Clinical trial results:
Phase II study on the feasibility and efficacy of R-DHAP + HD-MTX, combined with intrathecal rituximab, followed by autologous stem cell transplantation in patients with a recurrent aggressive B-cell lymphoma with CNS localisation

Summary

EudraCT number	2006-002141-37
Trial protocol	NL
Global end of trial date	17 May 2016

Results information

Result version number	v1 (current)
This version publication date	16 December 2022
First version publication date	16 December 2022

Trial information

Trial identification

Sponsor protocol code	HOVON 80 NHL

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	HOVON
Sponsor organisation address	De Boelelaan 1117, Amsterdam, Netherlands,
Public contact	HOVON Data Center, HOVON, hdc@erasmusmc.nl
Scientific contact	HOVON Data Center, HOVON, hdc@erasmusmc.nl

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	03 July 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2012
Global end of trial reached?	Yes
Global end of trial date	17 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess in a multicenter phase II study of patients with a recurrent or progressive B-cell lymphoma with CNS involvement:
The progression-free survival after R-DHAP-MTX + rituximab intrathecally followed by myelo-ablative chemotherapy and autologous peripheral blood stem cell transplantation.

Protection of trial subjects:	
Monitoring and Insurance	
Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	03 October 2006
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	Netherlands: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	37
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects gave written informed consent and were screened according to the inclusion- and exclusion criteria.

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: -

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

Dosage and administration details:

375mg/m2 on day 5.

Additionally 10mg i.t./i.ventr.:
Cycle 1; day -1, 4, 8, 11, 21.
Cycle 2; day -1, 5, 11, 21.
Cycle 3; day -1, 11, 25

Investigational medicinal product name	Cisplatine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

100mg/m2, 24 hrs continuous infusion on day 1.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

3000mg/m2, 1 hr infusion on day 15.

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

2g/m2 q 12 hrs (2 doses), 3 hrs infusion for every adminisation of 2g/m2 on day 2.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Tablet
Routes of administration	Oral use, Intravenous use, Intraventricular use

Dosage and administration details:

40mg/day, oral/i.v. on day 1, 2, 3, 4.

Additionally 4mg i.t./i.ventr:
Cycle 1; day -1, 4, 8, 11, 21.
Cycle 2; day -1, 5, 11, 21.
Cycle 3; day -1, 11, 25.

Number of subjects in period 1	Arm 1
Started	38
Completed	13
Not completed	25
Adverse reactions	7
Other	8
Lack of efficacy	10

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	38	38	
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)	37	37	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
median	57		
full range (min-max)	23 to 65	-	
Gender categorical Units: Subjects			
Female	17	17	
Male	21	21	

End points

End points reporting groups

Reporting group title	Arm 1

Reporting group description: -

Primary: Primary Endpoint

End point title	Primary Endpoint[1]

End point description:

End point type	Primary

End point timeframe:

See publication.

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: See attached chart/documents for results.

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Whole	36			

Attachments (see zip file)	Statistical data section from publication/HO80 Methods and List of reported non-SAE's/nonsaedata80-29Nov2022.pdf List of reported SAE's/saedata80-29Nov2022.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Please refer to Adverse event reporting additional description.

Adverse event reporting additional description:

All adverse events of Grade 2 or higher, except progression of disease, occurring during the protocol treatment period will be reported. Adverse events occurring after that period should also be reported if considered related to protocol treatment. Follow up of ongoing adverse events ends at day 30 following the last dose of protocol treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3

Reporting groups

Reporting group title	Experimental Group

Reporting group description: -

Serious adverse events	Experimental Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 36 (55.56%)		
number of deaths (all causes)	30		
number of deaths resulting from adverse events			
Vascular disorders			
Vascular disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General disorders and administration site conditions	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	4 / 36 (11.11%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 3		
Immune system disorders			
Immune system disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal			

disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Psychiatric disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Investigations	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Nervous system disorders			
Nervous system disorder	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	4 / 36 (11.11%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Blood and lymphatic system disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	4 / 36 (11.11%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: All combined, see SAE chart for details.		

subjects affected / exposed	3 / 36 (8.33%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatobiliary disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infections and infestations	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	7 / 36 (19.44%)		
occurrences causally related to treatment / all	4 / 10		
deaths causally related to treatment / all	1 / 4		

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

Non-serious adverse events	Experimental Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 36 (97.22%)		
Vascular disorders			
Vascular	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	7 / 36 (19.44%)		
occurrences (all)	8		
General disorders and administration site conditions			
Constitutional symptoms	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	12 / 36 (33.33%)		
occurrences (all)	14		
Pain	Additional description: All combined, see non-SAE chart for details.		

subjects affected / exposed	11 / 36 (30.56%)		
occurrences (all)	13		
Respiratory, thoracic and mediastinal disorders			
Pulmonary/upper respiratory	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Cardiac disorders			
Cardiac general	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	7 / 36 (19.44%)		
occurrences (all)	8		
Nervous system disorders			
Neurology	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	14 / 36 (38.89%)		
occurrences (all)	30		
Blood and lymphatic system disorders			
Blood/bone marrow	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	3		
Coagulation	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Hemorrhage/bleeding	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	4		
Lymphatics	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Ear and labyrinth disorders			
Auditory/ear	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Eye disorders			
Ocular/visual	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Gastrointestinal disorders			

Gastrointestinal	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	19 / 36 (52.78%)		
occurrences (all)	50		
Hepatobiliary disorders			
Hepatobiliary/pancreas	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatology/skin	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	4		
Renal and urinary disorders			
Renal/genitourinary	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	3		
Endocrine disorders			
Endocrine	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Musculoskeletal/soft tissue	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	5		
Infections and infestations			
Infection	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	26 / 36 (72.22%)		
occurrences (all)	64		
Metabolism and nutrition disorders			
Metabolic/laboratory	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	25 / 36 (69.44%)		
occurrences (all)	62		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2008	• p1,6: Telephone numbers and names statistician and datamanger changed • p14: In table 4 mg dose/day dexamethasone added to rituximab i.t. • p14: Rituximab i.t./i.ventr. diluted in NaCl to a concentration of 5 mg/ml in stead of 10 mg/ml • p16: Addition of dexamethasone and dilution of rituximab as indicated on p14 • p16: Addition of anti-histaminics to premedication before every i.t. treatment
02 June 2009	• p10: Addition of text: However, in a number of patients a temporary painful lumbosacral radiculopathy occurred after lumbar administration of 25 mg. Therefore the intrathecal dose will be limited to 10 mg.' • p14: In table first row deleted, in second row day –1 added to cycle 1 • p16: Dose escalation i.t. rituximab to 25 mg deleted dose will be continued at 10 mg

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported