Risk-based, response-adapted, Phase II open-label trial of nivolumab + brentuximab vedotin (N + Bv) for children, adolescents, and young adults with relapsed/refractory (R/R) CD30 + classic Hodgkin lymphoma (cHL) after failure of first-line therapy, followed by brentuximab + bendamustine (Bv + B) for participants with a suboptimal response.

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Ethical review	Approved WMO
Status	Completed
Health condition type	Lymphomas Hodgkin's disease
Study type	Interventional

Summary

ID

NL-OMON53072

Source
ToetsingOnline

Brief title
CA209-744

Condition

- Lymphomas Hodgkin's disease

Synonym
Hodgkin Lymphoma, Lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Hodgkin Disease, nivolumab

Outcome measures

Primary outcome

-Low Risk group: To describe the proportion of patients who remain free of certain cancer related complications, events and death at 3 years. This will be assessed by an independent blinded review group.

-Standard Risk group: To describe the proportion of patients who achieve a complete metabolic response (measured by medical imaging) before receiving high-dose chemotherapy followed by autologous stem cell transplant (HDCT/ASCT). This will be assessed by an independent blinded review group.

Secondary outcome

-To measure the overall response rate (ORR) (the proportion of patients whose cancer reduces or disappears after treatment) following 4 cycles of nivolumab and brentuximab vedotin. This will be assessed by an independent blinded review

group.

-To measure the proportion of patients whose disease does not progress at 3

years. This will be assessed by an independent blinded review group.

-Duration response (time from tumour response to disease progression) will be

evaluated for patients who achieved a response to treatment.

-The safety profile of nivolumab and brentuximab vedotin in children and young

adults with classic Hodgkin Lymphoma who have failed standard frontline

chemotherapy will be described.

Study description

Background summary

While the treatment of classic Hodgkin Lymphoma has improved dramatically over the past 20 years, with 5 year event free survival rates close to 90%, there is still a group of patients who either relapse or in whom first-line treatment fails. These patients currently have a poor outcome and there is currently an unmet need to improve the prognosis of this group of patients.

This is a study of nivolumab and brentuximab vedotin for children, adolescent and young adults with classic Hodgkin Lymphoma who have failed previous therapy, followed by brentuximab and bendamustine for those who did not receive an optimal response.

Approximately 100 patients will take part globally, 4 of these will be in the Netherlands. The study is sponsored by Bristol-Myers Squibb. The purpose of the study is to evaluate the safety and anti-tumour activity of combination therapy with nivolumab and brentuximab vedotin in a population of patients who have failed standard frontline chemotherapy.

Following a screening period, eligible patients will be given nivolumab and brentuximab vedotin every 3 weeks and depending on the patient*s response to treatment they may later be given brentuximab vedotin and bendamustine. Treatment will be given every three weeks and will be given 4 to 8 times in total. They may receive further treatments such as involved field radiation therapy and high dose chemotherapy followed by autologous stem cell transplant thereafter. Patients will be followed up for 3 years after they stop study

treatment.

Study objective

There are two treatment groups in this study: one with participants at low risk of deterioration and one with participants at standard risk of deterioration. The primary objective for each group is described below.

-Low Risk group: To describe the proportion of patients who remain free of certain cancer related complications, events and death at 3 years. This will be assessed by an independent blinded review group.

-Standard Risk group: To describe the proportion of patients who achieve a complete metabolic response (measured by medical imaging) before receiving high-dose chemotherapy followed by autologous stem cell transplant. This will be assessed by an independent blinded review group.

Study design

This is a risk-based, response-adapted phase II open label trial in children, adolescents and young adults with relapsed/refractory CD30+ classic Hodgkin Lymphoma (cHL) after failure of first line therapy.

There are three periods to the study: screening, treatment and follow-up.

SCREENING PERIOD
The screening period of the study can take up to 28 days to complete. Tests are to determine the patient*s eligibility to take part in the trial.
The screening tests/procedures include:
• Medical history and physical examination
• Vital signs measurement
• An assessment of how day to day activities are performed
• Blood and urine tests
• Pregnancy testing for women of child bearing potential (urine or blood sample)
•Request original samples of a tumour biopsy or undergo a biopsy procedure
•Tumour assessment by PET-CT
•Brain MRI may be performed if required

TREATMENT PERIOD
If it is safe and suitable for the patient to take part in the study as determined by the results of the screening tests/procedures mentioned above they will return to the hospital to receive treatment.

Patients will initially receive nivolumab at a dose of 3 mg/kg and brentuximab vedotin at 1.8 mg/kg every three weeks. Depending on the patient*s response to treatment they may later be given brentuximab vedotin (1.8 mg/kg) and

bendamustine (90 mg/m2) every three weeks. Treatment will be given for 4 to 8 doses in total. Thereafter patients may receive further treatments such as involved field radiation therapy and high-dose chemotherapy followed by autologous stem cell transplant.

A number of tests and procedures will be carried out during this period:
• Physical examination
• Vital signs measurement
• Review of any medications taken and any side effects experienced
• An assessment of how day to day activities are performed
• An assessment of the symptoms of disease
• Blood and urine tests
• Pregnancy testing for women of child bearing potential (urine or blood sample)
•Tumour assessment by PET-CT

FOLLOW-UP PERIOD
When patients stop or complete study treatment they will begin the last part of the study, the follow-up period. During this period the investigator will continue to assess the patient*s health condition.

Once treatment ends patients will be asked to come back to the hospital two more times, once about a month after they stop study treatment and the second time about two months after the first visit. During these visits some of the study procedures may be repeated including collection of blood and scans.

After the last two visits to the hospital, visits may be conducted over the phone. These will be conducted at 6, 12, 18, 24 and 36 months after they stop study treatment. Patients may need to go back to the hospital for scans for these visits.

A Data Monitoring Committee (DMC) will be established and meet regularly during the study to ensure that subject safety is carefully monitored and to provide oversight regarding safety and efficacy considerations.

Intervention

Nivolumab, brentuximab vedotin, and bendamustine in this study are considered investigational products.

Patients will initially receive nivolumab at a dose of 3 mg/kg and brentuximab vedotin at 1.8 mg/kg every three weeks. Depending on the patient*s response to treatment they may later be given brentuximab vedotin (1.8 mg/kg) and bendamustine (90 mg/m2) every three weeks. Treatment will be given for 4 to 8 doses in total. Thereafter patients may receive further treatments such as involved field radiation therapy and high-dose chemotherapy/autologous stem cell transplant.

Study burden and risks

As part of the trial, patients will be expected to attend multiple clinic visits where they will undergo physical examinations, vital sign measurements, blood tests for safety assessment, urine testing, pregnancy testing (for females of child bearing potential) and monitoring for adverse events. Patients will be asked to complete questionnaires about their quality of life. Blood will also be collected at certain visits for research purposes. There will be tumour imaging performed in the form of PET-CT and MRI. If there is no archive tumour tissue available or the sample was taken too long ago (more than 3 months), patients will be required to have a biopsy in order to participate. Patients may also receive involved field radiation therapy or high dose chemotherapy followed by autologous stem cell transplant.

The frequency of visits and number of procedures carried out during this trial would typically be considered over and above standard of care. The procedures are carried out by trained medical professionals and every effort will be made to minimise any risks or discomfort to the patient.

Treatment for cancer often has side effects, including some that are life threatening. To assure an ongoing favourable risk/benefit assessment for participants enrolled onto the study, an independent Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations. Additionally, the DMC will provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of participants enrolled in the study.

New Immune system targeted therapy (immunotherapies) such as nivolumab could potentially provide clinical benefit and improvements in the outcomes for patients with this disease (improvement in progression free and overall survival). However, with all experimental drugs and clinical trials, there are known and unknown risks. Study medication and procedure related risks are outlined in the patient information sheet in detail to ensure the patients are fully informed before agreeing to take part in the study.

Contacts

Public
Bristol-Myers Squibb

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Uxbridge UB8 1DH
GB
Scientific

Bristol-Myers Squibb

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

-Patients must provide written informed consent, children and adolescents should also give assent
-Males and females aged between 5 and 30 years, inclusive. Please note in the Netherlands, only patients aged between 5 to 18 inclusive will be included in the study.
-Women of child bearing potential must have a negative serum or urine pregnancy test within 24 hours prior to the start of study treatment
-Patients must have measurable classic Hodgkin lymphoma as documented by pathological and radiographic criteria
-Performance Level: Karnofsky above or equal to 50% for participants > 16 years of age or Lansky 50 for participants equal or less than16 years of age
-Patients must have received first line anti-cancer therapy that failed
-Patients must have adequate bone marrow, renal and hepatic function

Exclusion criteria

-Active, known, or suspected autoimmune disease, immunodeficiency or infection
-Active cerebral/meningeal disease related to the underlying malignancy
-Patients who failed more than one line of anti-cancer therapy or are treatment

naive
-Patients who previously received an allogeneic and/or autologous stem cell transplant for classic Hodgkin lymphoma
-Prior exposure to anti-PD1, anti-PDL1, anti-PD-L2, anti-CD137 or anti- CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
-Prior exposure to bendamustine

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	29-08-2017
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Adcetris
Generic name:	Brentuximab vedotin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Bendamustine HEXAL
Generic name:	Bendamustine hydrochloride
Registration:	Yes - NL outside intended use
Product type:	Medicine

Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-04-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-08-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	14-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-06-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	29-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-11-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-01-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-01-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-02-2023

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-09-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-12-2023
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
EudraCT	EUCTR2016-002347-41-NL
ClinicalTrials.gov	NCT02927769
CCMO	NL60079.078.17

Study results

Date completed: 28-05-2024

Results posted: 04-11-2024

First publication
01-01-1900