Very early FDG-PET-response adapted targeted therapy for advanced Hodgkin lymphoma: a single-arm phase II study

Published: 12-03-2019
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2023-508478-27-00 check the CTIS register for the current data. The main objective of this trial is to assess whether treatment adaptation based on a very early FDG-PET results in improved efficacy...

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

Summary

ID

NL-OMON50149

Source
ToetsingOnline

Brief title
COBRA

Condition

- Lymphomas Hodgkin's disease

Synonym
Hodgkin's disease, malignant lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: EORTC,Takeda

Intervention

Keyword: Advanced stage, Brentuximab, FDG-PET, Hodgkin Lymphoma

Outcome measures

Primary outcome

- Modified progression-free survival rate at 2 years after start of treatment

(2yr-mPFS).

The following are considered events for the primary endpoint:

progression/relapse;

start of new treatment for cHL when not in CR after completing protocol

treatment (including radiotherapy)

death from any cause.

Secondary outcome

- Patients with negative FDG-PET after 1 cycle of BrAVD (central assessment)

- Response rate according to Lugano Criteria at end of protocol treatment i.e.

after chemotherapy and after radiotherapy (if administered),

- Progression-free survival (where progression, relapse and death from any

cause are considered events).

- Overall survival

- Safety and tolerability

Exploratory:

- Response rate according to RECIL 2017

- To assess the degree of association between serum TARC level and FDG-PET

result both after one cycle of BrAVD among patients with pre-treatment TARC

elevation (see translational research in chapter 10)

- To identify markers that are potentially predictive for response or toxicity

or markers that can be used for treatment response monitoring (see

translational research chapter 10)

Study description

Background summary

Standard treatment for advanced Hodgkin lymphoma (HL) consists of chemotherapy: ABVD or escBEACOPP, followed by radiotherapy on FDG-PET positive residual disease after chemotherapy.

Although long-term progression free survival after escBEACOPP treatment (PFS 85-90%) is superior to ABVD (PFS 65-70%), escBEACOPP has more significant short-and long-term adverse effects than ABVD, and a potential difference in overall survival between patients treated with ABVD or escBEACOPP is debatable. Moreover comparable data is derived from studies in which individual treatment was not yet guided by the results of metabolic response during treatment by interim FDG-PET.

Currently, interim PET guidend treatment is standard of care for advanced HL. Adjustment of treatment, i.e. escalation of deëscalatie of treatment intensity is based on (metabolic) tumor response assessed by interim FDG-PET after 2 cycles of chemotherapy. FDG-PET after 1 cycle of chemotherapie (PET1) has recently been shown to have an even better negative predictive value. (NPV PET1: 98%, PET2: 90%)

Brentuximab-vedotin, an anti-CD30 Monoclonal antibody-toxine conjugate (vedotin) has high effectivity in HL. This drug is currently registered as 2nd or 3rd line treatment for HL. In up-front treatment for advanced HL, Brentuximab vetotin combined with AVD (without Bleomycine, i.e. BrAVD), was more effective than ABVD (phase III study); Brentuximab-vedotin incorporated in a escBEACOPP derived- ECADD combination (BrECADD) has been shown to be less toxic than escBEACOPP, and equally effective (phase II study).

Study objective

This study has been transitioned to CTIS with ID 2023-508478-27-00 check the CTIS register

for the current data.

The main objective of this trial is to assess whether treatment adaptation based on a very early FDG-PET results in improved efficacy while minimizing treatment toxicity in advanced stage HL patients treated with BV-containing regimens, BrAVD and BrECADD.
This will be primarily assessed by modified progression-free survival.

The secondary objectives are:
- To asses number of negative FDG-PET scans (Deauville score 1-3) after 1 cycle of BrAVD
- To assess response according to Lugano Criteria at end of protocol treatment i.e. after chemotherapy and after radiotherapy (if administered), as defined by FDG-PET/CT
- To assess the safety and tolerability of the different BV containing regimens
- To assess the safety and tolerability of radiotherapy in the context of BrAVD and BrECADD
- To assess efficacy in terms of PFS and OS

Exploratory objectives
- Response according to RECIL 2017
- To assess the degree of association between serum TARC level and FDG-PET result both after one cycle of BrAVD among patients with pre-treatment TARC elevation (see translational research in chapter 10)
- To identify markers that are potentially predictive for response or toxicity or markers that can be used for treatment response monitoring (see translational research chapter 10)

Study design

(see figure protocol chapter 4)

This is an international, open label, multi-center, single-arm phase II trial. Patients fulfilling the inclusion criteria, will be centrally registered at EORTC after written informed consent (IC) has been obtained.

