Clinical trial results:
International Study for Treatment of Standard Risk Childhood Relapsed ALL 2010 - A randomized Phase III Study Conducted by the Resistant Disease Committee of the International BFM Study Group

Summary

EudraCT number	2012-000793-30
Trial protocol	SE PT GB DE BE AT IE FI DK CZ IT NL FR PL ES NO
Global end of trial date	31 July 2023

Results information

Result version number	v1
This version publication date	26 September 2024
First version publication date	26 September 2024

Trial information

Trial identification

Sponsor protocol code	IntReALL-SR-2010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01802814
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité Universitätsmedizin Berlin
Sponsor organisation address	Campus Virchow Klinikum - Augustenburger Platz 1, Berlin, Germany, 13353
Public contact	PD Dr. Arend von Stackelberg, Charité Universitätsmedizin Berlin, +49 30450666833, arend.stackelberg@charite.de
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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	01 July 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2023
Global end of trial reached?	Yes
Global end of trial date	31 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Overall: Improvement of event-free survival (EFS) probabilities in childhood relapsed ALL
- Randomization 1: EFS of Arm A (ALL-REZ BFM 2002) versus B (ALLR3) in SR patients
- Randomization 2: Influence of epratuzumab on EFS in consolidation of SR patients

Protection of trial subjects:

This study was conducted in accordance with applicable laws and regulations including, but not limited to, the ethical principles that have their origins in the Declaration of Helsinki and the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP). Prior to recruitment of subjects, the relevant authorities and ethics committees had to approve and authorize this clinical trial. Amendments were only implemented after approval. Before the procedures mentioned in the protocol were performed, the subject or his/her parent/legal guardian had to sign and date the approved informed consent form according to the requirements of national law.
Post trial treatment is not different from the expected normal treatment of that condition.
After termination of the study, patients will be followed up by national children's cancer registries to capture safety relevant late effects, secondary malignancies and to have the opportunity to give feed back to the patients, if necessary. Patients who are off study continue to be observed including a report of death in order to allow the assessment of overall survival.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 May 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 35
Country: Number of subjects enrolled	Switzerland: 14
Country: Number of subjects enrolled	Israel: 21
Country: Number of subjects enrolled	Japan: 39
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Norway: 9
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Portugal: 17
Country: Number of subjects enrolled	United Kingdom: 4

Country: Number of subjects enrolled	Austria: 17
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Czechia: 22
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	Finland: 15
Country: Number of subjects enrolled	France: 141
Country: Number of subjects enrolled	Germany: 141
Country: Number of subjects enrolled	Italy: 179
Worldwide total number of subjects	693
EEA total number of subjects	577

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	501
Adolescents (12-17 years)	192
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with a first standard-risk (SR) ALL relapse aged 1 to 17 years were recruited in the trial from 23.10.2014 to 31.07.2020 in 17 countries (210 centers).

Pre-assignment

Screening details:

confirmed 1st relapsed B-cell or T-cell ALL;
less than 18 years of age;
meeting SR criteria: late isolated or late/early combined BCP BM relapse, late/early isolated extramedullary relapse;
enrollment in a participating centre;
written informed consent;
start of treatment falling into the study period;
no other clinical trials 30 days prior

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA)

Arm description:

SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA): Induction: SIA (F1, F2); Post induction: SCA1 and SCA2, 5 courses SCA3-7 (R1/2/1/2/1), 24 months maintenance (6MP, MTX) with 6 x TIT / 4 weeks. Cranial irradiation 18Gy for CNS relapse.

Arm type	Active comparator
Investigational medicinal product name	ALL-REZ BFM 2002 arm Prot II-IDA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Kit for radiopharmaceutical preparation, Solution for injection/infusion, Syrup, Tablet
Routes of administration	Intrathecal use, Intravenous use, Oral use, Percutaneous use

Dosage and administration details:

Induction: SIA (F1, F2);Consolidation: SCA1 and SCA2, 5 courses SCA3-7 (R1/2/1/2/1); Maintenance 24 months (6-MP, MTX) with 6 x TIT / 4 weeks. Cranial irradiation with 18 Gy for CNS relapse.

Arm title	SR arm B (UK-R3, arm mitoxantrone)

Arm description:

SR arm B (ALL R3):
Induction (1st randomization): SIB (phase I);
Consolidation: SCB1 and SCB2 (consolidation and intensification), 2 courses SCB3-4 (interim maintenance 1 and 2);
Maintenance 20 months (6-MP, MTX, 4-weekly VCR/DEX/IT reinduction pulses). Cranial irradiation with 18 Gy for CNS relapse.

Arm type	Experimental
Investigational medicinal product name	ALL R3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Kit for radiopharmaceutical preparation, Solution for injection/infusion, Syrup, Tablet
Routes of administration	Intrathecal use, Intravenous use, Oral use, Percutaneous use

Dosage and administration details:

Induction: SIB (phase I); Consolidation: SCB1 and SCB2 (consolidation and intensification), 2 courses SCB3-4 (interim maintenance 1 and 2); Maintenance 20 months (6-MP, MTX, 4-weekly VCR/DEX/IT reinduction pulses). Cranial irradiation with 18 Gy for CNS relapse.

Number of subjects in period 1[1]	SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA)	SR arm B (UK-R3, arm mitoxantrone)
Started	304	316
Completed	282	293
Not completed	22	23
no CR or death in CR without SCT	22	23

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Not all patients enrolled worldwide were evaluable in final report.

Baseline characteristics

Reporting groups	
Reporting group title	SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA)
Reporting group description:	
SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA): Induction: SIA (F1, F2); Post induction: SCA1 and SCA2, 5 courses SCA3-7 (R1/2/1/2/1), 24 months maintenance (6MP, MTX) with 6 x TIT / 4 weeks. Cranial irradiation 18Gy for CNS relapse.	
Reporting group title	SR arm B (UK-R3, arm mitoxantrone)
Reporting group description:	
SR arm B (ALL R3): Induction (1st randomization): SIB (phase I); Consolidation: SCB1 and SCB2 (consolidation and intensification), 2 courses SCB3-4 (interim maintenance 1 and 2); Maintenance 20 months (6-MP, MTX, 4-weekly VCR/DEX/IT reinduction pulses). Cranial irradiation with 18 Gy for CNS relapse.	

Reporting group values	SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA)	SR arm B (UK-R3, arm mitoxantrone)	Total
Number of subjects	304	316	620
Age categorical Units: Subjects			
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	230	221	451
Adolescents (12-17 years)	74	95	169
Adults (18-64 years)	0	0	0
Gender categorical Units: Subjects			
Female	104	104	208
Male	200	212	412

End points

End points reporting groups

Reporting group title	SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA)
Reporting group description:	
SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA): Induction: SIA (F1, F2); Post induction: SCA1 and SCA2, 5 courses SCA3-7 (R1/2/1/2/1), 24 months maintenance (6MP, MTX) with 6 x TIT / 4 weeks. Cranial irradiation 18Gy for CNS relapse.	
Reporting group title	SR arm B (UK-R3, arm mitoxantrone)
Reporting group description:	
SR arm B (ALL R3): Induction (1st randomization): SIB (phase I); Consolidation: SCB1 and SCB2 (consolidation and intensification), 2 courses SCB3-4 (interim maintenance 1 and 2); Maintenance 20 months (6-MP, MTX, 4-weekly VCR/DEX/IT reinduction pulses). Cranial irradiation with 18 Gy for CNS relapse.	

Primary: 4-year Event Free Survival probability - ITT

End point title	4-year Event Free Survival probability - ITT
End point description:	
The probability of Event Free Survival (pEFS) at 4 years was estimated according to the Kaplan-Meier method. The analysis was performed using the "intention to treat" (ITT) principle for all randomized study patients.	
End point type	Primary
End point timeframe:	
Event free survival (EFS) for is defined as the time from randomization to the first of induction failure, relapse, death from any cause or second malignancy or is censored at the date of last follow-up.	

End point values	SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA)	SR arm B (UK-R3, arm mitoxantrone)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	120		
Units: percentage				
number (confidence interval 95%)	68.6 (62.6 to 73.9)	69.0 (63.2 to 74.2)		

Statistical analyses

Statistical analysis title	Final analysis (Intention to treat)
Statistical analysis description:	
The log-rank test was used to compare the groups.	
Comparison groups	SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA) v SR arm B (UK-R3, arm mitoxantrone)

Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank

Secondary: 4-year Overall Survival probability - ITT

End point title	4-year Overall Survival probability - ITT

End point description:

The probability of Overall Survival (pOS) at 4 years was estimated according to the Kaplan-Meier method. The analysis was performed using the "intention to treat" (ITT) principle for all randomized study patients.

End point type	Secondary

End point timeframe:

Overall Survival (OS) is defined as the time from randomization to death from any cause. Stem-cell transplantation is not considered as event and is also not censored in the EFS/OS analyses.

End point values	SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA)	SR arm B (UK-R3, arm mitoxantrone)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	141		
Units: percentage				
number (confidence interval 95%)	84.0 (79.0 to 87.9)	84.8 (80.1 to 88.4)		

Statistical analyses

Statistical analysis title	Final analysis (Intention to treat)

Statistical analysis description:

The log-rank test was used to compare the groups.

Comparison groups	SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA) v SR arm B (UK-R3, arm mitoxantrone)
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first day of study treatment until end of study follow-up (3 years after treatment initiation).

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA)

Reporting group description:

SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA): Induction: SIA (F1, F2); Post induction: SCA1 and SCA2, 5 courses SCA3-7 (R1/2/1/2/1), 24 months maintenance (6MP, MTX) with 6 x TIT / 4 weeks. Cranial irradiation 18Gy for CNS relapse.

Reporting group title	SR arm B (UK-R3, arm mitoxantrone)

Reporting group description:

SR arm B (ALL R3):
Induction (1st randomization): SIB (phase I);
Consolidation: SCB1 and SCB2 (consolidation and intensification), 2 courses SCB3-4 (interim maintenance 1 and 2);
Maintenance 20 months (6-MP, MTX, 4-weekly VCR/DEX/IT reinduction pulses). Cranial irradiation with 18 Gy for CNS relapse.

Serious adverse events	SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA)	SR arm B (UK-R3, arm mitoxantrone)	
Total subjects affected by serious adverse events			
subjects affected / exposed	191 / 304 (62.83%)	213 / 316 (67.41%)	
number of deaths (all causes)	24	35	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify			
subjects affected / exposed	1 / 304 (0.33%)	3 / 316 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	2 / 304 (0.66%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Thromboembolic event			
subjects affected / exposed	3 / 304 (0.99%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Vascular disorders - Other, specify			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death NOS			
subjects affected / exposed	2 / 304 (0.66%)	6 / 316 (1.90%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 2	1 / 6	
Fever			
subjects affected / exposed	5 / 304 (1.64%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	3 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	4 / 304 (1.32%)	3 / 316 (0.95%)	
occurrences causally related to treatment / all	1 / 4	1 / 3	
deaths causally related to treatment / all	1 / 4	0 / 2	
Sudden death NOS			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Immune system disorders			

Allergic reaction			
subjects affected / exposed	5 / 304 (1.64%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylaxis treatment			
subjects affected / exposed	7 / 304 (2.30%)	7 / 316 (2.22%)	
occurrences causally related to treatment / all	7 / 7	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders - Other, specify			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cytokine release syndrome			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Adult respiratory distress syndrome			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Apnea			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 304 (0.33%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonitis			
subjects affected / exposed	4 / 304 (1.32%)	3 / 316 (0.95%)	
occurrences causally related to treatment / all	3 / 4	3 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	

Respiratory failure			
subjects affected / exposed	1 / 304 (0.33%)	3 / 316 (0.95%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
Bronchial infection			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	10 / 304 (3.29%)	19 / 316 (6.01%)	
occurrences causally related to treatment / all	9 / 10	18 / 19	
deaths causally related to treatment / all	0 / 0	1 / 2	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	2 / 304 (0.66%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 304 (0.00%)	3 / 316 (0.95%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Creatinine increased			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations - Other, specify			
subjects affected / exposed	2 / 304 (0.66%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Intestinal stoma site bleeding			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders - Other, specify			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure			
subjects affected / exposed	2 / 304 (0.66%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Edema cerebral			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	2 / 304 (0.66%)	3 / 316 (0.95%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrapyramidal disorder			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial hemorrhage			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Ischemia cerebrovascular			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders - Other,			

specify			
subjects affected / exposed	4 / 304 (1.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	2 / 304 (0.66%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	8 / 304 (2.63%)	4 / 316 (1.27%)	
occurrences causally related to treatment / all	8 / 8	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reversible posterior leukencephalopathy syndrome			
subjects affected / exposed	2 / 304 (0.66%)	3 / 316 (0.95%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders - Other, specify			
subjects affected / exposed	1 / 304 (0.33%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile neutropenia			
subjects affected / exposed	7 / 304 (2.30%)	21 / 316 (6.65%)	
occurrences causally related to treatment / all	11 / 11	25 / 26	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bone marrow hypocellular			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorders - Other, specify			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinopathy			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic hemorrhage			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colonic perforation			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophagitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders - Other, specify			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 304 (0.66%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis oral			
subjects affected / exposed	3 / 304 (0.99%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral pain			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	10 / 304 (3.29%)	9 / 316 (2.85%)	
occurrences causally related to treatment / all	9 / 10	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal hemorrhage			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			

subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomach pain			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typhlitis			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vomiting			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic necrosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal mucositis			
subjects affected / exposed	0 / 304 (0.00%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jejunal obstruction			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliay disorders - Other, specify			

subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders - Other, specify			
subjects affected / exposed	0 / 304 (0.00%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulceration			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic epidermal necrolysis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papulopustular rash			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle weakness right-sided			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Avascular necrosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	4 / 304 (1.32%)	4 / 316 (1.27%)	
occurrences causally related to treatment / all	2 / 4	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter related infection			
subjects affected / exposed	1 / 304 (0.33%)	4 / 316 (1.27%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis infection			
subjects affected / exposed	2 / 304 (0.66%)	3 / 316 (0.95%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			

subjects affected / exposed	2 / 304 (0.66%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other, specify			
subjects affected / exposed	5 / 304 (1.64%)	14 / 316 (4.43%)	
occurrences causally related to treatment / all	1 / 5	13 / 13	
deaths causally related to treatment / all	0 / 2	1 / 2	
Kidney infection			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Meningitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	40 / 304 (13.16%)	32 / 316 (10.13%)	
occurrences causally related to treatment / all	36 / 37	29 / 31	
deaths causally related to treatment / all	5 / 7	9 / 11	
Urinary tract infection			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	2 / 304 (0.66%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip infection			

subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal infection			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval infection			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycemia			
subjects affected / exposed	1 / 304 (0.33%)	6 / 316 (1.90%)	
occurrences causally related to treatment / all	1 / 1	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertriglyceridaemia			
subjects affected / exposed	5 / 304 (1.64%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalemia			
subjects affected / exposed	0 / 304 (0.00%)	4 / 316 (1.27%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA)	SR arm B (UK-R3, arm mitoxantrone)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	190 / 304 (62.50%)	142 / 316 (44.94%)	
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences (all)	1	1	
Hypotension			
subjects affected / exposed	2 / 304 (0.66%)	0 / 316 (0.00%)	
occurrences (all)	2	0	
Thromboembolic event			
subjects affected / exposed	7 / 304 (2.30%)	9 / 316 (2.85%)	
occurrences (all)	15	9	
Surgical and medical procedures			
Surgical and medical procedures - Other, specify			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	42 / 304 (13.82%)	43 / 316 (13.61%)	
occurrences (all)	48	54	
Pain			
subjects affected / exposed	0 / 304 (0.00%)	2 / 316 (0.63%)	
occurrences (all)	0	2	
Edema limbs			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Allergic reaction			

subjects affected / exposed	6 / 304 (1.97%)	6 / 316 (1.90%)	
occurrences (all)	6	7	
Anaphylaxis			
subjects affected / exposed	4 / 304 (1.32%)	3 / 316 (0.95%)	
occurrences (all)	4	3	
Immune system disorders - Other, specify			
subjects affected / exposed	1 / 304 (0.33%)	2 / 316 (0.63%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Pneumonitis			
subjects affected / exposed	0 / 304 (0.00%)	2 / 316 (0.63%)	
occurrences (all)	0	2	
Pulmonary edema			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Respiratory failure			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences (all)	1	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	2 / 304 (0.66%)	1 / 316 (0.32%)	
occurrences (all)	2	1	
Anxiety			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Confusion			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders - Other, specify			

subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Psychosis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences (all)	0	2	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	53 / 304 (17.43%)	56 / 316 (17.72%)	
occurrences (all)	84	82	
Cholesterol high			
subjects affected / exposed	4 / 304 (1.32%)	1 / 316 (0.32%)	
occurrences (all)	5	1	
Creatinine increased			
subjects affected / exposed	6 / 304 (1.97%)	8 / 316 (2.53%)	
occurrences (all)	6	8	
Fibrinogen decreased			
subjects affected / exposed	6 / 304 (1.97%)	0 / 316 (0.00%)	
occurrences (all)	11	0	
Investigations - Other, specify			
subjects affected / exposed	3 / 304 (0.99%)	4 / 316 (1.27%)	
occurrences (all)	21	5	
Lipase increased			
subjects affected / exposed	12 / 304 (3.95%)	2 / 316 (0.63%)	
occurrences (all)	16	2	
Lymphocyte count decreased			
subjects affected / exposed	2 / 304 (0.66%)	3 / 316 (0.95%)	
occurrences (all)	3	15	
Serum amylase increased			
subjects affected / exposed	3 / 304 (0.99%)	1 / 316 (0.32%)	
occurrences (all)	5	1	
Weight loss			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences (all)	0	3	
GGT increased			
subjects affected / exposed	5 / 304 (1.64%)	5 / 316 (1.58%)	
occurrences (all)	7	8	

Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications - Other, specify			
subjects affected / exposed	0 / 304 (0.00%)	2 / 316 (0.63%)	
occurrences (all)	0	2	
Cardiac disorders			
Cardiac disorders - Other, specify			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences (all)	0	1	
Pericardial effusion			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Edema cerebral			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Encephalopathy			
subjects affected / exposed	2 / 304 (0.66%)	0 / 316 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders - Other, specify			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Peripheral motor neuropathy			
subjects affected / exposed	4 / 304 (1.32%)	0 / 316 (0.00%)	
occurrences (all)	4	0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Seizure			

subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Vasovagal reaction			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Paresthesia			
subjects affected / exposed	16 / 304 (5.26%)	7 / 316 (2.22%)	
occurrences (all)	19	13	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders - Other, specify			
subjects affected / exposed	0 / 304 (0.00%)	5 / 316 (1.58%)	
occurrences (all)	0	11	
Febrile neutropenia			
subjects affected / exposed	11 / 304 (3.62%)	8 / 316 (2.53%)	
occurrences (all)	16	13	
Bone marrow hypocellular			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Hearing impaired			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences (all)	0	1	
Otitis media			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences (all)	0	1	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences (all)	0	1	
Eye disorders - Other, specify			
subjects affected / exposed	0 / 304 (0.00%)	2 / 316 (0.63%)	
occurrences (all)	0	2	
Uveitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Abdominal pain				
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)		
occurrences (all)	0	1		
Anal ulcer				
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)		
occurrences (all)	1	0		
Appendicitis				
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)		
occurrences (all)	1	1		
Appendicitis perforated				
subjects affected / exposed	2 / 304 (0.66%)	0 / 316 (0.00%)		
occurrences (all)	2	0		
Ascites				
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)		
occurrences (all)	1	0		
Colitis				
subjects affected / exposed	0 / 304 (0.00%)	2 / 316 (0.63%)		
occurrences (all)	0	2		
Diarrhoea				
subjects affected / exposed	30 / 304 (9.87%)	21 / 316 (6.65%)		
occurrences (all)	36	23		
Gastrointestinal disorders - Other, specify				
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)		
occurrences (all)	1	0		
Ileus				
subjects affected / exposed	2 / 304 (0.66%)	2 / 316 (0.63%)		
occurrences (all)	3	2		
Mucositis oral				
subjects affected / exposed	111 / 304 (36.51%)	121 / 316 (38.29%)		
occurrences (all)	156	156		
Nausea				
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)		
occurrences (all)	0	1		
Oral hemorrhage				

subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Pancreatitis			
subjects affected / exposed	8 / 304 (2.63%)	2 / 316 (0.63%)	
occurrences (all)	8	2	
Typhlitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	23 / 304 (7.57%)	13 / 316 (4.11%)	
occurrences (all)	26	14	
Pancreatic necrosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Anal mucositis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Bullous dermatitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders - Other, specify			
subjects affected / exposed	1 / 304 (0.33%)	2 / 316 (0.63%)	
occurrences (all)	1	2	
Skin ulceration			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences (all)	1	1	
Urticaria			
subjects affected / exposed	2 / 304 (0.66%)	0 / 316 (0.00%)	
occurrences (all)	2	0	
Rash maculo-papular			

subjects affected / exposed	4 / 304 (1.32%)	19 / 316 (6.01%)	
occurrences (all)	4	21	
Renal and urinary disorders			
Renal and urinary disorders - Other, specify			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences (all)	1	1	
Acute kidney injury			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Delayed puberty			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences (all)	0	1	
Hypothyroidism			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 316 (0.32%)	
occurrences (all)	0	1	
Infections and infestations			
Catheter related infection			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences (all)	1	1	
Sepsis			
subjects affected / exposed	4 / 304 (1.32%)	3 / 316 (0.95%)	
occurrences (all)	4	3	
Skin infection			
subjects affected / exposed	0 / 304 (0.00%)	2 / 316 (0.63%)	
occurrences (all)	0	2	

Vaginal infection			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Pancreas infection			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences (all)	1	1	
Lung infection			
subjects affected / exposed	1 / 304 (0.33%)	2 / 316 (0.63%)	
occurrences (all)	1	2	
Soft tissue infection			
subjects affected / exposed	0 / 304 (0.00%)	2 / 316 (0.63%)	
occurrences (all)	0	2	
Lip infection			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 304 (0.00%)	3 / 316 (0.95%)	
occurrences (all)	0	5	
Dehydration			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	13 / 304 (4.28%)	10 / 316 (3.16%)	
occurrences (all)	21	11	
Hypertriglyceridaemia			
subjects affected / exposed	17 / 304 (5.59%)	3 / 316 (0.95%)	
occurrences (all)	31	3	
Hyperuricaemia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 304 (0.00%)	3 / 316 (0.95%)	
occurrences (all)	0	6	
Hypocalcaemia			

subjects affected / exposed	2 / 304 (0.66%)	1 / 316 (0.32%)	
occurrences (all)	2	1	
Hypoglycaemia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 316 (0.00%)	
occurrences (all)	1	0	
Hypokalemia			
subjects affected / exposed	7 / 304 (2.30%)	10 / 316 (3.16%)	
occurrences (all)	11	13	
Hypomagnesaemia			
subjects affected / exposed	1 / 304 (0.33%)	1 / 316 (0.32%)	
occurrences (all)	1	1	
Hyponatraemia			
subjects affected / exposed	5 / 304 (1.64%)	5 / 316 (1.58%)	
occurrences (all)	9	5	
Hypophosphataemia			
subjects affected / exposed	2 / 304 (0.66%)	1 / 316 (0.32%)	
occurrences (all)	3	1	
Metabolism and nutrition disorders - Other, specify			
subjects affected / exposed	3 / 304 (0.99%)	4 / 316 (1.27%)	
occurrences (all)	3	7	
Iron overload			
subjects affected / exposed	0 / 304 (0.00%)	2 / 316 (0.63%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2015	Amended Protocol Version 1.9: Minor changes and clarifications.
01 November 2018	Amended Protocol Version 2.0: Stop of second randomization since 01.02.2019 due to discontinued supply of Epratuzumab. All patients receive the full standard chemotherapy of arm A or B. Recruitment time and follow-up time extended.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported