Clinical trial results:
Rituximab in Primary Central Nervous system Lymphoma.
A randomized HOVON / ALLG intergroup study

Summary

EudraCT number	2009-014722-42
Trial protocol	NL
Global end of trial date	21 December 2021

Results information

Result version number	v1 (current)
This version publication date	06 March 2024
First version publication date	06 March 2024

Trial information

Trial identification

Sponsor protocol code	HO105

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	HOVON
Sponsor organisation address	Dr. Molenwaterplein 40, Rotterdam, Netherlands,
Public contact	Dr. J.K. Doorduijn, HOVON Data Center, +31 (0)107041560, hovon@erasmusmc.nl
Scientific contact	Dr. J.K. Doorduijn, HOVON Data Center, +31 (0)107041560, hovon@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	30 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 May 2017
Global end of trial reached?	Yes
Global end of trial date	21 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assess the effect of the addition of rituximab to standard chemotherapy for PCNSL

Protection of trial subjects:

Monitoring and Insurance

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 July 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 30
Country: Number of subjects enrolled	New Zealand: 15
Country: Number of subjects enrolled	Netherlands: 157
Worldwide total number of subjects	202
EEA total number of subjects	157

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)	128
From 65 to 84 years	74
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 period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Control group

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	MBVP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

All patients will be treated with 2 courses of MBVP (total of 4 MTX doses) according to the schedule below. The 2nd course is scheduled 28 days after start of the previous course (at day 29):
Agent Dose/day Route Days
Methotrexate (HD-MTX) 3000 mg/m2 1 hr infusion i.v. 1,15
Teniposide 100 mg/m2 i.v. 2,3
BCNU 100 mg/m2 i.v. 4
Prednisolone 60 mg/m2 Orally or i.v. 1, 2, 3, 4, 5
The second HD-MTX dose is given 14 days after the first dose.

Arm title	Experimental group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Rituximab Mabthera
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intrathecal use

Dosage and administration details:

Rituximab 375 mg/m2 course 1: d 0,7,14,21 course 2: d 0, 14

Number of subjects in period 1	Control group	Experimental group
Started	101	101
Completed	75	76
Not completed	26	25
Unknown	3	4
Patients request	3	3
Adverse reaction	4	11
Lack of efficacy	16	7

Baseline characteristics

Reporting groups	
Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	202	202	
Age categorical			
Adults (26-70 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)	128	128	
From 65-84 years	74	74	
85 years and over	0	0	
Adults (26-70 years)	0	0	
Gender categorical			
Units: Subjects			
Female	91	91	
Male	111	111	

End points

End points reporting groups

Reporting group title	Control group
Reporting group description: -	
Reporting group title	Experimental group
Reporting group description: -	

Primary: Primary endpoint

End point title	Primary endpoint[1][2]
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

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: See attached chart/documents for results

End point values	Control group			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: Whole	199			

Attachments (see zip file)	saedata105-11Dec2023.pdf nonsaedata105-11Dec2023.pdf HO105_statistical data section form publication 30-06-2017

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events will be reported from the first study-related procedure until 30 days following the last dose of any drug or RT treatment from the protocol treatment schedule or until the start of subsequent systemic therapy for the disease under study,

Adverse event reporting additional description:

if earlier. Adverse events occurring after 30 days should also be reported if considered at least possibly related to the protocol treatment by the investigator. Special attention should be given to neurological and cognitive symptoms. Adverse Events have to be reported on the Adverse Events CRF.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Control group
Reporting group description: -	
Reporting group title	Experimental
Reporting group description: -	

Serious adverse events	Control group	Experimental	
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 100 (48.00%)	53 / 99 (53.54%)	
number of deaths (all causes)	64	55	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified	Additional description: All combined		
subjects affected / exposed	1 / 100 (1.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Vascular disorders			
Vascular disorders	Additional description: All combined		
subjects affected / exposed	2 / 100 (2.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General disorders	Additional description: All combined		

subjects affected / exposed	8 / 100 (8.00%)	4 / 99 (4.04%)	
occurrences causally related to treatment / all	4 / 8	3 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Immune system disorders			
Immune system disorders	Additional description: All combined		
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: All combined		
subjects affected / exposed	3 / 100 (3.00%)	5 / 99 (5.05%)	
occurrences causally related to treatment / all	2 / 3	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychiatric disorders	Additional description: All combined		
subjects affected / exposed	2 / 100 (2.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Investigations	Additional description: All combined		
subjects affected / exposed	1 / 100 (1.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: All combined		
subjects affected / exposed	3 / 100 (3.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders	Additional description: All combined		
subjects affected / exposed	2 / 100 (2.00%)	4 / 99 (4.04%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Nervous system disorders			

Nervous system disorders	Additional description: All combined		
subjects affected / exposed	11 / 100 (11.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	5 / 12	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders	Additional description: all combined		
subjects affected / exposed	6 / 100 (6.00%)	8 / 99 (8.08%)	
occurrences causally related to treatment / all	6 / 6	9 / 9	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: All combined		
subjects affected / exposed	4 / 100 (4.00%)	6 / 99 (6.06%)	
occurrences causally related to treatment / all	2 / 5	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders	Additional description: All combined		
subjects affected / exposed	1 / 100 (1.00%)	6 / 99 (6.06%)	
occurrences causally related to treatment / all	1 / 1	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal	Additional description: All combined		
subjects affected / exposed	1 / 100 (1.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations	Additional description: All combined		
subjects affected / exposed	20 / 100 (20.00%)	23 / 99 (23.23%)	
occurrences causally related to treatment / all	14 / 23	18 / 25	
deaths causally related to treatment / all	3 / 3	1 / 1	

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

Non-serious adverse events	Control group	Experimental	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 100 (79.00%)	82 / 99 (82.83%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms bening, malignant and unspecified	Additional description: All combined		
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Vascular disorders	Additional description: All combined		
subjects affected / exposed	18 / 100 (18.00%)	17 / 99 (17.17%)	
occurrences (all)	21	20	
Surgical and medical procedures			
Surgical and medical procedures	Additional description: All combined		
subjects affected / exposed	1 / 100 (1.00%)	5 / 99 (5.05%)	
occurrences (all)	1	6	
General disorders and administration site conditions			
General disorders and administration site conditions	Additional description: All combined		
subjects affected / exposed	26 / 100 (26.00%)	12 / 99 (12.12%)	
occurrences (all)	33	15	
Immune system disorders			
Immune system disorders	Additional description: All combined		
subjects affected / exposed	2 / 100 (2.00%)	0 / 99 (0.00%)	
occurrences (all)	2	0	
Social circumstances			
Social circumstances	Additional description: All combined		
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Reproductive system and breast disorders	Additional description: All combined		
subjects affected / exposed	1 / 100 (1.00%)	5 / 99 (5.05%)	
occurrences (all)	4	6	
Psychiatric disorders			
Psychiatric disorders	Additional description: All combined		
subjects affected / exposed	10 / 100 (10.00%)	10 / 99 (10.10%)	
occurrences (all)	11	11	
Investigations			

Investigations	Additional description: All combined		
subjects affected / exposed	29 / 100 (29.00%)	29 / 99 (29.29%)	
occurrences (all)	76	82	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: All combined		
subjects affected / exposed	4 / 100 (4.00%)	4 / 99 (4.04%)	
occurrences (all)	4	5	
Congenital, familial and genetic disorders			
Congenital, familial and genetic disorders	Additional description: All combined		
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Cardiac disorders	Additional description: All combined		
subjects affected / exposed	6 / 100 (6.00%)	5 / 99 (5.05%)	
occurrences (all)	7	5	
Nervous system disorders			
Nervous system disorders	Additional description: All combined		
subjects affected / exposed	23 / 100 (23.00%)	15 / 99 (15.15%)	
occurrences (all)	27	16	
Blood and lymphatic system disorders			
Blood and lymphatic disorders	Additional description: All combined		
subjects affected / exposed	19 / 100 (19.00%)	15 / 99 (15.15%)	
occurrences (all)	32	27	
Ear and labyrinth disorders			
Ear and labyrinth disorders	Additional description: All combined		
subjects affected / exposed	3 / 100 (3.00%)	2 / 99 (2.02%)	
occurrences (all)	3	2	
Eye disorders			
Eye disorders	Additional description: All combined		
subjects affected / exposed	9 / 100 (9.00%)	5 / 99 (5.05%)	
occurrences (all)	9	5	
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: All combined		
subjects affected / exposed	33 / 100 (33.00%)	37 / 99 (37.37%)	
occurrences (all)	47	56	
Hepatobiliary disorders			

Hepatobiliary disorders	Additional description: All combined		
subjects affected / exposed	1 / 100 (1.00%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders	Additional description: All combined		
subjects affected / exposed	12 / 100 (12.00%)	5 / 99 (5.05%)	
occurrences (all)	13	6	
Renal and urinary disorders			
Renal and urinary disorders	Additional description: All combined		
subjects affected / exposed	8 / 100 (8.00%)	15 / 99 (15.15%)	
occurrences (all)	9	20	
Endocrine disorders			
Endocrine disorders	Additional description: All combined		
subjects affected / exposed	1 / 100 (1.00%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders	Additional description: All combined		
subjects affected / exposed	9 / 100 (9.00%)	10 / 99 (10.10%)	
occurrences (all)	10	10	
Infections and infestations			
Infections and infestations	Additional description: All combined		
subjects affected / exposed	39 / 100 (39.00%)	33 / 99 (33.33%)	
occurrences (all)	62	51	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders	Additional description: All combined		
subjects affected / exposed	22 / 100 (22.00%)	24 / 99 (24.24%)	
occurrences (all)	40	43	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 May 2011	Safety reporting procedures, adding exclusion criterion, add sites
20 February 2013	- Adding the option for the participation of temporarily incapacitated patients. - A new monitoring plan.
10 March 2015	Change of investigator OLVG Amsterdam. New safety information about Rituximab and pregnancy prevention
29 March 2016	Change of investigator UMCG. -Longer conduct of quality of life and neuropsychological examination

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/30630772