Clinical trial results:
HD18 for advanced stages in Hodgkins Lymphoma

Summary

EudraCT number	2007-003187-22
Trial protocol	DE AT CZ NL
Global end of trial date	18 July 2019

Results information

Result version number	v1 (current)
This version publication date	24 July 2020
First version publication date	24 July 2020

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-908

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00515554
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	13 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the HD18 trial was to individualize treatment of patients with advanced-stage Hodgkin lymphoma (HL) by adapting it to early response.
The HD18 trial comprises of two independent studies for patients with a positive or negative PET after 2 cycles of eBEACOPP (PET-2), respectively.
The primary objective of the study in patients with positive PET-2 was to show superiority of the combined immuno-chemotherapy R-eBEACOPP compared with standard eBEACOPP in terms of progression-free survival (PFS).
The primary objective of the study in patients with negative PET-2 was to show non-inferiority of treatment with a reduced number of cycles compared with standard treatment in terms of PFS.

Protection of trial subjects:

Written informed consent before study entry, frequent DMC monitoring, hospitalization during first cycle and dexamethasone pre-treatment recommended for patients aged 40 years or older, mandatory prophylaxis during chemotherapy, dose reduction strategy in case of adverse events

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 May 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 37
Country: Number of subjects enrolled	Austria: 66
Country: Number of subjects enrolled	Czech Republic: 35
Country: Number of subjects enrolled	Germany: 1810
Country: Number of subjects enrolled	Switzerland: 153
Worldwide total number of subjects	2101
EEA total number of subjects	1948

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)	2101
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 14 May 2008 and 18 July 2014, 2101 patients were enrolled in 301 trial sites in 5 European countries.

Pre-assignment

Screening details:

Enrolled patients received 2 cycles eBEACOPP followed by PET/CT-based response assessment. After central review of PET-2, patients were randomly assigned to a treatment group based on their PET-2 result. Patients dropping out before or during central PET review were not randomized.

Pre-assignment period milestones

Number of subjects started	2101
Number of subjects completed	1964

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Protocol deviation: 39
Reason: Number of subjects	Revision of HL diagnosis: 21
Reason: Number of subjects	Registration error: 1
Reason: Number of subjects	Violation of inclusion or exclusion criteria: 35
Reason: Number of subjects	Independent disease entity: 5
Reason: Number of subjects	Other: 9
Reason: Number of subjects	Progressive disease: 1
Reason: Number of subjects	Adverse event, serious fatal: 7
Reason: Number of subjects	Adverse event, non-fatal: 18

Period 1

Period 1 title	Randomization
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: 8x eBEACOPP PET+

Arm description:

Standard treatment for PET-2-positive patients pre amendment 2: 8x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy

Arm type	Active comparator

Investigational medicinal product name	Bleomycin
Investigational medicinal product code	L01DC01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 10 mg/m² BSA on day 8 of each cycle	
Investigational medicinal product name	Etoposide
Investigational medicinal product code	L01CB01
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 200 mg/m² BSA on days 1-3 of each cycle	
Investigational medicinal product name	Doxorubicine
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 35 mg/m² BSA on day 1 of each cycle	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	L01AA01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 1250 mg/m² BSA on day 1 of each cycle	
Investigational medicinal product name	Vincristine
Investigational medicinal product code	L01CA02
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 1.4 mg/m² BSA on day 8 of each cycle	
Investigational medicinal product name	Procarbazine
Investigational medicinal product code	L01XB01
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 100 mg/m² BSA on days 1-7 of each cycle	
Investigational medicinal product name	Prednisone
Investigational medicinal product code	H02AB07
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use
Dosage and administration details: 40 mg/m² BSA on days 1-14 of each cycle	
Arm title	Arm B: 8x R-eBEACOPP PET+

Arm description:

Experimental treatment for PET-2-positive patients pre amendment 2: 8x R-eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy

Arm type	Experimental
Investigational medicinal product name	Bleomycin
Investigational medicinal product code	L01DC01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/m² BSA on day 8 of each cycle

Investigational medicinal product name	Etoposide
Investigational medicinal product code	L01CB01
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/m² BSA on days 1-3 of each cycle

Investigational medicinal product name	Doxorubicine
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

35 mg/m² BSA on day 1 of each cycle

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	L01AA01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1250 mg/m² BSA on day 1 of each cycle

Investigational medicinal product name	Vincristine
Investigational medicinal product code	L01CA02
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1.4 mg/m² BSA on day 8 of each cycle

Investigational medicinal product name	Procarbazine
Investigational medicinal product code	L01XB01
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

100 mg/m² BSA on days 1-7 of each cycle

Investigational medicinal product name	Prednisone
Investigational medicinal product code	H02AB07
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details: 40 mg/m² BSA on days 1-14 of each cycle	
Investigational medicinal product name	Rituximab
Investigational medicinal product code	L01XC02
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravascular use
Dosage and administration details: 375 mg/m² BSA on days 0 and 3 of cycle 4; 375 mg/m² BSA on day 1 of cycles 5-8	
Arm title	Arm A6: 6x eBEACOPP PET+
Arm description: Standard treatment for PET-2-positive patients post amendment 2: 6x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	
Arm type	Active comparator
Investigational medicinal product name	Bleomycin
Investigational medicinal product code	L01DC01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 10 mg/m² BSA on day 8 of each cycle	
Investigational medicinal product name	Etoposide
Investigational medicinal product code	L01CB01
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 200 mg/m² BSA on days 1-3 of each cycle	
Investigational medicinal product name	Doxorubicine
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 35 mg/m² BSA on day 1 of each cycle	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	L01AA01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 1250 mg/m² BSA on day 1 of each cycle	
Investigational medicinal product name	Vincristine
Investigational medicinal product code	L01CA02
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 1.4 mg/m² BSA on day 8 of each cycle	

Investigational medicinal product name	Procarbazine
Investigational medicinal product code	L01XB01
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

100 mg/m² BSA on days 1-7 of each cycle

Investigational medicinal product name	Prednisone
Investigational medicinal product code	H02AB07
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

40 mg/m² BSA on days 1-14 of each cycle

Arm title	Arm C: 8/6x eBEACOPP PET-

Arm description:

Standard treatment for PET-2-negative patients: 8x eBEACOPP pre amendment 2, 6x eBEACOPP post amendment 2, each in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy

Arm type	Active comparator
Investigational medicinal product name	Bleomycin
Investigational medicinal product code	L01DC01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/m² BSA on day 8 of each cycle

Investigational medicinal product name	Etoposide
Investigational medicinal product code	L01CB01
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/m² BSA on days 1-3 of each cycle

Investigational medicinal product name	Doxorubicine
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

35 mg/m² BSA on day 1 of each cycle

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	L01AA01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1250 mg/m² BSA on day 1 of each cycle

Investigational medicinal product name	Vincristine
Investigational medicinal product code	L01CA02
Other name	
Pharmaceutical forms	Solution for injection

Routes of administration	Intravenous use
Dosage and administration details: 1.4 mg/m² BSA on day 8 of each cycle	
Investigational medicinal product name	Procarbazine
Investigational medicinal product code	L01XB01
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 100 mg/m² BSA on days 1-7 of each cycle	
Investigational medicinal product name	Prednisone
Investigational medicinal product code	H02AB07
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use
Dosage and administration details: 40 mg/m² BSA on days 1-14 of each cycle	
Arm title	Arm D: 4x eBEACOPP PET-
Arm description: Experimental treatment for PET-2-negative patients: 4x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	
Arm type	Experimental
Investigational medicinal product name	Bleomycin
Investigational medicinal product code	L01DC01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 10 mg/m² BSA on day 8 of each cycle	
Investigational medicinal product name	Etoposide
Investigational medicinal product code	L01CB01
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 200 mg/m² BSA on days 1-3 of each cycle	
Investigational medicinal product name	Doxorubicine
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 35 mg/m² BSA on day 1 of each cycle	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	L01AA01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 1250 mg/m² BSA on day 1 of each cycle	

Investigational medicinal product name	Vincristine
Investigational medicinal product code	L01CA02
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1.4 mg/m² BSA on day 8 of each cycle

Investigational medicinal product name	Procarbazine
Investigational medicinal product code	L01XB01
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

100 mg/m² BSA on days 1-7 of each cycle

Investigational medicinal product name	Prednisone
Investigational medicinal product code	H02AB07
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

40 mg/m² BSA on days 1-14 of each cycle

Number of subjects in period 1	Arm A: 8x eBEACOPP PET+	Arm B: 8x R-eBEACOPP PET+	Arm A6: 6x eBEACOPP PET+
Started	220	220	511
Completed	217	217	506
Not completed	3	3	5
Revision of HL diagnosis	1	-	2
Adverse event, non-fatal	1	1	-
Violation of inclusion or exclusion criteria	-	-	2
Protocol deviation	1	2	1

Number of subjects in period 1	Arm C: 8/6x eBEACOPP PET-	Arm D: 4x eBEACOPP PET-
Started	508	505
Completed	504	501
Not completed	4	4
Revision of HL diagnosis	1	2
Adverse event, non-fatal	-	-
Violation of inclusion or exclusion criteria	1	1
Protocol deviation	2	1

Period 2

Period 2 title	Randomized treatment
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: 8x eBEACOPP PET+

Arm description:

Standard treatment for PET-2-positive patients pre amendment 2: 8x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy

Arm type	Active comparator
Investigational medicinal product name	Bleomycin
Investigational medicinal product code	L01DC01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/m² BSA on day 8 of each cycle

Investigational medicinal product name	Etoposide
Investigational medicinal product code	L01CB01
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/m² BSA on days 1-3 of each cycle

Investigational medicinal product name	Doxorubicine
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

35 mg/m² BSA on day 1 of each cycle

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	L01AA01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1250 mg/m² BSA on day 1 of each cycle

Investigational medicinal product name	Vincristine
Investigational medicinal product code	L01CA02
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1.4 mg/m² BSA on day 8 of each cycle

Investigational medicinal product name	Procarbazine
Investigational medicinal product code	L01XB01
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

100 mg/m² BSA on days 1-7 of each cycle

Investigational medicinal product name	Prednisone
Investigational medicinal product code	H02AB07
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

40 mg/m² BSA on days 1-14 of each cycle

Arm title	Arm B: 8x R-eBEACOPP PET+

Arm description:

Experimental treatment for PET-2-positive patients pre amendment 2: 8x R-eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy

Arm type	Experimental
Investigational medicinal product name	Bleomycin
Investigational medicinal product code	L01DC01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/m² BSA on day 8 of each cycle

Investigational medicinal product name	Etoposide
Investigational medicinal product code	L01CB01
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/m² BSA on days 1-3 of each cycle

Investigational medicinal product name	Doxorubicine
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

35 mg/m² BSA on day 1 of each cycle

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	L01AA01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1250 mg/m² BSA on day 1 of each cycle

Investigational medicinal product name	Vincristine
Investigational medicinal product code	L01CA02
Other name	
Pharmaceutical forms	Solution for injection

Routes of administration	Intravenous use
Dosage and administration details: 1.4 mg/m² BSA on day 8 of each cycle	
Investigational medicinal product name	Procarbazine
Investigational medicinal product code	L01XB01
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 100 mg/m² BSA on days 1-7 of each cycle	
Investigational medicinal product name	Prednisone
Investigational medicinal product code	H02AB07
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use
Dosage and administration details: 40 mg/m² BSA on days 1-14 of each cycle	
Investigational medicinal product name	Rituximab
Investigational medicinal product code	L01XC02
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravascular use
Dosage and administration details: 375 mg/m² BSA on days 0 and 3 of cycle 4; 375 mg/m² BSA on day 1 of cycles 5-8	
Arm title	Arm A6: 6x eBEACOPP PET+

Arm description:

Standard treatment for PET-2-positive patients post amendment 2: 6x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy

Arm type	Active comparator
Investigational medicinal product name	Bleomycin
Investigational medicinal product code	L01DC01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 10 mg/m² BSA on day 8 of each cycle	
Investigational medicinal product name	Etoposide
Investigational medicinal product code	L01CB01
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 200 mg/m² BSA on days 1-3 of each cycle	
Investigational medicinal product name	Doxorubicine
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 35 mg/m² BSA on day 1 of each cycle	

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	L01AA01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1250 mg/m² BSA on day 1 of each cycle

Investigational medicinal product name	Vincristine
Investigational medicinal product code	L01CA02
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1.4 mg/m² BSA on day 8 of each cycle

Investigational medicinal product name	Procarbazine
Investigational medicinal product code	L01XB01
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

100 mg/m² BSA on days 1-7 of each cycle

Investigational medicinal product name	Prednisone
Investigational medicinal product code	H02AB07
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

40 mg/m² BSA on days 1-14 of each cycle

Arm title	Arm C: 8/6x eBEACOPP PET-

Arm description:

Standard treatment for PET-2-negative patients: 8x eBEACOPP pre amendment 2, 6x eBEACOPP post amendment 2, each in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy

Arm type	Active comparator
Investigational medicinal product name	Bleomycin
Investigational medicinal product code	L01DC01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/m² BSA on day 8 of each cycle

Investigational medicinal product name	Etoposide
Investigational medicinal product code	L01CB01
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/m² BSA on days 1-3 of each cycle

Investigational medicinal product name	Doxorubicine
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Solution for infusion

Routes of administration	Intravenous use
Dosage and administration details: 35 mg/m² BSA on day 1 of each cycle	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	L01AA01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 1250 mg/m² BSA on day 1 of each cycle	
Investigational medicinal product name	Vincristine
Investigational medicinal product code	L01CA02
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 1.4 mg/m² BSA on day 8 of each cycle	
Investigational medicinal product name	Procarbazine
Investigational medicinal product code	L01XB01
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 100 mg/m² BSA on days 1-7 of each cycle	
Investigational medicinal product name	Prednisone
Investigational medicinal product code	H02AB07
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use
Dosage and administration details: 40 mg/m² BSA on days 1-14 of each cycle	
Arm title	Arm D: 4x eBEACOPP PET-

Arm description:

Experimental treatment for PET-2-negative patients: 4x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy

Arm type	Experimental
Investigational medicinal product name	Bleomycin
Investigational medicinal product code	L01DC01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 10 mg/m² BSA on day 8 of each cycle	
Investigational medicinal product name	Etoposide
Investigational medicinal product code	L01CB01
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 200 mg/m² BSA on days 1-3 of each cycle	

Investigational medicinal product name	Doxorubicine
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 35 mg/m² BSA on day 1 of each cycle	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	L01AA01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 1250 mg/m² BSA on day 1 of each cycle	
Investigational medicinal product name	Vincristine
Investigational medicinal product code	L01CA02
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 1.4 mg/m² BSA on day 8 of each cycle	
Investigational medicinal product name	Procarbazine
Investigational medicinal product code	L01XB01
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 100 mg/m² BSA on days 1-7 of each cycle	
Investigational medicinal product name	Prednisone
Investigational medicinal product code	H02AB07
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use
Dosage and administration details: 40 mg/m² BSA on days 1-14 of each cycle	

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: In the HD18 trial, all patients received initial 2 cycles of chemotherapy and were then randomized into one of two parallel treatment arms according to their PET-result. The baseline period only includes those patients who received randomized treatment within the study and are included in the efficacy analyses. Patients who dropped out before randomization are not included.

Number of subjects in period 2[2]	Arm A: 8x eBEACOPP PET+	Arm B: 8x R-eBEACOPP PET+	Arm A6: 6x eBEACOPP PET+
Started	217	217	506
Completed	186	180	442
Not completed	31	37	64
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	3	2	1
Physician decision	-	1	3
Adverse event, non-fatal	4	10	3

Incomplete documentation	6	9	20
Violation of inclusion or exclusion criteria	1	1	2
Not specified	-	-	-
Independent disease entity	1	-	4
Patients' wish	4	3	6
Lack of efficacy	2	2	2
Protocol deviation	10	9	23

Number of subjects in period 2[2]	Arm C: 8/6x eBEACOPP PET-	Arm D: 4x eBEACOPP PET-
Started	504	501
Completed	446	474
Not completed	58	27
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	1
Physician decision	-	2
Adverse event, non-fatal	10	2
Incomplete documentation	14	11
Violation of inclusion or exclusion criteria	2	1
Not specified	1	1
Independent disease entity	-	-
Patients' wish	23	6
Lack of efficacy	-	-
Protocol deviation	6	3

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: In HD18, all patients received 2 cycles of chemotherapy and were then randomized into one of two parallel treatment arms according to their PET result. All randomized patients are included in period 1 ("Randomization"). However, there were a small number of patients randomized despite prior protocol violation. These did not receive randomized treatment and have not been included in the efficacy analyses. Thus, the baseline period only includes patients receiving randomized treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: 8x eBEACOPP PET+
Reporting group description:	
Standard treatment for PET-2-positive patients pre amendment 2: 8x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	
Reporting group title	Arm B: 8x R-eBEACOPP PET+
Reporting group description:	
Experimental treatment for PET-2-positive patients pre amendment 2: 8x R-eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	
Reporting group title	Arm A6: 6x eBEACOPP PET+
Reporting group description:	
Standard treatment for PET-2-positive patients post amendment 2: 6x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	
Reporting group title	Arm C: 8/6x eBEACOPP PET-
Reporting group description:	
Standard treatment for PET-2-negative patients: 8x eBEACOPP pre amendment 2, 6x eBEACOPP post amendment 2, each in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	
Reporting group title	Arm D: 4x eBEACOPP PET-
Reporting group description:	
Experimental treatment for PET-2-negative patients: 4x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	

Reporting group values	Arm A: 8x eBEACOPP PET+	Arm B: 8x R-eBEACOPP PET+	Arm A6: 6x eBEACOPP PET+
Number of subjects	217	217	506
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)	217	217	506
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	88	86	211
Male	129	131	295
Ann Arbor Stage Units: Subjects			
IIA	0	1	0
IIB	49	54	96

IIIA	41	29	93
IIIB	58	51	118
IVA	20	26	63
IVB	49	56	136
ECOG Performance Status Units: Subjects			
ECOG 0	110	106	302
ECOG 1	101	104	185
ECOG 2	6	7	19
Large Mediastinal Mass Units: Subjects			
No	122	117	306
Yes	95	100	199
Missing	0	0	1
Extranodal disease Units: Subjects			
No	151	168	382
Yes	66	49	124
IPS Units: Subjects			
0-1	58	62	129
2-3	131	108	284
4-7	27	45	93
Missing	1	2	0
HL subtype Units: Subjects			
Classical HL	184	173	326
Nodular lymphocyte-predominant HL	4	12	15
Missing	29	32	165

Reporting group values	Arm C: 8/6x eBEACOPP PET-	Arm D: 4x eBEACOPP PET-	Total
Number of subjects	504	501	1945
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)	504	501	1945
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	189	188	762
Male	315	313	1183

Ann Arbor Stage Units: Subjects			
IIA	0	0	1
IIB	40	42	281
IIIA	156	156	475
IIIB	131	122	480
IVA	59	60	228
IVB	118	121	480
ECOG Performance Status Units: Subjects			
ECOG 0	319	314	1151
ECOG 1	174	181	745
ECOG 2	11	6	49
Large Mediastinal Mass Units: Subjects			
No	425	413	1383
Yes	79	88	561
Missing	0	0	1
Extranodal disease Units: Subjects			
No	424	441	1566
Yes	80	60	379
IPS Units: Subjects			
0-1	177	174	600
2-3	254	257	1034
4-7	71	68	304
Missing	2	2	7
HL subtype Units: Subjects			
Classical HL	365	364	1412
Nodular lymphocyte-predominant HL	26	27	84
Missing	113	110	449

End points

End points reporting groups

Reporting group title	Arm A: 8x eBEACOPP PET+
Reporting group description:	
Standard treatment for PET-2-positive patients pre amendment 2: 8x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	

Reporting group title	Arm B: 8x R-eBEACOPP PET+
Reporting group description:	
Experimental treatment for PET-2-positive patients pre amendment 2: 8x R-eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	

Reporting group title	Arm A6: 6x eBEACOPP PET+
Reporting group description:	
Standard treatment for PET-2-positive patients post amendment 2: 6x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	

Reporting group title	Arm C: 8/6x eBEACOPP PET-
Reporting group description:	
Standard treatment for PET-2-negative patients: 8x eBEACOPP pre amendment 2, 6x eBEACOPP post amendment 2, each in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	

Reporting group title	Arm D: 4x eBEACOPP PET-
Reporting group description:	
Experimental treatment for PET-2-negative patients: 4x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	

Reporting group title	Arm A: 8x eBEACOPP PET+
Reporting group description:	
Standard treatment for PET-2-positive patients pre amendment 2: 8x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	

Reporting group title	Arm B: 8x R-eBEACOPP PET+
Reporting group description:	
Experimental treatment for PET-2-positive patients pre amendment 2: 8x R-eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	

Reporting group title	Arm A6: 6x eBEACOPP PET+
Reporting group description:	
Standard treatment for PET-2-positive patients post amendment 2: 6x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	

Reporting group title	Arm C: 8/6x eBEACOPP PET-
Reporting group description:	
Standard treatment for PET-2-negative patients: 8x eBEACOPP pre amendment 2, 6x eBEACOPP post amendment 2, each in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	

Reporting group title	Arm D: 4x eBEACOPP PET-
Reporting group description:	
Experimental treatment for PET-2-negative patients: 4x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy	

Primary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival was defined as the time from completion of staging until progression, relapse, or death from any cause. If none of these events had occurred, progression-free survival was censored at the date of last information on the disease status. Progression-free survival was analyzed according to Kaplan-Meier. Analyses are based on the final data status after end of study and results may thus slightly differ from published values. Median observation time for progression-free survival for the entire study was 64 months. 5-year estimates and the respective 95% CIs will be reported.

End point type	Primary

End point timeframe:

5 years

End point values	Arm A: 8x eBEACOPP PET+	Arm B: 8x R-eBEACOPP PET+	Arm A6: 6x eBEACOPP PET+	Arm C: 8/6x eBEACOPP PET-
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	217	217	506	446[1]
Units: percent				
number (confidence interval 95%)	89.9 (85.7 to 94.1)	87.7 (83.1 to 92.4)	90.1 (87.2 to 92.9)	91.2 (88.4 to 93.9)

Notes:

[1] - PET-2-negative study: per-protocol analysis, severe protocol deviations excluded

End point values	Arm D: 4x eBEACOPP PET-			
Subject group type	Reporting group			
Number of subjects analysed	474[2]			
Units: percent				
number (confidence interval 95%)	93.0 (90.6 to 95.4)			

Notes:

[2] - PET-2-negative study: per-protocol analysis, severe protocol deviations excluded

Statistical analyses

Statistical analysis title	PET-2-positive study, superiority test

Statistical analysis description:

The primary objective of the study in patients with positive PET-2 was to show superiority of 8x R-eBEACOPP over 8x eBEACOPP. The trial was designed to detect an improvement of at least 15% in 5-year progression-free survival with a power of 80% and a two-sided significance level of 5%. Only patients with a positive PET-2 randomized to arms A and B (i.e. before amendment 2) are analyzed. PET-2-positive patients treated according to arm A6 post amendment 2 were separately analyzed descriptively.

Comparison groups	Arm A: 8x eBEACOPP PET+ v Arm B: 8x R-eBEACOPP PET+

Number of subjects included in analysis	434
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.4 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	2.32

Notes:

[3] - Superiority was tested using log-rank test on a 2-sided significance level of 5%.

[4] - Conclusion: The favourable outcome of patients treated with eBEACOPP could not be improved by adding rituximab after positive PET-2.

Statistical analysis title	PET-2-negative study, non-inferiority test

Statistical analysis description:

The primary objective of the study in patients with negative PET-2 was to show non-inferiority of 4x eBEACOPP over combined 8/6x eBEACOPP. We defined non-inferiority as an absolute difference of 6% in the 5-year progression-free survival estimates. The trial was designed to perform a per-protocol analysis (excluding severe protocol deviations) with a power of 80%.

Comparison groups	Arm C: 8/6x eBEACOPP PET- v Arm D: 4x eBEACOPP PET-
Number of subjects included in analysis	920
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Difference in 5-year estimates
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	5.5

Notes:

[5] - Non-inferiority would be established if the lower limit of the 2-sided 95% CI for the difference in 5-year progression-free survival was above -6%.
As the 95% CI for the 5-year difference excluded the predefined non-inferiority margin of -6%, non-inferiority of the shorter regimen could be concluded.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs of CTCAE grades 3/4 were assessed on the therapy administration CRFs for the duration of chemotherapy. SAEs were additionally assessed on specific forms, from first dose until 28 days after last dose unless at least possibly related.

