# Clinical trial results:
# A PHASE IB/II STUDY OF ESCALATING DOSES OF REVLIMID IN ASSOCIATION WITH R-CHOP (R2-CHOP) IN THE TREATMENT OF B-CELL LYMPHOMA

## Summary

| | |
|---|---|
| EudraCT number | 2007-007698-22 |
| Trial protocol | FR |
| Global end of trial date | 23 November 2015 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 14 January 2018 |
| First version publication date | 14 January 2018 |
| Summary attachment (see zip file) | CSR Synopsis (CSR_synopsis_R2CHOP_V1_LYSARC 20171221.pdf) |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | R2-CHOP |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00901615 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | LYSARC |
| Sponsor organisation address | CH Lyon Sud – Secteur Sainte Eugénie – Pav 6D, PIERRE-BENITE Cedex, France, 69495 |
| Public contact | Yvain ROBREAU, LYSARC, 33 4 72 66 93 33, |
| Scientific contact | Prof Hervé TILLY, LYSA, 33 2 32 08 22 00, |
| Sponsor organisation name | Centre Henri Becquerel |
| Sponsor organisation address | rue d'Amiens, ROUEN, France, 76038 |
| Public contact | Yvain ROBREAU, LYSARC<br>CH Lyon Sud – Secteur Sainte Eugénie – Pav 6D - 69495 PIERRE-BENITE Cedex - France, +33 4 72 66 93 33, |
| Scientific contact | Prof. Hervé TILLY, LYSA<br>CH Lyon Sud - Service d'Hématologie – Bâtiment 1 F 69495 PIERRE-BENITE Cedex , +33 2 32 08 22 00, |

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 | No |

| | |
|---|---|
| 1901/2006 apply to this trial? | |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 23 November 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 23 November 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the Phase Ib part of the study is to determine the recommended dose (RD) of lenalinomide (Revlimid) when administered in association with R-CHOP.
The primary objective of the Phase II part of the study is to assess the efficacy of the association of Revlimid and R-CHOP in a population of patients with follicular lymphoma as measured by the response rate at the end of treatment.

Protection of trial subjects:

salavge therapy if necessary

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 06 January 2009 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy, Scientific research |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | France: 108 |
| Worldwide total number of subjects | 108 |
| EEA total number of subjects | 108 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |

| | |
|---|---|
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 108 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Fom 06-Jan-2009 to 25-Jan-2012

### Pre-assignment

Screening details:

- Phase IB: Patients with one of the following B-cell Lymphoma, CD 20 positive:
  - Mantle cell, Marginal zone, follicular
  - Histological transformation from low grade to high grade
  - Diffuse large B cell
- Phase II: Patients with follicular lymphoma, WHO grade 1, 2 or 3a with at least one of the following signs requiring initiation of treatment

### Period 1

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

### Arms

| | |
|---|---|
| **Arm title** | R2-CHOP |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Revlimid |
| Investigational medicinal product code | Lenalidomide |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

2.5 mg, 5 mg and 10 mg strengths.
All patients were treated with R2-CHOP at a three-week interval for 6 cycles.

| **Number of subjects in period 1** | R2-CHOP |
|---|---|
| Started | 108 |
| Completed | 101 |
| Not completed | 7 |
| Consent withdrawn by subject | 2 |
| Adverse event, non-fatal | 1 |
| concurrent illness | 2 |
| Protocol deviation | 1 |
| Lack of efficacy | 1 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall trial |
|---|---|

Reporting group description: -

| Reporting group values | Overall trial | Total | |
|---|---|---|---|
| Number of subjects | 108 | 108 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 108 | 108 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous<br>Units: years | | | |
| median | 59 | | |
| full range (min-max) | 24 to 77 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 52 | 52 | |
| Male | 56 | 56 | |

### Subject analysis sets

| Subject analysis set title | Phase I part |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:
Subjects included in Phase I part

| Subject analysis set title | Phase II part |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:
Subjects included in phase II part

| Reporting group values | Phase I part | Phase II part | |
|---|---|---|---|
| Number of subjects | 28 | 80 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |

| | | | |
|---|---|---|---|
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 28 | 80 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| median | 58 | 60 | |
| full range (min-max) | 24 to 77 | 29 to 71 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 12 | 40 | |
| Male | 16 | 40 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | R2-CHOP |
| Reporting group description: - | |
| Subject analysis set title | Phase I part |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects included in Phase I part | |
| Subject analysis set title | Phase II part |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects included in phase II part | |

### Primary: Complete Response Rate at the End of Treatment According to Cheson 99

| | |
|---|---|
| End point title | Complete Response Rate at the End of Treatment According to Cheson 99[1] |
| End point description: | |
| End point type | Primary |
| End point timeframe: end of treatment | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Included in figure

| End point values | R2-CHOP | Phase II part | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 0[2] | | | |
| Units: Subjects with CR or CRu | | | | |
| CR or CRu | | 59 | | |
| Other | | 21 | | |

Notes:

[2] - Not applicable

### Statistical analyses

No statistical analyses for this end point

### Primary: Dose limiting toxicities (DLT)

| | |
|---|---|
| End point title | Dose limiting toxicities (DLT)[3] |
| End point description: | |
| End point type | Primary |
| End point timeframe: End of cycle 2 | |

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis

| **End point values** | R2-CHOP | Phase I part | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 0[4] | | | |
| Units: Subject presenting DLT | | | | |
| with DLT | | 6 | | |
| without DLT | | 21 | | |

Notes:

[4] - Not applicable

### Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Response Rate at the End of Treatment

| End point title | Overall Response Rate at the End of Treatment |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

End of treatment

| **End point values** | R2-CHOP | Phase II part | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 0[5] | | | |
| Units: Subjects with response | | | | |
| response (CR, CRu, PR) | | 75 | | |
| Other (SD, PD) | | 5 | | |

Notes:

[5] - Not applicable

### Statistical analyses

No statistical analyses for this end point

## Secondary: Progression free survival

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

60 months

| End point values | R2-CHOP | Phase II part | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 0[6] | | | |
| Units: Subjects presenting event | | | | |
| Event | | 18 | | |
| Censored | | 62 | | |

Notes:

[6] - Not applicable

| Attachments (see zip file) | PFS.png |
|---|---|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival

| End point title | Overall survival |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

60 months

| End point values | R2-CHOP | Phase II part | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 0[7] | | | |
| Units: Deaths | | | | |
| Dead | | 4 | | |
| Censored | | 76 | | |

Notes:

[7] - Not applicable

| Attachments (see zip file) | OS.png |
|---|---|

### Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Overall study | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 15.0 |

| Reporting groups | |
|---|---|
| Reporting group title | Phase I |
| Reporting group description: - | |
| Reporting group title | Phase II |
| Reporting group description: - | |

| Serious adverse events | Phase I | Phase II | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 27 (25.93%) | 21 / 80 (26.25%) | |
| number of deaths (all causes) | 0 | 4 | |
| number of deaths resulting from adverse events | 0 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasms benign, malignant and unspecified | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 6 / 80 (7.50%) | |
| occurrences causally related to treatment / all | 1 / 1 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Vascular disorders | | | |
| Vascular disorders | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| 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 | 2 / 27 (7.41%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |

| | | | |
|---|---|---|---|
| Immune system disorders ( | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Reproductive system and breast disorders | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 3 / 80 (3.75%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Investigations | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 2 / 80 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Injury, poisoning and procedural complications | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac disorders | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Blood and lymphatic system disorders | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 5 / 80 (6.25%) | |
| occurrences causally related to treatment / all | 1 / 2 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Eye disorders | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastrointestinal disorders | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 3 / 80 (3.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin and subcutaneous tissue disorders | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 2 / 80 (2.50%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal and urinary disorders ( | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 4 / 80 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infections and infestations | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 6 / 80 (7.50%) | |
| occurrences causally related to treatment / all | 2 / 2 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Phase I | Phase II | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 27 / 27 (100.00%) | 68 / 80 (85.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 7 / 80 (8.75%) | |
| occurrences (all) | 0 | 7 | |
| Vascular disorders | | | |
| VASCULAR DISORDERS | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 4 / 80 (5.00%) | |
| occurrences (all) | 2 | 7 | |
| Surgical and medical procedures | | | |
| SURGICAL AND MEDICAL PROCEDURES | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 80 (1.25%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 2 / 80 (2.50%) | |
| occurrences (all) | 3 | 2 | |
| Immune system disorders | | | |
| IMMUNE SYSTEM DISORDERS | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 80 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Reproductive system and breast disorders | | | |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 80 (1.25%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 3 / 80 (3.75%) | |
| occurrences (all) | 3 | 4 | |

| | | | |
|---|---|---|---|
| Investigations<br>INVESTIGATIONS<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 27 (0.00%)<br>0 | <br><br>4 / 80 (5.00%)<br>5 | |
| Injury, poisoning and procedural complications<br>INJURY, POISONING AND PROCEDURAL COMPLICATIONS<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 27 (0.00%)<br>0 | <br><br>1 / 80 (1.25%)<br>2 | |
| Cardiac disorders<br>CARDIAC DISORDERS<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 27 (3.70%)<br>1 | <br><br>2 / 80 (2.50%)<br>3 | |
| Nervous system disorders<br>NERVOUS SYSTEM DISORDERS<br>subjects affected / exposed<br>occurrences (all) | <br><br>3 / 27 (11.11%)<br>3 | <br><br>7 / 80 (8.75%)<br>8 | |
| Blood and lymphatic system disorders<br>BLOOD AND LYMPHATIC SYSTEM DISORDERS<br>subjects affected / exposed<br>occurrences (all) | <br><br>27 / 27 (100.00%)<br>88 | <br><br>68 / 80 (85.00%)<br>420 | |
| Eye disorders<br>EYE DISORDERS<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 27 (0.00%)<br>0 | <br><br>2 / 80 (2.50%)<br>3 | |
| Gastrointestinal disorders<br>GASTROINTESTINAL DISORDERS<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 27 (0.00%)<br>0 | <br><br>8 / 80 (10.00%)<br>12 | |
| Hepatobiliary disorders<br>HEPATOBILIARY DISORDERS<br>subjects affected / exposed<br>occurrences (all) | <br><br>2 / 27 (7.41%)<br>2 | <br><br>1 / 80 (1.25%)<br>1 | |
| Skin and subcutaneous tissue disorders<br>SKIN AND SUBCUTANEOUS TISSUE DISORDERS<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 27 (3.70%)<br>1 | <br><br>4 / 80 (5.00%)<br>5 | |
| Renal and urinary disorders | | | |

| | | | |
|---|---|---|---|
| RENAL AND URINARY DISORDERS<br>subjects affected / exposed<br>occurrences (all) | 0 / 27 (0.00%)<br>0 | 4 / 80 (5.00%)<br>4 | |
| Infections and infestations<br>INFECTIONS AND INFESTATIONS<br>subjects affected / exposed<br>occurrences (all) | 14 / 27 (51.85%)<br>14 | 29 / 80 (36.25%)<br>42 | |
| Metabolism and nutrition disorders<br>METABOLISM AND NUTRITION DISORDERS<br>subjects affected / exposed<br>occurrences (all) | 6 / 27 (22.22%)<br>6 | 3 / 80 (3.75%)<br>3 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 15 October 2008 | The first one concerns form corrections in the research protocol (mainly harmonizations between the synopsis and the text of the protocol and corrections of translation errors of measurement units), the submission of a patient booklet which was be distributed to the participants in the study and aimed at ensuring compliance with the test treatment, the collection of safety data (version 1 of 15 October 2008) and the modification of the investigator coordinator of the study, Professor Bertrand COIFFIER, by Professor Hervé TILLY and the modification of the principal investigator of the René Huguenin center of St Cloud, Dr. Maud JANVIER, by Dr. Carole SOUSSAIN. These modifications has been implemented in Protocol version 3 dated October 15, 2008. |
| 01 October 2009 | Second amendment concerns the addition of a dose level in Phase IB at 25 mg (indeed, the initially planned maximum level of 20 mg was well tolerated in the trial as in other trials studying the combination of Lenalidomide and Rituximab) and the addition of a cut-off date concerning the analysis of the primary criterion of Phase IB prior to that concerning the analysis of secondary criteria due to the earlier availability of data. These modifications has been implemented in Protocol version 4 dated October 1st, 2009. |
| 27 October 2010 | Third amendment concerns:<br>1. The transfer of the trial promotion to the Centre Henri Becquerel (Rouen, France).<br>2. Following the inclusion of all patients in Phase I, the primary endpoint data were analyzed. The Research Monitoring Committee recommended the 25 mg dose for Phase II with a schedule of dose adjustments for toxicity.<br>3. Five search locations are added and another has changed address.<br>4. In order to take into account the evolution of the practices, the protocol plan foreseen two cycles of rituximab alone for the end of the induction treatment and recommended the establishment of a maintenance treatment for the answering patients.<br>5. The PET-scan exam was added to the efficacy evaluation criteria as it now corresponds to the usual care of the patients involved in the research.<br>6. The safety information of the investigational drug was updated following the updating of the Investigator's Brochure.<br>These modifications has been implemented in Protocol version 5 dated October 27, 2010. |
| 30 August 2011 | Fourth amendment concerns<br>1. The conditions for reporting secondary malignancies and the conditions for reviewing the data by the DSMC following the recommendations of the AFSSAPS concerning the suspicion of risk of occurrence of secondary cancers dear to patients receiving lenalidomide.<br>2. The change of principal investigators in three research sites: the Principal Investigator of the Nancy Center, that of Paris St Louis and that of the Institut Curie have been modified.<br>3. The safety information of the investigational drug has been updated following updates to the Investigator Brochure version 14 and RCP version 20 of Revlimid.<br>These modifications has been implemented in Protocol version 6 dated August 30, 2011. |

| | |
|---|---|
| 16 December 2011 | Last amendment to the protocol concerns the updating of the product's safety information following the transmission of the new version of Investigator's Brochure No. 15 and RCP 22 by the product owner. For this purpose, a supplement of information leaflet of the patients has been written.<br>These modifications has been implemented in Protocol version 6.2 dated December 16, 2011. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/22733106