



## 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 |
| Scientific contact           | PD Dr. Arend von Stackelberg, Charité Universitätsmedizin Berlin, +49 30450666833, arend.stackelberg@charite.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:

## 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:

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### 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   |
| <b>Arm title</b>             | 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.

|                  |                                    |
|------------------|------------------------------------|
| <b>Arm title</b> | 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                            |

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**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.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | 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                                 |

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**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:<br>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:<br>SR arm B (ALL R3):<br>Induction (1st randomization): SIB (phase I);<br>Consolidation: SCB1 and SCB2 (consolidation and intensification), 2 courses SCB3-4 (interim maintenance 1 and 2);<br>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<br>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<br>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:<br>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:<br>SR arm B (ALL R3):<br>Induction (1st randomization): SIB (phase I);<br>Consolidation: SCB1 and SCB2 (consolidation and intensification), 2 courses SCB3-4 (interim maintenance 1 and 2);<br>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:<br>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:<br>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:<br>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<br>subjects affected / exposed               | 1 / 304 (0.33%) | 0 / 316 (0.00%) |  |
| occurrences causally related to<br>treatment / all                | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           |  |
| Investigations - Other, specify<br>subjects affected / exposed    | 2 / 304 (0.66%) | 0 / 316 (0.00%) |  |
| occurrences causally related to<br>treatment / all                | 0 / 2           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                     | 0 / 1           | 0 / 0           |  |
| Injury, poisoning and procedural<br>complications                 |                 |                 |  |
| Intestinal stoma site bleeding<br>subjects affected / exposed     | 1 / 304 (0.33%) | 0 / 316 (0.00%) |  |
| occurrences causally related to<br>treatment / all                | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           |  |
| Vascular access complication<br>subjects affected / exposed       | 1 / 304 (0.33%) | 1 / 316 (0.32%) |  |
| occurrences causally related to<br>treatment / all                | 1 / 1           | 1 / 1           |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           |  |
| Cardiac disorders   |                 |                 |  |
| Cardiac arrest<br>subjects affected / exposed                     | 0 / 304 (0.00%) | 1 / 316 (0.32%) |  |
| occurrences causally related to<br>treatment / all                | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 1           |  |
| Cardiac disorders - Other, specify<br>subjects affected / exposed | 0 / 304 (0.00%) | 1 / 316 (0.32%) |  |
| occurrences causally related to<br>treatment / all                | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           |  |
| Heart failure<br>subjects affected / exposed                      | 2 / 304 (0.66%) | 0 / 316 (0.00%) |  |
| occurrences causally related to<br>treatment / all                | 1 / 2           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                     | 0 / 1           | 0 / 0           |  |
| Sinus tachycardia<br>subjects affected / exposed                  | 1 / 304 (0.33%) | 0 / 316 (0.00%) |  |
| occurrences causally related to<br>treatment / all                | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>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<br>subjects affected / exposed                        | 0 / 304 (0.00%) | 1 / 316 (0.32%) |  |
| occurrences causally related to<br>treatment / all                             | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all                                  | 0 / 0           | 0 / 0           |  |
| White blood cell count decreased<br>subjects affected / exposed                | 1 / 304 (0.33%) | 1 / 316 (0.32%) |  |
| occurrences causally related to<br>treatment / all                             | 1 / 1           | 1 / 1           |  |
| deaths causally related to<br>treatment / all                                  | 0 / 0           | 0 / 0           |  |
| Eye disorders<br>Eye disorders - Other, specify<br>subjects affected / exposed | 0 / 304 (0.00%) | 1 / 316 (0.32%) |  |
| occurrences causally related to<br>treatment / all                             | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all                                  | 0 / 0           | 0 / 0           |  |
| Retinopathy<br>subjects affected / exposed                                     | 0 / 304 (0.00%) | 1 / 316 (0.32%) |  |
| occurrences causally related to<br>treatment / all                             | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                                  | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed    | 1 / 304 (0.33%) | 0 / 316 (0.00%) |  |
| occurrences causally related to<br>treatment / all                             | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                                  | 0 / 0           | 0 / 0           |  |
| Anal fistula<br>subjects affected / exposed                                    | 0 / 304 (0.00%) | 1 / 316 (0.32%) |  |
| occurrences causally related to<br>treatment / all                             | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all                                  | 0 / 0           | 0 / 0           |  |
| Colitis<br>subjects affected / exposed   | 1 / 304 (0.33%) | 0 / 316 (0.00%) |  |
| occurrences causally related to<br>treatment / all                             | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                                  | 0 / 0           | 0 / 0           |  |
| Colonic hemorrhage<br>subjects affected / exposed                              | 1 / 304 (0.33%) | 0 / 316 (0.00%) |  |
| occurrences causally related to<br>treatment / all                             | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>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           |  |
| Hepatobiliary 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 %

| <b>Non-serious adverse events</b>                     | SR arm A (ALL-REZ<br>BFM 2002 arm Prot<br>II-IDA) | SR arm B (UK-R3,<br>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<br>occurrences (all)  | 6 / 304 (1.97%)<br>6 | 6 / 316 (1.90%)<br>7 |  |
| Anaphylaxis<br>subjects affected / exposed<br>occurrences (all)                                 | 4 / 304 (1.32%)<br>4 | 3 / 316 (0.95%)<br>3 |  |
| Immune system disorders - Other,<br>specify<br>subjects affected / exposed<br>occurrences (all) | 1 / 304 (0.33%)<br>1 | 2 / 316 (0.63%)<br>2 |  |
| Respiratory, thoracic and mediastinal<br>disorders  |                      |                      |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 304 (0.33%)<br>1 | 0 / 316 (0.00%)<br>0 |  |
| Pneumonitis<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 304 (0.00%)<br>0 | 2 / 316 (0.63%)<br>2 |  |
| Pulmonary edema<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 304 (0.33%)<br>1 | 0 / 316 (0.00%)<br>0 |  |
| Pulmonary fibrosis<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 304 (0.33%)<br>1 | 0 / 316 (0.00%)<br>0 |  |
| Respiratory failure<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 304 (0.33%)<br>1 | 1 / 316 (0.32%)<br>1 |  |
| Psychiatric disorders   |                      |                      |  |
| Agitation<br>subjects affected / exposed<br>occurrences (all)                                   | 2 / 304 (0.66%)<br>2 | 1 / 316 (0.32%)<br>1 |  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 304 (0.33%)<br>1 | 0 / 316 (0.00%)<br>0 |  |
| Confusion<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 304 (0.33%)<br>1 | 0 / 316 (0.00%)<br>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<br>occurrences (all)   | 1 / 304 (0.33%)<br>1   | 0 / 316 (0.00%)<br>0  |  |
| Vasovagal reaction<br>subjects affected / exposed<br>occurrences (all)   | 1 / 304 (0.33%)<br>1   | 0 / 316 (0.00%)<br>0  |  |
| Paresthesia<br>subjects affected / exposed<br>occurrences (all)  | 16 / 304 (5.26%)<br>19 | 7 / 316 (2.22%)<br>13 |  |
| Blood and lymphatic system disorders<br>Blood and lymphatic system<br>disorders - Other, specify<br>subjects affected / exposed<br>occurrences (all) | 0 / 304 (0.00%)<br>0   | 5 / 316 (1.58%)<br>11 |  |
| Febrile neutropenia<br>subjects affected / exposed<br>occurrences (all)  | 11 / 304 (3.62%)<br>16 | 8 / 316 (2.53%)<br>13 |  |
| Bone marrow hypocellular<br>subjects affected / exposed<br>occurrences (all)   | 1 / 304 (0.33%)<br>1   | 0 / 316 (0.00%)<br>0  |  |
| Ear and labyrinth disorders<br>Hearing impaired<br>subjects affected / exposed<br>occurrences (all)  | 0 / 304 (0.00%)<br>0   | 1 / 316 (0.32%)<br>1  |  |
| Otitis media<br>subjects affected / exposed<br>occurrences (all)   | 0 / 304 (0.00%)<br>0   | 1 / 316 (0.32%)<br>1  |  |
| Eye disorders<br>Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 304 (0.00%)<br>0   | 1 / 316 (0.32%)<br>1  |  |
| Eye disorders - Other, specify<br>subjects affected / exposed<br>occurrences (all)   | 0 / 304 (0.00%)<br>0   | 2 / 316 (0.63%)<br>2  |  |
| Uveitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 304 (0.00%)<br>0   | 1 / 316 (0.32%)<br>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<br>occurrences (all)   | 4 / 304 (1.32%)<br>4 | 19 / 316 (6.01%)<br>21 |  |
| Renal and urinary disorders<br>Renal and urinary disorders - Other,<br>specify<br>subjects affected / exposed<br>occurrences (all) | 1 / 304 (0.33%)<br>1 | 1 / 316 (0.32%)<br>1   |  |
| Acute kidney injury<br>subjects affected / exposed<br>occurrences (all)  | 1 / 304 (0.33%)<br>1 | 0 / 316 (0.00%)<br>0   |  |
| Endocrine disorders<br>Adrenal insufficiency<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 304 (0.33%)<br>1 | 0 / 316 (0.00%)<br>0   |  |
| Delayed puberty<br>subjects affected / exposed<br>occurrences (all)  | 0 / 304 (0.00%)<br>0 | 1 / 316 (0.32%)<br>1   |  |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)   | 0 / 304 (0.00%)<br>0 | 1 / 316 (0.32%)<br>1   |  |
| Musculoskeletal and connective tissue<br>disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)                | 1 / 304 (0.33%)<br>1 | 0 / 316 (0.00%)<br>0   |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 304 (0.00%)<br>0 | 1 / 316 (0.32%)<br>1   |  |
| Infections and infestations<br>Catheter related infection<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 304 (0.33%)<br>1 | 1 / 316 (0.32%)<br>1   |  |
| Sepsis<br>subjects affected / exposed<br>occurrences (all)   | 4 / 304 (1.32%)<br>4 | 3 / 316 (0.95%)<br>3   |  |
| Skin infection<br>subjects affected / exposed<br>occurrences (all)   | 0 / 304 (0.00%)<br>0 | 2 / 316 (0.63%)<br>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 -<br>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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported