



Clinical trial results:

Freiburger ZNS-NHL Studie: Therapie für Patienten mit primären Non-Hodgkin Lymphomen des ZNS – Sequentielle Hochdosis-Chemotherapie mit autologer peripherer Blutstammzelltransplantation.

Freiburg ZNS-NHL Study: Therapy for Patients With Primary Non-Hodgkin Lymphoma of the CNS - Sequential High Dosage Chemotherapy With Autologous Peripheral Blood Stem Cell Plantation.

Summary

EudraCT number	2005-000615-99
Trial protocol	DE
Global end of trial date	02 March 2015

Results information

Result version number	v1 (current)
This version publication date	16 December 2020
First version publication date	16 December 2020

Trial information

Trial identification

Sponsor protocol code	00465
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00647049
WHO universal trial number (UTN)	-
Other trial identifiers	German Clinical Trials Register: DRKS00003748

Notes:

Sponsors

Sponsor organisation name	Medical Center - University of Freiburg
Sponsor organisation address	Breisacher Str. 153, Freiburg, Germany, 79110
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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	27 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 February 2015
Global end of trial reached?	Yes
Global end of trial date	02 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assessment of the efficacy of therapy with respect to the complete response rate 30 days after completion of the blood stem-cell transplantation. The study comprised two separate cohorts: 1. Newly diagnosed PCNSL15 and 2. Relapsed or refractory PCNSL. Here the results of the newly diagnosed cohort are reported. The results of the relapsed or refractory cohort are reported here: Kasenda B, Ihorst G, Schroers R, Korfel A, Schmidt-Wolf I, Egerer G, von Baumgarten L, Röth A, Bloehdorn J, Möhle R, Binder M, Keller U, Lamprecht M, Pfreundschuh M, Valk E, Fricker H, Schorb E, Fritsch K, Finke J, Illerhaus G. High-dose chemotherapy with autologous haematopoietic stem cell support for relapsed or refractory primary CNS lymphoma: a prospective multicentre trial by the German Cooperative PCNSL study group. *Leukemia*. 2017 Dec;31(12):2623-2629. doi: 10.1038/leu.2017.170. Epub 2017 May 31. PMID: 28559537.

Protection of trial subjects:

The study conformed to the Declaration of Helsinki. The local ethics committee at Freiburg University and the ethics committees at all participating centres approved the study protocol and all amendments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 January 2007
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	Germany: 79
Worldwide total number of subjects	79
EEA total number of subjects	79

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	78
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	79
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Number of subjects completed	79
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Period 1

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

Single arm study

Arms

Arm title	Newly diagnosed primary CNS
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Arm description:

First diagnosis of PCNSL: combined chemotherapy with methotrexate

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

375 mg/m²:

Sequential induction treatment: five courses: 7 days before first high-dose methotrexate course and days 0, 10, 20, and 30

Therapy continuation with AraC/TT (14 days after last treatment with MTX): at day 0 (first cycle) and day 21 (second cycle)

Therapy continuation with HD-BCNU/TT (21 days after last treatment with Arac/TT; day 43): at day 7 (first cycle) and day 21 (second cycle)

Investigational medicinal product name	Methotrexate
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Solution for infusion
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Routes of administration	Intravenous use
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Dosage and administration details:

Four courses of high-dose methotrexate 8000 mg/m² on days 1, 11, 21, and 31 with folinic acid rescue

Investigational medicinal product name	Folinic acid
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Tablet
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Routes of administration	Intravenous use, Oral use
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Dosage and administration details:

Rescue

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	Ara-C
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
3 g/m ² , days 2 and 3	
Investigational medicinal product name	Thiotepa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Within first cycle of R-AraC/TT therapy: 40 mg/m ² on day 2	
Within second cycle of R-AraC/TT therapy: 40 mg/m ² on day 23	
At day 4 and 5 of therapy continuation: 2x5 mg/kg/die	
Investigational medicinal product name	Carmustine
Investigational medicinal product code	
Other name	BCNU
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
400 mg/m ² at day 6 of therapy continuation (day 43)	
Investigational medicinal product name	Granulocyte Colony Stimulating Factor (G-CSF)
Investigational medicinal product code	
Other name	Neupogen
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Within first cycle of R-AraC/TT: from day 5 on: 5µg/kgKG (>70kg: 480µg, <70kg: 300µg)	
Within secondy cycle of R-AraC/TT: from day 26 on: G-CSF (Neupogen®) 1x/die s.c. bis WBC > 1000/µl	
5µg/kgKG (>70kg: 480µg, <70kg: 300µg)	
Investigational medicinal product name	Pegfilgrastim
Investigational medicinal product code	
Other name	Neulasta
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
6 mg. s.c. at day 4 of therapy continuation	

Number of subjects in period 1	Newly diagnosed primary CNS
Started	79
Completed	79

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)
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Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	79	79	
Age categorical Units: Subjects			
Adults (18-64 years)	78	78	
From 65-84 years	1	1	
Age continuous Units: years			
median	56		
inter-quartile range (Q1-Q3)	51 to 62	-	
Gender categorical Units: Subjects			
Female	35	35	
Male	44	44	

End points

End points reporting groups

Reporting group title	Newly diagnosed primary CNS
Reporting group description:	
First diagnosis of PCNSL: combined chemotherapy with methotrexate	

Primary: Complete response

End point title	Complete response ^[1]
End point description:	
Proportion of patients with complete response: 77.2%; 95% CI: 66.1-86.6	
End point type	Primary
End point timeframe:	
Best response 30 days after completion of HCT-ASCT	
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: This is a single-arm study, i. e. no group comparison possible.	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients	61			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete response achieved during induction

End point title	Complete response achieved during induction
End point description:	
Best response achieved during induction	
End point type	Secondary
End point timeframe:	
during induction	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients	21			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete response before entering HCT-ASCT

End point title	Complete response before entering HCT-ASCT
End point description:	
Best response before entering HCT-ASCT	
End point type	Secondary
End point timeframe:	
before entering HCT-ASCT	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients	18			

Statistical analyses

No statistical analyses for this end point

Secondary: Partial response achieved during induction

End point title	Partial response achieved during induction
End point description:	
End point type	Secondary
End point timeframe:	
Best response achieved during induction	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients	52			

Statistical analyses

No statistical analyses for this end point

Secondary: Partial response before entering HCT-ASCT

End point title	Partial response before entering HCT-ASCT
End point description:	
End point type	Secondary
End point timeframe:	
Best response before entering HCT-ASCT	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients	45			

Statistical analyses

No statistical analyses for this end point

Secondary: Stable disease achieved during induction

End point title	Stable disease achieved during induction
End point description:	
End point type	Secondary
End point timeframe:	
Best response achieved during induction	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Partial response

End point title	Partial response
End point description:	
End point type	Secondary
End point timeframe:	
Best response 30 days after HCT-ASCT	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Stable disease before entering HCT-ASCT

End point title	Stable disease before entering HCT-ASCT
End point description:	
End point type	Secondary
End point timeframe:	
Best response before entering HCT-ASCT	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Stable disease

End point title	Stable disease
End point description:	
End point type	Secondary
End point timeframe:	
Best reponse 30 days after HCT-ASCT	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Progressive disease achieved during induction

End point title	Progressive disease achieved during induction
End point description:	
End point type	Secondary
End point timeframe:	
Best reponse achieved during induction	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Progressive disease before entering HCT-ASCT

End point title	Progressive disease before entering HCT-ASCT
End point description:	
End point type	Secondary
End point timeframe:	
Best response before entering HCT-ASCT	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Progressive disease

End point title	Progressive disease
End point description:	
End point type	Secondary
End point timeframe:	
Best response 30 days after HCT-ASCT	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Thrombocytopenia during induction

End point title	Toxicity: Thrombocytopenia during induction
End point description:	
End point type	Secondary
End point timeframe:	
During induction	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients				
Grade 1 or 2	7			
Grade 3	12			
Grade 4	50			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Thrombocytopenia during HCT-ASCT

End point title	Toxicity: Thrombocytopenia during HCT-ASCT
End point description:	
End point type	Secondary
End point timeframe:	
During HCT-ASCT	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Number of patients				
Grade 1 or 2	1			
Grade 3	1			
Grade 4	67			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Leucopenia during induction

End point title	Toxicity: Leucopenia during induction
End point description:	
End point type	Secondary
End point timeframe:	
During induction	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients				
Grade 1 or 2	10			
Grade 3	24			
Grade 4	37			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Leucopenia during HCT-ASCT

End point title	Toxicity: Leucopenia during HCT-ASCT
End point description:	
End point type	Secondary
End point timeframe:	
During HCT-ASCT	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Number of patients				
Grade 1 or 2	2			
Grade 3	3			
Grade 4	68			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Anaemia during induction

End point title	Toxicity: Anaemia during induction
End point description:	
End point type	Secondary
End point timeframe:	
During induction	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients				
Grade 1 or 2	39			
Grade 3	37			
Grade 4	3			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Aneamia during HCT-ASCT

End point title	Toxicity: Aneamia during HCT-ASCT
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End point description:

End point type	Secondary
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End point timeframe:

During HCT-ASCT

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Number of patients				
Grade 1 or 2	32			
Grade 3	39			
Grade 4	2			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: GPT or ALT during induction

End point title	Toxicity: GPT or ALT during induction
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End point description:

GPT: glutamic-pyruvic transaminase; ALT: alanine aminotransferase

End point type	Secondary
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End point timeframe:

During induction

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients				
Grade 1 or 2	38			
Grade 3	27			
Grade 4	7			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: GPT or ALT during HCT-ASCT

End point title Toxicity: GPT or ALT during HCT-ASCT

End point description:

GPT: glutamic-pyruvic transaminase; ALT: alanine aminotransferase

End point type Secondary

End point timeframe:

During HCT-ASCT

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Number of patients				
Grade 3	3			
Grade 4	0			
Grade 5	0			
Grade 1 or 2	31			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Infections during induction

End point title Toxicity: Infections during induction

End point description:

End point type Secondary

End point timeframe:

During induction

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients				
Grade 1 or 2	0			
Grade 3	30			
Grade 4	2			
Grade 5	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Infections during HCT-ASCT

End point title	Toxicity: Infections during HCT-ASCT
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End point description:

End point type	Secondary
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End point timeframe:

During HCT-ASCT

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Number of patients				
Grade 1 or 2	6			
Grade 3	40			
Grade 4	2			
Grade 5	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Fever during induction

End point title	Toxicity: Fever during induction
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End point description:

End point type	Secondary
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End point timeframe:

During induction

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients				
Grade 1 or 2	0			
Grade 3	15			
Grade 4	1			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Fever during HCT-ASCT

End point title	Toxicity: Fever during HCT-ASCT
End point description:	
End point type	Secondary
End point timeframe:	
During HCT-ASCT	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Number of patients				
Grade 1 or 2	5			
Grade 3	50			
Grade 4	1			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Hyperbilirubinaemia during induction

End point title	Toxicity: Hyperbilirubinaemia during induction
End point description:	
End point type	Secondary
End point timeframe:	
During induction	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients				
Grade 1 or 2	8			
Grade 3	3			
Grade 4	0			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Hyperbilirubinaemia during HCT-ASCT

End point title	Toxicity: Hyperbilirubinaemia during HCT-ASCT
End point description:	
End point type	Secondary
End point timeframe:	
During HCT-ASCT	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Number of patients				
Grade 1 or 2	14			
Grade 3	0			
Grade 4	0			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Cardiac dysfunction during induction

End point title	Toxicity: Cardiac dysfunction during induction
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End point description:

End point type	Secondary
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End point timeframe:

During induction

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients				
Grade 1 or 2	0			
Grade 3	1			
Grade 4	1			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Cardiac dysfunction during HCT-ASCT

End point title	Toxicity: Cardiac dysfunction during HCT-ASCT
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End point description:

End point type	Secondary
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End point timeframe:

During HCT-ASCT

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Number of patients				
Grade 1 or 2	3			
Grade 3	1			
Grade 4	1			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Mucositis during induction

End point title Toxicity: Mucositis during induction

End point description:

End point type Secondary

End point timeframe:

During induction

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients				
Grade 1 or 2	27			
Grade 3	2			
Grade 4	0			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Mucositis during HCT-ASCT

End point title Toxicity: Mucositis during HCT-ASCT

End point description:

End point type Secondary

End point timeframe:

During HCT-ASCT

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Number of patients				
Grade 1 or 2	22			
Grade 3	23			
Grade 4	6			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Renal function (serum creatinine) during induction

End point title	Toxicity: Renal function (serum creatinine) during induction
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End point description:

End point type	Secondary
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End point timeframe:

During induction

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients				
Grade 1 or 2	24			
Grade 3	2			
Grade 4	0			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Renal function (serum creatinine) during HCT-ASCT

End point title	Toxicity: Renal function (serum creatinine) during HCT-ASCT
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End point description:

End point type	Secondary
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End point timeframe:

During HCT-ASCT

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Number of patients				
Grade 1 or 2	12			
Grade 3	0			
Grade 4	0			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Arrhythmias during induction

End point title	Toxicity: Arrhythmias during induction
End point description:	
End point type	Secondary
End point timeframe:	
During induction	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients				
Grade 1 or 2	0			
Grade 3	1			
Grade 4	0			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Arrhythmias during HCT-ASCT

End point title	Toxicity: Arrhythmias during HCT-ASCT
End point description:	
End point type	Secondary
End point timeframe:	
During HCT-ASCT	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Number of patients				
Grade 1 or 2	6			
Grade 3	3			
Grade 4	2			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Emesis during induction

End point title	Toxicity: Emesis during induction
End point description:	
End point type	Secondary
End point timeframe:	
During induction	

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients				
Grade 1 or 2	16			
Grade 3	1			
Grade 4	0			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Emesis during HCT-ASCT

End point title	Toxicity: Emesis during HCT-ASCT
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End point description:

End point type	Secondary
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End point timeframe:

During HCT-ASCT

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Number of patients				
Grade 1 or 2	29			
Grade 3	4			
Grade 4	0			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Nausea during induction

End point title	Toxicity: Nausea during induction
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End point description:

End point type	Secondary
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End point timeframe:

During induction

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of patients				
Grade 1 or 2	27			
Grade 3	1			
Grade 4	0			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity: Nausea during HCT-ASCT

End point title	Toxicity: Nausea during HCT-ASCT
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End point description:

End point type	Secondary
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End point timeframe:

During HCT-ASCT

End point values	Newly diagnosed primary CNS			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Number of patients				
Grade 1 or 2	35			
Grade 3	12			
Grade 4	0			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Final Analysis Population A

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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Reporting groups

Reporting group title	HCT-ASCT
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Reporting group description:

Patients received five courses of intravenous rituximab 375 mg/m² (7 days before first high-dose methotrexate course and then every 10 days) and four courses of intravenous high-dose methotrexate 8000 mg/m² (every 10 days) and then two courses of intravenous rituximab 375 mg/m² (day 1), cytarabine 3 g/m² (days 2 and 3), and thiotepa 40 mg/m² (day 3). 3 weeks after the last course, patients commenced intravenous HCT-ASCT (rituximab 375 mg/m² [day 1], carmustine 400 mg/m² [day 2], thiotepa 2 × 5 mg/kg [days 3 and 4], and infusion of stem cells [day 7]), irrespective of response status after induction.

Serious adverse events	HCT-ASCT		
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 79 (44.30%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events	4		
Vascular disorders			
hypertensive Krise			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
tiefe Beinvenenthrombose			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
mechanische Beatmung			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Fieber				
subjects affected / exposed	5 / 79 (6.33%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Generelle Verschlechterung des physischen Gesundheitszustandes				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Schleimhautentzündung				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ulkus				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
verzögerte Heilung				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Lungenembolie				
subjects affected / exposed	3 / 79 (3.80%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
respiratorische Insuffizienz				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Substanzbedingte psychotische Störung				

subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Wahnstoerung, unbestimmter Typ			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
C-reaktives Protein erhoeht			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia-Test positiv			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Koerpertemperatur erhoeht			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Kreatinin im Blut erhoeht			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fistel nach einem Eingriff			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Frakturen von Gesichtsknochen			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Sturz			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmie			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Koronararterienverschluss			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
akuter Myokardinfarkt			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ataxie			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Grand mal Konvulsion			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hemiparese			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydrozephalus			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Kleinhirnsyndrom			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Konvulsion			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stammhirnsyndrom			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subarachnoidalblutung			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemie			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukopenie			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombozytopenie			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoe			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Erbrechen			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uebelkeit			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis toxisch			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
akute Cholezystitis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Ausschlag mit Juckreiz			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nierenversagen akut			
subjects affected / exposed	3 / 79 (3.80%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Geraetebedingte Sepsis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Harnwegsinfektion			

subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hordeolum				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infektion im Zusammenhang mit einem medizinischen Geraet				
subjects affected / exposed	3 / 79 (3.80%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Klebsiella-Sepsis				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii-Pneumonie				
subjects affected / exposed	3 / 79 (3.80%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	1 / 1			
Pneumonie				
subjects affected / exposed	3 / 79 (3.80%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonie durch Pseudomonas				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	2 / 79 (2.53%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Sepsis durch Staphylokokken			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
akute Tonsillitis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
bronchopulmonale Aspergillose			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
pulmonale Sepsis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

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

Non-serious adverse events	HCT-ASCT		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 79 (44.30%)		
Vascular disorders			
Jugularvenenthrombose			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Thrombose			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Varizen			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Venenthrombose einer Extremitaet</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 79 (1.27%)</p> <p>1</p> <p>1 / 79 (1.27%)</p> <p>1</p>		
<p>Surgical and medical procedures</p> <p>Zahnextraktion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 79 (1.27%)</p> <p>1</p>		
<p>General disorders and administration site conditions</p> <p>Asthenie</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Fieber</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oedem</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Schmerz</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>generalisierte Oedeme</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>unerwuenschte Arzneimittelwirkung</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 79 (2.53%)</p> <p>2</p> <p>2 / 79 (2.53%)</p> <p>2</p> <p>3 / 79 (3.80%)</p> <p>3</p> <p>1 / 79 (1.27%)</p> <p>1</p> <p>2 / 79 (2.53%)</p> <p>2</p> <p>1 / 79 (1.27%)</p> <p>1</p>		
<p>Immune system disorders</p> <p>Immundefekt</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Ueberempfindlichkeit</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 79 (1.27%)</p> <p>1</p> <p>2 / 79 (2.53%)</p> <p>2</p>		
<p>Reproductive system and breast disorders</p>			

Balanoposthitis subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Metrorrhagie subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Respiratory, thoracic and mediastinal disorders			
Dysphonie subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Dyspnoe subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Epistaxis subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Lungenembolie subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Schluckauf subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Psychiatric disorders			
Angst subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Schlafstoerung subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Verwirrtheitszustand subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Investigations			
Bilirubin im Blut erhoelt subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		

Gewicht erhoeht subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Laktatdehydrogenase im Blut erhoeht subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Injury, poisoning and procedural complications subkutanes Haematom subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Cardiac disorders Sinustachykardie subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Nervous system disorders Affektion der Meningen subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Aufmerksamkeitsstoerungen subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Hemianopie subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Konvulsion subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Kopfschmerz subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Paraesthesie subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Ear and labyrinth disorders Lagerungsvertigo			

subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Eye disorders Sehen verschwommen subjects affected / exposed occurrences (all) Sehverschlechterung subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1 1 / 79 (1.27%) 1		
Gastrointestinal disorders Blutstuhl subjects affected / exposed occurrences (all) Darmdivertikel haemorrhagisch subjects affected / exposed occurrences (all) Diarrhoe subjects affected / exposed occurrences (all) Enterokolitis subjects affected / exposed occurrences (all) Erbrechen subjects affected / exposed occurrences (all) Gastritis subjects affected / exposed occurrences (all) Ileus spastisch subjects affected / exposed occurrences (all) Pankreatitis subjects affected / exposed occurrences (all) Subileus	1 / 79 (1.27%) 1 1 / 79 (1.27%) 1 3 / 79 (3.80%) 3 1 / 79 (1.27%) 1 2 / 79 (2.53%) 3 2 / 79 (2.53%) 2 1 / 79 (1.27%) 1 1 / 79 (1.27%) 1		

subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Uebelkeit			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	3		
gastrointestinale Entzündung			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Hepatobiliary disorders			
Steatosis hepatis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Erythem			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Hautläsion			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Pruritus generalisiert			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Urtikaria			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
makuloöser Ausschlag			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgie			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Bursitis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Rückenschmerzen			

subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Schmerz in einer Extremität			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Schmerzen des Muskel- und Skelettsystems			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Clostridium difficile-Kolitis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Erysipel			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Gastroenteritis durch Norovirus			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Gastrointestinalinfektion			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Harnwegsinfektion			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Herpesvirus-Infektion			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Infektion			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Pneumonie			

subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Septischer Schock			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Staphylokokkeninfektion			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
bakterielle Infektion			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
oral Herpes			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
pseudomembranoese Kolitis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Fluessigkeitsretention			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 February 2008	In addition to chemotherapy, the monoclonal antibody rituximab is administered to all patients with CD-20 positive primary cerebral lymphomas. The side effects of AraC listed in the introduction were complemented and the side effects of Thiotepa corrected. The timepoint for lumbar puncture were corrected. The remission criteria of Macdonald et al were replaced by the remission criteria established by the International Primary CNS Lymphoma Collaborative Group (IPCG) specifically for PCNSL. The target criteria evaluation is not affected by this.
29 July 2009	Study population: Number of participants was increased from 39 to 80.

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/27476790>

<http://www.ncbi.nlm.nih.gov/pubmed/28559537>