Clinical trial results:
A phase II study of R-CHOP with intensive CNS prophylaxis and scrotal irradiation in patients with primary testicular diffuse large B-cell lymphoma

Summary

EudraCT number	2009-011789-26
Trial protocol	IT
Global end of trial date	29 September 2023

Results information

Result version number	v1
This version publication date	24 October 2024
First version publication date	24 October 2024
Summary attachment (see zip file)	IELSG30 Synopsis Results (IELSG30 Results_synopsys.pdf)

Trial information

Trial identification

Sponsor protocol code	IELSG30

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00945724
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	International Extranodal Lymphoma Study Group (IELSG)
Sponsor organisation address	Via Vincenzo Vela 6, Bellinzona, Switzerland, 6500
Public contact	Uffici Studi FIL, Fondazione Italiana Linfomi - ETS, +39 0599769918, startup@filinf.it
Scientific contact	Uffici Studi FIL, Fondazione Italiana Linfomi - ETS, +39 0599769918, startup@filinf.it

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	29 August 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 September 2023
Global end of trial reached?	Yes
Global end of trial date	29 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate safety and feasibility of the R-CHOP regimen in combination with intrathecal liposomal cytarabine and systemic intermediate-dose methotrexate followed by loco-regional radiotherapy in untreated patient with stage I and II Primary Testicular Lymphoma

Protection of trial subjects:

Guidelines for dose modifications were included in the study protocol, in order to minimize any possible risks for the patients.
All concomitant medications for medical conditions other than B-NHL are permitted, as clinically indicated.
All supportive therapies other than anti-cancer treatment needed for the management of patients enrolled in this study are permitted

During treatment the following therapies were recommended as concomitant therapy:
- Premedication for rituximab infusion with paracetamol and diphenhydramine is mandatory before each infusion of rituximab, because it may reduce infusion reactions.
- Use of corticosteroids is allowed as pre-medication for rituximab infusion.
- Pre-phase therapy is recommended in older patients (>65 years) with PDN 100 mg/die for 10 days and VCR 1.5 mg total dose
- G-CSF or Peg-Filgrastim as primary prophylaxis for the prevention of febrile neutropenia in older (>65 years) patients and in
presence of neutropenia < 1.0 x 109/L.
- Cotrimoxazole BACTRIM 3 tablets/week (or 1 x 2/day for two days/week) or Pentamidine aerosol every 15 days in patients with Bactrim allergy or in patients with G6PD deficiency throughout the treatment and consolidation phase.
- Platelets and red blood cell transfusion in case of Hb < 8 g/dL or Plts < 10 x 109/L.
- Laxatives and other prebiotics and probiotics to prevent constipation and should be administered according to standard practice
- Antiemetic agents

Background therapy:

- Antiviral prophylaxis with acyclovir 800-1200 mg at day since the beginning of therapy in patients with herpes virus infection reactivation. Additional prophylaxis with levofloxacin or ciprofloxacin to be administered in case of neutropenia <1.0 x 109/l.
- In patients with Ab antiHBcAg +, Ab antiHBsAg +/- prophylaxis against hepatitis B reactivation with Lamivudine 100 mg/die from the start of the treatment to one year after the end of the treatment.

Evidence for comparator: -

Actual start date of recruitment	27 September 2009
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	Italy: 47

Country: Number of subjects enrolled	Switzerland: 7
Worldwide total number of subjects	54
EEA total number of subjects	47

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)	27
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment lasted from 27 September 2009 to 13 July 2017.

Pre-assignment

Screening details:

Fifty four patients were screened and all were enrolled and treated.

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	Arm 1

Arm description:

Weeks 1 -15
All patients treated with 6 cycles of R-CHOP (CHOP21) on days 0/1 to 5, to be repeated every 21 days
Intratecal (IT) Chemotherapy: liposomal cytarabine on day 0 of cycles 2, 3, 4 and 5 of R-CHOP
Weeks 18 - 22
High Dose (HD) Methotrexate (MTX) Days 0 - 4 of two 14 days cycles
From Week 25
Scrotal prophylactic radio therapy (RT) to the contralateral testis.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m2 on day o or day 1 of R-CHOP regimen for six 21 days cycles

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

Dosage and administration details:

750 mg/m2 on day1 of of R-CHOP regimen for six 21 days cycles

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 mg/m2 of R-CHOP regimen for six 21 days cycles

