



Clinical trial results:

A phase 2 study of brentuximab vedotin in combination with standard of care treatment (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [RCHOP]) or RCHP (rituximab, cyclophosphamide, doxorubicin, and prednisone) as front-line therapy in patients with diffuse large B-cell lymphoma (DLBCL)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-004741-54 |
| Trial protocol | CZ ES IT |
| Global end of trial date | 01 May 2017 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 13 May 2018 |
| First version publication date | 13 May 2018 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | SGN35-017 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01925612 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Seattle Genetics, Inc |
| Sponsor organisation address | 21823 30th Dr SE, Bothell, United States, 98021-3907 |
| Public contact | Chief Medical Officer, Seattle Genetics, Inc, 001 855-473-2436, medinfo@seagen.com |
| Scientific contact | Chief Medical Officer, Seattle Genetics, Inc, 001 855-473-2436, medinfo@seagen.com |

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 | 15 March 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 May 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To assess the antitumor activity of brentuximab vedotin administered in combination with RCHOP or RCHP, and in combination with RCHP versus RCHOP alone, as measured by the CR rate at the end of treatment per investigator assessment in treatment-naïve patients with high-intermediate or high risk systemic DLBCL

To assess the safety profile of brentuximab vedotin administered at dose levels of 1.2 mg/kg versus 1.8 mg/kg in combination with RCHOP or brentuximab vedotin 1.8 mg/kg in combination with RCHP in treatment-naïve patients with high-intermediate or high risk systemic DLBCL

Protection of trial subjects:

The protocol for this study was designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The conduct of all aspects of the study, including methods for obtaining informed consent, were also in accordance with principles enunciated in the declaration, the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP), and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in Title 21 CFR Parts 11, 50, 54, 56, and 312. The consent form approved by each IRB/IEC included all elements required by the applicable regional laws and regulations, including a statement that Seattle Genetics, Inc. and authorities had access to patient records. Consent was obtained from all patients before any protocol-required procedures were performed, including any procedure not part of normal patient care.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 01 August 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Poland: 2 |
| Country: Number of subjects enrolled | Czech Republic: 2 |
| Country: Number of subjects enrolled | Italy: 1 |
| Country: Number of subjects enrolled | United States: 80 |
| Worldwide total number of subjects | 85 |
| EEA total number of subjects | 5 |

Notes:

| Subjects enrolled per age group | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 39 |
| From 65 to 84 years | 46 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled from 30-Aug-2013 through 28-Nov-2016.

Pre-assignment

Screening details:

The population to be studied includes treatment-naïve patients with systemic de novo or transformed DLBCL or follicular non-Hodgkin lymphoma (NHL) grade 3b.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

Part 1 was randomized and open-label.

Part 2 was non-randomized and open-label.

Part 3 was randomized and open-label.

Arms

| | |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Part 1: BV (1.2 mg/kg) + RCHOP |

Arm description:

Part 1 of the study is randomized and open-label. Brentuximab vedotin was administered at 1.2mg/kg in combination with standard RCHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Brentuximab vedotin |
| Investigational medicinal product code | |
| Other name | Adcetris, SGN-35 |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1.2mg/kg every 3 weeks by IV infusion

| | |
|--|-----------------------|
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

375 mg/m² every 3 weeks by IV infusion for up to 6 cycles.

| | |
|--|----------------------------------|
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

750 mg/m² every 3 weeks by IV infusion for up to 6 cycles.

| | |
|--|-------------|
| Investigational medicinal product name | Doxorubicin |
| Investigational medicinal product code | |
| Other name | |

| | |
|--|--|
| Pharmaceutical forms | Dispersion for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 50 mg/m ² every 3 weeks by IV infusion for up to 6 cycles. | |
| Investigational medicinal product name | Vincristine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 1.4 mg/m ² every 3 weeks by IV infusion for up to 6 cycles (dose capped at 2 mg total). | |
| Investigational medicinal product name | Prednisone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 100 mg on Days 1 to 5 of each 3-week cycle, orally for up to 6 cycles. | |
| Arm title | Part 1: BV (1.8 mg/kg) + RCHOP |
| Arm description: | |
| Part 1 of the study is a randomized and open-label. Brentuximab vedotin was administered at 1.8 mg/kg in combination with standard RCHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). | |
| Arm type | Experimental |
| Investigational medicinal product name | Brentuximab vedotin |
| Investigational medicinal product code | |
| Other name | Adcetris, SGN-35 |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 1.8mg/kg every 3 weeks by IV infusion | |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 375 mg/m ² every 3 weeks by IV infusion for up to 6 cycles. | |
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 750 mg/m ² every 3 weeks by IV infusion for up to 6 cycles. | |
| Investigational medicinal product name | Doxorubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Dispersion for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 50 mg/m ² every 3 weeks by IV infusion for up to 6 cycles. | |

| | |
|---|--|
| Investigational medicinal product name | Vincristine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 1.4 mg/m ² every 3 weeks by IV infusion for up to 6 cycles (dose capped at 2 mg total). | |
| Investigational medicinal product name | Prednisone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 100 mg on Days 1 to 5 of each 3-week cycle, orally for up to 6 cycles. | |
| Arm title | Part 2: BV (1.8 mg/kg) + RCHP |
| Arm description: | |
| Part 2 of the study was non-randomized and open-label. Brentuximab vedotin (1.8 mg/kg) was administered in combination with RCHP chemotherapy (rituximab, cyclophosphamide, doxorubicin, and prednisone). | |
| Arm type | Experimental |
| Investigational medicinal product name | Brentuximab vedotin |
| Investigational medicinal product code | |
| Other name | Adcetris, SGN-35 |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 1.8mg/kg every 3 weeks by IV infusion | |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 375 mg/m ² every 3 weeks by IV infusion for up to 6 cycles. | |
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 750 mg/m ² every 3 weeks by IV infusion for up to 6 cycles. | |
| Investigational medicinal product name | Doxorubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Dispersion for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 50 mg/m ² every 3 weeks by IV infusion for up to 6 cycles. | |
| Investigational medicinal product name | Prednisone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

100 mg on Days 1 to 5 of each 3-week cycle, orally for up to 6 cycles.

| | |
|------------------|-------------------------------|
| Arm title | Part 3: BV (1.8 mg/kg) + RCHP |
|------------------|-------------------------------|

Arm description:

Part 3 of the study was randomized and open-label. Brentuximab vedotin (1.8 mg/kg) was administered in combination with RCHP chemotherapy.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Brentuximab vedotin |
| Investigational medicinal product code | |
| Other name | Adcetris, SGN-35 |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1.8mg/kg every 3 weeks by IV infusion

| | |
|--|-----------------------|
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

375 mg/m² every 3 weeks by IV infusion for up to 6 cycles.

| | |
|--|----------------------------------|
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

750 mg/m² every 3 weeks by IV infusion for up to 6 cycles.

| | |
|--|-------------------------|
| Investigational medicinal product name | Doxorubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Dispersion for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

50 mg/m² every 3 weeks by IV infusion for up to 6 cycles.

| | |
|--|------------|
| Investigational medicinal product name | Prednisone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

100 mg on Days 1 to 5 of each 3-week cycle, orally for up to 6 cycles.

| | |
|------------------|---------------|
| Arm title | Part 3: RCHOP |
|------------------|---------------|

Arm description:

Part 3 of the study was randomized and open-label. RCHOP chemotherapy was administered alone.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|----------------------------------|
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 375 mg/m ² every 3 weeks by IV infusion for up to 6 cycles. | |
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 750 mg/m ² every 3 weeks by IV infusion for up to 6 cycles. | |
| Investigational medicinal product name | Doxorubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Dispersion for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 50 mg/m ² every 3 weeks by IV infusion for up to 6 cycles. | |
| Investigational medicinal product name | Vincristine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 1.4 mg/m ² every 3 weeks by IV infusion for up to 6 cycles (dose capped at 2 mg total). | |
| Investigational medicinal product name | Prednisone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 100 mg on Days 1 to 5 of each 3-week cycle, orally for up to 6 cycles. | |

| Number of subjects in period 1 | Part 1: BV (1.2 mg/kg) + RCHOP | Part 1: BV (1.8 mg/kg) + RCHOP | Part 2: BV (1.8 mg/kg) + RCHP |
|---------------------------------------|--------------------------------|--------------------------------|-------------------------------|
| Started | 29 | 22 | 11 |
| Completed | 25 | 18 | 10 |
| Not completed | 4 | 4 | 1 |
| Adverse event, serious fatal | 1 | 1 | - |
| Adverse event, non-fatal | 2 | 2 | - |
| Progressive Disease | 1 | 1 | 1 |

| Number of subjects in period 1 | Part 3: BV (1.8 mg/kg) + RCHP | Part 3: RCHOP |
|---------------------------------------|-------------------------------|---------------|
| Started | 11 | 12 |

| | | |
|------------------------------|----|----|
| Completed | 10 | 10 |
| Not completed | 1 | 2 |
| Adverse event, serious fatal | 1 | 2 |
| Adverse event, non-fatal | - | - |
| Progressive Disease | - | - |

Baseline characteristics

Reporting groups

| | |
|--|--------------------------------|
| Reporting group title | Part 1: BV (1.2 mg/kg) + RCHOP |
| Reporting group description: Part 1 of the study is randomized and open-label. Brentuximab vedotin was administered at 1.2mg/kg in combination with standard RCHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). | |
| Reporting group title | Part 1: BV (1.8 mg/kg) + RCHOP |
| Reporting group description: Part 1 of the study is a randomized and open-label. Brentuximab vedotin was administered at 1.8 mg/kg in combination with standard RCHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). | |
| Reporting group title | Part 2: BV (1.8 mg/kg) + RCHP |
| Reporting group description: Part 2 of the study was non-randomized and open-label. Brentuximab vedotin (1.8 mg/kg) was administered in combination with RCHP chemotherapy (rituximab, cyclophosphamide, doxorubicin, and prednisone). | |
| Reporting group title | Part 3: BV (1.8 mg/kg) + RCHP |
| Reporting group description: Part 3 of the study was randomized and open-label. Brentuximab vedotin (1.8 mg/kg) was administered in combination with RCHP chemotherapy. | |
| Reporting group title | Part 3: RCHOP |
| Reporting group description: Part 3 of the study was randomized and open-label. RCHOP chemotherapy was administered alone. | |

| Reporting group values | Part 1: BV (1.2 mg/kg) + RCHOP | Part 1: BV (1.8 mg/kg) + RCHOP | Part 2: BV (1.8 mg/kg) + RCHP |
|----------------------------------|--------------------------------|--------------------------------|-------------------------------|
| Number of subjects | 29 | 22 | 11 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 10 | 11 | 7 |
| 65 years and over | 19 | 11 | 4 |
| Age continuous | | | |
| Units: years | | | |
| median | 70 | 64 | 59 |
| full range (min-max) | 33 to 80 | 21 to 81 | 22 to 78 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 13 | 6 | 4 |
| Male | 16 | 16 | 7 |
| Ethnicity | | | |
| NIH/OMB | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 4 | 2 | 1 |
| Not Hispanic or Latino | 25 | 18 | 8 |
| Unknown or Not Reported | 0 | 2 | 2 |
| Race | | | |
| NIH/OMB | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 1 | 1 |

| | | | |
|---|----|----|----|
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 1 | 1 | 1 |
| White | 27 | 17 | 8 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 1 | 3 | 1 |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| United States | 29 | 22 | 11 |
| Czechia | 0 | 0 | 0 |
| Poland | 0 | 0 | 0 |
| Italy | 0 | 0 | 0 |
| ECOG Performance Status | | | |
| Units: Subjects | | | |
| Zero | 5 | 4 | 1 |
| One | 16 | 12 | 4 |
| Two | 8 | 6 | 6 |

| Reporting group values | Part 3: BV (1.8 mg/kg) + RCHP | Part 3: RCHOP | Total |
|---|-------------------------------|---------------|-------|
| Number of subjects | 11 | 12 | 85 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 5 | 6 | 39 |
| 65 years and over | 6 | 6 | 46 |
| Age continuous | | | |
| Units: years | | | |
| median | 68 | 65 | |
| full range (min-max) | 46 to 74 | 41 to 80 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 10 | 6 | 39 |
| Male | 1 | 6 | 46 |
| Ethnicity | | | |
| NIH/OMB | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 1 | 8 |
| Not Hispanic or Latino | 11 | 11 | 73 |
| Unknown or Not Reported | 0 | 0 | 4 |
| Race | | | |
| NIH/OMB | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 2 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 1 | 0 | 4 |
| White | 10 | 12 | 74 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 5 |
| Region of Enrollment | | | |
| Units: Subjects | | | |

| | | | |
|-------------------------|---|----|----|
| United States | 8 | 10 | 80 |
| Czechia | 1 | 1 | 2 |
| Poland | 2 | 0 | 2 |
| Italy | 0 | 1 | 1 |
| ECOG Performance Status | | | |
| Units: Subjects | | | |
| Zero | 4 | 4 | 18 |
| One | 4 | 3 | 39 |
| Two | 3 | 5 | 28 |

End points

End points reporting groups

| | |
|--|--------------------------------|
| Reporting group title | Part 1: BV (1.2 mg/kg) + RCHOP |
| Reporting group description: Part 1 of the study is randomized and open-label. Brentuximab vedotin was administered at 1.2mg/kg in combination with standard RCHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). | |
| Reporting group title | Part 1: BV (1.8 mg/kg) + RCHOP |
| Reporting group description: Part 1 of the study is a randomized and open-label. Brentuximab vedotin was administered at 1.8 mg/kg in combination with standard RCHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). | |
| Reporting group title | Part 2: BV (1.8 mg/kg) + RCHP |
| Reporting group description: Part 2 of the study was non-randomized and open-label. Brentuximab vedotin (1.8 mg/kg) was administered in combination with RCHP chemotherapy (rituximab, cyclophosphamide, doxorubicin, and prednisone). | |
| Reporting group title | Part 3: BV (1.8 mg/kg) + RCHP |
| Reporting group description: Part 3 of the study was randomized and open-label. Brentuximab vedotin (1.8 mg/kg) was administered in combination with RCHP chemotherapy. | |
| Reporting group title | Part 3: RCHOP |
| Reporting group description: Part 3 of the study was randomized and open-label. RCHOP chemotherapy was administered alone. | |

Primary: Complete Remission Rate

| | |
|--|--|
| End point title | Complete Remission Rate ^[1] |
| End point description: Number (count) of participants that achieved complete remission according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). | |
| End point type | Primary |
| End point timeframe: Up to 6 months | |
| Notes: | |

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Within-group analysis

| End point values | Part 1: BV (1.2 mg/kg) + RCHOP | Part 1: BV (1.8 mg/kg) + RCHOP | Part 2: BV (1.8 mg/kg) + RCHP | Part 3: BV (1.8 mg/kg) + RCHP |
|------------------------------|--------------------------------|--------------------------------|-------------------------------|-------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 29 | 22 | 11 | 11 |
| Units: Count of Participants | 20 | 16 | 9 | 6 |

| End point values | Part 3: RCHOP | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |

| | | | | |
|------------------------------|---|--|--|--|
| Units: Count of Participants | 8 | | | |
|------------------------------|---|--|--|--|

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Adverse Events

| | |
|-----------------|--|
| End point title | Incidence of Adverse Events ^[2] |
|-----------------|--|

End point description:

Number (count) of participants that experienced at least 1 adverse event.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 6 months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Data for this end point were summarized per protocol.

| End point values | Part 1: BV (1.2 mg/kg) + RCHOP | Part 1: BV (1.8 mg/kg) + RCHOP | Part 2: BV (1.8 mg/kg) + RCHP | Part 3: BV (1.8 mg/kg) + RCHP |
|------------------------------|--------------------------------|--------------------------------|-------------------------------|-------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 29 | 22 | 11 | 11 |
| Units: Count of Participants | 29 | 22 | 11 | 11 |

| End point values | Part 3: RCHOP | | | |
|------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: Count of Participants | 12 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Laboratory Abnormalities

| | |
|-----------------|--|
| End point title | Incidence of Laboratory Abnormalities ^[3] |
|-----------------|--|

End point description:

Number (count) of participants that experienced a Grade 3 or higher maximum post-baseline laboratory toxicity (hematology and chemistry)

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 6 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Data for this end point were summarized per protocol.

| End point values | Part 1: BV (1.2 mg/kg) + RCHOP | Part 1: BV (1.8 mg/kg) + RCHOP | Part 2: BV (1.8 mg/kg) + RCHP | Part 3: BV (1.8 mg/kg) + RCHP |
|--|--------------------------------|--------------------------------|-------------------------------|-------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 29 | 22 | 11 | 11 |
| Units: Count of Participants | | | | |
| Any Hematology Test | 10 | 16 | 4 | 6 |
| Lymphocytes (x10 ³ /uL) | 8 | 15 | 3 | 4 |
| Absolute Neutrophil Count (x10 ³ /uL) | 4 | 4 | 1 | 2 |
| Neutrophils (x10 ³ /uL) | 4 | 4 | 1 | 2 |
| Leukocytes (x10 ³ /uL) | 3 | 2 | 1 | 1 |
| Hemoglobin (x10 ³ /uL) | 0 | 1 | 0 | 1 |
| Platelets (x10 ³ /uL) | 1 | 1 | 0 | 0 |
| Any Chemistry Test | 4 | 7 | 2 | 1 |
| Glucose (mg/dL) | 3 | 5 | 0 | 0 |
| Potassium (mEq)/L | 0 | 2 | 1 | 1 |
| Calcium (mg/dL) | 1 | 1 | 0 | 0 |
| Sodium (mEq/L) | 0 | 2 | 0 | 0 |
| Alanine Aminotransferase (IU/L) | 0 | 0 | 1 | 0 |

| End point values | Part 3: RCHOP | | | |
|--|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: Count of Participants | | | | |
| Any Hematology Test | 4 | | | |
| Lymphocytes (x10 ³ /uL) | 4 | | | |
| Absolute Neutrophil Count (x10 ³ /uL) | 0 | | | |
| Neutrophils (x10 ³ /uL) | 0 | | | |
| Leukocytes (x10 ³ /uL) | 1 | | | |
| Hemoglobin (x10 ³ /uL) | 0 | | | |
| Platelets (x10 ³ /uL) | 0 | | | |
| Any Chemistry Test | 3 | | | |
| Glucose (mg/dL) | 1 | | | |
| Potassium (mEq)/L | 2 | | | |
| Calcium (mg/dL) | 0 | | | |
| Sodium (mEq/L) | 0 | | | |
| Alanine Aminotransferase (IU/L) | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

| | |
|-----------------|-------------------------|
| End point title | Objective Response Rate |
|-----------------|-------------------------|

End point description:

Number (count) of participants that achieved complete or partial remission at the end of treatment according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 6 months

| End point values | Part 1: BV (1.2 mg/kg) + RCHOP | Part 1: BV (1.8 mg/kg) + RCHOP | Part 2: BV (1.8 mg/kg) + RCHP | Part 3: BV (1.8 mg/kg) + RCHP |
|------------------------------|--------------------------------|--------------------------------|-------------------------------|-------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 29 | 22 | 11 | 11 |
| Units: Count of Participants | 23 | 19 | 10 | 10 |

| End point values | Part 3: RCHOP | | | |
|------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: Count of Participants | 9 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

| | |
|-----------------|---------------------------|
| End point title | Progression-free Survival |
|-----------------|---------------------------|

End point description:

Median progression-free survival (in months) and observed minimum-maximum range.

Insufficient data to determine median value in all arms. Arms and full ranges listed below:

Part 1: BV (1.2 mg/kg) + RCHOP (0.62, 40.21+)

Part 1: BV (1.8mg/kg) + RCHOP (1.28, 39.85+)

Part 2: BV (1.8 mg/kg) + RCHP (3.35, 24.34+)

Part 3: BV (1.8 mg/kg) + RCHP (3.25, 15.41+)

Part 3: RCHOP (1.25, 16.43+)

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 4 years

| End point values | Part 1: BV (1.2 mg/kg) + RCHOP | Part 1: BV (1.8 mg/kg) + RCHOP | Part 2: BV (1.8 mg/kg) + RCHP | Part 3: BV (1.8 mg/kg) + RCHP |
|-------------------------------|--------------------------------|--------------------------------|-------------------------------|-------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 29 | 22 | 11 | 11 |
| Units: Months | | | | |
| median (full range (min-max)) | 999 (0.62 to 999) | 999 (1.28 to 999) | 999 (3.35 to 999) | 999 (3.25 to 999) |

| End point values | Part 3: RCHOP | | | |
|-------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: Months | | | | |
| median (full range (min-max)) | 999 (1.25 to 999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

| | |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

Median progression-free survival (in months) and observed minimum-maximum range.

Insufficient data to calculate median for 3 arms. Arms and full ranges are listed here:

Part 1: BV (1.2 mg/kg) + RCHOP (0.62, 42.79)

Part 2: BV (1.8 mg/kg) + RCHP (16.56, 25.76)

Part 3: BV (1.8 mg/kg) + RCHP (3.25, 16.85)

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 4 years

| End point values | Part 1: BV (1.2 mg/kg) + RCHOP | Part 1: BV (1.8 mg/kg) + RCHOP | Part 2: BV (1.8 mg/kg) + RCHP | Part 3: BV (1.8 mg/kg) + RCHP |
|-------------------------------|--------------------------------|--------------------------------|-------------------------------|-------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 29 | 22 | 11 | 11 |
| Units: Months | | | | |
| median (full range (min-max)) | 999 (0.62 to 999) | 18.1 (1.28 to 44.29) | 999 (16.56 to 999) | 999 (3.25 to 999) |

| End point values | Part 3: RCHOP | | | |
|------------------|---------------|--|--|--|
|------------------|---------------|--|--|--|

| | | | | |
|-------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: Months | | | | |
| median (full range (min-max)) | 4.6 (1.25 to 19.22) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from study Day 1 (predose) through the EOT visit or 30 days after the last study treatment (mono- or combination therapy), whichever was later. However, all protocol-related AEs were collected from the time of informed consent.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

Reporting groups

| | |
|--------------------------------|--------------------------------|
| Reporting group title | Part 1: BV (1.2 mg/kg) + RCHOP |
| Reporting group description: - | |
| Reporting group title | Part 1: BV (1.8 mg/kg) + RCHOP |
| Reporting group description: - | |
| Reporting group title | Part 2: BV (1.8 mg/kg) + RCHP |
| Reporting group description: - | |
| Reporting group title | Part 3: BV (1.8 mg/kg) + RCHP |
| Reporting group description: - | |
| Reporting group title | Part 3: RCHOP |
| Reporting group description: - | |

| Serious adverse events | Part 1: BV (1.2 mg/kg) + RCHOP | Part 1: BV (1.8 mg/kg) + RCHOP | Part 2: BV (1.8 mg/kg) + RCHP |
|---|--------------------------------|--------------------------------|-------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 29 (55.17%) | 14 / 22 (63.64%) | 5 / 11 (45.45%) |
| number of deaths (all causes) | 6 | 7 | 1 |
| number of deaths resulting from adverse events | 1 | 2 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colorectal cancer metastatic | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Myelodysplastic syndrome | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus test positive | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiomyopathy | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Guillain-Barre syndrome | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Febrile neutropenia | | | |
| subjects affected / exposed | 8 / 29 (27.59%) | 8 / 22 (36.36%) | 2 / 11 (18.18%) |
| occurrences causally related to treatment / all | 10 / 13 | 9 / 13 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic colitis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Stevens-Johnson syndrome | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 22 (9.09%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Bronchiolitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia infection | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pantoea agglomerans infection | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Part 3: BV (1.8 mg/kg) + RCHP | Part 3: RCHOP | |
|---|-------------------------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 11 (36.36%) | 4 / 12 (33.33%) | |
| number of deaths (all causes) | 1 | 2 | |
| number of deaths resulting from adverse events | 1 | 2 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colorectal cancer metastatic | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus test positive | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Guillain-Barre syndrome | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Nausea | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic colitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Stevens-Johnson syndrome | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia sepsis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchiolitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pantoea agglomerans infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Part 1: BV (1.2 mg/kg) + RCHOP | Part 1: BV (1.8 mg/kg) + RCHOP | Part 2: BV (1.8 mg/kg) + RCHP |
|---|--------------------------------|--------------------------------|-------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 29 / 29 (100.00%) | 22 / 22 (100.00%) | 11 / 11 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 1 | 2 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 6 / 22 (27.27%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 9 | 0 |
| Flushing | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 0 | 1 |
| Hot flush | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 | 1 |
| Hypertension | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 17 / 29 (58.62%) | 16 / 22 (72.73%) | 7 / 11 (63.64%) |
| occurrences (all) | 28 | 30 | 7 |
| Asthenia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 8 / 29 (27.59%) | 7 / 22 (31.82%) | 0 / 11 (0.00%) |
| occurrences (all) | 19 | 8 | 0 |
| Chills | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | 4 / 22 (18.18%) | 3 / 11 (27.27%) |
| occurrences (all) | 12 | 4 | 3 |
| Oedema peripheral | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | 7 / 22 (31.82%) | 1 / 11 (9.09%) |
| occurrences (all) | 9 | 8 | 2 |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 29 (20.69%) | 6 / 22 (27.27%) | 1 / 11 (9.09%) |
| occurrences (all) | 9 | 6 | 1 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 3 / 22 (13.64%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 3 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 2 |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| Pain | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 22 (9.09%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Malaise | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Throat irritation | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 22 (0.00%) | 4 / 11 (36.36%) |
| occurrences (all) | 2 | 0 | 4 |
| Dyspnoea | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | 9 / 22 (40.91%) | 0 / 11 (0.00%) |
| occurrences (all) | 7 | 12 | 0 |
| Cough | | | |

| | | | |
|------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 29 (10.34%) | 4 / 22 (18.18%) | 1 / 11 (9.09%) |
| occurrences (all) | 3 | 7 | 1 |
| Nasal congestion | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Respiratory tract irritation | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 1 / 22 (4.55%) | 1 / 11 (9.09%) |
| occurrences (all) | 3 | 1 | 1 |
| Sinus congestion | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 | 1 |
| Upper-airway cough syndrome | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 0 | 1 |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 22 (9.09%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 22 (9.09%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 22 (4.55%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Hiccups | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 22 (9.09%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | 8 / 22 (36.36%) | 2 / 11 (18.18%) |
| occurrences (all) | 7 | 8 | 2 |

| | | | |
|--|------------------------|-----------------------|----------------------|
| Anxiety subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 | 4 / 22 (18.18%) 5 | 0 / 11 (0.00%) 0 |
| Confusional state subjects affected / exposed occurrences (all) | 4 / 29 (13.79%) 4 | 2 / 22 (9.09%) 2 | 0 / 11 (0.00%) 0 |
| Depression subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 | 1 / 22 (4.55%) 1 | 0 / 11 (0.00%) 0 |
| Investigations | | | |
| Weight decreased subjects affected / exposed occurrences (all) | 10 / 29 (34.48%) 16 | 8 / 22 (36.36%) 13 | 1 / 11 (9.09%) 1 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 22 (0.00%) 0 | 2 / 11 (18.18%) 3 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 22 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| International normalised ratio increased subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 22 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 3 | 0 / 22 (0.00%) 0 | 1 / 11 (9.09%) 2 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 22 (0.00%) 0 | 1 / 11 (9.09%) 2 |
| Injury, poisoning and procedural complications | | | |
| Fall subjects affected / exposed occurrences (all) | 4 / 29 (13.79%) 5 | 1 / 22 (4.55%) 1 | 0 / 11 (0.00%) 0 |
| Contusion subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 22 (0.00%) 0 | 1 / 11 (9.09%) 1 |

| | | | |
|-------------------------------|------------------|------------------|-----------------|
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 8 / 29 (27.59%) | 4 / 22 (18.18%) | 0 / 11 (0.00%) |
| occurrences (all) | 9 | 4 | 0 |
| Palpitations | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 3 | 0 | 1 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 3 / 22 (13.64%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Nervous system disorders | | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 16 / 29 (55.17%) | 15 / 22 (68.18%) | 6 / 11 (54.55%) |
| occurrences (all) | 25 | 27 | 6 |
| Headache | | | |
| subjects affected / exposed | 6 / 29 (20.69%) | 6 / 22 (27.27%) | 3 / 11 (27.27%) |
| occurrences (all) | 7 | 6 | 5 |
| Dizziness | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 8 / 22 (36.36%) | 1 / 11 (9.09%) |
| occurrences (all) | 6 | 9 | 1 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 8 / 22 (36.36%) | 0 / 11 (0.00%) |
| occurrences (all) | 11 | 14 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 5 / 22 (22.73%) | 2 / 11 (18.18%) |
| occurrences (all) | 6 | 5 | 2 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 0 / 22 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 3 | 0 | 2 |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 22 (4.55%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 2 | 1 |
| Syncope | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoaesthesia | | | |

| | | | |
|---|------------------------|------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Paraesthesia subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia subjects affected / exposed occurrences (all) | 10 / 29 (34.48%) 27 | 7 / 22 (31.82%) 20 | 4 / 11 (36.36%) 5 |
| Anaemia subjects affected / exposed occurrences (all) | 9 / 29 (31.03%) 26 | 7 / 22 (31.82%) 20 | 2 / 11 (18.18%) 5 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 5 / 29 (17.24%) 20 | 3 / 22 (13.64%) 19 | 2 / 11 (18.18%) 2 |
| Leukopenia subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 13 | 4 / 22 (18.18%) 16 | 0 / 11 (0.00%) 0 |
| Febrile neutropenia subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 0 / 22 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Ear and labyrinth disorders | | | |
| Ear pain subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 | 2 / 22 (9.09%) 2 | 0 / 11 (0.00%) 0 |
| Eye disorders | | | |
| Lacrimation increased subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 3 / 22 (13.64%) 4 | 0 / 11 (0.00%) 0 |
| Vision blurred subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 2 / 22 (9.09%) 2 | 0 / 11 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 14 / 29 (48.28%) 24 | 15 / 22 (68.18%) 23 | 8 / 11 (72.73%) 9 |
| Diarrhoea | | | |

| | | | |
|----------------------------------|------------------|------------------|-----------------|
| subjects affected / exposed | 14 / 29 (48.28%) | 15 / 22 (68.18%) | 3 / 11 (27.27%) |
| occurrences (all) | 19 | 23 | 4 |
| Constipation | | | |
| subjects affected / exposed | 8 / 29 (27.59%) | 9 / 22 (40.91%) | 6 / 11 (54.55%) |
| occurrences (all) | 9 | 12 | 6 |
| Vomiting | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | 14 / 22 (63.64%) | 2 / 11 (18.18%) |
| occurrences (all) | 9 | 17 | 2 |
| Stomatitis | | | |
| subjects affected / exposed | 8 / 29 (27.59%) | 3 / 22 (13.64%) | 3 / 11 (27.27%) |
| occurrences (all) | 10 | 4 | 3 |
| Abdominal pain | | | |
| subjects affected / exposed | 6 / 29 (20.69%) | 3 / 22 (13.64%) | 0 / 11 (0.00%) |
| occurrences (all) | 6 | 3 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 1 | 0 | 2 |
| Haemorrhoids | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 22 (4.55%) | 2 / 11 (18.18%) |
| occurrences (all) | 2 | 1 | 2 |
| Oral pain | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 22 (9.09%) | 2 / 11 (18.18%) |
| occurrences (all) | 1 | 2 | 2 |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 3 / 22 (13.64%) | 1 / 11 (9.09%) |
| occurrences (all) | 5 | 3 | 2 |
| Dry mouth | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 3 / 22 (13.64%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 3 / 22 (13.64%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 22 (9.09%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Epigastric discomfort | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Tongue discolouration | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Abdominal distension | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 22 (9.09%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Toothache | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 22 (9.09%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 5 / 29 (17.24%) | 9 / 22 (40.91%) | 8 / 11 (72.73%) |
| occurrences (all) | 6 | 10 | 10 |
| Dry skin | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 22 (4.55%) | 2 / 11 (18.18%) |
| occurrences (all) | 2 | 2 | 2 |
| Night sweats | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 2 / 22 (9.09%) | 2 / 11 (18.18%) |
| occurrences (all) | 4 | 2 | 2 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 22 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 2 | 0 | 2 |
| Pruritus | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 3 / 22 (13.64%) | 1 / 11 (9.09%) |
| occurrences (all) | 3 | 3 | 2 |
| Blister | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 0 | 1 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|----------------------|----------------------|---------------------|
| Hyperhidrosis subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 2 / 22 (9.09%) 2 | 0 / 11 (0.00%) 0 |
| Renal and urinary disorders | | | |
| Micturition urgency subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 22 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Renal failure subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 22 (4.55%) 1 | 1 / 11 (9.09%) 1 |
| Pollakiuria subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 4 | 1 / 22 (4.55%) 1 | 0 / 11 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 5 / 29 (17.24%) 6 | 4 / 22 (18.18%) 4 | 1 / 11 (9.09%) 1 |
| Muscle spasms subjects affected / exposed occurrences (all) | 6 / 29 (20.69%) 7 | 2 / 22 (9.09%) 2 | 0 / 11 (0.00%) 0 |
| Myalgia subjects affected / exposed occurrences (all) | 4 / 29 (13.79%) 5 | 4 / 22 (18.18%) 7 | 0 / 11 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 5 / 29 (17.24%) 5 | 2 / 22 (9.09%) 2 | 0 / 11 (0.00%) 0 |
| Bone pain subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 | 3 / 22 (13.64%) 3 | 0 / 11 (0.00%) 0 |
| Flank pain subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 2 | 1 / 22 (4.55%) 2 | 1 / 11 (9.09%) 1 |
| Pain in extremity subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 1 / 22 (4.55%) 1 | 0 / 11 (0.00%) 0 |
| Muscular weakness | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 2 / 22 (9.09%) 2 | 0 / 11 (0.00%) 0 |
| Infections and infestations | | | |
| Candida infection | | | |
| subjects affected / exposed | 5 / 29 (17.24%) | 5 / 22 (22.73%) | 2 / 11 (18.18%) |
| occurrences (all) | 8 | 7 | 2 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 22 (4.55%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 1 | 1 |
| Oral candidiasis | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 2 / 22 (9.09%) | 1 / 11 (9.09%) |
| occurrences (all) | 4 | 2 | 1 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 2 |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 22 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral herpes | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 0 / 22 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 22 (9.09%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | 10 / 22 (45.45%) | 2 / 11 (18.18%) |
| occurrences (all) | 10 | 15 | 2 |
| Dehydration | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 29 (10.34%) | 9 / 22 (40.91%) | 2 / 11 (18.18%) |
| occurrences (all) | 3 | 11 | 3 |
| Hypokalaemia | | | |
| subjects affected / exposed | 6 / 29 (20.69%) | 5 / 22 (22.73%) | 1 / 11 (9.09%) |
| occurrences (all) | 10 | 8 | 1 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 5 / 22 (22.73%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 8 | 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 22 (9.09%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 6 | 1 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 22 (9.09%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 22 (9.09%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 3 / 22 (13.64%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 11 | 0 |

| Non-serious adverse events | Part 3: BV (1.8 mg/kg) + RCHP | Part 3: RCHOP | |
|---|-------------------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 11 (100.00%) | 12 / 12 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Flushing | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 3 / 12 (25.00%) | |
| occurrences (all) | 2 | 4 | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 3 | |
| Chills | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 12 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Throat irritation | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | 4 / 12 (33.33%) | |
| occurrences (all) | 3 | 4 | |
| Cough | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 12 (16.67%) | |
| occurrences (all) | 1 | 2 | |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 12 (16.67%) | |
| occurrences (all) | 1 | 2 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory tract irritation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 12 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Sinus congestion | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Upper-airway cough syndrome | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pleural effusion | | | |

