



## Clinical trial results: HD18 for advanced stages in Hodgkins Lymphoma Summary

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

### Results information

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

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | Uni-Koeln-908 |
|-----------------------|---------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00515554 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 13 February 2020 |
| Is this the analysis of the primary completion data? | No               |

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

Notes:

## General information about the trial

Main objective of the trial:

The aim of the HD18 trial was to individualize treatment of patients with advanced-stage Hodgkin lymphoma (HL) by adapting it to early response.

The HD18 trial comprises of two independent studies for patients with a positive or negative PET after 2 cycles of eBEACOPP (PET-2), respectively.

The primary objective of the study in patients with positive PET-2 was to show superiority of the combined immuno-chemotherapy R-eBEACOPP compared with standard eBEACOPP in terms of progression-free survival (PFS).

The primary objective of the study in patients with negative PET-2 was to show non-inferiority of treatment with a reduced number of cycles compared with standard treatment in terms of PFS.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

## Population of trial subjects

### Subjects enrolled per country

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

Notes:

| <b>Subjects enrolled per age group</b>    |      |
|---|------|
| In utero                                  | 0    |
| Preterm newborn - gestational age < 37 wk | 0    |
| Newborns (0-27 days)                      | 0    |
| Infants and toddlers (28 days-23 months)  | 0    |
| Children (2-11 years)                     | 0    |
| Adolescents (12-17 years)                 | 0    |
| Adults (18-64 years)                      | 2101 |
| From 65 to 84 years                       | 0    |
| 85 years and over                         | 0    |

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Pre-assignment period milestones

|                              |      |
|------------------------------|------|
| Number of subjects started   | 2101 |
| Number of subjects completed | 1964 |

### Pre-assignment subject non-completion reasons

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

### Period 1

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

Blinding implementation details:

Not applicable

### Arms

|                              |                         |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes                     |
| <b>Arm title</b>             | Arm A: 8x eBEACOPP PET+ |

Arm description:

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

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|   |                                       |
|---|---------------------------------------|
| Investigational medicinal product name              | Bleomycin                             |
| Investigational medicinal product code              | L01DC01                               |
| Other name  |                                       |
| Pharmaceutical forms                                | Powder for solution for injection     |
| Routes of administration                            | Intravenous use                       |
| Dosage and administration details:                  |                                       |
| 10 mg/m <sup>2</sup> BSA on day 8 of each cycle     |                                       |
| Investigational medicinal product name              | Etoposide                             |
| Investigational medicinal product code              | L01CB01                               |
| Other name  |                                       |
| Pharmaceutical forms                                | Concentrate for solution for infusion |
| Routes of administration                            | Intravenous use                       |
| Dosage and administration details:                  |                                       |
| 200 mg/m <sup>2</sup> BSA on days 1-3 of each cycle |                                       |
| Investigational medicinal product name              | Doxorubicine                          |
| Investigational medicinal product code              | L01DB01                               |
| Other name  |                                       |
| Pharmaceutical forms                                | Solution for infusion                 |
| Routes of administration                            | Intravenous use                       |
| Dosage and administration details:                  |                                       |
| 35 mg/m <sup>2</sup> BSA on day 1 of each cycle     |                                       |
| Investigational medicinal product name              | Cyclophosphamide                      |
| Investigational medicinal product code              | L01AA01                               |
| Other name  |                                       |
| Pharmaceutical forms                                | Powder for solution for injection     |
| Routes of administration                            | Intravenous use                       |
| Dosage and administration details:                  |                                       |
| 1250 mg/m <sup>2</sup> BSA on day 1 of each cycle   |                                       |
| Investigational medicinal product name              | Vincristine                           |
| Investigational medicinal product code              | L01CA02                               |
| Other name  |                                       |
| Pharmaceutical forms                                | Solution for injection                |
| Routes of administration                            | Intravenous use                       |
| Dosage and administration details:                  |                                       |
| 1.4 mg/m <sup>2</sup> BSA on day 8 of each cycle    |                                       |
| Investigational medicinal product name              | Procarbazine                          |
| Investigational medicinal product code              | L01XB01                               |
| Other name  |                                       |
| Pharmaceutical forms                                | Capsule, hard                         |
| Routes of administration                            | Oral use                              |
| Dosage and administration details:                  |                                       |
| 100 mg/m <sup>2</sup> BSA on days 1-7 of each cycle |                                       |
| Investigational medicinal product name              | Prednisone                            |
| Investigational medicinal product code              | H02AB07                               |
| Other name  |                                       |
| Pharmaceutical forms                                | Oral drops                            |
| Routes of administration                            | Oral use                              |
| Dosage and administration details:                  |                                       |
| 40 mg/m <sup>2</sup> BSA on days 1-14 of each cycle |                                       |
| <b>Arm title</b>                                    | Arm B: 8x R-eBEACOPP PET+             |

Arm description:

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

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

Dosage and administration details:

10 mg/m<sup>2</sup> BSA on day 8 of each cycle

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

Dosage and administration details:

200 mg/m<sup>2</sup> BSA on days 1-3 of each cycle

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

Dosage and administration details:

35 mg/m<sup>2</sup> BSA on day 1 of each cycle

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

Dosage and administration details:

1250 mg/m<sup>2</sup> BSA on day 1 of each cycle

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

Dosage and administration details:

1.4 mg/m<sup>2</sup> BSA on day 8 of each cycle

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

Dosage and administration details:

100 mg/m<sup>2</sup> BSA on days 1-7 of each cycle

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

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

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name   | Procarbazine                          |
| Investigational medicinal product code   | L01XB01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Capsule, hard                         |
| Routes of administration   | Oral use                              |
| Dosage and administration details:<br>100 mg/m <sup>2</sup> BSA on days 1-7 of each cycle  |                                       |
| Investigational medicinal product name   | Prednisone                            |
| Investigational medicinal product code   | H02AB07                               |
| Other name   |                                       |
| Pharmaceutical forms   | Oral drops                            |
| Routes of administration   | Oral use                              |
| Dosage and administration details:<br>40 mg/m <sup>2</sup> BSA on days 1-14 of each cycle  |                                       |
| <b>Arm title</b>   | Arm C: 8/6x eBEACOPP PET-             |
| Arm description:<br>Standard treatment for PET-2-negative patients: 8x eBEACOPP pre amendment 2, 6x eBEACOPP post amendment 2, each in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual <sup>18</sup> F-FDG uptake after chemotherapy |                                       |
| Arm type   | Active comparator                     |
| Investigational medicinal product name   | Bleomycin                             |
| Investigational medicinal product code   | L01DC01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Powder for solution for injection     |
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:<br>10 mg/m <sup>2</sup> BSA on day 8 of each cycle  |                                       |
| Investigational medicinal product name   | Etoposide                             |
| Investigational medicinal product code   | L01CB01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Concentrate for solution for infusion |
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:<br>200 mg/m <sup>2</sup> BSA on days 1-3 of each cycle  |                                       |
| Investigational medicinal product name   | Doxorubicine                          |
| Investigational medicinal product code   | L01DB01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Solution for infusion                 |
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:<br>35 mg/m <sup>2</sup> BSA on day 1 of each cycle  |                                       |
| Investigational medicinal product name   | Cyclophosphamide                      |
| Investigational medicinal product code   | L01AA01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Powder for solution for injection     |
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:<br>1250 mg/m <sup>2</sup> BSA on day 1 of each cycle  |                                       |
| Investigational medicinal product name   | Vincristine                           |
| Investigational medicinal product code   | L01CA02                               |
| Other name   |                                       |
| Pharmaceutical forms   | Solution for injection                |



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

|   |                        |
|---|------------------------|
| Investigational medicinal product name  | Vincristine            |
| Investigational medicinal product code  | L01CA02                |
| Other name  |                        |
| Pharmaceutical forms  | Solution for injection |
| Routes of administration  | Intravenous use        |
| Dosage and administration details:<br>1.4 mg/m <sup>2</sup> BSA on day 8 of each cycle    |                        |
| Investigational medicinal product name  | Procarbazine           |
| Investigational medicinal product code  | L01XB01                |
| Other name  |                        |
| Pharmaceutical forms  | Capsule, hard          |
| Routes of administration  | Oral use               |
| Dosage and administration details:<br>100 mg/m <sup>2</sup> BSA on days 1-7 of each cycle |                        |
| Investigational medicinal product name  | Prednisone             |
| Investigational medicinal product code  | H02AB07                |
| Other name  |                        |
| Pharmaceutical forms  | Oral drops             |
| Routes of administration  | Oral use               |
| Dosage and administration details:<br>40 mg/m <sup>2</sup> BSA on days 1-14 of each cycle |                        |

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

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

**Period 2**

|                                  |                         |
|----------------------------------|-------------------------|
| Period 2 title                   | Randomized treatment    |
| Is this the baseline period?     | Yes <sup>[1]</sup>      |
| Allocation method                | Randomised - controlled |
| Blinding used                    | Not blinded             |
| Blinding implementation details: |                         |
| Not applicable                   |                         |

**Arms**

|                              |                         |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes                     |
| <b>Arm title</b>             | Arm A: 8x eBEACOPP PET+ |

Arm description:

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

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

Dosage and administration details:

10 mg/m<sup>2</sup> BSA on day 8 of each cycle

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

Dosage and administration details:

200 mg/m<sup>2</sup> BSA on days 1-3 of each cycle

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

Dosage and administration details:

35 mg/m<sup>2</sup> BSA on day 1 of each cycle

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

Dosage and administration details:

1250 mg/m<sup>2</sup> BSA on day 1 of each cycle

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

Dosage and administration details:

1.4 mg/m<sup>2</sup> BSA on day 8 of each cycle

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name   | Procarbazine                          |
| Investigational medicinal product code   | L01XB01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Capsule, hard                         |
| Routes of administration   | Oral use                              |
| Dosage and administration details:<br>100 mg/m <sup>2</sup> BSA on days 1-7 of each cycle  |                                       |
| Investigational medicinal product name   | Prednisone                            |
| Investigational medicinal product code   | H02AB07                               |
| Other name   |                                       |
| Pharmaceutical forms   | Oral drops                            |
| Routes of administration   | Oral use                              |
| Dosage and administration details:<br>40 mg/m <sup>2</sup> BSA on days 1-14 of each cycle  |                                       |
| <b>Arm title</b>   | Arm B: 8x R-eBEACOPP PET+             |
| Arm description:<br>Experimental treatment for PET-2-positive patients pre amendment 2: 8x R-eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual <sup>18</sup> F-FDG uptake after chemotherapy |                                       |
| Arm type   | Experimental                          |
| Investigational medicinal product name   | Bleomycin                             |
| Investigational medicinal product code   | L01DC01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Powder for solution for injection     |
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:<br>10 mg/m <sup>2</sup> BSA on day 8 of each cycle  |                                       |
| Investigational medicinal product name   | Etoposide                             |
| Investigational medicinal product code   | L01CB01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Concentrate for solution for infusion |
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:<br>200 mg/m <sup>2</sup> BSA on days 1-3 of each cycle  |                                       |
| Investigational medicinal product name   | Doxorubicine                          |
| Investigational medicinal product code   | L01DB01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Solution for infusion                 |
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:<br>35 mg/m <sup>2</sup> BSA on day 1 of each cycle  |                                       |
| Investigational medicinal product name   | Cyclophosphamide                      |
| Investigational medicinal product code   | L01AA01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Powder for solution for injection     |
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:<br>1250 mg/m <sup>2</sup> BSA on day 1 of each cycle  |                                       |
| Investigational medicinal product name   | Vincristine                           |
| Investigational medicinal product code   | L01CA02                               |
| Other name   |                                       |
| Pharmaceutical forms   | Solution for injection                |

|   |                                       |
|---|---------------------------------------|
| Routes of administration  | Intravenous use                       |
| Dosage and administration details:  |                                       |
| 1.4 mg/m <sup>2</sup> BSA on day 8 of each cycle  |                                       |
| Investigational medicinal product name  | Procarbazine                          |
| Investigational medicinal product code  | L01XB01                               |
| Other name  |                                       |
| Pharmaceutical forms  | Capsule, hard                         |
| Routes of administration  | Oral use                              |
| Dosage and administration details:  |                                       |
| 100 mg/m <sup>2</sup> BSA on days 1-7 of each cycle   |                                       |
| Investigational medicinal product name  | Prednisone                            |
| Investigational medicinal product code  | H02AB07                               |
| Other name  |                                       |
| Pharmaceutical forms  | Oral drops                            |
| Routes of administration  | Oral use                              |
| Dosage and administration details:  |                                       |
| 40 mg/m <sup>2</sup> BSA on days 1-14 of each cycle   |                                       |
| Investigational medicinal product name  | Rituximab                             |
| Investigational medicinal product code  | L01XC02                               |
| Other name  |                                       |
| Pharmaceutical forms  | Concentrate for solution for infusion |
| Routes of administration  | Intravascular use                     |
| Dosage and administration details:  |                                       |
| 375 mg/m <sup>2</sup> BSA on days 0 and 3 of cycle 4; 375 mg/m <sup>2</sup> BSA on day 1 of cycles 5-8  |                                       |
| <b>Arm title</b>  | Arm A6: 6x eBEACOPP PET+              |
| Arm description:  |                                       |
| Standard treatment for PET-2-positive patients post amendment 2: 6x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual <sup>18</sup> F-FDG uptake after chemotherapy |                                       |
| Arm type  | Active comparator                     |
| Investigational medicinal product name  | Bleomycin                             |
| Investigational medicinal product code  | L01DC01                               |
| Other name  |                                       |
| Pharmaceutical forms  | Powder for solution for injection     |
| Routes of administration  | Intravenous use                       |
| Dosage and administration details:  |                                       |
| 10 mg/m <sup>2</sup> BSA on day 8 of each cycle   |                                       |
| Investigational medicinal product name  | Etoposide                             |
| Investigational medicinal product code  | L01CB01                               |
| Other name  |                                       |
| Pharmaceutical forms  | Concentrate for solution for infusion |
| Routes of administration  | Intravenous use                       |
| Dosage and administration details:  |                                       |
| 200 mg/m <sup>2</sup> BSA on days 1-3 of each cycle   |                                       |
| Investigational medicinal product name  | Doxorubicine                          |
| Investigational medicinal product code  | L01DB01                               |
| Other name  |                                       |
| Pharmaceutical forms  | Solution for infusion                 |
| Routes of administration  | Intravenous use                       |
| Dosage and administration details:  |                                       |
| 35 mg/m <sup>2</sup> BSA on day 1 of each cycle   |                                       |

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name   | Cyclophosphamide                      |
| Investigational medicinal product code   | L01AA01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Powder for solution for injection     |
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:<br>1250 mg/m <sup>2</sup> BSA on day 1 of each cycle  |                                       |
| Investigational medicinal product name   | Vincristine                           |
| Investigational medicinal product code   | L01CA02                               |
| Other name   |                                       |
| Pharmaceutical forms   | Solution for injection                |
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:<br>1.4 mg/m <sup>2</sup> BSA on day 8 of each cycle   |                                       |
| Investigational medicinal product name   | Procarbazine                          |
| Investigational medicinal product code   | L01XB01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Capsule, hard                         |
| Routes of administration   | Oral use                              |
| Dosage and administration details:<br>100 mg/m <sup>2</sup> BSA on days 1-7 of each cycle  |                                       |
| Investigational medicinal product name   | Prednisone                            |
| Investigational medicinal product code   | H02AB07                               |
| Other name   |                                       |
| Pharmaceutical forms   | Oral drops                            |
| Routes of administration   | Oral use                              |
| Dosage and administration details:<br>40 mg/m <sup>2</sup> BSA on days 1-14 of each cycle  |                                       |
| <b>Arm title</b>   | Arm C: 8/6x eBEACOPP PET-             |
| Arm description:<br>Standard treatment for PET-2-negative patients: 8x eBEACOPP pre amendment 2, 6x eBEACOPP post amendment 2, each in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual <sup>18</sup> F-FDG uptake after chemotherapy |                                       |
| Arm type   | Active comparator                     |
| Investigational medicinal product name   | Bleomycin                             |
| Investigational medicinal product code   | L01DC01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Powder for solution for injection     |
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:<br>10 mg/m <sup>2</sup> BSA on day 8 of each cycle  |                                       |
| Investigational medicinal product name   | Etoposide                             |
| Investigational medicinal product code   | L01CB01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Concentrate for solution for infusion |
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:<br>200 mg/m <sup>2</sup> BSA on days 1-3 of each cycle  |                                       |
| Investigational medicinal product name   | Doxorubicine                          |
| Investigational medicinal product code   | L01DB01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Solution for infusion                 |

|  |                                       |
|--|---------------------------------------|
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:   |                                       |
| 35 mg/m <sup>2</sup> BSA on day 1 of each cycle  |                                       |
| Investigational medicinal product name   | Cyclophosphamide                      |
| Investigational medicinal product code   | L01AA01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Powder for solution for injection     |
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:   |                                       |
| 1250 mg/m <sup>2</sup> BSA on day 1 of each cycle  |                                       |
| Investigational medicinal product name   | Vincristine                           |
| Investigational medicinal product code   | L01CA02                               |
| Other name   |                                       |
| Pharmaceutical forms   | Solution for injection                |
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:   |                                       |
| 1.4 mg/m <sup>2</sup> BSA on day 8 of each cycle   |                                       |
| Investigational medicinal product name   | Procarbazine                          |
| Investigational medicinal product code   | L01XB01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Capsule, hard                         |
| Routes of administration   | Oral use                              |
| Dosage and administration details:   |                                       |
| 100 mg/m <sup>2</sup> BSA on days 1-7 of each cycle  |                                       |
| Investigational medicinal product name   | Prednisone                            |
| Investigational medicinal product code   | H02AB07                               |
| Other name   |                                       |
| Pharmaceutical forms   | Oral drops                            |
| Routes of administration   | Oral use                              |
| Dosage and administration details:   |                                       |
| 40 mg/m <sup>2</sup> BSA on days 1-14 of each cycle  |                                       |
| <b>Arm title</b>   | Arm D: 4x eBEACOPP PET-               |
| Arm description:   |                                       |
| Experimental treatment for PET-2-negative patients: 4x eBEACOPP in 21-day intervals; 30 Gy radiotherapy recommended for lesions of at least 2.5 cm in the largest diameter with residual <sup>18</sup> F-FDG uptake after chemotherapy |                                       |
| Arm type   | Experimental                          |
| Investigational medicinal product name   | Bleomycin                             |
| Investigational medicinal product code   | L01DC01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Powder for solution for injection     |
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:   |                                       |
| 10 mg/m <sup>2</sup> BSA on day 8 of each cycle  |                                       |
| Investigational medicinal product name   | Etoposide                             |
| Investigational medicinal product code   | L01CB01                               |
| Other name   |                                       |
| Pharmaceutical forms   | Concentrate for solution for infusion |
| Routes of administration   | Intravenous use                       |
| Dosage and administration details:   |                                       |
| 200 mg/m <sup>2</sup> BSA on days 1-3 of each cycle  |                                       |

|   |                                   |
|---|-----------------------------------|
| Investigational medicinal product name  | Doxorubicine                      |
| Investigational medicinal product code  | L01DB01                           |
| Other name  |                                   |
| Pharmaceutical forms  | Solution for infusion             |
| Routes of administration  | Intravenous use                   |
| Dosage and administration details:<br>35 mg/m <sup>2</sup> BSA on day 1 of each cycle     |                                   |
| Investigational medicinal product name  | Cyclophosphamide                  |
| Investigational medicinal product code  | L01AA01                           |
| Other name  |                                   |
| Pharmaceutical forms  | Powder for solution for injection |
| Routes of administration  | Intravenous use                   |
| Dosage and administration details:<br>1250 mg/m <sup>2</sup> BSA on day 1 of each cycle   |                                   |
| Investigational medicinal product name  | Vincristine                       |
| Investigational medicinal product code  | L01CA02                           |
| Other name  |                                   |
| Pharmaceutical forms  | Solution for injection            |
| Routes of administration  | Intravenous use                   |
| Dosage and administration details:<br>1.4 mg/m <sup>2</sup> BSA on day 8 of each cycle    |                                   |
| Investigational medicinal product name  | Procarbazine                      |
| Investigational medicinal product code  | L01XB01                           |
| Other name  |                                   |
| Pharmaceutical forms  | Capsule, hard                     |
| Routes of administration  | Oral use                          |
| Dosage and administration details:<br>100 mg/m <sup>2</sup> BSA on days 1-7 of each cycle |                                   |
| Investigational medicinal product name  | Prednisone                        |
| Investigational medicinal product code  | H02AB07                           |
| Other name  |                                   |
| Pharmaceutical forms  | Oral drops                        |
| Routes of administration  | Oral use                          |
| Dosage and administration details:<br>40 mg/m <sup>2</sup> BSA on days 1-14 of each cycle |                                   |

Notes:

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

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

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



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

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

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: In HD18, all patients received 2 cycles of chemotherapy and were then randomized into one of two parallel treatment arms according to their PET result. All randomized patients are included in period 1 ("Randomization"). However, there were a small number of patients randomized despite prior protocol violation. These did not receive randomized treatment and have not been included in the efficacy analyses. Thus, the baseline period only includes patients receiving randomized treatment.

## Baseline characteristics

### Reporting groups

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

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

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

| <b>Reporting group values</b>                         | Arm C: 8/6x<br>eBEACOPP PET- | Arm D: 4x<br>eBEACOPP PET- | Total |
|---|------------------------------|----------------------------|-------|
| Number of subjects                                    | 504                          | 501                        | 1945  |
| Age categorical                                       |                              |                            |       |
| Units: Subjects                                       |                              |                            |       |
| In utero  | 0                            | 0                          | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                            | 0                          | 0     |
| Newborns (0-27 days)                                  | 0                            | 0                          | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0                            | 0                          | 0     |
| Children (2-11 years)                                 | 0                            | 0                          | 0     |
| Adolescents (12-17 years)                             | 0                            | 0                          | 0     |
| Adults (18-64 years)                                  | 504                          | 501                        | 1945  |
| From 65-84 years                                      | 0                            | 0                          | 0     |
| 85 years and over                                     | 0                            | 0                          | 0     |
| Gender categorical                                    |                              |                            |       |
| Units: Subjects                                       |                              |                            |       |
| Female  | 189                          | 188                        | 762   |
| Male  | 315                          | 313                        | 1183  |

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

## End points

### End points reporting groups

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

## Primary: Progression-free survival

|                 |                           |
|-----------------|---------------------------|
| End point title | Progression-free survival |
|-----------------|---------------------------|

End point description:

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

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

5 years

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

Notes:

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

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

Notes:

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

## Statistical analyses

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

Statistical analysis description:

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

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

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

Notes:

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

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

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | PET-2-negative study, non-inferiority test |
|-----------------------------------|--|

Statistical analysis description:

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

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

Notes:

[5] - Non-inferiority would be established if the lower limit of the 2-sided 95% CI for the difference in 5-year progression-free survival was above -6%.

As the 95% CI for the 5-year difference excluded the predefined non-inferiority margin of -6%, non-inferiority of the shorter regimen could be concluded.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 10.1   |

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Arm A: 8x eBEACOPP PET+ |
|-----------------------|-------------------------|

Reporting group description:

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

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

Reporting group description:

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

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Arm A6: 6x eBEACOPP PET+ |
|-----------------------|--------------------------|

Reporting group description:

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

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

Reporting group description:

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

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Arm D: 4x eBEACOPP PET- |
|-----------------------|-------------------------|

Reporting group description:

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

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Arm 0: Non-randomized patients |
|-----------------------|--------------------------------|

Reporting group description:

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

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



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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

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

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

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

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

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

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

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

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

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

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

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

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

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

Notes:

### Limitations and caveats

None reported

### Online references

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

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