Phase I-II study combining Brentuximab Vedotin with second line salvage chemotherapy (R-DHAP) in CD30 positive diffuse large B-cell lymphoma patients refractory to first line chemotherapy or in first relapse who are eligible for high dose treatment followed by autologous stem cell transplantation. Transplant BRaVE NHL

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This study has been transitioned to CTIS with ID 2023-510556-22-00 check the CTIS register for the current data. Lead in phase 1Primary objective:• To identify the feasibility and RDL (recommended dose level) of brentuximab vedotin in combination...

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

Summary

ID

NL-OMON46902

Source
ToetsingOnline

Brief title
HOVON 136 NHL/ Transplant BRaVE NHL

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
aggressive B-cell lymphoma, Diffuse large B-cell lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: Subsidie aangevraagd bij KWF;Takeda,Takeda

Intervention

Keyword: Brentuximab vedotin, CD30, DLBCL, Relapse

Outcome measures

Primary outcome

Phase 1 part

Primary endpoint

• The rate of patients with serious toxicity during cycle 1-2 of the

combination BV-R-DHAP

Phase 2 part

Primary efficacy endpoint

• Metabolic CR rate (PET-CT) after the third cycle of BV-R-DHAP salvage therapy

Primary feasibility/toxicity endpoints

• Rate of grade 3/4 non-hematological toxicity, including neurotoxicity after

each cycle of BV-R-DHAP

Secondary outcome

Phase 1 part

Secondary endpoints

• (Serious) Adverse Events during combination treatment

• Time to hematological recovery after each cycle of BV-R-DHAP

• Time to recovery from non-hematological toxicity after each cycle of BV-R-DHAP

• Administration of treatment: dose reductions, interval between cycles,

discontinuation rate

• Rate of successful PBSC collection (>= 2x106 CD34+ cells/kg) after the third

cycle of BV-R-DHAP

Phase 2 part

Secondary efficacy endpoints

• Overall response rate (PR + CR) after the third cycle of BV-R-DHAP salvage

therapy (based on the results of the FDG-PET/CT scan)

• Overall response rate (PR + CR) after ASCT (based on the results of the

FDG-PET/CT scan)

• Metabolic CR rate (PET-CT) after ASCT

• Fraction of patients (CR/PR) eligible for ASCT who actually undergo ASCT

• Progression free survival (PFS), Event free survival (EFS), Overall survival

(OS

Secondary feasibility/toxicity endpoints

• (Serious) Adverse Events during the combination treatment

• Time to hematological recovery after each cycle of BV + R-DHAP

• Administration of treatment: dose reductions, interval between courses,

discontinuation rate

• Rate of successful PBSC collection (>= 2 x106 CD34+ cells/kg) after the second

or third cycle of BV-R-DHAP

• Time to hematological recovery after ASCT

• (Serious) Adverse Events after ASCT

Study description

Background summary

Patients with primary refractory or relapse diffuse large B-cell lymphoma (DLBCL) after R-CHOP have a dismal prognosis. Only 25% long term survivors are observed after salvage with high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). CD30 expression is observed in 30% of refractory/relapse DLBCL. Monotherapy with brentuximab vedotin is effective in relapse CD30 positive DLBCL. The addition of brentuximab vedotin to R-DHAP might improve the prognosis of these patients.

Study objective

This study has been transitioned to CTIS with ID 2023-510556-22-00 check the CTIS register for the current data.

Lead in phase 1
Primary objective:
• To identify the feasibility and RDL (recommended dose level) of brentuximab vedotin in combination with R-DHAP
Secondary objective:
• To assess the toxicity of brentuximab vedotin in combination with R-DHAP
• To assess the success rate of autologous peripheral blood stem cell harvest after brentuximab vedotin-R-DHAP

Phase 2
Primary objective:

• To evaluate the efficacy of the combination of brentuximab vedotin and R-DHAP as salvage treatment in relapse/refractory DLBCL patients in terms of metabolic CR rate after the third cycle
• To establish the rate of CTCAE grade 3/4 non-hematological toxicity, including neurotoxicity after each cycle of brentuximab vedotin-R-DHAP
Secondary objectives:
• To asses the overall response rate (ORR) after 3 cycles and after ASCT
• To assess the toxicity profile of brentuximab vedotin in combination with R-DHAP
• To assess hematological recovery after each cycle of brentuximab vedotin-R-DHAP
• To assess the success rate of harvesting an autologous peripheral blood stem cell graft
• To assess the fraction of patients (CR/PR) eligible for ASCT who actually undergo ASCT
• To assess peripheral blood neutrophil and platelet recovery after ASCT
• To evaluate the progression free survival (PFS), event free survival (EFS), and overall survival (OS)
• To identify predictive factors for response, PFS, EFS and OS (exploratory analysis)

Study design

Phase I-II, multicenter, prospective, non-randomized

Intervention

Patients will receive brentuximab vedotin in combination with R-DHAP, followed in responsive patients by high dose chemotherapy and ASCT

Study burden and risks

The prognosis of patients with refractory and relapse DLBCL is dismal. Only 25% long term survivors are observed after salvage with high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). In approximately 30% of relapse DLBCL the CD30 antigen is expressed. Brentuximab vedotin has shown promising activity in DLBCL after relapse. Addition of brentuximab vedotin may improve the prognosis for these patients.The hypothesis of this study is that combination treatment with brentuximab vedotin and R-DHAP will induce higher metabolic CR rates. Increasing metabolic CR rates prior to ASCT is expected to improve PFS and OS. Risk for the patient relate to drug specific side-effects, in particular relevant hematological toxicity and increased risk of polyneuropathy. Patients will undergo extra diagnostic procedures, such as extra laboratory controls (blood counts and chemistry), one extra PET-CT scan and two extra CT scans.

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

• CD30 positive DLBCL, i.e. more than 1% of DLBCL cells CD30 positive according to the WHO classification 2008:.
- CD30 positive DLBCL, including EBV positive DLBCL
- CD30 positive primary mediastinal B-cell lymphoma
• Primary refractory to or in first relapse after first line therapy with R-CHOP or R-CHOP-like therapy
• Age >= 18 years (upper age limit for ASCT at the discretion of the participating center)
• Measurable disease: on CT scan at least 1 lesion/node with a long axis of > 1.5 cm and at least one positive lesion on 18F-FDG PET scan
• WHO performance status 0-2
• Adequate hepatic function:
• Adequate renal function:

• Adequate bone marrow function:
• Hemoglobin must be >= 8 g/dL (5.0 mmol/L), transfusion is allowed
• Eligible for high-dose chemotherapy and ASCT
• Resolution of relevant toxicities from first-line therapy
• Life expectancy of > 3 months with treatment
• Negative pregnancy test at study entry, if applicable
• Female patient is either post-menopausal for at least 1 year before screening visit or surgically sterile or if of childbearing potential, agrees to practice 2 effective methods of contraception, at the same time, or agrees to completely abstain from heterosexual intercourse, from the time of signing the informed consent through 12 months after the last dose of study drug
• Male patients, even if surgically sterilized, (i.e. status post vasectomy) agree to practice effective barrier contraception, or agrees to completely abstain from heterosexual intercourse, during the entire study period and through 12 months after the last dose of study drug
• Written informed consent
• Patient is capable of giving informed consent

Exclusion criteria

• Peripheral sensory or motor neuropathy grade >= 2
• Known cerebral or meningeal disease (NHL or any other etiology), including signs and symptoms of progressive multifocal leukoencephalopathy (PML)
• Symptomatic neurological disease compromising normal activities of daily living or requiring medications
• Transformed lymphoma
• DLBCL after organ transplantation
• Immunodeficiency-associated B-cell lymphoproliferative disease
• Use of other investigational agents within at least 5 half-lives of the most recent agent used prior to study entry
• Treatment with myelosuppressive chemotherapy or biological therapy <= 4 weeks before study entry
• Female patients who are breast feeding
• History of another malignancy less than 3 years before study inclusion, or previously diagnosed with another malignancy and have evidence of residual disease, with the exception of non-melanoma skin cancer, completely resected melanoma TNMpT1 and carcinoma in situ of the uterine cervix
• Known hypersensitivity to recombinant proteins, murine proteins, or to any excipient contained in the drug formulation of brentuximab vedotin
• Active hepatitis B or C infection
• HIV positivity
• Radiation therapy within 8 weeks prior to start of protocol treatment. Emergency radiation therapy is allowed, as long as measurable disease (at non-irradiated sites) persists
• Patients with a serious psychiatric disorder that could, in the investigator's opinion, potentially interfere with the completion of treatment according to protocol

• Major organ dysfunction, unless NHL-related
• Patients who have any severe and/or uncontrolled medical condition or other conditions that could affect their participation in the study
• Thyroid abnormalities when thyroid function cannot be maintained in the normal range by medication
• Current participation in another clinical trial interfering with this trial
• Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule
• Claustrophobia to the extent that PET-CT is impossible

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-07-2018
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Adcetris
Generic name:	Brentuximab Vedotin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	18-04-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-09-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-11-2024
Application type:	Amendment
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
EU-CTR	CTIS2023-510556-22-00
EudraCT	EUCTR2016-001211-21-NL
CCMO	NL58172.078.16