| | | | |
|--|---------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| Dysphonia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| Epistaxis subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 | |
| Hiccups subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 | |
| Anxiety subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 1 / 12 (8.33%) 1 | |
| Confusional state subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| Depression subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Investigations Weight decreased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 3 / 12 (25.00%) 3 | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| International normalised ratio increased | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 2 | 0 / 12 (0.00%) 0 | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 2 | 0 / 12 (0.00%) 0 | |
| Contusion subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 3 | 0 / 12 (0.00%) 0 | |
| Cardiac disorders | | | |
| Tachycardia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 | |
| Palpitations subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| Atrial fibrillation subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 | |
| Nervous system disorders | | | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 4 / 11 (36.36%) 6 | 4 / 12 (33.33%) 4 | |
| Headache subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 3 | 1 / 12 (8.33%) 1 | |
| Dizziness subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 2 | 3 / 12 (25.00%) 3 | |
| Peripheral motor neuropathy | | | |

| | | | |
|--------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 12 (16.67%) | |
| occurrences (all) | 1 | 2 | |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 2 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 11 (36.36%) | 2 / 12 (16.67%) | |
| occurrences (all) | 4 | 4 | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | 1 / 12 (8.33%) | |
| occurrences (all) | 8 | 1 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|--|--|---|--|
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| Eye disorders Lacrimation increased subjects affected / exposed occurrences (all) Vision blurred subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 | |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Haemorrhoids subjects affected / exposed occurrences (all) Oral pain | 4 / 11 (36.36%) 6 6 / 11 (54.55%) 8 1 / 11 (9.09%) 1 2 / 11 (18.18%) 2 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 | 2 / 12 (16.67%) 2 1 / 12 (8.33%) 1 5 / 12 (41.67%) 5 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Dysphagia | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 12 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Epigastric discomfort | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Tongue discolouration | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Toothache | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | 3 / 12 (25.00%) | |
| occurrences (all) | 3 | 4 | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Night sweats | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|---|----------------------|----------------------|--|
| Skin hyperpigmentation subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| Pruritus subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 2 / 12 (16.67%) 2 | |
| Blister subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 2 | 0 / 12 (0.00%) 0 | |
| Rash subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Urticaria subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 | |
| Renal and urinary disorders Micturition urgency subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 | |
| Renal failure subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| Pollakiuria subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 2 / 12 (16.67%) 3 | |
| Muscle spasms subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| Myalgia | | | |

| | | | |
|-----------------------------------|-----------------|----------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Infections and infestations | | | |
| Candida infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 12 (8.33%) | |
| occurrences (all) | 2 | 1 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |

| | | | |
|--|----------------------|----------------------|--|
| Pneumocystis jirovecii pneumonia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| Oral herpes subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| Sinusitis subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 2 | 3 / 12 (25.00%) 3 | |
| Dehydration subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 3 | 1 / 12 (8.33%) 1 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 3 | 2 / 12 (16.67%) 3 | |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 2 | 1 / 12 (8.33%) 2 | |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 12 (8.33%) 4 | |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |
| Hyponatraemia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 19 June 2013 | <ul style="list-style-type: none">• Removed CD30 expression by local pathology laboratory as a screening assessment, for operational ease. CD30 expression was still evaluated by central pathology laboratory.• Removed randomization stratification by CD30 expression because it was unlikely that significant imbalances would be observed between treatment arms.• Clarified that the optional malignant lymphoma biopsy may be requested for patients who progress at any time during their participation on the study.• Clarified the definition of PFS and associated censoring rules. |
| 04 November 2013 | <ul style="list-style-type: none">• Clarified the permissible use of corticosteroids prior to first dose• Clarified that routine vaccination was permitted as long as the vaccine did not contain live microorganisms• Added serology for hepatitis B surface antigen and anti-hepatitis B core antibody to the screening assessments to ensure exclusion of patients who are positive for either hepatitis B surface antigen or anti-hepatitis B core antibody because of the risk of hepatitis B reactivation in patients treated with rituximab• Clarified the definition of study treatment-related AEs• Clarified that certain AEs may be followed until resolution, return to baseline, or study closure |
| 26 February 2014 | <ul style="list-style-type: none">• Revised protocol to define high-intermediate and high risk patients based on standard IPI or age-adjusted IPI• Clarified to show that all samples provided by patients may be used to evaluate disease-related biomarkers, including baseline tumor specimens and not just those specimens taken on treatment |
| 14 January 2015 | <ul style="list-style-type: none">• Added new part to the study (Part 2) to assess safety, efficacy, and PK of BV + RCHP; numerous sections of the protocol were updated |
| 10 August 2015 | <ul style="list-style-type: none">• Added new part to the study (Part 3) to assess safety and antitumor activity of BV + RCHP versus RCHOP alone; numerous sections of the protocol were updated• Revised Inclusion criterion No. 7 to clarify patients must use 2 effective contraception methods during the study• Revised Exclusion criterion No. 12 to allow patients with negative PCR assay• Added instructions regarding testing for hepatitis B PCR assay and concomitant therapy with antiviral prophylaxis |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported