Clinical trial results:
An international phase II trial assessing tolerability and efficacy of sequential Methotrexate-Aracytin-based combination and R-ICE combination, followed by high-dose chemotherapy supported by autologous stem cell transplant, in patients with systemic B-cell lymphoma with central nervous system involvement at diagnosis or relapse (MARIETTA regimen)

Summary

EudraCT number	2014-003031-19
Trial protocol	IT NL
Global end of trial date	22 March 2024

Results information

Result version number	v1 (current)
This version publication date	06 June 2025
First version publication date	06 June 2025
Summary attachment (see zip file)	IELSG42 Results - Synopsis (IELSG42 Results Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	IELSG42

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02329080
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	IELSG Operations Office, International Extranodal Lymphoma Study Group (IELSG) , 0041 58 666 7321, ielsg@ior.usi.ch
Scientific contact	IELSG Operations Office, International Extranodal Lymphoma Study Group (IELSG) , 0041 58 666 7321, ielsg@ior.usi.ch

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	12 May 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 March 2024
Global end of trial reached?	Yes
Global end of trial date	22 March 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of a new sequential combination of high-dose methotrexate (HD-MTX)-AraC-based chemoimmunotherapy, followed by R-ICE regimen, and by high-dose chemotherapy supported by Autologous Stem Cell Transplantation (ASCT).

Protection of trial subjects:

Guidelines for dose modifications and dose delays were included in the study protocol, in order to minimize any possible
risks for the patients.
The following supportive therapies could be delivered: antiemetics, analgesics, antibiotics, anticonvulsants, sedatives, anti-hyperuricemic agents as well as other therapies to control metabolic and malnutrition disturbances.
Antimicrobial prophylaxis should follow Institutional guidelines since the variability in endemic or epidemic distribution of infectious agents. However, oral antiviral (Acyclovir 400 mg bid), antifungine (Fluconazole 200 mg/d) and antipneumocystic (Trimethoprim 160 mg and sulfamethoxazole 800 mg, thrice per week) prophylaxis was suggested.
Conventional doses of G-CSF from day 6th to 12th of every course associated with antibiotic prophylaxis as per local practice (same period) were also suggested.
Platelet transfusion were performed when counts was <10 x 109/L, or <20 x 109/L in case of fever or active bleeding. RBC transfusion were performed with haemoglobin <8.0 g/dL or in selected patients with higher levels according to physician’s preference

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 March 2015
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	Switzerland: 1
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Italy: 54
Worldwide total number of subjects	79
EEA total number of subjects	58

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)	52
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment lasted from 30 March 2015 to 03 August 2018

Pre-assignment

Screening details:

During the recrutment period 79 patients were enrolled and 75 of them were treated

Period 1

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

Arms

Arm title	Arm 1

Arm description:

Experimental treatment was started within 3 weeks of baseline assessment of target lesions. Treatment included 6 cycles of chemoimmunotherapy, the first 3 cycles with an HDMTX- based combination followed by other 3 cycles of R-ICE combination and finally a BCNU-thiotepa containing conditioning and subsequent ASCT. The interval between the first day of 2 consecutive cycles was 3 weeks. The interval between the last chemoimmunotherapy cycle and conditioning was 4-6 weeks

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Intrathecal use

Dosage and administration details:

3.5 mg/m2 on day 1 of HDMTX combination for 3 cycles of 3 weeks
If liposomal cytarabine is not available, standard intrathecal chemotherapy with 50 mg Hydrocortisone + methotrexate 10-12 mg + cytarabine 40-50 mg is administered on Day 4 of each cycle of HDMTX and R-ICE combination

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 0 of HDMTX combination for 3 cycles lasting 3 weeks
375 mg/m2 on Day 1 of R-ICE combination for 3 cycles lasting 3 weeks

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use, Intravenous use

Dosage and administration details:

4g/m2 on Day 2 and 3 of HDMTX combination for 3 cycles lasting 3 weeks
If liposomal cytarabine is not available, standard intrathecal chemotherapy with 50 mg Hydrocortisone + methotrexate 10-12 mg + cytarabine 40-50 mg is administered on Day 4 of each cycle of HDMTX and R-ICE combination

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

Dosage and administration details:

5 mg/m2 on Day 2 of R-ICE combination for 3 cycles lasting 3 weeks

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

Dosage and administration details:

800 mg on Day 2 of R-ICE combination for 3 cycles lasting 3 weeks

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

Dosage and administration details:

100 mg/m2 on Day 1,2 and 3 of R-ICE combination for 3 cycles lasting 3 weeks

Investigational medicinal product name	Thiotepa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

