Clinical trial results:
Targeted BEACOPP variants in patients with newly diagnosed advanced classical Hodgkin Lymphoma

Summary

EudraCT number	2011-005082-21
Trial protocol	DE
Global end of trial date	15 October 2016

Results information

Result version number	v1 (current)
This version publication date	08 April 2020
First version publication date	08 April 2020

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-1491

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01569204
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus Magnus-Platz, Köln, Germany, 50923
Public contact	Trial Coordination Center of the German Hodgkin Study Group (GHSG), German Hodgkin Study Group (GHSG), 0049 22147888200, ghsg@uk-koeln.de
Scientific contact	Trial Coordination Center of the German Hodgkin Study Group (GHSG), German Hodgkin Study Group (GHSG), 0049 22147888200, ghsg@uk-koeln.de

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	Final
Date of interim/final analysis	03 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the trial was to implement the antibody-drug conjugate brentuximab vedotin into the first-line treatment of patients with advanced classical Hodgkin lymphoma. The combination of targeted drugs such as brentuximab vedotin with conventional chemotherapy might allow reducing the doses of classical chemotherapeutic substances without compromising treatment efficacy. One major goal of this trial is to generate a novel BEACOPP-based treatment protocol to serve as comparator in the next GHSG treatment optimization trial for patients with newly diagnosed advanced classical Hodgkin lymphoma (HD21).

Protection of trial subjects:

Written informed consent before study entry, frequent DMC monitoring, hospitalization during first cycle recommended, mandatory prophylaxis during chemotherapy, dose reduction strategy in case of adverse events

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 October 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 104
Worldwide total number of subjects	104
EEA total number of subjects	104

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)	104
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 26 October 2012 and 15 May 2014, a total of 104 patients with newly diagnosed advanced-stage Hodgkin lymphoma were recruited in 20 trial sites in Germany.

Pre-assignment

Screening details:

Main inclusion criteria: previously untreated classical Hodgkin lymphoma in advanced stages, normal organ function, life expectancy >3 months. Main exclusion criteria: severe pulmonary or cardiac disease, HIV positivity, WBC count <3x10/L, platelet count <100x10/L, bilirubin >2 mg/dL, AST or ALT >100 U/L, pregnancy or lactation, ECOG >2.

Period 1

Period 1 title	Randomized study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BrECAPP

Arm description:

Six 21-day cycles of BrECAPP

Arm type	Experimental
Investigational medicinal product name	Brentuximab vedotin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.8 mg/kg body weight on day 1 of each 21-day cycle, calculated with the patient's actual weight up to 100 kg.
Patients with a weight of more than 100 kg receive the maximum dose of 180 mg of brentuximab vedotin.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/m² body surface area on days 2-4 of each 21-day cycle. The maximum upper limit for the calculation of chemotherapy is fixed at a body surface of 2.1 m², even if the calculated body surface exceeds this.
Etoposide phosphate may be applied as etoposide-equivalent dose: 113 mg etoposide phosphate is equivalent to 100 mg etoposide. This difference is due to different molecular weights.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1250 mg/m² body surface area on day 2 of each 21-day cycle. The maximum upper limit for the calculation of chemotherapy is fixed at a body surface of 2.1 m², even if the calculated body surface exceeds this.

Uromitexan according to current standards is obligatory. The patient should ingest 2.5 liters of fluid on the day of administration.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

35 mg/m² body surface area on day 2 of each 21-day cycle. The maximum upper limit for the calculation of chemotherapy is fixed at a body surface of 2.1 m², even if the calculated body surface exceeds this.

Investigational medicinal product name	Procarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

100 mg/m² body surface area on days 2-8 of each 21-day cycle. The maximum upper limit for the calculation of chemotherapy is fixed at a body surface of 2.1 m², even if the calculated body surface exceeds this.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40 mg/m² body surface area on days 2-15 of each 21-day cycle. The maximum upper limit for the calculation of chemotherapy is fixed at a body surface of 2.1 m², even if the calculated body surface exceeds this.

Arm title	BrECADD

Arm description:

Six 21-day cycles of BrECADD

Arm type	Experimental
Investigational medicinal product name	Brentuximab vedotin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.8 mg/kg body weight on day 1 of each 21-day cycle, calculated with the patient's actual weight up to 100 kg.
Patients with a weight of more than 100 kg receive the maximum dose of 180 mg of brentuximab vedotin.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

150 mg/m² body surface area on days 2-4 of each 21-day cycle. The maximum upper limit for the calculation of chemotherapy is fixed at a body surface of 2.1 m², even if the calculated body surface exceeds this.
Etoposide phosphate may be applied as etoposide-equivalent dose: 113 mg etoposide phosphate is equivalent to 100 mg etoposide. This difference is due to different molecular weights.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1250 mg/m² body surface area on day 2 of each 21-day cycle. The maximum upper limit for the calculation of chemotherapy is fixed at a body surface of 2.1 m², even if the calculated body surface exceeds this.
Uromitexan according to current standards is obligatory. The patient should ingest 2.5 liters of fluid on the day of administration.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

40 mg/m² body surface area on day 2 of each 21-day cycle. The maximum upper limit for the calculation of chemotherapy is fixed at a body surface of 2.1 m², even if the calculated body surface exceeds this.

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion, Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

250 mg/m² body surface area on days 3-4 of each 21-day cycle. The maximum upper limit for the calculation of chemotherapy is fixed at a body surface of 2.1 m², even if the calculated body surface exceeds this.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

40 mg/m² body surface area on days 2-5 of each 21-day cycle. The maximum upper limit for the calculation of chemotherapy is fixed at a body surface of 2.1 m², even if the calculated body surface exceeds this.

Number of subjects in period 1	BrECAPP	BrECADD
Started	52	52
Started randomized treatment	50	52
Completed	48	52
Not completed	4	0
Consent withdrawn by subject	1	-
Physician decision	1	-
Adverse event, non-fatal	1	-
Violation of I/E criteria	1	-

Baseline characteristics

Reporting groups	
Reporting group title	BrECAPP
Reporting group description: Six 21-day cycles of BrECAPP	
Reporting group title	BrECADD
Reporting group description: Six 21-day cycles of BrECADD	

Reporting group values	BrECAPP	BrECADD	Total
Number of subjects	52	52	104
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	52	52	104
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	29.5	28.5	
full range (min-max)	18 to 60	18 to 59	-
Gender categorical Units: Subjects			
Female	21	20	41
Male	31	32	63
Ann Arbor stage Units: Subjects			
IIB	10	8	18
IIIA	15	9	24
IIIB	8	12	20
IVA	5	5	10
IVB	14	18	32
Large mediastinal mass Units: Subjects			
No	31	31	62
Yes	21	21	42
Extranodal disease Units: Subjects			
No	41	37	78
Yes	11	15	26
At least 3 nodal areas involved			

Units: Subjects			
No	8	10	18
Yes	44	42	86
Elevated ESR Units: Subjects			
No	21	13	34
Yes	31	39	70
International prognostic score Units: Subjects			
0-2	35	33	68
3-7	17	19	36
WHO activity index Units: Subjects			
0 (fully active)	23	18	41
1 (able to do light work)	27	34	61
2 (unable to do light work)	2	0	2

End points

End points reporting groups

Reporting group title	BrECAPP
Reporting group description: Six 21-day cycles of BrECAPP	
Reporting group title	BrECADD
Reporting group description: Six 21-day cycles of BrECADD	

Primary: Complete response to chemotherapy

End point title	Complete response to chemotherapy[1]

End point description:

We defined complete response as the achievement of either complete remission, partial remission with residual lymphoma less than 2.5 cm, or PET negativity (Deauville score 1-3) after chemotherapy, according to central review.
Both arms were analyzed separately.
Assuming a complete response in 90% in each arm, we would be able to test the null hypothesis "complete response rate is 70% or lower" with a one-sided significance level of 2.5% and a power of 90% per arm. We calculated one-sided 97.5% Clopper-Pearson exact binominal CIs for observed responses in order to exclude the benchmark of 70%.

End point type	Primary

End point timeframe:

The CT-based restaging was scheduled within the last week of the last chemotherapy cycle. In patients with residual lymphoma of 2.5 cm or larger, a PET scan was to be performed at least 3 weeks after the end of the last chemotherapy cycle.

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: This is a phase-2 study with 2 regimens to be evaluated independently. There is no arm comparison but 2 single-arm analyses, which cannot be entered in the system.
Analyses were as follows:
The null hypothesis H0 "Complete response rate<=70%" was tested versus a one-sided alternative via a one-sided 97.5% CI per arm.
The lower confidence limits were 73% and 77%, respectively, and thus both above the efficacy benchmark.
In conclusion, both null hypotheses could be rejected.

End point values	BrECAPP	BrECADD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[2]	52		
Units: subjects				
Yes	42	46		
No	7	6		

Notes:

[2] - 3/52 patients excluded: 2 did not receive any study treatment, 1 violated I/E criteria

Statistical analyses

No statistical analyses for this end point

Primary: Complete remission

End point title	Complete remission[3]

End point description:

We defined complete remission as complete remission after completion of study treatment or, in case of residual lymphoma after completion of study treatment, freedom from progression without additional treatment for at least 6 months.
Both arms were analyzed separately.
The co-primary efficacy endpoint was only to be tested if the null hypothesis for complete response could not be rejected.
Assuming a complete remission rate of 95% for each arm, we would be able to test the null hypothesis "complete remission rate is 80% or lower" with a one-sided significance level of 2.5% and a power of 90% per arm. To this end, one-sided 97.5% Clopper-Pearson exact binominal CIs for observed remissions would be calculated in order to exclude the benchmark of 80%.

End point type	Primary

End point timeframe:

Within 6 months after end of study treatment

Notes:

[3] - 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: The co-primary efficacy endpoint "complete remission" was only to be tested if the null hypothesis for the primary endpoint "complete response" could not be rejected. As the null hypothesis for "complete response" could be rejected for both regimens, a confirmative test of "complete remission" was not done.

End point values	BrECAPP	BrECADD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[4]	52		
Units: patients				
Yes	46	46		
No	3	6		

Notes:

[4] - 3/52 patients excluded: 2 did not receive any study treatment, 1 violated I/E criteria

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival is defined as time from randomization to disease progression or death from any cause and censored at the date of last tumor assessment for patients alive without progressive disease.

End point type	Secondary

End point timeframe:

18-months progression-free survival will be reported.

End point values	BrECAPP	BrECADD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[5]	52		
Units: percent				
number (confidence interval 95%)	95 (85 to 100)	89 (77 to 100)		

Notes:
[5] - 3/52 patients excluded: 2 did not receive any study treatment, 1 violated I/E criteria

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All events up to 30 days after end of treatment had to be reported. Events that occured later than 30 days after the end of treatment had to be reported if causality was rated at least as "possible".

Adverse event reporting additional description:

AEs were assessed on the therapy administration CRFs. SAEs were additionally assessed on specific forms. SAEs may thus be reported twice; non-serious and SAEs might include duplicate events and do not add up to a total number of AEs.
Hospitalization in connection with therapeutic measures of the trial and deaths from HL were no SAEs in this trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups

Reporting group title	BrECAPP

Reporting group description:

Six 21-day cycles of BrECAPP

Reporting group title	BrECADD

Reporting group description:

Six 21-day cycles of BrECADD

Serious adverse events	BrECAPP	BrECADD	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 50 (42.00%)	18 / 52 (34.62%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	0	
Investigations			
Investigations			
subjects affected / exposed	5 / 50 (10.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	0 / 50 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures			

subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	7 / 50 (14.00%)	9 / 52 (17.31%)	
occurrences causally related to treatment / all	9 / 9	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	4 / 50 (8.00%)	3 / 52 (5.77%)	
occurrences causally related to treatment / all	4 / 4	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Immune system disorders			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	3 / 50 (6.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Musculoskeletal and connective tissue disorders			
subjects affected / exposed	1 / 50 (2.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	6 / 50 (12.00%)	7 / 52 (13.46%)	
occurrences causally related to treatment / all	6 / 6	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	BrECAPP	BrECADD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)	51 / 52 (98.08%)	
Nervous system disorders			
Nervous system disorders, sensory			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	16 / 50 (32.00%)	18 / 52 (34.62%)	
occurrences (all)	37	41	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	47 / 50 (94.00%)	50 / 52 (96.15%)	
occurrences (all)	234	251	
Thrombocytopenia			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			

subjects affected / exposed	45 / 50 (90.00%)	43 / 52 (82.69%)	
occurrences (all)	190	180	
Leukopenia			
subjects affected / exposed	48 / 50 (96.00%)	46 / 52 (88.46%)	
occurrences (all)	232	222	
General disorders and administration site conditions			
Drug fever			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 50 (10.00%)	2 / 52 (3.85%)	
occurrences (all)	7	3	
Gastrointestinal disorders			
Nausea or vomiting			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	22 / 50 (44.00%)	19 / 52 (36.54%)	
occurrences (all)	46	32	
Mucositis			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 50 (24.00%)	9 / 52 (17.31%)	
occurrences (all)	14	11	
Gastrointestinal tract disorder			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 50 (28.00%)	16 / 52 (30.77%)	
occurrences (all)	18	18	
Respiratory, thoracic and mediastinal disorders			
Respiratory tract disorders			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 50 (10.00%)	8 / 52 (15.38%)	
occurrences (all)	6	13	
Hepatobiliary disorders			

Hepatobiliary disorders alternative dictionary used: NCI CTCAE 4.0 alternative assessment type: Non-systematic subjects affected / exposed[1] occurrences (all)	8 / 48 (16.67%) 26	7 / 44 (15.91%) 26	
Skin and subcutaneous tissue disorders Skin disorders alternative dictionary used: NCI CTCAE 4.0 alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 5	2 / 52 (3.85%) 2	
Infections and infestations Infection alternative dictionary used: NCI CTCAE 4.0 alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	11 / 50 (22.00%) 14	13 / 52 (25.00%) 21	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Documentation of hepatobiliary disorders was introduced with an amendment of the case report form concerning acute AEs 3 months after start of recruitment. Thus, a small number of patients have no documented information about these AEs.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2012	Updated procedures for cases of peripheral neuropathy and PML, updated contact information for reporting of SAEs and pregnancies, added information on product complaints, reduction of obligatory pause between prephase and start of treatment from 7 to 2 days
16 September 2013	Addition of adverse reaction "acute pancreatitis" to the ICF following important drug warning for brentuximab vedotin, updated IB
04 February 2014	Adaption of the reference level for the evaluation of PET for radiotherapy recommendation

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/29133014