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details: 1.3 mg/m2 (2mg dose max) on day 1 of R-CHOP regimen for six of 21 days cycles	
Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 40 mg/m2 on days 1 -5 of R-Chop regimen for six 21 days cycles	
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intratracheal use
Dosage and administration details: 50 mg on day 0 of cycles 2, 3, 4 and 5 of R-Chop 21 cycles	
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 1.5 g/m2 Days 0 - 4 of two 14 days cycles	

Number of subjects in period 1	Arm 1
Started	54
Completed	45
Not completed	9
Consent withdrawn by subject	2
Physician decision	1
Adverse event, non-fatal	5
Second malignancy	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1
Reporting group description:	
Weeks 1 -15 All patients treated with 6 cycles of R-CHOP (CHOP21) on days 0/1 to 5, to be repeated every 21 days Intratecal (IT) Chemotherapy: liposomal cytarabine on day 0 of cycles 2, 3, 4 and 5 of R-CHOP Weeks 18 - 22 High Dose (HD) Methotrexate (MTX) Days 0 - 4 of two 14 days cycles From Week 25 Scrotal prophylactic radio therapy (RT) to the contralateral testis.	

Reporting group values	Arm 1	Total	
Number of subjects	54	54	
Age categorical 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)	27	27	
From 65-84 years	27	27	
85 years and over	0	0	
Arm 1	0	0	
Age continuous Units: years			
median	66		
full range (min-max)	37 to 79	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	54	54	
Ann Arbor Stage Units: Subjects			
Stage I	32	32	
Stage II	22	22	
Bilateral testicular location Units: Subjects			
Bilateral testicular location	1	1	
No Bilateral testicular location	53	53	
B symptoms Units: Subjects			
Presence of B symptoms	2	2	
No presence of B symptoms	52	52	
Serum lactate dehydrogenase (LDH) Units: Subjects			

> normal upper value	7	7	
</= normal upper value	47	47	
Serun Beta2-microglobulin Units: Subjects			
> normal upper value	8	8	
</= normal upper value	40	40	
Not recorded	6	6	

Subject analysis sets

Subject analysis set title	R-CHOP + lyposomal cytarabine
Subject analysis set type	Full analysis
Subject analysis set description: Subjects treated with R-CHOP (CHOP21)	
Subject analysis set title	HD-MTX
Subject analysis set type	Full analysis
Subject analysis set description: Subjects treated with HD-MTX	

Reporting group values	R-CHOP + lyposomal cytarabine	HD-MTX	
Number of subjects	54	48	
Age categorical 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)	27	26	
From 65-84 years	27	22	
85 years and over	0	0	
Arm 1	54	48	
Age continuous Units: years			
median			
full range (min-max)			
Gender categorical Units: Subjects			
Female	0	0	
Male	54	48	
Ann Arbor Stage Units: Subjects			
Stage I			
Stage II			
Bilateral testicular location Units: Subjects			
Bilateral testicular location			
No Bilateral testicular location			

B symptoms Units: Subjects			
Presence of B symptoms No presence of B symptoms			
Serum lactate dehydrogenase (LDH) Units: Subjects			
> normal upper value </= normal upper value			
Serun Beta2-microglobulin Units: Subjects			
> normal upper value </= normal upper value Not recorded			

End points

End points reporting groups

Reporting group title	Arm 1

Reporting group description:

Weeks 1 -15
All patients treated with 6 cycles of R-CHOP (CHOP21) on days 0/1 to 5, to be repeated every 21 days
Intratecal (IT) Chemotherapy: liposomal cytarabine on day 0 of cycles 2, 3, 4 and 5 of R-CHOP
Weeks 18 - 22
High Dose (HD) Methotrexate (MTX) Days 0 - 4 of two 14 days cycles
From Week 25
Scrotal prophylactic radio therapy (RT) to the contralateral testis.

Subject analysis set title	R-CHOP + lyposomal cytarabine
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects treated with R-CHOP (CHOP21)

Subject analysis set title	HD-MTX
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects treated with HD-MTX

Primary: Feasibility

End point title	Feasibility[1]

End point description:

AEs causing withdrawal from study treatment

End point type	Primary

End point timeframe:

From treatment start to the 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: No statistical analysis was planned or conducted for this endpoint.
The final sample size, identifying a clinically relevant 15% improvement in PFS , was 54 patients, in a single-arm study, resulting in a 15% increase in PFS (from 67% to 82%), with a power of 80% and α at .05 (1-sided).

End point values	Arm 1	R-CHOP + lyposomal cytarabine	HD-MTX	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	54	54	48	
Units: Subjects				
Subjects discontinuing treatment for toxicity	6	3	3	

Statistical analyses

No statistical analyses for this end point

Secondary: 5 year cumulative incidence of progression

End point title	5 year cumulative incidence of progression

End point description:

Cumulative incidence of progression was measured from the date of achievement of a remission to the date of relapse until 5 years from study entry;

End point type	Secondary

End point timeframe:

From the first documented response to relapse until 5 years from study entry

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Percentage				
number (confidence interval 95%)	6 (2 to 16)			

Statistical analyses

No statistical analyses for this end point

Secondary: 5 years progression free survival (PFS)

End point title	5 years progression free survival (PFS)

End point description:

PFS was meausered from time of study entry until lymphoma relapse/progression, or death because of any cause

End point type	Secondary

End point timeframe:

From study entry until 5 years after

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Percentage				
number (confidence interval 95%)	91 (79 to 96)			

Statistical analyses

No statistical analyses for this end point

Secondary: 5 years Overall survival (OS)

End point title	5 years Overall survival (OS)

End point description:

OS was measured from study entry until the date of death from any cause

End point type	Secondary

End point timeframe:
From study entry until 5 years after

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Percentage				
number (confidence interval 95%)	92 (81 to 97)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From the date of informed consent signature until 30 days after the end of treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	5.1

Reporting groups

Reporting group title	Safety population

Reporting group description:

All patients who have received at least one dose of treatment will be considered as Safety Population

Reporting group title	R-CHOP + IT lyposomal cytarabine

Reporting group description: -

Reporting group title	HD-MTX

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The R-CHOP21 treatment was well tolerated, with no unexpected side effects and only a few AEs reported

Serious adverse events	Safety population	R-CHOP + IT lyposomal cytarabine	HD-MTX
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 54 (35.19%)	17 / 54 (31.48%)	3 / 48 (6.25%)
number of deaths (all causes)	12	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Increase of neutrophilis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 54 (1.85%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostatic Cancer			
subjects affected / exposed	1 / 54 (1.85%)	1 / 54 (1.85%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Thrombosis			

subjects affected / exposed	1 / 54 (1.85%)	1 / 54 (1.85%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 54 (1.85%)	1 / 54 (1.85%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 54 (1.85%)	1 / 54 (1.85%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac general pericardial effusion			
subjects affected / exposed	1 / 54 (1.85%)	1 / 54 (1.85%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 54 (1.85%)	1 / 54 (1.85%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CNS cerebrovascular ischemia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 54 (1.85%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy			
subjects affected / exposed	1 / 54 (1.85%)	1 / 54 (1.85%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 54 (1.85%)	1 / 54 (1.85%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial hemorrhage			

subjects affected / exposed	1 / 54 (1.85%)	0 / 54 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	4 / 54 (7.41%)	4 / 54 (7.41%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	4 / 4	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Mucositis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 54 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site reaction/extravasation changes			
subjects affected / exposed	1 / 54 (1.85%)	1 / 54 (1.85%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	1 / 54 (1.85%)	1 / 54 (1.85%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 54 (1.85%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 54 (1.85%)	1 / 54 (1.85%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pharyngitis			

subjects affected / exposed	1 / 54 (1.85%)	1 / 54 (1.85%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 54 (1.85%)	0 / 54 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute urinary retention			
subjects affected / exposed	1 / 54 (1.85%)	1 / 54 (1.85%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 54 (3.70%)	2 / 54 (3.70%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Safety population	R-CHOP + IT lyposomal cytarabine	HD-MTX
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)	0 / 54 (0.00%)	0 / 48 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2009	The main purpose of this amendment was to revise the Schedule of Events, as the IT administration did not reflect what was stated in the previous protocol text. Additionally, a Steering Committee was included
10 May 2010	This amendment was implemented to remove certain hematology and blood chemistry evaluations and to correct some typographical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
29 August 2012	The trial was temporary halted due to a temporary withdrawal of Depocyte in the EU. Patients on treatment during trial suspension were treated with non liposomal ARA-C intra-tecal.	19 August 2013

Notes:

Limitations and caveats

None reported