabthera
Generic name:	Rituximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA
Generic name:	Inotuzumab Ozogamicin

Ethics review

Approved WMO Date:	12-09-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2010-020147-12-NL
ClinicalTrials.gov	NCT01232556
CCMO	NL34594.078.11