30 mg/m2 on day 4 of HDMTX combination for 3 cycles lasting 3 weeks
5 mg/Kg on days -6 and -5 of conditioning regimen

Investigational medicinal product name	Carmustine
Investigational medicinal product code	
Other name	BCNU
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m2 on Day - 6 of the conditioning regimen

Investigational medicinal product name	Liposomal Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intrathecal use

Dosage and administration details:

50 mg on Day 5 of HDMTX combination for 3 cycles lasting 3 weeks
50 mg on Day 4 of R-ICE combination for 3 cycles lasting 3 weeks

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

Dosage and administration details:

In case of BCNU unavailability, 3.2 mg/kg on days -4, -3 and -2 of the conditioning regimen

Investigational medicinal product name	Hydrocortisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intrathecal use

Dosage and administration details:

If liposomal cytarabine is not available, standard intrathecal combination with 50 mg Hydrocortisone + methotrexate 10-12 mg + cytarabine 40-50 mg is administered on on Day 4 of each cycle of HDMTX and R-ICE combination.

Number of subjects in period 1[1]	Arm 1
Started	75
Completed	37
Not completed	38
Adverse event, serious fatal	4
Physician decision	2
Adverse event, non-fatal	1
Partial response	4
Complete response	4
Lost to follow-up	1
Lack of efficacy	22

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Four patients were excluded after enrolment before the start of study treatment because of unrelated laboratory abnormalities (two patients), disease only at flow cytometry examination of the cerebrospinal fluid (one), and death at the same time as registration (one).

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (Overall period)

Reporting group description: -

Reporting group values	Overall trial (Overall period)	Total	
Number of subjects	75	75	
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)	50	50	
From 65-84 years	25	25	
85 years and over	0	0	
Age continuous Units: years			
median	58		
full range (min-max)	23 to 70	-	
Gender categorical Units: Subjects			
Female	37	37	
Male	38	38	
CNS involvement at presentation Units: Subjects			
CNS involvement at presentation	32	32	
No CNS involvement at presentation	43	43	
Isolated CNS relapse Units: Subjects			
Isolated CNS relapse	15	15	
No Isolated CNS relapse	60	60	
Concomitant CNS-systemic localisation Units: Subjects			
Concomitant CNS-systemic localisation	28	28	
No Concomitant CNS-systemic localisation	47	47	
HBV or HCV seropositivity Units: Subjects			
HBV or HCV seropositivity	2	2	
No HBV or HCV seropositivity	73	73	
CNS site of disease - Brain parenchima Units: Subjects			

Brain parenchima	34	34	
No brain parenchima	41	41	
CNS site of disease - Cerebrospinal fluid or meninges Units: Subjects			
Cerebrospinal fluid or meninges	8	8	
No Cerebrospinal fluid or meninges	67	67	
CNS sites of disease - Spinal cord Units: Subjects			
Spinal cord	2	2	
No Spinal cord	73	73	
CNS sites of disease - Eyes Units: Subjects			
Eyes	2	2	
No eyes	73	73	
CNS sites of disease - Brain and cerebrospinal fluid or meninges Units: Subjects			
Brain and cerebrospinal fluid or meninges	13	13	
No brain and cerebrospinal fluid or meninges	62	62	
CNS sites of disease - Brain and eyes Units: Subjects			
Brain and eyes	10	10	
No brain and eyes	65	65	
CNS sites of disease - Brain, cerebrospinal fluid and eyes Units: Subjects			
Brain, cerebrospinal fluid and eyes	6	6	
No Brain, cerebrospinal fluid and eyes	69	69	
ECOG-PS			
Eastern Cooperative Oncology Group Performance Status (ECOG-PS)			
Units: Subjects			
ECOG-PS > 1	28	28	
ECOG-PS </= 1	47	47	
Number of extranodal organs involved (other than CNS) Units: Subjects			
Number of extranodal organs involved >1	23	23	
Number of extranodal organs involved </=1	52	52	
High LDH serum concentration Units: Subjects			
High LDH serum concentration	37	37	
No High LDH serum concentration	38	38	
Advanced stage Units: Subjects			
Advanced stage	60	60	
No advanced stage	15	15	
International Prognostic Index (IPI) Units: Subjects			

Low IPI risk	14	14	
Low-intermediate IPI risk	18	18	
High-intermediate IPI risk	26	26	
High IPI risk	17	17	

End points

End points reporting groups

Reporting group title	Arm 1

Reporting group description:

Experimental treatment was started within 3 weeks of baseline assessment of target lesions. Treatment included 6 cycles of chemoimmunotherapy, the first 3 cycles with an HDMTX- based combination followed by other 3 cycles of R-ICE combination and finally a BCNU-thiotepa containing conditioning and subsequent ASCT. The interval between the first day of 2 consecutive cycles was 3 weeks. The interval between the last chemoimmunotherapy cycle and conditioning was 4-6 weeks

Primary: 1 year progression free survival (PFS)

End point title	1 year progression free survival (PFS)[1]

End point description:

End point type	Primary

End point timeframe:

At 1 year from enrolment

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: Single arm trial

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: Percentage				
number (confidence interval 95%)	58 (55 to 61)			

Statistical analyses

No statistical analyses for this end point

Secondary: 2-year progression-free survival (PFS)

End point title	2-year progression-free survival (PFS)

End point description:

End point type	Secondary

End point timeframe:

At 2 years after trial entry

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: Percentage				
number (confidence interval 95%)	46 (39 to 53)			

Statistical analyses

No statistical analyses for this end point

Secondary: 2 year overall survival (OS)

End point title	2 year overall survival (OS)

End point description:

End point type	Secondary

End point timeframe:

At 2 years from treatment starts

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: Percentage				
number (confidence interval 95%)	46 (39 to 53)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From trial inclusion until 30 days after end of treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Safety evaluable population

Reporting group description: -

Serious adverse events	Safety evaluable population		
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 75 (61.33%)		
number of deaths (all causes)	50		
number of deaths resulting from adverse events	4		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatremia			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Poorly differentiated adenocarcinoma			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Bleeding			

subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thromboembolic event			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Neurological toxicity			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Brain ischemic stroke			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bleeding brain lesion			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration			

site conditions				
Fatigue				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fever				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				
subjects affected / exposed	16 / 75 (21.33%)			
occurrences causally related to treatment / all	23 / 23			
deaths causally related to treatment / all	0 / 0			
Neutropenic fever				
subjects affected / exposed	3 / 75 (4.00%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bicytopenia				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Gastrointestinal bleeding				

subjects affected / exposed	2 / 75 (2.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Vomiting and diarrhea			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Microperforation of the bowel			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bowel perforation			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute renal failure			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Septic arthritis			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Septic shock			
subjects affected / exposed	3 / 75 (4.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	1 / 1		

Interstitial pneumonia				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	13 / 75 (17.33%)			
occurrences causally related to treatment / all	12 / 15			
deaths causally related to treatment / all	1 / 3			
Pneumonia				
subjects affected / exposed	3 / 75 (4.00%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus infection				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus reactivation				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	2 / 75 (2.67%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Adenovirus infection				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fungal chest infection				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				

subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter related infection			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tuberculosis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety evaluable population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 75 (96.00%)		
Vascular disorders			
Vascular Disorders			
subjects affected / exposed	15 / 75 (20.00%)		
occurrences (all)	23		
Cardiac disorders			
Cardiac Disorders			
subjects affected / exposed	8 / 75 (10.67%)		
occurrences (all)	16		
Nervous system disorders			
Nervous System Disorders			
subjects affected / exposed	24 / 75 (32.00%)		
occurrences (all)	67		
Blood and lymphatic system disorders			
Blood and Lymphatic System Disorders G3-4			
subjects affected / exposed	51 / 75 (68.00%)		
occurrences (all)	327		
General disorders and administration site conditions			

General Disorders and Administration Site Conditions subjects affected / exposed occurrences (all)	55 / 75 (73.33%) 121		
Eye disorders Eye Disorders subjects affected / exposed occurrences (all)	5 / 75 (6.67%) 6		
Gastrointestinal disorders Gastrointestinal Disorders subjects affected / exposed occurrences (all)	35 / 75 (46.67%) 116		
Respiratory, thoracic and mediastinal disorders Respiratory Thoracic and Mediastinal Disorders subjects affected / exposed occurrences (all)	9 / 75 (12.00%) 13		
Skin and subcutaneous tissue disorders Skin and Subcutaneous Tissue Disorders subjects affected / exposed occurrences (all)	15 / 75 (20.00%) 15		
Renal and urinary disorders Renal and Urinary Disorders subjects affected / exposed occurrences (all)	7 / 75 (9.33%) 12		
Infections and infestations Infections and Infestations subjects affected / exposed occurrences (all)	28 / 75 (37.33%) 65		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2017	Amendment No. 3 (protocol version 4.0) This amendment was implemented in all four countries. The reasons of the amendment were to correct the infusion duration of cytarabine, and to clarify the dose of folinic acid and the capped dose of carboplatin. In addition, it was suggested a radiotherapy treatment in case of progressive disease and the schedule and methods for disease evaluation was clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported