Clinical trial results:
HD16 for early stages in Hodgkins Lymphoma

Summary

EudraCT number	2007-004474-24
Trial protocol	DE NL AT
Global end of trial date	29 December 2020

Results information

Result version number	v1 (current)
This version publication date	02 September 2021
First version publication date	02 September 2021

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-987

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00736320
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	06 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The HD16 trial had 2 co-primary objectives regarding the treatment of early-stage favorable Hodgkin lymphoma (HL). The first question addressed whether radiotherapy could be omitted from standard combined-modality treatment (CMT) in patients with a negative PET after 2 cycles of ABVD (PET-2) without a clinically relevant loss of tumor control in terms of non-inferior progression-free survival (PFS). Second, the HD16 trial aimed to assess whether a positive PET-2 represented a risk factor for PFS among patients treated with CMT.

Protection of trial subjects:

Written informed consent before study entry, frequent IDMC monitoring, central expert review of PET-2

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 November 2009
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: 19
Country: Number of subjects enrolled	Austria: 43
Country: Number of subjects enrolled	Germany: 1025
Country: Number of subjects enrolled	Switzerland: 63
Worldwide total number of subjects	1150
EEA total number of subjects	1087

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)	1079
From 65 to 84 years	71
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 25 Nov 2009 and 29 Dec 2015, 1150 patients were enrolled in 250 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, IIA, or IIB without pre-defined risk factors, ECOG performance status <= 2, and age at study entry 18-75 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, Data analyst, Assessor

Blinding implementation details:

Patients and investigators as well as the central response assessment panel and data analysts were masked to treatment allocation until central review of the PET-2 examination had been completed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard CMT

Arm description:

Standard combined-modality treatment (CMT): Patients randomized to this arm were assigned to receive 2 cycles of ABVD chemotherapy followed by centrally reviewed PET/CT-based restaging (PET-2) and 20 Gy involved-field radiotherapy (IF-RT).

Arm type	Active comparator
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

25 mg/m² BSA on day 1 and 15 of each 28-day cycle

Investigational medicinal product name	Bleomycin
Investigational medicinal product code	L01DC01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

10 mg/m² BSA on day 1 and 15 of each 28-day cycle

Investigational medicinal product name	Vinblastine
Investigational medicinal product code	L01CA01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

6 mg/m² BSA on day 1 and 15 of each 28-day cycle

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	L01AX04
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m² BSA on day 1 and 15 of each 28-day cycle

Arm title	PET-2-guided treatment

Arm description:

PET-2-guided treatment: Patients randomized to this arm were assigned to receive 2 cycles of ABVD chemotherapy followed by centrally reviewed PET/CT-based restaging (PET-2). Only in case of a positive PET-2 in terms of a Deauville score of 3 or higher, chemotherapy was followed by consolidating 20 Gy IF-RT.

Arm type	Experimental
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

25 mg/m² BSA on day 1 and 15 of each 28-day cycle

Investigational medicinal product name	Bleomycin
Investigational medicinal product code	L01DC01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

10 mg/m² BSA on day 1 and 15 of each 28-day cycle

Investigational medicinal product name	Vinblastine
Investigational medicinal product code	L01CA01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

6 mg/m² BSA on day 1 and 15 of each 28-day cycle

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	L01AX04
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m² BSA on day 1 and 15 of each 28-day cycle

Number of subjects in period 1	Standard CMT	PET-2-guided treatment
Started	575	575
Completed	573	566
Not completed	2	9
Consent withdrawn by subject	-	1
Disconfirmation of diagnosis	2	8

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, Data analyst, Assessor

Blinding implementation details:

Patients and investigators as well as the central response assessment panel and data analysts were masked to treatment allocation until central review of the PET-2 examination had been completed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard CMT

Arm description:

Standard combined-modality treatment (CMT): Patients randomized to this arm were assigned to receive 2 cycles of ABVD chemotherapy followed by centrally reviewed PET/CT-based restaging (PET-2) and 20 Gy involved-field radiotherapy (IF-RT).

Arm type	Active comparator
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

25 mg/m² BSA on day 1 and 15 of each 28-day cycle

Investigational medicinal product name	Bleomycin
Investigational medicinal product code	L01DC01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

10 mg/m² BSA on day 1 and 15 of each 28-day cycle

Investigational medicinal product name	Vinblastine
Investigational medicinal product code	L01CA01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

6 mg/m² BSA on day 1 and 15 of each 28-day cycle

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	L01AX04
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m² BSA on day 1 and 15 of each 28-day cycle

Arm title	PET-2-guided treatment

Arm description:

PET-2-guided treatment: Patients randomized to this arm were assigned to receive 2 cycles of ABVD chemotherapy followed by centrally reviewed PET/CT-based restaging (PET-2). Only in case of a positive PET-2 in terms of a Deauville score of 3 or higher, chemotherapy was followed by consolidating 20 Gy IF-RT.

Arm type	Experimental
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

25 mg/m² BSA on day 1 and 15 of each 28-day cycle

Investigational medicinal product name	Bleomycin
Investigational medicinal product code	L01DC01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

10 mg/m² BSA on day 1 and 15 of each 28-day cycle

Investigational medicinal product name	Vinblastine
Investigational medicinal product code	L01CA01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

6 mg/m² BSA on day 1 and 15 of each 28-day cycle

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	L01AX04
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m² BSA on day 1 and 15 of each 28-day 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 those who did not start study treatment were excluded from all analyses including baseline characteristics.

Number of subjects in period 2[2]	Standard CMT	PET-2-guided treatment
Started	573	566
Completed	501	506
Not completed	72	60
Consent withdrawn by subject	4	2
Protocol deviation	67	58
Lack of efficacy	1	-

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	Standard CMT
Reporting group description:	
Standard combined-modality treatment (CMT): Patients randomized to this arm were assigned to receive 2 cycles of ABVD chemotherapy followed by centrally reviewed PET/CT-based restaging (PET-2) and 20 Gy involved-field radiotherapy (IF-RT).	
Reporting group title	PET-2-guided treatment
Reporting group description:	
PET-2-guided treatment: Patients randomized to this arm were assigned to receive 2 cycles of ABVD chemotherapy followed by centrally reviewed PET/CT-based restaging (PET-2). Only in case of a positive PET-2 in terms of a Deauville score of 3 or higher, chemotherapy was followed by consolidating 20 Gy IF-RT.	

Reporting group values	Standard CMT	PET-2-guided treatment	Total
Number of subjects	573	566	1139
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)	543	528	1071
From 65-84 years	30	38	68
85 years and over	0	0	0
Age continuous Units: years			
median	38	37	
full range (min-max)	18 to 75	18 to 75	-
Gender categorical Units: Subjects			
Female	241	244	485
Male	332	322	654
Ann Arbor stage Units: Subjects			
IA	164	145	309
IB	24	22	46
IIA	358	367	725
IIB	27	32	59
ECOG performance status Units: Subjects			
ECOG 0	529	519	1048
ECOG 1	43	47	90
ECOG 2	1	0	1
Histologic subtype			

Units: Subjects			
Classical HL	433	409	842
Nodular lymphocyte-predominant HL	43	54	97
Not done	97	103	200

End points

End points reporting groups

Reporting group title	Standard CMT

Reporting group description:

Standard combined-modality treatment (CMT): Patients randomized to this arm were assigned to receive 2 cycles of ABVD chemotherapy followed by centrally reviewed PET/CT-based restaging (PET-2) and 20 Gy involved-field radiotherapy (IF-RT).

Reporting group title	PET-2-guided treatment

Reporting group description:

PET-2-guided treatment: Patients randomized to this arm were assigned to receive 2 cycles of ABVD chemotherapy followed by centrally reviewed PET/CT-based restaging (PET-2). Only in case of a positive PET-2 in terms of a Deauville score of 3 or higher, chemotherapy was followed by consolidating 20 Gy IF-RT.

Reporting group title	Standard CMT

Reporting group description:

Standard combined-modality treatment (CMT): Patients randomized to this arm were assigned to receive 2 cycles of ABVD chemotherapy followed by centrally reviewed PET/CT-based restaging (PET-2) and 20 Gy involved-field radiotherapy (IF-RT).

Reporting group title	PET-2-guided treatment

Reporting group description:

PET-2-guided treatment: Patients randomized to this arm were assigned to receive 2 cycles of ABVD chemotherapy followed by centrally reviewed PET/CT-based restaging (PET-2). Only in case of a positive PET-2 in terms of a Deauville score of 3 or higher, chemotherapy was followed by consolidating 20 Gy IF-RT.

Subject analysis set title	Standard CMT - PET-2-negative PP
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol population of patients assigned to the standard CMT group with negative PET-2 in terms of Deauville score 1-2. These patients received standard CMT with 2 cycles of ABVD chemotherapy and 20 Gy involved-field radiotherapy.

Subject analysis set title	PET-2-guided treatment - PET-2-negative PP
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol population of patients assigned to the PET-2-guided treatment group with negative PET-2 in terms of Deauville score 1-2. These patients received 2 cycles of ABVD chemotherapy alone.

Subject analysis set title	CMT cohort with negative PET-2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients with a negative PET-2 (in terms of a Deauville score of 1-2) assigned to receive CMT (i.e. only from the standard CMT group)

Subject analysis set title	CMT cohort with positive PET-2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients with a positive PET-2 in terms of a Deauville score of 3 or higher assigned to receive CMT (i.e. from both the standard CMT and PET-2-guided treatment groups)

Primary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival was defined as the time from completion of all staging examinations 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 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.

End point type	Primary

End point timeframe:

5 years

End point values	Standard CMT - PET-2-negative PP	PET-2-guided treatment - PET-2-negative PP	CMT cohort with negative PET-2	CMT cohort with positive PET-2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	328	300	353	340
Units: Percent				
number (confidence interval 95%)	94.2 (91.6 to 96.9)	86.7 (82.5 to 90.9)	94.0 (91.4 to 96.6)	90.3 (86.9 to 93.6)

Statistical analyses

Statistical analysis title	Non-inferiority of PET-2-guided treatment

Statistical analysis description:

Non-inferiority analysis regarding the omission of radiotherapy in patients with a negative PET-2: Non-inferiority of ABVD alone over standard CMT would be established if the upper limit of the 2-sided 95% CI for the hazard ratio was below the pre-defined non-inferiority margin of 3.01 in a per-protocol analysis of the PET-2-negative patient population. Hazard ratio and 95% CI were obtained from univariate Cox regression.

Comparison groups	PET-2-guided treatment - PET-2-negative PP v Standard CMT - PET-2-negative PP
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Hazard ratio (HR)
Point estimate	2.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	3.51

Statistical analysis title	Prognostic impact of PET-2

Statistical analysis description:

Analysis of the prognostic impact of PET-2: A two-sided log-rank test regarding progression-free survival on a significance level of 5% was to be performed comparing groups defined by PET-2 result (i.e. Deauville score 1-2 vs. Deauville score 3 or higher) among all patients assigned to receive CMT.

Comparison groups	CMT cohort with positive PET-2 v CMT cohort with negative PET-2

Number of subjects included in analysis	693
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.16
upper limit	3.32

Notes:

[1] - Sensitivity analysis: Cox regression model adjusted for the stratification factors age, sex, B symptoms, disease localization, albumin level and bulky disease, HR=1.96, 95% CI 1.16-3.32, p=0.012.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) of CTCAE grades 3/4 were assessed on the therapy administraion CRFs for the duration of study therapy. 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, non-serious AEs and 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	Standard CMT

Reporting group description:

Standard combined-modality treatment (CMT): Patients randomized to this arm were assigned to receive 2 cycles of ABVD chemotherapy followed by centrally reviewed PET/CT-based restaging (PET-2) and 20 Gy involved-field radiotherapy (IF-RT).

Reporting group title	PET-2-guided treatment

Reporting group description:

PET-2-guided treatment: Patients randomized to this arm were assigned to receive 2 cycles of ABVD chemotherapy followed by centrally reviewed PET/CT-based restaging (PET-2). Only in case of a positive PET-2 in terms of a Deauville score of 3 or higher, chemotherapy was followed by consolidating 20 Gy IF-RT.

Serious adverse events	Standard CMT	PET-2-guided treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	71 / 571 (12.43%)	51 / 561 (9.09%)	
number of deaths (all causes)	14	9	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified			
subjects affected / exposed	0 / 571 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	9 / 571 (1.58%)	10 / 561 (1.78%)	
occurrences causally related to treatment / all	8 / 9	11 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	21 / 571 (3.68%)	11 / 561 (1.96%)	
occurrences causally related to treatment / all	21 / 23	10 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Immune system disorderorders			
subjects affected / exposed	0 / 571 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	0 / 571 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	8 / 571 (1.40%)	5 / 561 (0.89%)	
occurrences causally related to treatment / all	6 / 8	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	2 / 571 (0.35%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Investigations			
subjects affected / exposed	1 / 571 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			

subjects affected / exposed	3 / 571 (0.53%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	1 / 571 (0.18%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	2 / 571 (0.35%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood and lymphatic disorders			
subjects affected / exposed	7 / 571 (1.23%)	5 / 561 (0.89%)	
occurrences causally related to treatment / all	6 / 7	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	11 / 571 (1.93%)	4 / 561 (0.71%)	
occurrences causally related to treatment / all	8 / 12	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	0 / 571 (0.00%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	1 / 571 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Endocrine disorders			

subjects affected / exposed	0 / 571 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	7 / 571 (1.23%)	3 / 561 (0.53%)	
occurrences causally related to treatment / all	3 / 7	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	10 / 571 (1.75%)	13 / 561 (2.32%)	
occurrences causally related to treatment / all	11 / 11	15 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	3 / 571 (0.53%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Standard CMT	PET-2-guided treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	156 / 571 (27.32%)	141 / 561 (25.13%)	
Blood and lymphatic system disorders			
Leukopenia			
alternative dictionary used: NCI CTCAE 3.0			
alternative assessment type: Systematic			
subjects affected / exposed[1]	103 / 554 (18.59%)	100 / 542 (18.45%)	
occurrences (all)	131	131	
General disorders and administration site conditions			
Nausea or vomiting			
alternative dictionary used: NCI CTCAE 3.0			
alternative assessment type: Systematic			

subjects affected / exposed[2]	29 / 554 (5.23%)	20 / 542 (3.69%)	
occurrences (all)	37	23	
Gastrointestinal disorders			
Mucositis			
alternative dictionary used: NCI CTCAE 3.0			
alternative assessment type: Systematic			
subjects affected / exposed[3]	9 / 554 (1.62%)	3 / 542 (0.55%)	
occurrences (all)	9	6	
Gastrointestinal disorder			
alternative dictionary used: NCI CTCAE 3.0			
alternative assessment type: Systematic			
subjects affected / exposed[4]	9 / 554 (1.62%)	9 / 542 (1.66%)	
occurrences (all)	11	11	
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
alternative dictionary used: NCI CTCAE 3.0			
alternative assessment type: Systematic			
subjects affected / exposed[5]	10 / 554 (1.81%)	12 / 542 (2.21%)	
occurrences (all)	10	13	
Infections and infestations			
Infection			
alternative dictionary used: NCI CTCAE 3.0			
alternative assessment type: Systematic			
subjects affected / exposed[6]	11 / 554 (1.99%)	14 / 542 (2.58%)	
occurrences (all)	12	16	

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 adverse events 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) adverse events 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 adverse events 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) adverse events 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.
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[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 adverse events 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) adverse events 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.
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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2009	Reduction of radiotherapy dose from 30 Gy to 20 Gy based on the results of the GHSG HD10 trial
17 July 2015	Extension of recruitment period and sample size, rearrangement of statistical test hierarchy and adaption of test parameters for reasons of feasibility, all based on recommendations by the independent DMC
14 August 2017	Extension of individual follow-up period until the end of the study for all patients who would provide separate informed consent

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/3149875