Adverse event reporting additional description:

Please note that SAEs may be reported twice, on the therapy administration CRF and again on the SAE form. Thus, the "non-serious" AEs and the SAEs might include duplicate events and do not add up to a total number of AEs.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups

Reporting group title	Arm A: 8x eBEACOPP PET+

Reporting group description:

Standard treatment for PET-2-positive patients pre amendment 2: 8x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy

Reporting group title	Arm B: 8x R-eBEACOPP PET+

Reporting group description:

Experimental treatment for PET-2-positive patients pre amendment 2: 8x R-eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy

Reporting group title	Arm A6: 6x eBEACOPP PET+

Reporting group description:

Standard treatment for PET-2-positive patients post amendment 2: 6x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy

Reporting group title	Arm C: 8/6x eBEACOPP PET-

Reporting group description:

Standard treatment for PET-2-negative patients: 8x eBEACOPP pre amendment 2, 6x eBEACOPP post amendment 2, each in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy

Reporting group title	Arm D: 4x eBEACOPP PET-

Reporting group description:

Experimental treatment for PET-2-negative patients: 4x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy

Reporting group title	Arm 0: Non-randomized patients

Reporting group description:

In HD18, patients were randomized after the second cycle of eBEACOPP. Thus, also non-randomized patients might have received study treatment and were analyzed for safety. Out of 137 non-randomized patients, 102 have received study treatment.

Serious adverse events	Arm A: 8x eBEACOPP PET+	Arm B: 8x R-eBEACOPP PET+	Arm A6: 6x eBEACOPP PET+
Total subjects affected by serious adverse events			
subjects affected / exposed	101 / 219 (46.12%)	95 / 220 (43.18%)	194 / 509 (38.11%)
number of deaths (all causes)	9	17	15

number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 219 (1.83%)	1 / 220 (0.45%)	2 / 509 (0.39%)
occurrences causally related to treatment / all	4 / 4	1 / 1	2 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Vascular disorders			
Vascular disorders			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 219 (3.20%)	10 / 220 (4.55%)	17 / 509 (3.34%)
occurrences causally related to treatment / all	6 / 8	7 / 10	15 / 19
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Surgical and medical procedures			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 219 (0.91%)	0 / 220 (0.00%)	0 / 509 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General disorders and administration site conditions			
alternative assessment type: Systematic			
subjects affected / exposed	22 / 219 (10.05%)	17 / 220 (7.73%)	27 / 509 (5.30%)
occurrences causally related to treatment / all	23 / 26	17 / 19	23 / 28
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Immune system disorders			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 219 (0.91%)	1 / 220 (0.45%)	7 / 509 (1.38%)
occurrences causally related to treatment / all	1 / 2	0 / 1	4 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			

Reproductive system and breast disorders			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 219 (0.00%)	0 / 220 (0.00%)	1 / 509 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 219 (2.74%)	9 / 220 (4.09%)	8 / 509 (1.57%)
occurrences causally related to treatment / all	6 / 6	8 / 9	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychiatric disorders			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 219 (0.91%)	3 / 220 (1.36%)	3 / 509 (0.59%)
occurrences causally related to treatment / all	2 / 2	3 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Investigations			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 219 (1.37%)	0 / 220 (0.00%)	3 / 509 (0.59%)
occurrences causally related to treatment / all	3 / 3	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Injury, poisioning and procedural complications			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 219 (0.46%)	2 / 220 (0.91%)	1 / 509 (0.20%)
occurrences causally related to treatment / all	0 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac disorders			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 219 (0.00%)	3 / 220 (1.36%)	4 / 509 (0.79%)
occurrences causally related to treatment / all	0 / 0	3 / 4	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Nervous system disorders			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 219 (0.91%)	4 / 220 (1.82%)	6 / 509 (1.18%)
occurrences causally related to treatment / all	1 / 2	3 / 4	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
alternative assessment type: Systematic			
subjects affected / exposed	42 / 219 (19.18%)	37 / 220 (16.82%)	78 / 509 (15.32%)
occurrences causally related to treatment / all	54 / 56	48 / 50	98 / 98
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Ear and labyrinth disorders			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 219 (0.00%)	1 / 220 (0.45%)	0 / 509 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye disorders			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 219 (0.00%)	0 / 220 (0.00%)	0 / 509 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal disorders			
alternative assessment type: Systematic			
subjects affected / exposed	17 / 219 (7.76%)	12 / 220 (5.45%)	24 / 509 (4.72%)
occurrences causally related to treatment / all	17 / 18	11 / 13	22 / 29
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Hepatobiliary disorders			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 219 (0.46%)	1 / 220 (0.45%)	0 / 509 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 219 (1.37%)	2 / 220 (0.91%)	3 / 509 (0.59%)
occurrences causally related to treatment / all	3 / 3	2 / 2	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal and urinary disorders			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 219 (1.37%)	1 / 220 (0.45%)	1 / 509 (0.20%)
occurrences causally related to treatment / all	1 / 3	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Endocrine disorders			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 219 (0.00%)	0 / 220 (0.00%)	1 / 509 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 219 (1.83%)	6 / 220 (2.73%)	13 / 509 (2.55%)
occurrences causally related to treatment / all	1 / 5	2 / 6	4 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infections and infestations			
alternative assessment type: Systematic			

