Clinical trial results:
Phase I/II feasibility study combining Brentuximab Vedotin (Adcetris) with second line salvage chemotherapy (DHAP) in Hodgkin lymphoma patients refractory to first line chemotherapy or in first relapse who are eligible for high dose treatment followed by autologous peripheral blood stem cell transplantation

Summary

EudraCT number	2012-003097-45
Trial protocol	NL DK FR
Global end of trial date	21 September 2020

Results information

Result version number	v1 (current)
This version publication date	10 August 2022
First version publication date	10 August 2022
Summary attachment (see zip file)	Combining brentuximab vedotin with dexamethasone, high-dose cytarabine and cisplatin as salvage treatment in relapsed or refractory Hodgkin lymphoma: the phase II HOVON/LLPC Transplant BRaVE study (haematol.2019.243238.full.pdf)

Trial information

Trial identification

Sponsor protocol code	NL40688.018.12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02280993
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Academic Medical Center
Sponsor organisation address	Meibergdreef 9, Amsterdam, Netherlands, 1105AZ
Public contact	Roberto Liu, Academic Medical Center, 00 31205665950, r.d.liu@amsterdamumc.nl
Scientific contact	Roberto Liu, Academic Medical Center, 00 31205665950, r.d.liu@amsterdamumc.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	20 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase II

- To demonstrate the efficacy and safety of BV in combination with DHAP as salvage treatment (establish the fraction of responding patients – metabolic CR – as judged by PET-CT after the third cycle, and establish the rate of grade ¾ non-hematological toxicity, including neurotoxicity).

Protection of trial subjects:

The Data Safety Monitoring Board will advise the Principal Investigator and the Co-PI about the continuation of the study. The DSMB will evaluate the general progress and the feasibility of the study, the quality and completeness of the data, side effects and safety.
The DSMB consists of at least 3 members, among whom (at least) one statistician and minimally two physicians. The members of the DSMB are invited on personal title on the basis of their expert knowledge of the disease involved and/or the research methodology. Members of the DSMB will have ample experience with phase I/II clinical trials.
The members of the DSMB will not be involved in the study or work in a hospital department participating in the study.
The DSMB reports their written recommendations to the trial statistician. The report may consist of a confidential and a public part, where the confidential part contains references to unblinded data, if there are any. The trial statistician forwards the public part of the DSMB recommendation to the Principal Investigator and the Co-PI. The DSMB recommendations are not binding.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 35
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 17
Worldwide total number of subjects	55
EEA total number of subjects	55

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	54
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

During phase II a total of 55 patients were included in the period between 23-10-2015 and 25-07-2017.

Pre-assignment

Screening details:

All patients provided written informed consent. The study enrolled patients aged ≥18 years with histologically confirmed CD30 positive cHL by local pathology assessment, either having primary refractory disease or a first relapse after first-line chemotherapy. Central pathology review was performed by two experienced hematopathologists.

Pre-assignment period milestones

Number of subjects started	55
Number of subjects completed	55

Period 1

Period 1 title	Phase II (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Salvage treatment during phase II

Arm description:

Salvage treatment during phase II

Arm type	Experimental
Investigational medicinal product name	Brentuximab vedotin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.8 mg/kg, IV, day 1

Number of subjects in period 1	Salvage treatment during phase II
Started	55
Completed	55

Baseline characteristics

Reporting groups	
Reporting group title	Phase II

Reporting group description: -

Reporting group values	Phase II	Total	
Number of subjects	55	55	
Age categorical Units: Subjects			
Adults (18-64 years)		0	
Age continuous			
Patient characteristics - age			
Units: years median full range (min-max)	 29 19 to 71	 -	
Gender categorical Units: Subjects			
Female	27	27	
Male	28	28	

End points

End points reporting groups

Reporting group title	Salvage treatment during phase II
Reporting group description: Salvage treatment during phase II	

Primary: Metabolic CR rate (PET-CT) after the third cycle of BV-DHAP reinduction therapy

End point title	Metabolic CR rate (PET-CT) after the third cycle of BV-DHAP reinduction therapy[1]
End point description:	
End point type	Primary
End point timeframe: After the third cycle of BV-DHAP reinduction therapy	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no comparison between groups, only descriptive evaluation of metabolic CR rate, no direct comparison. The statistical analysis for an endpoint is thus not mandatory. This is why the statistical analysis was deleted (after consulting Sjennie Daelmans).

End point values	Salvage treatment during phase II			
Subject group type	Reporting group			
Number of subjects analysed	52[2]			
Units: Whole	52			

Notes:

[2] - 55 patients were included in the phase II part, 3 patients were not evaluable for response.

Attachments (see zip file)	Final publication/haematol.2019.243238.full.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events of all grades regardless relationship to investigational product occurring from the the first study-related procedure until 30 days to end of treatment evaluation.

Adverse event reporting additional description:

Adverse events occurring after 30 days should also be reported if considered at least possibly related to the investigational medicinal product by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Phase II

Reporting group description: -

Serious adverse events	Phase II		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 55 (32.73%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Investigations			
Elevated liver enzymes			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	9 / 55 (16.36%)		
occurrences causally related to treatment / all	9 / 9		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea/vomiting			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal function disorder			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Periodic paralysis (hypokalemia)			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Phase II		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 55 (36.36%)		
Investigations			
Increased liver enzymes			
subjects affected / exposed	10 / 55 (18.18%)		
occurrences (all)	10		
Elektrolyte disorders			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	14 / 55 (25.45%)		
occurrences (all)	14		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Malaise			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea/vomiting			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Diarrhea			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Renal and urinary disorders			
Renal function disorder			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Myalgia shoulder			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Paralysis (hypokalemia)			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		

Infections and infestations			
Sepsis			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Infection			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2015	1. The use of long-acting G-CSF (Neulasta) after the 1st and 3rd course of Brentuximab Vedotin + DHAP and after autologous stemcell transplantation is now obligatory to reduce the prolonged period of grade 4 granulocytopenia that was observed in the initial patients in the phase I part of the study who did not receive the growth factor : See section 5.2.2 and 5.4.3 in the protocol. NB. After course 2 all patients receive G-CSF in view of stem cell harvesting. 2. The definition of DLT has been extended : see section 5.2.3 , the Table in section 7.2 and section 17.7 in the protocol dealing with long-lasting granulocytopenia despite growth factor treatment after BV + DHAP. 3. Eligibility criteria for high dose BEAM chemotherapy followed by autologous stemcell transplantation have now been introduced in a new section in the protocol : 5.4.1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32273476