



## Clinical trial results:

### Randomized phase III study of a treatment driven by early PET response compared to a treatment not monitored by early PET in patients with Ann Arbor Stage III-IV or high risk IIB Hodgkin lymphoma

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2010-022844-19    |
| Trial protocol           | FR BE             |
| Global end of trial date | 30 September 2019 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 07 February 2023 |
| First version publication date | 07 February 2023 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | AHL2011 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01358747 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |                                                                            |
|------------------------------|----------------------------------------------------------------------------|
| Sponsor organisation name    | Centre Hospitalier Universitaire de Dijon                                  |
| Sponsor organisation address | 1 boulevard Jeanne d'Arc, DIJON CEDEX, France, 21079                       |
| Public contact               | Project Management, LYSARC, contact@lysarc.org                             |
| Scientific contact           | Project Management, Pr Olivier Casasnovas, olivier.casasnovas@chu-dijon.fr |

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                       | 19 April 2019     |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 30 September 2019 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

Demonstrate the non inferiority in term of progression free survival (PFS) of a therapeutic strategy driven by PET with a ABVD conventional dose chemotherapy for patients reaching a negative PET after 2 cycles of BEACOPPesc, compared to a treatment not monitored by early PET delivering 6 cycles of BEACOPPesc.

Protection of trial subjects:

DSMC periodically reviewed the safety and efficacy data from the trial prepared by the independent statistician. All data presented at the meeting were confidential. Following each meeting the DSMC prepared a report and may recommended changes in the trial conduct.

Background therapy: -

Evidence for comparator: -

|                                                           |             |
|-----------------------------------------------------------|-------------|
| Actual start date of recruitment                          | 19 May 2011 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | Yes         |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Belgium: 765 |
| Country: Number of subjects enrolled | France: 58   |
| Worldwide total number of subjects   | 823          |
| EEA total number of subjects         | 823          |

Notes:

### Subjects enrolled per age group

|                                           |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 16  |
| Adults (18-64 years)                      | 807 |
| From 65 to 84 years                       | 0   |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

88 study centers in France and Belgium.

Date first subject first visit: 19 May 2011

Date last subject completed: 29 April 2019

### Pre-assignment

Screening details:

Male or female adult (aged 16 to 60 years old) subjects with histologically proven HL not previously treated, with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 1, or 2, and life expectancy  $\geq$  90 days were eligible for participation in the study

### Period 1

|                              |                          |
|------------------------------|--------------------------|
| Period 1 title               | Overall (overall period) |
| Is this the baseline period? | Yes                      |
| Allocation method            | Randomised - controlled  |
| Blinding used                | Not blinded              |

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | Standard Arm |

Arm description:

Patients were treated by a BEACOPPesc regimen every 3 weeks for 4 cycles. A PET was performed after 2 cycles of chemotherapy (PET2) with no decisional value, and after 4 cycles with decisional value.

In case of PET4 negative result, patient received 2 additional cycles of BEACOPPesc delivered every 3 weeks

In case of PET4 positive result, patient received a salvage therapy

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

Dosage and administration details:

10 mg/m<sup>2</sup> at Day 8

|                                        |                          |
|----------------------------------------|--------------------------|
| Investigational medicinal product name | Etoposide                |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Suspension for injection |
| Routes of administration               | Intravenous use          |

Dosage and administration details:

200 mg/m<sup>2</sup> at days 1, 2 and 3

|                                        |                          |
|----------------------------------------|--------------------------|
| Investigational medicinal product name | Doxorubicin              |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Suspension for injection |
| Routes of administration               | Intravenous use          |

Dosage and administration details:

35 mg/ m<sup>2</sup> on day 1

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| Investigational medicinal product name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Cyclophosphamide               |
| Investigational medicinal product code                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                |
| Other name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                |
| Pharmaceutical forms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Solution for injection in vial |
| Routes of administration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Intravenous use                |
| Dosage and administration details:<br>1250 mg/m2 on day 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                |
| Investigational medicinal product name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Vincristine                    |
| Investigational medicinal product code                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                |
| Other name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                |
| Pharmaceutical forms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Solution for injection in vial |
| Routes of administration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Intravenous use                |
| Dosage and administration details:<br>1.4 mg/m2 on day 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                |
| Investigational medicinal product name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Procarbazine                   |
| Investigational medicinal product code                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                |
| Other name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                |
| Pharmaceutical forms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Capsule, hard                  |
| Routes of administration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Oral use                       |
| Dosage and administration details:<br>Dosage: 100 mg/m2<br>Administration: Daily from Day 1 of each cycle to day 7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                |
| Investigational medicinal product name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Prednisone                     |
| Investigational medicinal product code                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                |
| Other name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                |
| Pharmaceutical forms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Capsule, hard                  |
| Routes of administration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Oral use                       |
| Dosage and administration details:<br>Dosage: 40mg/m2<br>Administration: Daily from Day 1 of each cycle to day 8 and day 9 to day 14                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                |
| Investigational medicinal product name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Lenograstim                    |
| Investigational medicinal product code                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                |
| Other name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                |
| Pharmaceutical forms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Solution for injection         |
| Routes of administration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Cutaneous use                  |
| Dosage and administration details:<br>5 microgr/kg/day start on day 9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                |
| <b>Arm title</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Experimental arm               |
| Arm description:<br>Patients were treated by a BEACOPPesc regimen every 3 weeks for 2 cycles followed by a PET scan (PET2).<br><br>After PET2 central review:<br><ul style="list-style-type: none"> <li>- In case of positive PET2, the treatment was completed by 2 additional cycles of BEACOPPesc (induction treatment = 4 x BEACOPPesc)</li> <li>- In case of negative PET2, the treatment was completed by 2 cycles of ABVD delivered every 4 weeks (induction treatment = 2 x BEACOPPesc + 2 x ABVD).</li> </ul> After PET4 central review:<br><ul style="list-style-type: none"> <li>- In case of positive PET4, a salvage therapy was decided by the investigator</li> <li>- In case of negative PET4 : <ul style="list-style-type: none"> <li>- if PET2 was negative, treatment was completed by 2 cycles of ABVD (induction treatment = 2 x BEACOPPesc + 4 x ABVD).</li> <li>- if PET2 was positive, treatment was completed by 2 cycles of BEACOPPesc (induction treatment = 4 x BEACOPPesc)</li> </ul> </li> </ul> |                                |
| Arm type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Experimental                   |

|                                                                             |                                |
|-----------------------------------------------------------------------------|--------------------------------|
| Investigational medicinal product name                                      | Bleomycin                      |
| Investigational medicinal product code                                      |                                |
| Other name                                                                  |                                |
| Pharmaceutical forms                                                        | Suspension for injection       |
| Routes of administration                                                    | Intravenous use                |
| Dosage and administration details:                                          |                                |
| 10 mg/m <sup>2</sup> at Day 8                                               |                                |
| Investigational medicinal product name                                      | Etoposide                      |
| Investigational medicinal product code                                      |                                |
| Other name                                                                  |                                |
| Pharmaceutical forms                                                        | Suspension for injection       |
| Routes of administration                                                    | Intravenous use                |
| Dosage and administration details:                                          |                                |
| 200 mg/m <sup>2</sup> at days 1, 2 and 3                                    |                                |
| Investigational medicinal product name                                      | Doxorubicin                    |
| Investigational medicinal product code                                      |                                |
| Other name                                                                  |                                |
| Pharmaceutical forms                                                        | Suspension for injection       |
| Routes of administration                                                    | Intravenous use                |
| Dosage and administration details:                                          |                                |
| 35 mg/ m <sup>2</sup> on day 1                                              |                                |
| Investigational medicinal product name                                      | Cyclophosphamide               |
| Investigational medicinal product code                                      |                                |
| Other name                                                                  |                                |
| Pharmaceutical forms                                                        | Solution for injection in vial |
| Routes of administration                                                    | Intravenous use                |
| Dosage and administration details:                                          |                                |
| 1250 mg/m <sup>2</sup> on day 1                                             |                                |
| Investigational medicinal product name                                      | Vincristine                    |
| Investigational medicinal product code                                      |                                |
| Other name                                                                  |                                |
| Pharmaceutical forms                                                        | Solution for injection in vial |
| Routes of administration                                                    | Intravenous use                |
| Dosage and administration details:                                          |                                |
| 1.4 mg/m <sup>2</sup> on day 1                                              |                                |
| Investigational medicinal product name                                      | Procarbazine                   |
| Investigational medicinal product code                                      |                                |
| Other name                                                                  |                                |
| Pharmaceutical forms                                                        | Capsule, hard                  |
| Routes of administration                                                    | Oral use                       |
| Dosage and administration details:                                          |                                |
| Dosage: 100 mg/m <sup>2</sup>                                               |                                |
| Administration: Daily from Day 1 of each cycle to day 7                     |                                |
| Investigational medicinal product name                                      | Prednisone                     |
| Investigational medicinal product code                                      |                                |
| Other name                                                                  |                                |
| Pharmaceutical forms                                                        | Capsule, hard                  |
| Routes of administration                                                    | Oral use                       |
| Dosage and administration details:                                          |                                |
| Dosage: 40mg/m <sup>2</sup>                                                 |                                |
| Administration: Daily from Day 1 of each cycle to day 8 and day 9 to day 14 |                                |

|                                        |                          |
|----------------------------------------|--------------------------|
| Investigational medicinal product name | Lenograstim              |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Solution for injection   |
| Routes of administration               | Cutaneous use            |
| Dosage and administration details:     |                          |
| 5 microgr/kg/day start on day 9        |                          |
| Investigational medicinal product name | Doxorubicin              |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Suspension for injection |
| Routes of administration               | Intravenous use          |
| Dosage and administration details:     |                          |
| 25 mg/ m2 on day 1 and day 15          |                          |
| Investigational medicinal product name | Bleomycin                |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Suspension for injection |
| Routes of administration               | Intravenous use          |
| Dosage and administration details:     |                          |
| 10 mg/m2 on day 1 and day 15           |                          |
| Investigational medicinal product name | Vinblastine              |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Solution for infusion    |
| Routes of administration               | Intravenous use          |
| Dosage and administration details:     |                          |
| 6 mg/m2 on day 1 and day 15            |                          |
| Investigational medicinal product name | Dacarbazine              |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Solution for infusion    |
| Routes of administration               | Intravenous use          |
| Dosage and administration details:     |                          |
| 375 mg/m2 on day 1 and day 15          |                          |

| <b>Number of subjects in period 1</b> | Standard Arm | Experiimental arm |
|---------------------------------------|--------------|-------------------|
| Started                               | 413          | 410               |
| Completed                             | 342          | 359               |
| Not completed                         | 71           | 51                |
| Consent withdrawn by subject          | 4            | 3                 |
| Physician decision                    | 2            | 3                 |
| death                                 | 4            | 2                 |
| Adverse event, non-fatal              | 28           | 4                 |
| other                                 | 4            | 3                 |
| Lack of efficacy                      | 26           | 19                |

|                    |   |    |
|--------------------|---|----|
| Protocol deviation | 3 | 17 |
|--------------------|---|----|



## Baseline characteristics

### Reporting groups

|                                |         |
|--------------------------------|---------|
| Reporting group title          | Overall |
| Reporting group description: - |         |

| Reporting group values                             | Overall  | Total |  |
|----------------------------------------------------|----------|-------|--|
| Number of subjects                                 | 823      | 823   |  |
| Age categorical                                    |          |       |  |
| Units: Subjects                                    |          |       |  |
| In utero                                           |          | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) |          | 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)                               |          | 0     |  |
| From 65-84 years                                   |          | 0     |  |
| 85 years and over                                  |          | 0     |  |
| Subjects                                           |          | 0     |  |
| Age continuous                                     |          |       |  |
| Units: years                                       |          |       |  |
| arithmetic mean                                    | 32.9     |       |  |
| full range (min-max)                               | 16 to 60 | -     |  |
| Gender categorical                                 |          |       |  |
| Units: Subjects                                    |          |       |  |
| Female                                             | 307      | 307   |  |
| Male                                               | 516      | 516   |  |

### Subject analysis sets

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | ITT                |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

The ITT set contains all patients who were formally randomized regardless whether they have received treatment or not (following an intent-to-treat principle).

Patients are analyzed according to the treatment arm they were randomized to receive.

The ITT set is used for the efficacy analysis.

| Reporting group values                             | ITT |  |  |
|----------------------------------------------------|-----|--|--|
| Number of subjects                                 | 823 |  |  |
| Age categorical                                    |     |  |  |
| Units: Subjects                                    |     |  |  |
| In utero                                           |     |  |  |
| Preterm newborn infants (gestational age < 37 wks) |     |  |  |
| Newborns (0-27 days)                               |     |  |  |

|                                                                                                                                                                             |                  |  |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|--|--|
| Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over<br>Subjects |                  |  |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>full range (min-max)                                                                                                   | 32.9<br>16 to 60 |  |  |
| Gender categorical<br>Units: Subjects                                                                                                                                       |                  |  |  |
| Female<br>Male                                                                                                                                                              | 307<br>516       |  |  |

## End points

### End points reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Standard Arm |
|-----------------------|--------------|

Reporting group description:

Patients were treated by a BEACOPPesc regimen every 3 weeks for 4 cycles. A PET was performed after 2 cycles of chemotherapy (PET2) with no decisional value, and after 4 cycles with decisional value.

In case of PET4 negative result, patient received 2 additional cycles of BEACOPPesc delivered every 3 weeks

In case of PET4 positive result, patient received a salvage therapy

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Experimental arm |
|-----------------------|------------------|

Reporting group description:

Patients were treated by a BEACOPPesc regimen every 3 weeks for 2 cycles followed by a PET scan (PET2).

After PET2 central review:

- In case of positive PET2, the treatment was completed by 2 additional cycles of BEACOPPesc (induction treatment = 4 x BEACOPPesc)

- In case of negative PET2, the treatment was completed by 2 cycles of ABVD delivered every 4 weeks (induction treatment = 2 x BEACOPPesc + 2 x ABVD).

After PET4 central review:

- In case of positive PET4, a salvage therapy was decided by the investigator

- In case of negative PET4 :

- if PET2 was negative, treatment was completed by 2 cycles of ABVD (induction treatment = 2 x BEACOPPesc + 4 x ABVD).

- if PET2 was positive, treatment was completed by 2 cycles of BEACOPPesc (induction treatment = 4 x BEACOPPesc)

|                            |     |
|----------------------------|-----|
| Subject analysis set title | ITT |
|----------------------------|-----|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

The ITT set contains all patients who were formally randomized regardless whether they have received treatment or not (following an intent-to-treat principle).

Patients are analyzed according to the treatment arm they were randomized to receive.

The ITT set is used for the efficacy analysis.

### Primary: PFS

|                 |     |
|-----------------|-----|
| End point title | PFS |
|-----------------|-----|

End point description:

The primary endpoint was progression-free survival. PFS was measured from the date of randomization to the date of first documented progression of the lymphoma in non-responding patients, relapse for CR patients or death from any cause without progression, whichever occurs first

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

End point timeframe:

5-year progression-free survival

| End point values                          | Standard Arm        | Experimental arm    |  |  |
|-------------------------------------------|---------------------|---------------------|--|--|
| Subject group type                        | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed               | 413                 | 410                 |  |  |
| Units: percent                            |                     |                     |  |  |
| arithmetic mean (confidence interval 95%) | 87.5 (83.9 to 90.4) | 86.7 (83.0 to 89.7) |  |  |

|                                   |         |
|-----------------------------------|---------|
| <b>Attachments (see zip file)</b> | PFS.png |
|-----------------------------------|---------|

## Statistical analyses

|                                   |                                       |
|-----------------------------------|---------------------------------------|
| <b>Statistical analysis title</b> | Comparison according to treatment arm |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

Based on a Cox model, the Hazard Ratio (HR) of patients in experimental treatment are compared to patients in standard arm.

|                                         |                                 |
|-----------------------------------------|---------------------------------|
| Comparison groups                       | Standard Arm v Experimental arm |
| Number of subjects included in analysis | 823                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[1]</sup>  |
| P-value                                 | = 0.64                          |
| Method                                  | Logrank                         |
| Parameter estimate                      | Hazard ratio (HR)               |
| Point estimate                          | 1.071                           |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.738                           |
| upper limit                             | 1.554                           |

Notes:

[1] - The Com-Nougue non-inferiority test for PFS gave a similar conclusion in the ITT population by rejecting the null hypothesis (p=0.0037).

