Clinical trial results:
Dose densified chemoimmunotherapy with early CNS prophylaxis in patients less than 65 years with high risk (aaIPI2) 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/m2 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/m2 (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 2daily 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/m2 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/m2 i.v. day 1-3	
Investigational medicinal product name	Pegfilgastrim
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/m2 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:

DepoCyte 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 hemorrage			
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	(5.1.2011 first approval for the study) Amendment 01 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	Amendment 02 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	Amendment 03 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