# 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<br>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<br>Units: years | | | |
| median | 38 | 37 | |
| full range (min-max) | 18 to 75 | 18 to 75 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 241 | 244 | 485 |
| Male | 332 | 322 | 654 |
| Ann Arbor stage<br>Units: Subjects | | | |
| IA | 164 | 145 | 309 |
| IB | 24 | 22 | 46 |
| IIA | 358 | 367 | 725 |
| IIB | 27 | 32 | 59 |
| ECOG performance status<br>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.
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.

[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.
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.
[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 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.

## 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