All patients will receive 1 cycle of BrAVD followed by a FDG-PET with low-dose CT scan (PET1). Further treatment will be based on the centrally revised PET1 results scored according to the Deauville 5 point score (DS) as follows:
1. If PET1-negative (Deauville score: 1-3): patients will receive an additional 5 cycles of BrAVD
2. If PET1-positive (Deauville score: 4-5): patients will switch treatment and receive 6 cycles of BrECADD

Radiotherapy will be applied only to patients with residual PET positivity (Deauville score 4 or 5) at the end of chemotherapy. Only sites of residual PET

positive disease will be irradiated.

Intervention

see study design

All patients will receive 1 cycle of BrAVD followed by a FDG-PET with low-dose CT scan (PET1). Further treatment will be based on the centrally revised PET1 results scored according to the Deauville 5 point score (DS) as follows:
1. If PET1-negative (Deauville score: 1-3): patients will receive an additional 5 cycles of BrAVD
2. If PET1-positive (Deauville score: 4-5): patients will switch treatment and receive 6 cycles of BrECADD

Radiotherapy will be applied only to patients with residual PET positivity (Deauville score 4 or 5) at the end of chemotherapy. Only sites of residual PET positive disease will be irradiated.

Study burden and risks

The diagnostic work-up and evaluation of treatment (before, during and after protocol treatment) will differ only minimally from the standard of care (see E).

The risk of Brentuximab-Vedotin mainly consists in the possible occurrence of (largely reversible) polyneuropathy. Patients will be closely monitored during treatment and adaptation of BV dose according to signs and symptoms of polyneuropathy is extensively described in the protocol (see p 36 protocol).

BrECADD, the treatment for patients with a PET positive interim scan after 1 cycle of BrAVD will replace escBEACOPP which is currently standard of care for patients in daily practice with a positive interim PET scan after 2 cycles of ABVD. BrECADD has been shown to be equally effective but less toxic than escBEACOPP.

Contacts

Public
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue E. Mounier 83/11
Brussel 1200
BE
Scientific

European Organisation for Research in Treatment of Cancer (EORTC)

Avenue E. Mounier 83/11
Brussel 1200
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Classical Hodgkin lymphoma, histologically proven, previously untreated
- Staged by FDG-PET with diagnostic-quality CT (i.v. contrast).
- Clinical stages according to Lugano 2014 and based on FDG/PET CT:
> Stage IIB with large mediastinal mass > 1/3 max transverse diameter thorax and/or extranodal lesion(s)
> Stage III - IV
- Age >=18 and <=60
- WHO performance status 0-2 (Appendix C)
- Adequate organ function (for specification see 3.1.1 protocol page 24)
- Absence of any medical, psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.
- Participation in translational research is mandatory and therefore patient must consent for it.
- Negative pregnancy serum test < 72 h prior to 1st treatment (WOCBP)
- Willing to comply with birth control methods (protocol 3.1.1.) during the study and 6 months after last treatment dose
- Written informed consent

Exclusion criteria

- Cerebral or meningeal disease (HL or any other etiology), including signs or

symptoms of Progressive Multifocal Leukoencephalopathy
- Symptomatic neurologic disease compromising normal activities of daily living or requiring medications
- Sensory or motor peripheral neuropathy >= grade 2 according to CTCAE version 5.0
- Cardiovascular conditions (specifications see protocol 3.1.2 p 25)
- Poorly controlled diabetes mellitus (HbA1c > 7.5 % or a fasting blood sugar > 200 mg/dL).
- Any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics within 2 weeks prior to registration.
- Known HIV infection, chronic active hepatitis C, HBV positivity (HBsAg+ patients; HBsAg- HBcAb+/HBV DNA+ patients). Note: HBsAg-/HBV DNA - patients are eligible; patients who are seropositive due to vaccination are eligible
- Concomitant or previous malignancies within the past 5 years, with the exception of adequately treated carcinoma in situ of the cervix , non-melanoma skin cancer.
- Previous treatment with anti CD30 antibodies
- Known hypersensitivity to any excipient contained in Brentuximab Vedotin formulation and other study drugs.
- Concurrent anti-cancer treatment or use of any investigational agent(s)

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):	19-12-2019
Enrollment:	38
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:	Dacarbazine
Generic name:	Dacarbazine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Doxorubicin
Generic name:	Adriamycin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Endoxan
Generic name:	Cyclophosphamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Vinblastine
Generic name:	Vinblastine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-03-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-11-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-06-2021

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-01-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-03-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-08-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	CTIS2023-508478-27-00
EudraCT	EUCTR2017-000498-35-NL
ClinicalTrials.gov	NCT03517137
CCMO	NL67858.042.18