



Clinical trial results:

Dose densified chemoimmunotherapy with early CNS prophylaxis in patients less than 65 years with high risk (aalPI2) Diffuse Large B-Cell Lymphoma. (NLG-LBC05, CHIC)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2010-023125-38 |
| Trial protocol | SE FI NO DK |
| Global end of trial date | 14 May 2020 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 20 November 2024 |
| First version publication date | 20 November 2024 |
| Summary attachment (see zip file) | CHIC, Summary of results (CHIC, Summary of results, 11.2.2020.pdf) |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | NLG-LBC05 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01325194 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | CHIC: NLG-LB05 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Hospital district of Helsinki and Uusimaa |
| Sponsor organisation address | Haartmaninkatu 4, Helsinki, Finland, 00290 |
| Public contact | Sirpa Leppä, Nordic Lymphoma Group, +358 504270820, sirpa.leppa@helsinki.fi |
| Scientific contact | Sirpa Leppä, Nordic Lymphoma Group, +358 504270820, sirpa.leppa@helsinki.fi |

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 | 14 May 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 14 May 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 May 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Time to treatment failure from date of registration.
CNS relapse rate at 1,5 years.

Protection of trial subjects:

Patient protection

The responsible investigators will ensure that this study is conducted in agreement with either the declaration of Helsinki (Tokyo, Venice and Hong Kong amendments), or the laws and the regulations of the countries, whichever provide the greatest protection of the patient. The protocol has been written, and the study will be conducted according to the guidelines for Good Clinical Practice issued by the European Union. As a pre-requirement for implementation, the protocol will have to be approved by the local, regional or national Ethical Review Boards according to the existing national and local regulatory requirements.

Background therapy:

A mainstay of therapy has been CHOP chemotherapy regimen, which is as effective as and less toxic than more intensive regimens (2-4). With a CHOP-like therapy, approximately 50% of all patients are cured. Recently, combination of rituximab, a monoclonal antibody targeting CD20, with CHOP has led to a marked improvement of survival.

Evidence for comparator:

This was a phase II study without a direct comparator. Instead the study results were compared to the recent CRY 04 study . Previous reduced CNS relapse rate in a phase II study with a historical control does not prove the importance of prophylaxis and should ideally be confirmed in an adequately sized phase III study. However, such a study cannot be performed within the Nordic community within a reasonable time. Internationally it was not possible to agree upon a treatment plan for a multicentre prospective randomized study due lack of conformity concerning treatment recommendations for this treatment group.

| | |
|---|---------------|
| Actual start date of recruitment | 14 March 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Norway: 46 |
| Country: Number of subjects enrolled | Sweden: 5 |
| Country: Number of subjects enrolled | Denmark: 33 |
| Country: Number of subjects enrolled | Finland: 55 |
| Worldwide total number of subjects | 139 |
| EEA total number of subjects | 139 |

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) | 139 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Recruitment started 14.3.2011, stopped 31.12.2014

Pre-assignment

Screening details:

Main inclusion criteria:

- Age ≥ 18 - < 65 years
- Histologically confirmed CD20+ diffuse large B-cell lymphoma
- Advanced stage

Pre-assignment period milestones

| | |
|------------------------------|-----|
| Number of subjects started | 139 |
| Number of subjects completed | 139 |

Period 1

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

Blinding implementation details:

No blinding

Arms

| | |
|-----------|---------------------------|
| Arm title | Phase II single arm study |
|-----------|---------------------------|

Arm description:

Patients are given a pre-phase medication consisting of dexamethasone, rituximab and vincristine, followed by two cycles of high dose methotrexate with CHOP/CHOD and rituximab, and four cycles of CHOEP/CHOED with rituximab. In addition, one course of high dose cytarabine and rituximab, and three courses of liposomal cytarabine (DepoCyte®) are given. The courses should be given with a two week interval if possible.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Methotrexate 3 g/m² i.v. as a 3 hour infusion. Folic acid rescue (leucovorin) is given after 24 hours,

| | |
|--|---|
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cyclophosphamide 750 mg/m² i.v. day 1

| | |
|--|---|
| Investigational medicinal product name | Doxorubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |

| | |
|--|---|
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Doxorubicin 50 mg/m ² i.v. day 1 | |
| Investigational medicinal product name | Vincristine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Vincristine 1.4 mg/m ² (max. 2.0 mg) i.v. day 1 | |
| Investigational medicinal product name | Prednisone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Prednisone 100 mg po days 1-5 OR Dexamethasone 10 mg x 2 daily p.o. (alternatively betamethasone 8 mg x 2 daily p.o.) days 1-5 in courses including DepoCyte | |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Rituximab 375 mg/m ² i.v. day 1 | |
| Investigational medicinal product name | Etoposide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Etoposide 100 mg/m ² i.v. day 1-3 | |
| Investigational medicinal product name | Pegfilgrastim |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| Long lasting G-CSF (pegfilgrastim, Neulasta®) 48 hours after chemotherapy course 1 and 2, 24 hours after the 3-day CHOEP courses and the 2-day High dose AraC courses. | |
| Investigational medicinal product name | Cytarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Cytarabine 3 g/m ² i.v. x 2 for 2 days (in total four times). Cytarabine is given as a 1-hour infusion every 12-hour in 500 ml glucose 5%. | |
| Investigational medicinal product name | DepoCyte |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |

| | |
|--------------------------|-----------------|
| Routes of administration | Intrathecal use |
|--------------------------|-----------------|

Dosage and administration details:

DepoCyt 50 mg by intraspinal route.

| Number of subjects in period 1 | Phase II single arm study |
|---------------------------------------|---------------------------|
| Started | 139 |
| Completed | 126 |
| Not completed | 13 |
| Adverse event, non-fatal | 9 |
| Lack of efficacy | 4 |

Baseline characteristics

Reporting groups

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

| Reporting group values | Overall trial | Total | |
|--|---------------|-------|--|
| Number of subjects | 139 | 139 | |
| Age categorical | | | |
| Adults, 18-64 years | | | |
| 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) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Adults 18-64 | 139 | 139 | |
| Age continuous | | | |
| Units: years | | | |
| median | 56 | | |
| full range (min-max) | 20 to 64 | - | |
| Gender categorical | | | |
| 51 women, 88 men were included in the study | | | |
| Units: Subjects | | | |
| Female | 51 | 51 | |
| Male | 88 | 88 | |
| Large B-cell lymphoma | | | |
| Units: Subjects | | | |
| DLBCL | 113 | 113 | |
| TCRB | 5 | 5 | |
| PMBCL | 8 | 8 | |
| Intravascular | 1 | 1 | |
| Follicular lymphoma, grade 3B | 5 | 5 | |
| Not reviewed, not recorded | 7 | 7 | |

Subject analysis sets

| | |
|----------------------------|---------------|
| Subject analysis set title | Analysis |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The main analysis included those registered patients that started the protocol treatment.

TTF as well as the secondary endpoints Overall Survival and Time to Progression, will be presented using Kaplan-Meier curves and the effect of clinical and biological prognostic factors will be analysed by means of Cox regression. Toxicity and incidence of CNS-relapse will be shown in descriptive tables. The study

results will be compared to the recent CRY 04 study. The aims of the study are to at least achieve the 3-year TTF of the CRY04 study and with a substantial reduction of the CNS relapse rate with the use of early systemic and intrathecal CNS prophylaxis. A reduced CNS relapse rate in a phase II study with a historical control will not prove the importance of prophylaxis and should ideally be confirmed in an adequately sized phase III study.

| Reporting group values | Analysis | | |
|---|----------|--|--|
| Number of subjects | 139 | | |
| Age categorical | | | |
| Adults, 18-64 years | | | |
| 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 | | |
| Adults 18-64 | 139 | | |
| Age continuous | | | |
| Units: years | | | |
| median | 56 | | |
| full range (min-max) | 20 to 64 | | |
| Gender categorical | | | |
| 51 women, 88 men were included in the study | | | |
| Units: Subjects | | | |
| Female | 51 | | |
| Male | 88 | | |
| Large B-cell lymphoma | | | |
| Units: Subjects | | | |
| DLBCL | 113 | | |
| TCRB | 5 | | |
| PMBCL | 8 | | |
| Intravascular | 1 | | |
| Follicular lymphoma, grade 3B | 5 | | |
| Not reviewed, not recorded | 7 | | |

End points

End points reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Phase II single arm study |
|-----------------------|---------------------------|

Reporting group description:

Patients are given a pre-phase medication consisting of dexamethasone, rituximab and vincristine, followed by two cycles of high dose methotrexate with CHOP/CHOD and rituximab, and four cycles of CHOEP/CHOED with rituximab. In addition, one course of high dose cytarabine and rituximab, and three courses of liposomal cytarabine (DepoCyte®) are given. The courses should be given with a two week interval if possible.

| | |
|----------------------------|----------|
| Subject analysis set title | Analysis |
|----------------------------|----------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The main analysis included those registered patients that started the protocol treatment. TTF as well as the secondary endpoints Overall Survival and Time to Progression, will be presented using Kaplan-Meier curves and the effect of clinical and biological prognostic factors will be analysed by means of Cox regression. Toxicity and incidence of CNS-relapse will be shown in descriptive tables. The study results will be compared to the recent CRY 04 study. The aims of the study are to at least achieve the 3-year TTF of the CRY04 study and with a substantial reduction of the CNS relapse rate with the use of early systemic and intrathecal CNS prophylaxis. A reduced CNS relapse rate in a phase II study with a historical control will not prove the importance of prophylaxis and should ideally be confirmed in an adequately sized phase III study.

Primary: Three – year - time to treatment failure (TTF)

| | |
|-----------------|--|
| End point title | Three – year - time to treatment failure (TTF) |
|-----------------|--|

End point description:

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

End point timeframe:

Time to treatment failure

Interval between the registration date and the date of documented progression or lack of response, first relapse, death for any reason or discontinuation/change of therapy because of toxicity, whichever occurs first. Otherwise

| End point values | Phase II single arm study | Analysis | | |
|-----------------------------|---------------------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 139 | 139 | | |
| Units: months | | | | |
| number (not applicable) | 139 | 139 | | |

Statistical analyses

| | |
|----------------------------|-----|
| Statistical analysis title | TTF |
|----------------------------|-----|

Statistical analysis description:

Time to treatment failure

Interval between the registration date and the date of documented progression or lack of response, first relapse, death for any reason or discontinuation/change of therapy because of toxicity, whichever occurs first. Otherwise, patients will be censored at the last date they were known to be alive. For patients not responding at any time point on study treatment, TTF is defined as 1 day.

| | |
|-------------------|--------------------------------------|
| Comparison groups | Phase II single arm study v Analysis |
|-------------------|--------------------------------------|

| | |
|---|-----------------------|
| Number of subjects included in analysis | 278 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | = 0.03 ^[2] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.42 |
| upper limit | 0.96 |

Notes:

[1] - survival

[2] - Comparison is done with historical control.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events with excerpts occurring during the treatment period and until the end of the last treatment administration

Adverse event reporting additional description:

Serious adverse events will be reported until 30 days after the last course of chemotherapy.

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

Dictionary used

| | |
|-----------------|------|
| Dictionary name | CTCA |
|-----------------|------|

| | |
|--------------------|-----|
| Dictionary version | 3.0 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | AEs (> grade 2) |
|-----------------------|-----------------|

Reporting group description: -

| Serious adverse events | AEs (> grade 2) | | |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 139 (6.47%) | | |
| number of deaths (all causes) | 23 | | |
| number of deaths resulting from adverse events | 4 | | |
| Vascular disorders | | | |
| Subdural hematoma | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| GI hemorrhage | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Infections and infestations | | | |
| Multiorgan failure | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Septisemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 139 (1.44%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Unspecified toxicity | | | |
| subjects affected / exposed | 4 / 139 (2.88%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Progressive multifocal neuroencephalopathy | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |

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

| | | | |
|---|---|--|--|
| Non-serious adverse events | AEs (> grade 2) | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 79 / 139 (56.83%) | | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | Additional description: In the case of this trial, treatment consist of dose densified immunochemotherapy which results in adverse events such as hematological toxicity. Therefore we consider this part irrelevant. | | |
| subjects affected / exposed | 79 / 139 (56.83%) | | |
| occurrences (all) | 560 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 28 November 2011 | <p>(5.1.2011 first approval for the study)</p> <p>Amendment 01</p> <ol style="list-style-type: none">1. New inclusion criterion for Danish and Swedish centres: Epidural lymphoma.2. New exclusion criterion: Conditions that may be compatible with impaired cerebrospinal fluid flow.3. Addition of two rituximab courses (one extra during pre-phase on day -4 and one during 7th course with high-dose cytarabine).4. Increased dose of dexamethasone during CHOD or CHOED courses. Dexamethasone can be substituted with equipotent amount of betamethasone.5. Option to delay second R-CHOP course with 1-2 days.6. Common Terminology Criteria for Adverse Events v.3.0 (CTCAE) (Appendix 3).7. Revised methotrexate excretion table (Appendix 4).8. Sampling of cerebrospinal fluid for freezing |
| 20 September 2012 | <p>Amendment 02</p> <ol style="list-style-type: none">1. Administration of DepoCyte omitted from the protocol.2. CHOED courses changed to CHOEP (Dxm changed to Prednisone in courses 1, 3 and 5).3. Number of study population increased from 170.4. Inclusion criteria for Danish centres have been revised to be the same as in Finland and Norway.5. List of local PIs in Denmark has been updated (Appendix 1 on page 34). |

| | |
|-------------------|---|
| 01 September 2013 | <p>Amendment 03</p> <ol style="list-style-type: none"> 1. Administration of DepoCyte is reimplemented to the protocol in Denmark, Finland and Norway as in protocol version 3. 2. CHOEP courses changed to CHOED (Prednisone changed to Dxm in courses 1, 3 and 5). 3. Revised methotrexate excretion table (Appendix 4). 4. Study will be continued until the end of 2014. New planned sample size is 130. 5. Prephase can be initiated before registration if clinically needed. 6. Treatment and particularly possible DepoCyte associated side effects are recorded using a specific patient questionnaire after cycles 1, 3 and 5 at the beginning of the following cycle. 7. Contact information for the protocol secretariat to register patients and report SAEs has been changed. 8. List of local PIs and study centres in Sweden has been updated (Appendix 1 on page 33). |
|-------------------|---|

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/32380536>