



## Clinical trial results:

### Freiburger Studie zur Behandlung von Primären ZNS-Lymphomen bei Patienten über 65 Jahre: Methotrexat-basierte Chemo-Immuntherapie mit anschließender Erhaltungstherapie

#### - PRIMAIN-Studie -

#### Summary

EudraCT number	2008-007645-31
Trial protocol	DE
Global end of trial date	05 August 2015

#### Results information

Result version number	v1 (current)
This version publication date	10 September 2020
First version publication date	10 September 2020

#### Trial information

##### Trial identification

Sponsor protocol code	00591
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00989352
WHO universal trial number (UTN)	-
Other trial identifiers	German Clinical Trials Register: DRKS00000582

Notes:

##### Sponsors

Sponsor organisation name	Medical Center - University of Freiburg
Sponsor organisation address	Breisacher Str. 153, Freiburg, Germany, 79110
Public contact	Elvira Burger-Martin, Medical Center - University of Freiburg, +49 761 27073780, elvira.burger@uniklinik-freiburg.de
Scientific contact	Prof. Dr. Gerald Illerhaus, Klinikum Stuttgart, +49 711 27830456, g.illerhaus@klinikum-stuttgart.de

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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	16 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 June 2015
Global end of trial reached?	Yes
Global end of trial date	05 August 2015
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

The primary end point was the Complete remission rate measured after 3 cycles of R-MPL (rituximab, HD-MTX, procarbazine and lomustine). Secondary end points were toxicity, neurotoxicity as evaluated by the mini-mental status test (MMST), quality of life (QoL) using the European Organization for Research and Treatment of Cancer QoL core questionnaire (EORTC QLQ-C30 Version 3.0)<sup>10</sup> and QLQ-BN20 for brain cancer, best response achieved during immuno-chemotherapy, PFS defined as time from the start of treatment until progression or death from any cause whichever occurred first and overall survival (OS) defined as time from the start of treatment until death from any cause.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 November 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	Germany: 107
Worldwide total number of subjects	107
EEA total number of subjects	107

Notes:

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**Subjects enrolled per age group**

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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)	0
From 65 to 84 years	106

85 years and over	1
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## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

Number of subjects started	107
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Number of subjects completed	107
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### Period 1

Period 1 title	Overall (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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### Arms

Arm title	R-MPL / R-MP
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Arm description:

One cycle of R-MPL consisted of rituximab 375 mg/m<sup>2</sup> infused in 90 min on day – 6 (only at the beginning of treatment), days 1, 15 and 29; HD-MTX 3 g/m<sup>2</sup> over 4 h on days 2, 16 and 30; lomustine 110 mg/m<sup>2</sup> orally on day 2, and procarbazine 60 mg/m<sup>2</sup> orally on days 2–11. started. Cycles were repeated every 42 days with 3 cycles planned in total. Maintenance treatment with procarbazine 100 mg for 5 days (6 cycles repeated on day 29) was started on day 43 of the last R-MPL cycle. After protocol amendment, lomustine was omitted and all patients were treated with R-MP.

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	Infusion
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Routes of administration	Intravenous use
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Dosage and administration details:

375 mg/m<sup>2</sup> infused in 90 min on day – 6 (only at the beginning of treatment), days 1, 15 and 29.

Investigational medicinal product name	Highdose methotrexate (HD-MTX)
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Infusion
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Routes of administration	Intravenous use
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Dosage and administration details:

3 g/m<sup>2</sup> over 4 h on days 2, 16 and 30.

Investigational medicinal product name	Lomustine
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Capsule
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Routes of administration	Oral use
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Dosage and administration details:

110 mg/m<sup>2</sup> orally on day 2.

Investigational medicinal product name	Procarbazine
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

60 mg/m<sup>2</sup> orally on days 2–11.

