Clinical trial results:
HD17 for Intermediate Stage Hodgkin Lymphoma - Treatment Optimization Trial in the First-Line Treatment of intermediate Stage Hodgkin lymhoma; Therapy stratification by means of FDG-PET

Summary

EudraCT number	2007-005920-34
Trial protocol	DE NL AT
Global end of trial date	21 March 2020

Results information

Result version number	v1 (current)
This version publication date	24 March 2021
First version publication date	24 March 2021

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-1014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01356680
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus Magnus-Platz, Köln, Germany, 50923
Public contact	German Hodgkin Study Group (GHSG), Trial Coordination Center of the German Hodgkin Study Group (GHSG), 0049 22147888200, ghsg@uk-koeln.de
Scientific contact	German Hodgkin Study Group (GHSG), Trial Coordination Center of the 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	30 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 March 2020
Global end of trial reached?	Yes
Global end of trial date	21 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the HD17 trial was to individualize the treatment of patients with intermediate-stage Hodgkin lymphoma (HL) by PET-guided treatmet, omitting radiotherapy in PET-negative patients after completion of 4 chemotherapy cycles (PET4). The primary objective of the study was to show non-inferiority of the PET-guided strategy in terms of progression-free survival (PFS). The second objective of the study was to confirm PET4-positivity as risk factor for PFS in patients treated with combined modality treatment (CMT).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2012
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	Switzerland: 84
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Austria: 45
Country: Number of subjects enrolled	Germany: 963
Worldwide total number of subjects	1100
EEA total number of subjects	1016

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)	1100
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 13 January 2012 and 21 March 2017, 1100 patients were recruited in 224 trial sites in 4 European countries.

Pre-assignment

Screening details:

Main entry criteria were histologically proven primary Hodgkin lymphoma (HL), clinical stages (CS) IA, IB, or IIA with pre-defined risk factor, ECOG performance status <= 2, and age at study entry 18-60 years.

Period 1

Period 1 title	Randomization
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Patients and investigators as well as the central response assessment committee were masked to treatment allocation until central review of the PET4 examination had been completed.

Arms

Are arms mutually exclusive?	Yes
Arm title	A: Standard CMT

Arm description:

Standard CMT = combined modality treatment (chemotherapy followed by consolidating radiotherapy)

Patients randomized to arm A were assigned to receive 2+2 chemotherapy (2 cycles eBEACOPP followed by 2 cycles ABVD) and 30 Gy IFRT (involved-field radiotherapy)

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	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/m2 BSA on days 1-3 of each eBEACOPP 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 eBEACOPP 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 eBEACOPP 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 on day 8 of each eBEACOPP 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 on days 1-7 of each eBEACOPP 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 eBEACOPP cycle

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

Dosage and administration details:
25 mg/m2 BSA on days 1+15 of each ABVD cycle

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

Dosage and administration details:
6 mg/m2 BSA on days 1+15 of each ABVD cycle

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	DTIC

Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m2 BSA on days 1+15 of each ABVD cycle

Arm title	B: PET4-stratified treatment

Arm description:

PET4-stratified treatment= chemotherapy only in case of PET4-negativity and standard CMT in case of PET4-positivity at the restaging after chemotherapy

Patients randomized to arm B were assigned to receive standard 2+2 chemotherapy (2 cycles eBEACOPP followed by 2 cycles ABVD) and - in case of PET4-positivity - followed by consolidating 30 GY INRT (involved-node radiotherapy).

PET4-positivity was defined as Deauville score (DS) 3 or 4 at the PET/CT-based restaging 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	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/m2 BSA on days 1-3 of each eBEACOPP 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 eBEACOPP 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 eBEACOPP 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 on day 8 of each eBEACOPP 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 on days 1-7 of each eBEACOPP 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 eBEACOPP cycle

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 days 1+15 of each ABVD 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:
25 mg/m2 BSA on days 1+15 of each ABVD cycle

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

Dosage and administration details:
6 mg/m2 BSA on days 1+15 of each ABVD cycle

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

Dosage and administration details:
375 mg/m2 BSA on days 1+15 of each ABVD cycle

Number of subjects in period 1	A: Standard CMT	B: PET4-stratified treatment
Started	548	552
Completed	546	550
Not completed	2	2
withdrawal before start of treatment	1	1
Hodgkin lymphoma diagnosis disconfirmed	1	1

Period 2

Period 2 title	ITT
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	A: Standard CMT

Arm description:

Standard CMT = combined modality treatment (chemotherapy followed by consolidating radiotherapy) Patients randomized to arm A were assigned to receive 2+2 chemotherapy (2 cycles eBEACOPP followed by 2 cycles ABVD) and 30 Gy IFRT (involved-field radiotherapy)

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	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/m2 BSA on days 1-3 of each eBEACOPP 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 eBEACOPP 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 eBEACOPP 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 on day 8 of each eBEACOPP 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 on days 1-7 of each eBEACOPP 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 eBEACOPP cycle	
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	Doxorubicine
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 25 mg/m2 BSA on days 1+15 of each ABVD cycle	
Investigational medicinal product name	Vinblastine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: 6 mg/m2 BSA on days 1+15 of each ABVD cycle	
Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	DTIC
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:	
375 mg/m2 BSA on days 1+15 of each ABVD cycle	

Arm title	B: PET4-stratified treatment

Arm description:

PET4-stratified treatment= chemotherapy only in case of PET4-negativity and standard CMT in case of PET4-positivity at the restaging after chemotherapy

Patients randomized to arm B were assigned to receive standard 2+2 chemotherapy (2 cycles eBEACOPP followed by 2 cycles ABVD) and - in case of PET4-positivity - followed by consolidating 30 GY INRT (involved-node radiotherapy).
PET4-positivity was defined as Deauville score (DS) 3 or 4 at the PET/CT-based restaging 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	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
200 mg/m2 BSA on days 1-3 of each eBEACOPP 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 eBEACOPP 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 eBEACOPP 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 on day 8 of each eBEACOPP 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 on days 1-7 of each eBEACOPP 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 eBEACOPP cycle

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 days 1+15 of each ABVD 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:

25 mg/m2 BSA on days 1+15 of each ABVD cycle

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

Dosage and administration details:

6 mg/m2 BSA on days 1+15 of each ABVD cycle

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

Dosage and administration details:

375 mg/m2 BSA on days 1+15 of each ABVD cycle

Notes:

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

Justification: Randomized patients with disconfirmed HL or who did not start study treatment were excluded from all analyses and are not reported.

Number of subjects in period 2[2]	A: Standard CMT	B: PET4-stratified treatment
Started	546	550
Completed	428	477
Not completed	118	73
Adverse event, serious fatal	-	1
acute toxicity of chemotherapy	2	1
early-stage or advanced-stage HL	49	39
violation of other inclusion criteria	2	2
no PET4 for other reasons	5	11
Protocol deviation	60	19

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: Patients with disconfirmed HL diagnosis and those who did not receive any study treatment were excluded from all analyses are not reported in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	A: Standard CMT
Reporting group description:	
Standard CMT = combined modality treatment (chemotherapy followed by consolidating radiotherapy) Patients randomized to arm A were assigned to receive 2+2 chemotherapy (2 cycles eBEACOPP followed by 2 cycles ABVD) and 30 Gy IFRT (involved-field radiotherapy)	
Reporting group title	B: PET4-stratified treatment
Reporting group description:	
PET4-stratified treatment= chemotherapy only in case of PET4-negativity and standard CMT in case of PET4-positivity at the restaging after chemotherapy Patients randomized to arm B were assigned to receive standard 2+2 chemotherapy (2 cycles eBEACOPP followed by 2 cycles ABVD) and - in case of PET4-positivity - followed by consolidating 30 GY INRT (involved-node radiotherapy). PET4-positivity was defined as Deauville score (DS) 3 or 4 at the PET/CT-based restaging after chemotherapy.	

Reporting group values	A: Standard CMT	B: PET4-stratified treatment	Total
Number of subjects	546	550	1096
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)	546	550	1096
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	294	294	588
Male	252	256	508
Ann Arbor Stage Units: Subjects			
IA	20	18	38
IB	18	12	30
IIA	374	376	750
IIB	134	143	277
IIIA	0	1	1
ECOG Performance Units: Subjects			
ECOG: 0	448	444	892
ECOG:1	98	102	200
ECOG: 2	0	4	4
ECOG: >2	0	0	0
Large mediastinal mass			

Units: Subjects			
No	448	449	897
Yes	98	101	199
Elevated erythrocyte sedimentation rate Units: Subjects			
No	303	298	601
Yes	243	252	495
>= 3 nodal areas involved Units: Subjects			
No	153	150	303
Yes	393	400	793
Infra-diaphragmatic disease Units: Subjects			
No	511	517	1028
Yes	35	33	68
Bulky disease Units: Subjects			
No	263	245	508
Yes	283	305	588
Histologic subtype Units: Subjects			
Nodular sclerosis	210	211	421
Mixed cellularity	54	46	100
Lymphocyte-depleted	1	0	1
Lymphocyte-rich	8	7	15
unspecified classical HL	59	52	111
Nodular lymphocyte-predominant HL	7	7	14
not recorded	207	227	434

End points

End points reporting groups

Reporting group title	A: Standard CMT

Reporting group description:

Standard CMT = combined modality treatment (chemotherapy followed by consolidating radiotherapy)

Patients randomized to arm A were assigned to receive 2+2 chemotherapy (2 cycles eBEACOPP followed by 2 cycles ABVD) and 30 Gy IFRT (involved-field radiotherapy)

Reporting group title	B: PET4-stratified treatment

Reporting group description:

PET4-stratified treatment= chemotherapy only in case of PET4-negativity and standard CMT in case of PET4-positivity at the restaging after chemotherapy

Patients randomized to arm B were assigned to receive standard 2+2 chemotherapy (2 cycles eBEACOPP followed by 2 cycles ABVD) and - in case of PET4-positivity - followed by consolidating 30 GY INRT (involved-node radiotherapy).

PET4-positivity was defined as Deauville score (DS) 3 or 4 at the PET/CT-based restaging after chemotherapy.

Reporting group title	A: Standard CMT

Reporting group description:

Standard CMT = combined modality treatment (chemotherapy followed by consolidating radiotherapy)
Patients randomized to arm A were assigned to receive 2+2 chemotherapy (2 cycles eBEACOPP followed by 2 cycles ABVD) and 30 Gy IFRT (involved-field radiotherapy)

Reporting group title	B: PET4-stratified treatment

Reporting group description:

PET4-stratified treatment= chemotherapy only in case of PET4-negativity and standard CMT in case of PET4-positivity at the restaging after chemotherapy

Patients randomized to arm B were assigned to receive standard 2+2 chemotherapy (2 cycles eBEACOPP followed by 2 cycles ABVD) and - in case of PET4-positivity - followed by consolidating 30 GY INRT (involved-node radiotherapy).
PET4-positivity was defined as Deauville score (DS) 3 or 4 at the PET/CT-based restaging after chemotherapy.

Subject analysis set title	Arm A (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

Arm A: standard combined modality treatment (PP)

Subject analysis set title	Arm B (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

Arm B: experimental PET4-stratified treatment

Subject analysis set title	Arm A - PET4-negative (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

Arm A: standard CMT (2+2 chemotherapy followed by consolidating 30 Gy IF-RT)

Subject analysis set title	Arm B - PET4-negative (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

Arm B: experimental treatment omitting consolidating radiotherapy for PET4-negative patients

Subject analysis set title	CMT PET4-negative (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

PET4-negative arm A patients: combined modality treatment
PET4-negativity was defined as Deauville Score (DS) <3 in the trial protocol.

Subject analysis set title	CMT PET4-positive (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All PET4-positive patients. All received combined modality treatment.
Arm A: 2+2 followed by 30 Gy IF-RT
Arm B: 2+2 followed by 30 Gy IN-RT

PET4-positivity was defined as Deauville Score (DS) 3 or 4 in the trial protocol.

Primary: Progression-free survival (PFS) - PP analysis

End point title	Progression-free survival (PFS) - PP analysis

End point description:

This is a per-protocol analysis of Progression-free survival (PFS). Patients without regular PET4 review or with protocol violation after the PET4 result had been documented where excluded. PFS was defined as the time from study entry until progression, relapse, or death from any cause. If none of these events had occurred, PFS was censored at the date of last information on disease status. PFS 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 was months. 5-year estimates and the rspective 95% CIs will be reported.

End point type	Primary

End point timeframe:

5 years

End point values	Arm A (PP)	Arm B (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	435[1]	479[2]		
Units: percent				
number (confidence interval 95%)	97.4 (95.0 to 98.7)	94.5 (91.5 to 96.5)		

Notes:

[1] - Patients in arm A received standard CMT (2 x eBEACOPP + 2 x ABVD, followed by 30 Gy IF-RT)

[2] - PET4-stratified treatment (2+2 chemotherapy for all. Omission of 30 Gy IN-RT if PET4-negative)

Statistical analyses

Statistical analysis title	Non-inferiority test

Statistical analysis description:

Non-inferiority would be established if the lower limit of the 2-sided 95%-CI for the difference in 5-year PFS was above -8%.

Comparison groups	Arm A (PP) v Arm B (PP)
Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Difference in 5-year estimates
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	0.1

Notes:

[3] - Non-inferiority would be established if the lower limit of the 2-sided 95%-CI for the difference in 5-year PFS was above -8%.
As the 95%-CI for the 5-year difference excluded the pedefined non-inferiority margin of -8%, non-inferiority of the PET4-stratified treatment strategy could be concluded

Primary: Progression-free survival (PFS)- PP analysis of PET4-negative patients

End point title	Progression-free survival (PFS)- PP analysis of PET4-negative patients

End point description:

The second primary objective of the trial was to demonstrate non-inferiority of 2+2-chemotherapy over combined modality treatment (2+2 + IF-RT) for patients with a complete metabolic response after chemotherapy (PET4-negative patients).

End point type	Primary

End point timeframe:

5-years

End point values	Arm A - PET4-negative (PP)	Arm B - PET4-negative (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	318	333		
Units: percent				
number (confidence interval 95%)	97.9 (94.9 to 99.1)	94.9 (91.2 to 97.0)		

Statistical analyses

Statistical analysis title	Non-inferiority test for PET4-negative patients
Comparison groups	Arm A - PET4-negative (PP) v Arm B - PET4-negative (PP)
Number of subjects included in analysis	651
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Difference in 5-year estimates
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	0.3

Notes:

[4] - As the 95%-CI for the 5-year difference excluded the predefined non-inferiority margin of -8%, non-inferiority of 2+2 over CMT could be concluded for PET4-negative patients

Primary: Progression-free survival (PFS) - ITT analysis of CMT-treated patients

End point title	Progression-free survival (PFS) - ITT analysis of CMT-treated patients

End point description:

The third primary objective of the trial was do demonstrate the negative-prognostic value of PET4-positivity in an ITT-analysis of all PET4-positive arm A and arm B patients and PET-negative arm B patients (all assigned to combined modality treatment).

End point type	Primary

End point timeframe:

5-years

End point values	CMT PET4-negative (ITT)	CMT PET4-positive (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	318	328		
Units: percent				
number (confidence interval 95%)	97.9 (94.9 to 99.1)	94.7 (91.0 to 96.9)		

Statistical analyses

Statistical analysis title	Comparison of PET4-negative and PET4-positive pts.
Comparison groups	CMT PET4-negative (ITT) v CMT PET4-positive (ITT)
Number of subjects included in analysis	646
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.01
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	9

Notes:

[5] - Kaplan-Meier analysis of PFS-curves : Comparison of PET4-positive and PET4-negative patients treated with 2+2 followed by consolidating radiotherapy.

Secondary: Progression-free survival (PFS) - ITT analysis

End point title	Progression-free survival (PFS) - ITT analysis

End point description:

This is an intention-to treat analysis of Progression-free survival (PFS) which was defined as the time from study entry until progression, relapse, or death from any cause. If none of these events had occurred, PFS was censored at the date of last information on disease status. PFS 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 was 52 months. 5-year estimates and the respective 95% CIs will be reported.

End point type	Secondary

End point timeframe:

5 years

End point values	A: Standard CMT	B: PET4-stratified treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	546[6]	550[7]		
Units: percent				
number (confidence interval 95%)	96.7 (94.4 to 98.0)	94.0 (91.2 to 95.9)		

Notes:

[6] - ITT analysis

[7] - ITT

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs of CTCAE grades 3/4 were assessed on the therapy administraion CRFs for the duration of chemotherapy. SAEs were addditionally 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 administraion 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 - Safety Set

Reporting group description:

Patients randomized to standard treatment (2+2 chemotherapy + 30 Gy IF-RT).
Patients with disconfirmed HL diagnosis or without documented chemotherapy-CRF were excluded from analysis.

Reporting group title	Arm B - Safety set

Reporting group description:

Patients randomized to PET4-stratified treatment (2+2 chemotherapy followed by 30Gy INRT only in case of PET4-positivity).
Patients with disconfirmed HL diagnosis or without documented chemotherapy-CRF were excluded from analysis.

Serious adverse events	Arm A - Safety Set	Arm B - Safety set	
Total subjects affected by serious adverse events			
subjects affected / exposed	161 / 544 (29.60%)	164 / 543 (30.20%)	
number of deaths (all causes)	5	5	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 544 (0.18%)	0 / 543 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular disorders			
alternative assessment type: Systematic			

subjects affected / exposed	11 / 544 (2.02%)	18 / 543 (3.31%)	
occurrences causally related to treatment / all	11 / 12	14 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medicalprocedures			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 544 (0.55%)	0 / 543 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General disorders and administration site conditions			
alternative assessment type: Systematic			
subjects affected / exposed	39 / 544 (7.17%)	37 / 543 (6.81%)	
occurrences causally related to treatment / all	40 / 44	36 / 38	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Immune system disorder			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 544 (0.92%)	5 / 543 (0.92%)	
occurrences causally related to treatment / all	4 / 5	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
alternative assessment type: Systematic			
subjects affected / exposed	9 / 544 (1.65%)	8 / 543 (1.47%)	
occurrences causally related to treatment / all	10 / 11	8 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychiatric disorder			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 544 (0.37%)	1 / 543 (0.18%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Investigations			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 544 (1.29%)	7 / 543 (1.29%)	
occurrences causally related to treatment / all	5 / 7	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 544 (1.10%)	1 / 543 (0.18%)	
occurrences causally related to treatment / all	2 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 544 (1.10%)	2 / 543 (0.37%)	
occurrences causally related to treatment / all	5 / 7	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorders			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 544 (0.92%)	4 / 543 (0.74%)	
occurrences causally related to treatment / all	4 / 5	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
alternative assessment type: Systematic			
subjects affected / exposed	56 / 544 (10.29%)	64 / 543 (11.79%)	
occurrences causally related to treatment / all	74 / 76	82 / 82	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorder			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 544 (0.00%)	1 / 543 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorder			
alternative assessment type: Systematic			
subjects affected / exposed	37 / 544 (6.80%)	36 / 543 (6.63%)	
occurrences causally related to treatment / all	39 / 46	38 / 43	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disorder			
subjects affected / exposed	1 / 544 (0.18%)	0 / 543 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 544 (0.18%)	3 / 543 (0.55%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 544 (0.18%)	2 / 543 (0.37%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 544 (1.29%)	9 / 543 (1.66%)	
occurrences causally related to treatment / all	1 / 10	3 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Infections and infestations			
alternative assessment type: Systematic			
subjects affected / exposed	28 / 544 (5.15%)	36 / 543 (6.63%)	
occurrences causally related to treatment / all	32 / 35	37 / 38	
deaths causally related to treatment / all	0 / 0	1 / 1	
Metabolism and nutrition disorders			
Metabolism and nutrion disorders			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 544 (0.18%)	0 / 543 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Arm A - Safety Set	Arm B - Safety set	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	455 / 544 (83.64%)	455 / 543 (83.79%)	
Blood and lymphatic system disorders			
Leukopenia			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[1]	436 / 531 (82.11%)	444 / 530 (83.77%)	
occurrences (all)	1006	1027	
Anemia			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[2]	46 / 531 (8.66%)	64 / 530 (12.08%)	
occurrences (all)	63	89	
Thrombocytopenia			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[3]	139 / 531 (26.18%)	176 / 530 (33.21%)	
occurrences (all)	208	265	
Gastrointestinal disorders			
Nausea/Vomiting			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[4]	38 / 531 (7.16%)	29 / 530 (5.47%)	
occurrences (all)	52	33	

Infections and infestations			
Infection			
alternative dictionary used: NCI CTCAE 3.0			
subjects affected / exposed[5]	32 / 531 (6.03%)	40 / 530 (7.55%)	
occurrences (all)	33	43	

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 habe been excluded from te "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 for 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 for 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 for 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 for 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
24 July 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? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33539742