subjects affected / exposed	31 / 219 (14.16%)	36 / 220 (16.36%)	77 / 509 (15.13%)
occurrences causally related to treatment / all	36 / 37	43 / 43	91 / 92
deaths causally related to treatment / all	1 / 1	3 / 3	0 / 0
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 219 (0.46%)	0 / 220 (0.00%)	1 / 509 (0.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm C: 8/6x eBEACOPP PET-	Arm D: 4x eBEACOPP PET-	Arm 0: Non-randomized patients
Total subjects affected by serious adverse events			
subjects affected / exposed	190 / 507 (37.48%)	147 / 502 (29.28%)	39 / 102 (38.24%)
number of deaths (all causes)	29	11	9
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 507 (0.79%)	4 / 502 (0.80%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	3 / 4	4 / 4	1 / 1
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Vascular disorders			
Vascular disorders			
alternative assessment type: Systematic			
subjects affected / exposed	26 / 507 (5.13%)	18 / 502 (3.59%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	22 / 29	15 / 20	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Surgical and medical procedures			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 507 (0.39%)	0 / 502 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

General disorders and administration site conditions			
alternative assessment type: Systematic			
subjects affected / exposed	26 / 507 (5.13%)	27 / 502 (5.38%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	30 / 31	26 / 28	2 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Immune system disorders			
Immune system disorders			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 507 (1.58%)	4 / 502 (0.80%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	7 / 8	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Reproductive system and breast disorders			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 507 (0.00%)	1 / 502 (0.20%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
alternative assessment type: Systematic			
subjects affected / exposed	22 / 507 (4.34%)	4 / 502 (0.80%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	20 / 23	3 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Psychiatric disorders			
Psychiatric disorders			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 507 (0.00%)	3 / 502 (0.60%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Investigations			
alternative assessment type: Systematic			

subjects affected / exposed	4 / 507 (0.79%)	5 / 502 (1.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	4 / 4	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Injury, poisioning and procedural complications			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 507 (0.20%)	2 / 502 (0.40%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac disorders			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 507 (1.18%)	3 / 502 (0.60%)	3 / 102 (2.94%)
occurrences causally related to treatment / all	7 / 7	2 / 6	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Nervous system disorders			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 507 (1.38%)	3 / 502 (0.60%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	7 / 7	2 / 4	2 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
alternative assessment type: Systematic			
subjects affected / exposed	68 / 507 (13.41%)	65 / 502 (12.95%)	10 / 102 (9.80%)
occurrences causally related to treatment / all	83 / 84	79 / 79	11 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Ear and labyrinth disorders			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 507 (0.00%)	0 / 502 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
Eye disorders			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 507 (0.00%)	0 / 502 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal disorders			
alternative assessment type: Systematic			
subjects affected / exposed	33 / 507 (6.51%)	15 / 502 (2.99%)	4 / 102 (3.92%)
occurrences causally related to treatment / all	35 / 35	13 / 15	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatobiliary disorders			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 507 (0.00%)	0 / 502 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 507 (1.18%)	2 / 502 (0.40%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	7 / 10	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal and urinary disorders			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 507 (0.39%)	5 / 502 (1.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	2 / 2	3 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Endocrine disorders			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 507 (0.00%)	0 / 502 (0.00%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
alternative assessment type: Systematic			
subjects affected / exposed	11 / 507 (2.17%)	7 / 502 (1.39%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	3 / 12	1 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infections and infestations			
alternative assessment type: Systematic			
subjects affected / exposed	67 / 507 (13.21%)	29 / 502 (5.78%)	18 / 102 (17.65%)
occurrences causally related to treatment / all	72 / 77	29 / 31	18 / 18
deaths causally related to treatment / all	5 / 5	0 / 0	5 / 5
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 507 (0.39%)	0 / 502 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm A: 8x eBEACOPP PET+	Arm B: 8x R-eBEACOPP PET+	Arm A6: 6x eBEACOPP PET+
Total subjects affected by non-serious adverse events			
subjects affected / exposed	214 / 219 (97.72%)	213 / 220 (96.82%)	486 / 509 (95.48%)
Nervous system disorders			
Nervous system disorder			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[1]	20 / 218 (9.17%)	21 / 220 (9.55%)	49 / 505 (9.70%)
occurrences (all)	38	36	87
Blood and lymphatic system disorders			

Leukopenia			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[2]	207 / 218 (94.95%)	211 / 220 (95.91%)	470 / 505 (93.07%)
occurrences (all)	1054	1128	1933
Anaemia			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[3]	115 / 218 (52.75%)	134 / 220 (60.91%)	261 / 505 (51.68%)
occurrences (all)	315	382	622
Thrombocytopenia			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[4]	158 / 218 (72.48%)	167 / 220 (75.91%)	327 / 505 (64.75%)
occurrences (all)	532	606	1023
Gastrointestinal disorders			
Nausea or vomiting			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[5]	19 / 218 (8.72%)	22 / 220 (10.00%)	33 / 505 (6.53%)
occurrences (all)	25	50	53
Mucositis			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[6]	20 / 218 (9.17%)	16 / 220 (7.27%)	25 / 505 (4.95%)
occurrences (all)	30	23	27
Infections and infestations			
Infection			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[7]	51 / 218 (23.39%)	43 / 220 (19.55%)	56 / 505 (11.09%)
occurrences (all)	67	57	69

Non-serious adverse events	Arm C: 8/6x eBEACOPP PET-	Arm D: 4x eBEACOPP PET-	Arm 0: Non-randomized patients
Total subjects affected by non-serious adverse events			
subjects affected / exposed	491 / 507 (96.84%)	461 / 502 (91.83%)	89 / 102 (87.25%)
Nervous system disorders			
Nervous system disorder			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[1]	52 / 505 (10.30%)	17 / 499 (3.41%)	0 / 84 (0.00%)
occurrences (all)	96	25	0
Blood and lymphatic system disorders			

Leukopenia			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[2]	469 / 505 (92.87%)	439 / 499 (87.98%)	66 / 84 (78.57%)
occurrences (all)	2249	1296	110
Anaemia			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[3]	276 / 505 (54.65%)	195 / 499 (39.08%)	18 / 84 (21.43%)
occurrences (all)	662	345	25
Thrombocytopenia			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[4]	364 / 505 (72.08%)	286 / 499 (57.31%)	36 / 84 (42.86%)
occurrences (all)	1360	617	48
Gastrointestinal disorders			
Nausea or vomiting			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[5]	49 / 505 (9.70%)	32 / 499 (6.41%)	9 / 84 (10.71%)
occurrences (all)	83	42	10
Mucositis			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[6]	39 / 505 (7.72%)	28 / 499 (5.61%)	7 / 84 (8.33%)
occurrences (all)	56	38	8
Infections and infestations			
Infection			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[7]	75 / 505 (14.85%)	40 / 499 (8.02%)	11 / 84 (13.10%)
occurrences (all)	104	51	11

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: Non-serious AEs were documented on the same CRF reporting treatment administration. This CRF is missing in a small number of patients. As we do not have any information on (non-serious) AEs in these patients, they have been excluded from the "exposed" cohort.

[2] - 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: Non-serious AEs were documented on the same CRF reporting treatment administration. This CRF is missing in a small number of patients. As we do not have any information on (non-serious) AEs in these patients, they have been excluded from the "exposed" cohort.

[3] - 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: Non-serious AEs were documented on the same CRF reporting treatment administration. This CRF is missing in a small number of patients. As we do not have any information on (non-serious) AEs in these patients, they have been excluded from the "exposed" cohort.

[4] - 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: Non-serious AEs were documented on the same CRF reporting treatment administration. This CRF is missing in a small number of patients. As we do not have any information on (non-serious) AEs in these patients, they have been excluded from the "exposed" cohort.
[5] - 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: Non-serious AEs were documented on the same CRF reporting treatment administration. This CRF is missing in a small number of patients. As we do not have any information on (non-serious) AEs in these patients, they have been excluded from the "exposed" cohort.
[6] - 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: Non-serious AEs were documented on the same CRF reporting treatment administration. This CRF is missing in a small number of patients. As we do not have any information on (non-serious) AEs in these patients, they have been excluded from the "exposed" cohort.
[7] - 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: Non-serious AEs were documented on the same CRF reporting treatment administration. This CRF is missing in a small number of patients. As we do not have any information on (non-serious) AEs in these patients, they have been excluded from the "exposed" cohort.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2009	Implementation of additional PET for PET-2-negative patients with residual lesions after end of chemotherapy; introduction of obligatory prephase treatment with dexamethasone for patients older than 40 years and extended prophylaxis
22 September 2011	Implementation of the results of the preceding GHSG HD15 trial: Therapy in the standard arms A and C was changed from 8 to 6 cycles eBEACOPP. Randomization for patients with positive PET-2 was stopped because the required sample size for superiority test was reached and PET-2-positive patients were subsequently treated with standard of 6x eBEACOPP.
21 December 2012	Recruitment of 500 additional patients in order to reach sufficient power for the analysis of PET-2-negative patients; current information regarding adjuvant medication (Levofloxacin) was taken into account.
14 April 2014	Adaption of the reference level for the evaluation of PET for radiotherapy recommendation
11 September 2017	Enable the documentation of follow-up data of all patients until the global end of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 October 2012	Originally planned recruitment completed on 19-Oct-2012. Reassessment of assumptions - another 500 patients required in order to analyze the study question for PET-2-negative patients with sufficient power. Recruitment paused until amendment was approved.	24 January 2013

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28236583

http://www.ncbi.nlm.nih.gov/pubmed/29061295