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Any episode of any grade of toxicities, related to a Serious Adverse Event must be reported as "Serious Adverse Event"

· Non-serious adverse events not to be reported.

· The following events are not to be reported as SAE if require hospitalization le

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 15     |

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | BEACOPP only |
|-----------------------|--------------|

Reporting group description:

patients who received BEACOPP only and who performed cycle 1

|                       |                |
|-----------------------|----------------|
| Reporting group title | BEACOPP + ABVD |
|-----------------------|----------------|

Reporting group description: -

| Serious adverse events                                              | BEACOPP only       | BEACOPP + ABVD    |  |
|---------------------------------------------------------------------|--------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                    |                   |  |
| subjects affected / exposed                                         | 160 / 458 (34.93%) | 97 / 361 (26.87%) |  |
| number of deaths (all causes)                                       | 19                 | 10                |  |
| number of deaths resulting from adverse events                      | 6                  | 2                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                   |  |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) |                    |                   |  |
| subjects affected / exposed                                         | 7 / 458 (1.53%)    | 3 / 361 (0.83%)   |  |
| occurrences causally related to treatment / all                     | 8 / 8              | 3 / 3             |  |
| deaths causally related to treatment / all                          | 2 / 3              | 1 / 2             |  |
| Vascular disorders                                                  |                    |                   |  |
| VASCULAR DISORDERS                                                  |                    |                   |  |
| subjects affected / exposed                                         | 11 / 458 (2.40%)   | 9 / 361 (2.49%)   |  |
| occurrences causally related to treatment / all                     | 3 / 12             | 0 / 11            |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0             |  |
| General disorders and administration site conditions                |                    |                   |  |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS                |                    |                   |  |

|                                                                                                    |                  |                  |  |
|----------------------------------------------------------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                                                                        | 30 / 458 (6.55%) | 16 / 361 (4.43%) |  |
| occurrences causally related to treatment / all                                                    | 13 / 37          | 10 / 18          |  |
| deaths causally related to treatment / all                                                         | 0 / 0            | 0 / 0            |  |
| Immune system disorders<br>IMMUNE SYSTEM DISORDERS                                                 |                  |                  |  |
| subjects affected / exposed                                                                        | 4 / 458 (0.87%)  | 5 / 361 (1.39%)  |  |
| occurrences causally related to treatment / all                                                    | 2 / 4            | 5 / 5            |  |
| deaths causally related to treatment / all                                                         | 0 / 0            | 0 / 0            |  |
| Reproductive system and breast disorders<br>REPRODUCTIVE SYSTEM AND BREAST DISORDERS               |                  |                  |  |
| subjects affected / exposed                                                                        | 2 / 458 (0.44%)  | 0 / 361 (0.00%)  |  |
| occurrences causally related to treatment / all                                                    | 1 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all                                                         | 0 / 0            | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders<br>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS |                  |                  |  |
| subjects affected / exposed                                                                        | 19 / 458 (4.15%) | 15 / 361 (4.16%) |  |
| occurrences causally related to treatment / all                                                    | 14 / 21          | 11 / 18          |  |
| deaths causally related to treatment / all                                                         | 1 / 2            | 0 / 0            |  |
| Injury, poisoning and procedural complications<br>INJURY, POISONING AND PROCEDURAL COMPLICATIONS   |                  |                  |  |
| subjects affected / exposed                                                                        | 2 / 458 (0.44%)  | 3 / 361 (0.83%)  |  |
| occurrences causally related to treatment / all                                                    | 2 / 2            | 1 / 3            |  |
| deaths causally related to treatment / all                                                         | 0 / 0            | 0 / 0            |  |
| Cardiac disorders<br>CARDIAC DISORDERS                                                             |                  |                  |  |
| subjects affected / exposed                                                                        | 8 / 458 (1.75%)  | 10 / 361 (2.77%) |  |
| occurrences causally related to treatment / all                                                    | 3 / 8            | 3 / 11           |  |
| deaths causally related to treatment / all                                                         | 1 / 1            | 0 / 1            |  |
| Nervous system disorders<br>NERVOUS SYSTEM DISORDERS                                               |                  |                  |  |
| subjects affected / exposed                                                                        | 3 / 458 (0.66%)  | 3 / 361 (0.83%)  |  |
| occurrences causally related to treatment / all                                                    | 2 / 3            | 3 / 4            |  |
| deaths causally related to treatment / all                                                         | 0 / 0            | 0 / 0            |  |

|                                                                                                    |                  |                 |  |
|----------------------------------------------------------------------------------------------------|------------------|-----------------|--|
| Blood and lymphatic system disorders<br>BLOOD AND LYMPHATIC SYSTEM DISORDERS                       |                  |                 |  |
| subjects affected / exposed                                                                        | 29 / 458 (6.33%) | 1 / 361 (0.28%) |  |
| occurrences causally related to treatment / all                                                    | 30 / 33          | 13 / 14         |  |
| deaths causally related to treatment / all                                                         | 0 / 0            | 0 / 0           |  |
| Eye disorders<br>EYE DISORDERS                                                                     |                  |                 |  |
| subjects affected / exposed                                                                        | 0 / 458 (0.00%)  | 1 / 361 (0.28%) |  |
| occurrences causally related to treatment / all                                                    | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all                                                         | 0 / 0            | 0 / 0           |  |
| Gastrointestinal disorders<br>GASTROINTESTINAL DISORDERS                                           |                  |                 |  |
| subjects affected / exposed                                                                        | 20 / 458 (4.37%) | 8 / 361 (2.22%) |  |
| occurrences causally related to treatment / all                                                    | 21 / 26          | 7 / 9           |  |
| deaths causally related to treatment / all                                                         | 0 / 0            | 0 / 0           |  |
| Hepatobiliary disorders<br>HEPATOBIILIARY DISORDERS                                                |                  |                 |  |
| subjects affected / exposed                                                                        | 5 / 458 (1.09%)  | 1 / 361 (0.28%) |  |
| occurrences causally related to treatment / all                                                    | 4 / 6            | 0 / 1           |  |
| deaths causally related to treatment / all                                                         | 0 / 0            | 0 / 0           |  |
| Skin and subcutaneous tissue disorders<br>SKIN AND SUBCUTANEOUS TISSUE DISORDERS                   |                  |                 |  |
| subjects affected / exposed                                                                        | 3 / 458 (0.66%)  | 5 / 361 (1.39%) |  |
| occurrences causally related to treatment / all                                                    | 3 / 3            | 3 / 6           |  |
| deaths causally related to treatment / all                                                         | 0 / 0            | 0 / 0           |  |
| Renal and urinary disorders<br>RENAL AND URINARY DISORDERS                                         |                  |                 |  |
| subjects affected / exposed                                                                        | 6 / 458 (1.31%)  | 1 / 361 (0.28%) |  |
| occurrences causally related to treatment / all                                                    | 1 / 6            | 0 / 1           |  |
| deaths causally related to treatment / all                                                         | 0 / 0            | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders<br>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS |                  |                 |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 7 / 458 (1.53%)   | 4 / 361 (1.11%)   |  |
| occurrences causally related to treatment / all | 7 / 10            | 2 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Infections and infestations</b>              |                   |                   |  |
| <b>INFECTIONS AND INFESTATIONS</b>              |                   |                   |  |
| subjects affected / exposed                     | 90 / 458 (19.65%) | 42 / 361 (11.63%) |  |
| occurrences causally related to treatment / all | 91 / 121          | 43 / 56           |  |
| deaths causally related to treatment / all      | 2 / 2             | 1 / 1             |  |
| <b>Metabolism and nutrition disorders</b>       |                   |                   |  |
| <b>METABOLISM AND NUTRITION DISORDERS</b>       |                   |                   |  |
| subjects affected / exposed                     | 2 / 458 (0.44%)   | 1 / 361 (0.28%)   |  |
| occurrences causally related to treatment / all | 2 / 2             | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                           | BEACOPP only        | BEACOPP + ABVD      |  |
|-------------------------------------------------------------|---------------------|---------------------|--|
| Total subjects affected by non-serious adverse events       |                     |                     |  |
| subjects affected / exposed                                 | 458 / 458 (100.00%) | 361 / 361 (100.00%) |  |
| <b>Vascular disorders</b>                                   |                     |                     |  |
| Vascular disorders                                          |                     |                     |  |
| subjects affected / exposed                                 | 68 / 458 (14.85%)   | 59 / 361 (16.34%)   |  |
| occurrences (all)                                           | 68                  | 59                  |  |
| <b>General disorders and administration site conditions</b> |                     |                     |  |
| General disorders and administration site conditions        |                     |                     |  |
| subjects affected / exposed                                 | 354 / 458 (77.29%)  | 275 / 361 (76.18%)  |  |
| occurrences (all)                                           | 354                 | 275                 |  |
| <b>Immune system disorders</b>                              |                     |                     |  |
| Immune system disorders                                     |                     |                     |  |
| subjects affected / exposed                                 | 8 / 458 (1.75%)     | 11 / 361 (3.05%)    |  |
| occurrences (all)                                           | 8                   | 11                  |  |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |                     |                     |  |
| Respiratory, thoracic and mediastinal disorders             |                     |                     |  |



|                                                                                                                                         |                               |                           |  |
|-----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                                        | 146 / 458 (31.88%)<br>146     | 104 / 361 (28.81%)<br>104 |  |
| Investigations<br>Investigations<br>subjects affected / exposed<br>occurrences (all)                                                    | 199 / 458 (43.45%)<br>199     | 152 / 361 (42.11%)<br>152 |  |
| Cardiac disorders<br>Cardiac disorders<br>subjects affected / exposed<br>occurrences (all)                                              | 40 / 458 (8.73%)<br>40        | 28 / 361 (7.76%)<br>28    |  |
| Nervous system disorders<br>Nervous system disorders<br>subjects affected / exposed<br>occurrences (all)                                | 157 / 458 (34.28%)<br>157     | 123 / 361 (34.07%)<br>123 |  |
| Blood and lymphatic system disorders<br>Blood and lymphatic system<br>disorders<br>subjects affected / exposed<br>occurrences (all)     | 458 / 458<br>(100.00%)<br>458 | 358 / 361 (99.17%)<br>358 |  |
| Gastrointestinal disorders<br>Gastro-intestinal disorders<br>subjects affected / exposed<br>occurrences (all)                           | 365 / 458 (79.69%)<br>365     | 305 / 361 (84.49%)<br>305 |  |
| Hepatobiliary disorders<br>Hepatobiliary disorders<br>subjects affected / exposed<br>occurrences (all)                                  | 9 / 458 (1.97%)<br>9          | 4 / 361 (1.11%)<br>4      |  |
| Skin and subcutaneous tissue disorders<br>Skin and subcutaneous tissue<br>disorders<br>subjects affected / exposed<br>occurrences (all) | 138 / 458 (30.13%)<br>138     | 115 / 361 (31.86%)<br>115 |  |
| Renal and urinary disorders<br>Renal and urinary disorders<br>subjects affected / exposed<br>occurrences (all)                          | 31 / 458 (6.77%)<br>31        | 16 / 361 (4.43%)<br>16    |  |
| Infections and infestations<br>Infections and infestations                                                                              |                               |                           |  |

|                                                                                                                              |                           |                           |  |
|------------------------------------------------------------------------------------------------------------------------------|---------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                             | 198 / 458 (43.23%)<br>198 | 145 / 361 (40.17%)<br>145 |  |
| Metabolism and nutrition disorders<br>Metabolism and nutrition disorders<br>subjects affected / exposed<br>occurrences (all) | 70 / 458 (15.28%)<br>70   | 35 / 361 (9.70%)<br>35    |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                  |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|
| 20 October 2011 | Version 2.0 (20 October 2011)<br>Removal of LH dosage in men under the age of 45 and participating in the fertility study. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30658935>