<b>Number of subjects in period 1</b>	R-MPL / R-MP
Started	107
Completed	107

## Baseline characteristics

### Reporting groups

Reporting group title	Overall
Reporting group description: -	

Reporting group values	Overall	Total	
Number of subjects	107	107	
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)	0	0	
From 65-84 years	106	106	
85 years and over	1	1	
Age continuous			
Units: years			
median	73		
full range (min-max)	66 to 85	-	
Gender categorical			
Units: Subjects			
Female	50	50	
Male	57	57	

### Subject analysis sets

Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Five patients were excluded because of systemic lymphoma involvement at registration or having a diagnosis of relapsed PCNSL. Finally, 107 eligible patients were included in the ITT population.

Reporting group values	Intention to treat		
Number of subjects	107		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	106		
85 years and over	1		
Age continuous			
Units: years			
median	73		
full range (min-max)	66 to 85		
Gender categorical			
Units: Subjects			
Female	50		
Male	57		

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## End points

### End points reporting groups

Reporting group title	R-MPL / R-MP
Reporting group description: One cycle of R-MPL consisted of rituximab 375 mg/m <sup>2</sup> infused in 90 min on day – 6 (only at the beginning of treatment), days 1, 15 and 29; HD-MTX 3 g/m <sup>2</sup> over 4 h on days 2, 16 and 30; lomustine 110 mg/m <sup>2</sup> orally on day 2, and procarbazine 60 mg/m <sup>2</sup> orally on days 2–11. started. Cycles were repeated every 42 days with 3 cycles planned in total. Maintenance treatment with procarbazine 100 mg for 5 days (6 cycles repeated on day 29) was started on day 43 of the last R-MPL cycle. After protocol amendment, lomustine was omitted and all patients were treated with R-MP.	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: Five patients were excluded because of systemic lymphoma involvement at registration or having a diagnosis of relapsed PCNSL. Finally, 107 eligible patients were included in the ITT population.	

### Primary: Complete remission

End point title	Complete remission <sup>[1]</sup>
End point description:	
End point type	Primary
End point timeframe: after 3 cycles	
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 study. The primary end point was analysed by calculating the CR rate with the two-sided 95% confidence interval (CI) based on the binomial distribution. Based on 107 evaluable patients, the null hypothesis (CR probability was 0.4 at a significance level alpha = 10%) could be rejected if the number of observed CRs is 50.	

End point values	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients	38			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Partial remission

End point title	Partial remission
End point description:	
End point type	Secondary
End point timeframe: after 3 cycles	



End point values	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients	15			

### 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: after 3 cycles	

End point values	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients	0			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progressive disease / relapse

End point title	Progressive disease / relapse
End point description:	
End point type	Secondary
End point timeframe: after 3 cycles	

<b>End point values</b>	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients	12			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Complete remission, best response achieved

End point title	Complete remission, best response achieved
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End point description:

End point type	Secondary
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End point timeframe:

Best response achieved during immuno-chemotherapy.

<b>End point values</b>	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients	45			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Partial remission, best response achieved

End point title	Partial remission, best response achieved
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End point description:

End point type	Secondary
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End point timeframe:

Best response achieved during immuno-chemotherapy.

<b>End point values</b>	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients	34			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Stable disease, best response achieved

End point title	Stable disease, best response achieved
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End point description:

End point type	Secondary
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End point timeframe:

Best response achieved during immuno-chemotherapy.

<b>End point values</b>	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients	1			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progressive disease, best response achieved

End point title	Progressive disease, best response achieved
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End point description:

End point type	Secondary
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End point timeframe:

Best response achieved during immuno-chemotherapy.

<b>End point values</b>	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients	2			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free survival

End point title	Progression-free survival
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End point description:

End point type	Secondary
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End point timeframe:

Time from the start of treatment until progression or death from any cause whichever occurred first.

<b>End point values</b>	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Months				
median (confidence interval 95%)	10.3 (6.5 to 15.9)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free survival, 1-year rate %

End point title	Progression-free survival, 1-year rate %
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End point description:

End point type	Secondary
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End point timeframe:

Time from the start of treatment until progression or death from any cause whichever occurred first.

<b>End point values</b>	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Rate (%)				
number (confidence interval 95%)	46.3 (36.8 to 55.8)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progressive-free survival, 2-year rate %

End point title	Progressive-free survival, 2-year rate %
End point description:	

End point type	Secondary
End point timeframe:	
time from the start of treatment until progression or death from any cause whichever occurred first.	

<b>End point values</b>	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Rate (%)				
number (confidence interval 95%)	37.3 (28.0 to 46.6)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival

End point title	Overall survival
End point description:	

End point type	Secondary
End point timeframe:	
Time from the start of treatment until death from any cause.	

<b>End point values</b>	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Months				
median (confidence interval 95%)	20.7 (10.7 to 44.8)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival, 1-year rate %

End point title	Overall survival, 1-year rate %
End point description:	
End point type	Secondary
End point timeframe:	
Time from the start of treatment until death from any cause.	

<b>End point values</b>	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Rates (%)				
number (confidence interval 95%)	56.7 (47.2 to 66.1)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival, 2-year rate %

End point title	Overall survival, 2-year rate %
End point description:	
End point type	Secondary
End point timeframe:	
Time from the start of treatment until death from any cause.	

<b>End point values</b>	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Rates (%)				
number (confidence interval 95%)	47.0 (37.3 to 56.7)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Toxicity: Leukopenia

End point title	Toxicity: Leukopenia
End point description:	
End point type	Secondary
End point timeframe: during treatment	

<b>End point values</b>	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients				
Grade 1	10			
Grade 2	20			
Grade 3	44			
Grade 4	15			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Toxicity: Anaemia

End point title	Toxicity: Anaemia
End point description:	
End point type	Secondary
End point timeframe: during treatment	

End point values	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients				
Grade 1	12			
Grade 2	51			
Grade 3	33			
Grade 4	2			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Toxicity: Thrombocytopenia

End point title	Toxicity: Thrombocytopenia
End point description:	
End point type	Secondary
End point timeframe: during treatment	

End point values	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients				
Grade 1	21			
Grade 2	13			
Grade 3	20			
Grade 4	11			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Toxicity: Infections

End point title	Toxicity: Infections
End point description:	
End point type	Secondary
End point timeframe: during treatment	



<b>End point values</b>	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients				
Grade 1	5			
Grade 2	20			
Grade 3	32			
Grade 4	3			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Toxicity: Transaminases

End point title	Toxicity: Transaminases
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End point description:

End point type	Secondary
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End point timeframe:

during treatment

<b>End point values</b>	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients				
Grade 1	34			
Grade 2	24			
Grade 3	24			
Grade 4	3			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Toxicity: Hyperbilirubinaemia

End point title	Toxicity: Hyperbilirubinaemia
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End point description:

End point type	Secondary
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End point timeframe:  
during treatment

End point values	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients				
Grade 1	18			
Grade 2	2			
Grade 3	0			
Grade 4	0			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Toxicity: Renal impairment (serum creatinine)

End point title Toxicity: Renal impairment (serum creatinine)

End point description:

End point type Secondary

End point timeframe:

during treatment

End point values	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients				
Grade 1	31			
Grade 2	21			
Grade 3	6			
Grade 4	0			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Toxicity: Mucositis

End point title Toxicity: Mucositis

End point description:

End point type	Secondary
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End point timeframe:  
during treatment

End point values	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients				
Grade 1	15			
Grade 2	14			
Grade 3	8			
Grade 4	0			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Toxic deaths

End point title	Toxic deaths
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End point description:

End point type	Secondary
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End point timeframe:  
during treatment

End point values	Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of patients	9			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Complete study

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	R-MPL
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Reporting group description:

Rituximab (375 mg/m<sup>2</sup>, days 1, 15, 29), high-dose methotrexate (3 g/m<sup>2</sup> days 2, 16, 30), procarbazine (60 mg/m<sup>2</sup> days 2-11) and lomustine (110 mg/m<sup>2</sup>, day 2)

Reporting group title	R-MP
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Reporting group description:

Rituximab (375 mg/m<sup>2</sup>, days 1, 15, 29), high-dose methotrexate (3 g/m<sup>2</sup> days 2, 16, 30), procarbazine (60 mg/m<sup>2</sup> days 2-11)

Serious adverse events	R-MPL	R-MP	
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 69 (59.42%)	26 / 38 (68.42%)	
number of deaths (all causes)	41	18	
number of deaths resulting from adverse events	10	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Progression einer Neubildung			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Fieber			
subjects affected / exposed	2 / 69 (2.90%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	2 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generelle Verschlechterung des physischen Gesundheitszustandes			
subjects affected / exposed	3 / 69 (4.35%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	3 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	

Schleimhautentzuendung			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Versagen mehrerer Organe			
subjects affected / exposed	2 / 69 (2.90%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lungenembolie			
subjects affected / exposed	2 / 69 (2.90%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Orientierungsstoerung			
subjects affected / exposed	1 / 69 (1.45%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wahn			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Alaninaminotransferase anomal			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Allgemeinzustand nach der Eastern Cooperative Oncology Group verschlechtert			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin erniedrigt			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kreatinin im Blut erhoeht			
subjects affected / exposed	0 / 69 (0.00%)	2 / 38 (5.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nierenfunktionstest anomal			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminasen erhoeht			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fraktur eines Lendenwirbels			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Frakturen von Gesichtsknochen			

subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sturz			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
subdurales Haematom			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myokardinfarkt			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perikarderguss			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
akuter Myokardinfarkt			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
akutes Koronarsyndrom			
subjects affected / exposed	1 / 69 (1.45%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hirnoedem			
subjects affected / exposed	2 / 69 (2.90%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hirnstammischaemie			

subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Koma			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Konvulsion			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparese			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
transitorische ischaemische Attacke			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
zerebrale Thrombose			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
febrile Neutropenie			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Analblutung			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoe			



subjects affected / exposed	2 / 69 (2.90%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dickdarmperforation			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erbrechen			
subjects affected / exposed	0 / 69 (0.00%)	2 / 38 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Magengeschwuer			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss Syndrom			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uebelkeit			
subjects affected / exposed	0 / 69 (0.00%)	2 / 38 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
akutes Abdomen			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
erosive Duodenitis			

subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrooesophageale Refluxerkrankung			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Arzneimittelbedingter Leberschaden			
subjects affected / exposed	2 / 69 (2.90%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Ausschlag			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ausschlag generalisiert			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nierenfunktionsbeeinträchtigung			
subjects affected / exposed	2 / 69 (2.90%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nierenversagen			
subjects affected / exposed	2 / 69 (2.90%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nierenversagen akut			
subjects affected / exposed	3 / 69 (4.35%)	4 / 38 (10.53%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations Bakterielle Harnwegsinfektion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 69 (1.45%) 1 / 1 0 / 0	 0 / 38 (0.00%) 0 / 0 0 / 0	
Bakterielle Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 69 (1.45%) 1 / 1 1 / 1	 0 / 38 (0.00%) 0 / 0 0 / 0	
Bronchopneumonie subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 69 (0.00%) 0 / 0 0 / 0	 1 / 38 (2.63%) 0 / 1 0 / 0	
Candidose des Oesophagus subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 69 (1.45%) 0 / 1 0 / 0	 0 / 38 (0.00%) 0 / 0 0 / 0	
Clostridium difficile-Infektion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 69 (1.45%) 1 / 1 0 / 0	 0 / 38 (0.00%) 0 / 0 0 / 0	
Cytomegalovirus hepatitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 69 (1.45%) 1 / 1 0 / 0	 0 / 38 (0.00%) 0 / 0 0 / 0	
Divertikulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 69 (1.45%) 1 / 1 0 / 0	 0 / 38 (0.00%) 0 / 0 0 / 0	
Enterokokken-Bakteriaemie subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 69 (1.45%) 1 / 1 0 / 0	 0 / 38 (0.00%) 0 / 0 0 / 0	
Gastroenteritis durch Norovirus			

subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Geraetebedingte Sepsis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Harnwegsinfektion			
subjects affected / exposed	0 / 69 (0.00%)	3 / 38 (7.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infektion			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infektion an der Katheterstelle			
subjects affected / exposed	1 / 69 (1.45%)	2 / 38 (5.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infektion im Zusammenhang mit einem medizinischen Geraet			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella-Sepsis			

subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsielleninfektion			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii-Pneumonie			
subjects affected / exposed	3 / 69 (4.35%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonie			
subjects affected / exposed	8 / 69 (11.59%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	3 / 9	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonie durch Klebsiella			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	5 / 69 (7.25%)	3 / 38 (7.89%)	
occurrences causally related to treatment / all	3 / 5	1 / 3	
deaths causally related to treatment / all	2 / 2	0 / 2	
Sepsis durch Staphylokokken			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septischer Schock			

subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wundinfektion			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Zystitis escherichia			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
atypische Pneumonie			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
febrile Infektion			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
orale Candidose			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonale Sepsis			
subjects affected / exposed	2 / 69 (2.90%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	2 / 2	1 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 69 (4.35%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

<b>Non-serious adverse events</b>	R-MPL	R-MP	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 69 (28.99%)	13 / 38 (34.21%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
zerebrales Hygrom			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Vascular disorders			
Hypotonie			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Venenthrombose einer Extremität			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Arzneimittelunverträglichkeit			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Fieber			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
grippeähnliche Erkrankung			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Schlaflosigkeit			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Investigations			
Leukozytenzahl erniedrigt			

subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Transaminasen erhoeht			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Schilddruesenunterfunktion nach einem Eingriff			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Sturz			
subjects affected / exposed	3 / 69 (4.35%)	0 / 38 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Ataxie			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
periphere sensorische Neuropathie			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Leukopenie			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Neutropenie			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Hoersturz			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Vertigo			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	



Eye disorders			
Papillenoedem			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
ischaemische Neuropathie des Nervus opticus			
subjects affected / exposed	0 / 69 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoe			
subjects affected / exposed	1 / 69 (1.45%)	1 / 38 (2.63%)	
occurrences (all)	1	1	
Enterokolitis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Uebelkeit			
subjects affected / exposed	2 / 69 (2.90%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Arzneimittelwirkung mit Eosinophilie und systemischen Symptomen			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Ausschlag			
subjects affected / exposed	1 / 69 (1.45%)	1 / 38 (2.63%)	
occurrences (all)	2	1	
Ekzem asteatotisch			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Medikamentenausschlag			
subjects affected / exposed	1 / 69 (1.45%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			

Harnverhaltung subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 1	0 / 38 (0.00%) 0	
Endocrine disorders			
Androgenmangel subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0	1 / 38 (2.63%) 1	
Diabetes insipidus subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0	1 / 38 (2.63%) 1	
Infections and infestations			
Bakteraemie subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 1	0 / 38 (0.00%) 0	
Bronchitis subjects affected / exposed occurrences (all)	2 / 69 (2.90%) 3	0 / 38 (0.00%) 0	
Gastroenteritis durch Clostridien subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 1	0 / 38 (0.00%) 0	
Gastroenteritis durch Norovirus subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 1	0 / 38 (0.00%) 0	
Harnwegsinfektion subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0	1 / 38 (2.63%) 1	
Herpes zoster subjects affected / exposed occurrences (all)	2 / 69 (2.90%) 2	0 / 38 (0.00%) 0	
Infektion der oberen Atemwege subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 1	1 / 38 (2.63%) 1	
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 1	0 / 38 (0.00%) 0	
Pneumonie durch Herpes simplex			

subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 1	0 / 38 (0.00%) 0	
Zystitis escherichia subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0	1 / 38 (2.63%) 1	
ophthalmischer Herpes zoster subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 1	0 / 38 (0.00%) 0	
oral Herpes subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0	1 / 38 (2.63%) 2	
Metabolism and nutrition disorders Hyponatraemie subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0	1 / 38 (2.63%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2012	1. Increase of sample size; 2. Dropping Lomustine from the therapy protocol due to several reported adverse and serious adverse events associated with treatment (mainly haematological toxicities and infections).

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/2784313>