



Clinical trial results:

Open-label, uncontrolled Phase II trial of intravenous PI3K inhibitor BAY 80-6946 in patients with relapsed, indolent or aggressive Non-Hodgkin's lymphomas

Summary

| | |
|--------------------------|--|
| EudraCT number | 2012-002602-52 |
| Trial protocol | GB FI DE BE ES IT SE PL AT PT HU DK IE GR LU |
| Global end of trial date | 18 May 2023 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 29 May 2024 |
| First version publication date | 29 May 2024 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | BAY80-6946/16349 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01660451 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368 |
| Public contact | Therapeutic Area Head, Bayer AG, 49 30 300139003, clinical-trials-contact@bayer.com |
| Scientific contact | Therapeutic Area Head, Bayer AG, 49 30 300139003, clinical-trials-contact@bayer.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 | 18 May 2023 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 18 May 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The objective of study part A was to evaluate the efficacy and safety of copanlisib in patients with indolent or aggressive NHL who have progressed after standard therapy. The objective of study part B was to evaluate the efficacy and safety of copanlisib in patients with indolent B-cell NHL relapsed after, or refractory to widely used approved therapies in standard practice.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 31 October 2012 |
| 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: 7 |
| Country: Number of subjects enrolled | Portugal: 1 |
| Country: Number of subjects enrolled | Spain: 15 |
| Country: Number of subjects enrolled | Sweden: 2 |
| Country: Number of subjects enrolled | United Kingdom: 33 |
| Country: Number of subjects enrolled | Austria: 1 |
| Country: Number of subjects enrolled | Belgium: 26 |
| Country: Number of subjects enrolled | Bulgaria: 3 |
| Country: Number of subjects enrolled | Finland: 15 |
| Country: Number of subjects enrolled | France: 49 |
| Country: Number of subjects enrolled | Germany: 26 |
| Country: Number of subjects enrolled | Greece: 6 |
| Country: Number of subjects enrolled | Hungary: 10 |
| Country: Number of subjects enrolled | Ireland: 1 |
| Country: Number of subjects enrolled | Italy: 38 |
| Country: Number of subjects enrolled | Australia: 3 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Canada: 20 |
| Country: Number of subjects enrolled | Hong Kong: 2 |
| Country: Number of subjects enrolled | Israel: 12 |
| Country: Number of subjects enrolled | Korea, Republic of: 11 |
| Country: Number of subjects enrolled | New Zealand: 1 |
| Country: Number of subjects enrolled | Russian Federation: 14 |
| Country: Number of subjects enrolled | Singapore: 4 |
| Country: Number of subjects enrolled | Türkiye: 10 |
| Country: Number of subjects enrolled | United States: 28 |
| Worldwide total number of subjects | 338 |
| EEA total number of subjects | 200 |

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) | 162 |
| From 65 to 84 years | 170 |
| 85 years and over | 6 |

Subject disposition

Recruitment

Recruitment details:

Part A-Study enrolled subjects from 41 study centers in 10 countries, between 19 NOV 2012 (first subject first visit [FPFV]) and 13 AUG 2018 (last subject last visit [LPLV]). Part B-Study enrolled subjects from 81 study centers in 24 countries, between 04 NOV 2013 (FPFV) and 18 MAY 2023 (LPLV),

Pre-assignment

Screening details:

Part A: 125 subjects were screened, 41 were screened but never assigned to treatment. Total 84 were assigned to treatment. Part B: 213 subjects were screened, 70 were screened but never assigned to treatment. Total 143 were assigned to treatment, of them 1 was suspected as fraudulent and excluded from analysis sets. Therefore 142 were evaluable.

Period 1

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

Arms

| | |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Part A: Indolent NHL/CLL |

Arm description:

Subjects with indolent Non-Hodgkin's lymphoma/Chronic lymphocytic leukemia [iNHL/CLL] received copanlisib 0.8 milligram per kilogram (mg/kg), maximum 65 mg, intravenous (IV) infusion dosing over 1 hour in 100 milliliter (mL) normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas by Cheson et al. 1999, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.

| | |
|--|----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Copanlisib (Aliqopa) |
| Investigational medicinal product code | BAY80-6946 |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Dosing was weekly for the first 3 weeks (on Days 1, 8, and 15) of a 28-day cycle, followed by a 1-week break (i.e., no infusion on Day 22).

| | |
|------------------|------------------------|
| Arm title | Part A: Aggressive NHL |
|------------------|------------------------|

Arm description:

Subjects with aggressive NHL (aNHL) received copanlisib 0.8 mg/kg, maximum 65 mg, IV infusion dosing over 1 hour in 100 mL normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas by Cheson et al. 1999, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.

| | |
|--|----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Copanlisib (Aliqopa) |
| Investigational medicinal product code | BAY 80-6946 |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Dosing was weekly for the first 3 weeks (on Days 1, 8, and 15) of a 28-day cycle, followed by a 1-week break (i.e., no infusion on Day 22).

| | |
|--|----------------------|
| Arm title | Part B: Indolent NHL |
| Arm description: | |
| Subjects with indolent B-cell NHL received copanlisib fixed 60 mg or 0.8 mg/kg, IV infusion dosing over 1 hour in 100 mL normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Revised Response Criteria for Malignant Lymphoma by Cheson et al., 2007, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study. | |
| Arm type | Experimental |
| Investigational medicinal product name | Copanlisib (Aliqopa) |
| Investigational medicinal product code | BAY 80-6946 |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Dosing was weekly for the first 3 weeks (on Days 1, 8, and 15) of a 28-day cycle, followed by a 1-week break (i.e., no infusion on Day 22).

| Number of subjects in period 1^[1] | Part A: Indolent NHL/CLL | Part A: Aggressive NHL | Part B: Indolent NHL |
|---|--------------------------|------------------------|----------------------|
| Started | 33 | 51 | 142 |
| Completed | 0 | 0 | 0 |
| Not completed | 33 | 51 | 142 |
| Progressive disease – radiological progression | 12 | 23 | 50 |
| Physician decision | 1 | 2 | 5 |
| Trial closure | - | - | 1 |
| Protocol Deviation | - | - | 1 |
| AE not related to clinical disease progression | 13 | 10 | 40 |
| Progressive disease – clinical progression | 4 | 10 | 9 |
| Consent withdrawn by subject | 1 | 1 | 20 |
| Death | 1 | - | 1 |
| Other | - | - | 1 |
| AE related to clinical disease progression | 1 | 3 | 11 |
| Switching to other therapy | - | 1 | 1 |
| Sponsor Decision | - | - | 1 |
| Protocol deviation | - | 1 | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: In study part A, 125 subjects were screened, 41 were screened but never assigned to treatment, total 84 were assigned to treatment. In study part B, 213 subjects were screened, 70 were screened but never assigned to treatment, total 143 were assigned to treatment, of them 1 was suspected as fraudulent and excluded from analysis sets. Therefore 142 were evaluable.

Baseline characteristics

Reporting groups

| | |
|---|--------------------------|
| Reporting group title | Part A: Indolent NHL/CLL |
| Reporting group description: | |
| Subjects with indolent Non-Hodgkin's lymphoma/Chronic lymphocytic leukemia [iNHL/CLL] received copanlisib 0.8 milligram per kilogram (mg/kg), maximum 65 mg, intravenous (IV) infusion dosing over 1 hour in 100 milliliter (mL) normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas by Cheson et al. 1999, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study. | |
| Reporting group title | Part A: Aggressive NHL |
| Reporting group description: | |
| Subjects with aggressive NHL (aNHL) received copanlisib 0.8 mg/kg, maximum 65 mg, IV infusion dosing over 1 hour in 100 mL normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas by Cheson et al. 1999, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study. | |
| Reporting group title | Part B: Indolent NHL |
| Reporting group description: | |
| Subjects with indolent B-cell NHL received copanlisib fixed 60 mg or 0.8 mg/kg, IV infusion dosing over 1 hour in 100 mL normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Revised Response Criteria for Malignant Lymphoma by Cheson et al., 2007, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study. | |

| Reporting group values | Part A: Indolent NHL/CLL | Part A: Aggressive NHL | Part B: Indolent NHL |
|-------------------------|--------------------------|------------------------|----------------------|
| Number of subjects | 33 | 51 | 142 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 11 | 27 | 78 |
| From 65-84 years | 21 | 22 | 64 |
| 85 years and over | 1 | 2 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 66.7 | 62.2 | 61.4 |
| standard deviation | ± 9.8 | ± 15.5 | ± 12.1 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 18 | 22 | 71 |
| Male | 15 | 29 | 71 |
| Race | | | |
| Units: Subjects | | | |
| Asian | 0 | 0 | 15 |
| White | 25 | 40 | 120 |
| Unknown or Not Reported | 8 | 11 | 7 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 2 | 2 | 6 |
| Not Hispanic or Latino | 21 | 36 | 124 |
| Unknown or Not Reported | 10 | 13 | 12 |

| | | | |
|-------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 226 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 116 | | |
| From 65-84 years | 107 | | |
| 85 years and over | 3 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 111 | | |
| Male | 115 | | |
| Race | | | |
| Units: Subjects | | | |
| Asian | 15 | | |
| White | 185 | | |
| Unknown or Not Reported | 26 | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 10 | | |
| Not Hispanic or Latino | 181 | | |
| Unknown or Not Reported | 35 | | |

End points

End points reporting groups

| | |
|--|----------------------------------|
| Reporting group title | Part A: Indolent NHL/CLL |
| Reporting group description: Subjects with indolent Non-Hodgkin's Lymphoma/Chronic lymphocytic leukemia [iNHL/CLL] received copanlisib 0.8 milligram per kilogram (mg/kg), maximum 65 mg, intravenous (IV) infusion dosing over 1 hour in 100 milliliter (mL) normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas by Cheson et al. 1999, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study. | |
| Reporting group title | Part A: Aggressive NHL |
| Reporting group description: Subjects with aggressive NHL (aNHL) received copanlisib 0.8 mg/kg, maximum 65 mg, IV infusion dosing over 1 hour in 100 mL normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas by Cheson et al. 1999, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study. | |
| Reporting group title | Part B: Indolent NHL |
| Reporting group description: Subjects with indolent B-cell NHL received copanlisib fixed 60 mg or 0.8 mg/kg, IV infusion dosing over 1 hour in 100 mL normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Revised Response Criteria for Malignant Lymphoma by Cheson et al., 2007, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study. | |
| Subject analysis set title | Full analysis set (FAS) - Part A |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All subjects assigned to study treatment. | |
| Subject analysis set title | Full analysis set (FAS) - Part B |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All subjects assigned to study treatment. | |
| Subject analysis set title | Safety analysis set (SAF)-Part A |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All FAS subjects with at least one study drug administration. | |
| Subject analysis set title | Safety analysis set (SAF)-Part B |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All FAS subjects with at least one study drug administration. | |
| Subject analysis set title | Per protocol set (PPS)- Part A |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All subjects with drug administration that were evaluable for objective tumor response (OR) and that had no major protocol deviation effecting the primary efficacy evaluation. At least one post baseline tumor assessment was available in order to consider the patient evaluable. Subjects who were not evaluable for tumor response and who discontinued due to a drug-related toxicity, death or progression by clinical judgment before disease was re-evaluated were also to be considered evaluable. The detailed definitions and the assignment of subjects to this analysis set were based on the Validity Review Meeting. | |

Primary: Objective Response Rate (ORR) Based on Independent Review-Part A

| | |
|-----------------|--|
| End point title | Objective Response Rate (ORR) Based on Independent Review-Part A ^{[1][2]} |
|-----------------|--|

End point description:

Objective response rate was defined as the proportion of participants with a best response rating of complete response (CR), unconfirmed complete response (CRu) or partial response (PR), based on the Report of an International Workshop to Standardize Response Criteria for non-Hodgkins Lymphomas, Cheson, 1999, as evaluated by the Independent Response Adjudication Committee (IRAC). For chronic lymphocytic leukemia (CLL) patients Hallek criteria (2008) were used and assessed by investigator.

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

End point timeframe:

Baseline up to the last patient has completed the 16 weeks of treatment

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: Descriptive statistics were done, no inferential statistical analyses were performed.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part A arms.

| End point values | Part A: Indolent NHL/CLL | Part A: Aggressive NHL | | |
|----------------------------------|--------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 ^[3] | 48 ^[4] | | |
| Units: Percentage | | | | |
| number (confidence interval 90%) | 43.75 (28.73 to 59.68) | 27.08 (16.83 to 39.57) | | |

Notes:

[3] - PPS

[4] - PPS

Statistical analyses

No statistical analyses for this end point

Primary: ORR Based on Independent Review-Part B

| | |
|-----------------|--|
| End point title | ORR Based on Independent Review-Part B ^{[5][6]} |
|-----------------|--|

End point description:

Objective response rate was defined as the proportion of participants with a best response rating of CR or PR, based on the International Working Group Revised response Criteria for Malignant Lymphoma, Cheson 2007.

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

End point timeframe:

Baseline up to the last patient has completed the 16 weeks of treatment

Notes:

[5] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

| End point values | Part B: Indolent NHL | | | |
|----------------------------------|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 142 ^[7] | | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | 59.15 (50.60 to 67.32) | | | |

Notes:

[7] - FAS

Statistical analyses

No statistical analyses for this end point

Primary: ORR Based on Investigator Assessment-Part A

| | |
|-----------------|---|
| End point title | ORR Based on Investigator Assessment-Part A ^{[8][9]} |
|-----------------|---|

End point description:

Objective response rate was defined as the proportion of participants with a best response rating of CR, CRu or PR, based on the Report of an International Workshop to Standardize Response Criteria for non-Hodgkins Lymphomas, Cheson, 1999. For CLL patients Hallek criteria (2008) were used and assessed by investigator.

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

End point timeframe:

Baseline up to the last patient has completed the 16 weeks of treatment

Notes:

[8] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part A arms.

| End point values | Part A: Indolent NHL/CLL | Part A: Aggressive NHL | | |
|----------------------------------|--------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 ^[10] | 48 ^[11] | | |
| Units: Percentage | | | | |
| number (confidence interval 90%) | 46.88 (31.54 to 62.66) | 31.25 (20.35 to 43.97) | | |

Notes:

[10] - PPS

[11] - PPS

Statistical analyses

No statistical analyses for this end point

Primary: ORR Based on Investigator Assessment-Part B

| | |
|-----------------|---|
| End point title | ORR Based on Investigator Assessment-Part B ^{[12][13]} |
|-----------------|---|

End point description:

Objective response rate was defined as the proportion of participants with a best response rating of CR or PR, based on the International Working Group Revised response Criteria for Malignant Lymphoma, Cheson 2007.

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

End point timeframe:

Baseline up to the last patient has completed the 16 weeks of treatment

Notes:

[12] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

| End point values | Part B: Indolent NHL | | | |
|----------------------------------|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 142 ^[14] | | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | 51.41 (42.88 to 59.87) | | | |

Notes:

[14] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Based on Independent Review-Part A

| | |
|-----------------|---|
| End point title | Duration of Response (DOR) Based on Independent Review-Part A ^[15] |
|-----------------|---|

End point description:

Duration of response (DOR) was defined as the time (in days) from the date of the first observed tumor response of CR or PR (whichever was noted earlier) to first subsequent disease progression (either first progressive disease [PD], first clinical progression or first adverse event [AE] associated with clinical disease progression) or death caused by disease progression, if this death occurred before progression was documented. All deaths were considered as 'caused by disease progression' except deaths with the reason "other" or "AE not related to disease progression. "99999" denotes value can't be estimated.

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

End point timeframe:

Baseline up to approximately 6 years

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part A arms.

| End point values | Part A: Indolent NHL/CLL | Part A: Aggressive NHL | | |
|----------------------------------|--------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 ^[16] | 14 ^[17] | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 322 (61 to 99999) | 99999 (61 to 99999) | | |

Notes:

[16] - PPS

[17] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: DOR Based on Independent Review-Part B

| | |
|-----------------|--|
| End point title | DOR Based on Independent Review-Part B ^[18] |
|-----------------|--|

End point description:

Duration of response (DOR) was defined as the time (in days) from the date of the first observed tumor response of CR or PR (whichever was noted earlier) to first subsequent disease progression (either first progressive disease [PD], first clinical progression or first adverse event [AE] associated with clinical disease progression) or death caused by disease progression, if this death occurred before progression was documented. All deaths were considered as 'caused by disease progression' except deaths with the reason "other" or "AE not related to disease progression."

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

End point timeframe:

Baseline up to approximately 10 years

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

| End point values | Part B: Indolent NHL | | | |
|----------------------------------|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 85 ^[19] | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 14.9 (9.2 to 22.6) | | | |

Notes:

[19] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: DOR Based on Investigator Assessment-Part A

| | |
|-----------------|---|
| End point title | DOR Based on Investigator Assessment-Part A ^[20] |
|-----------------|---|

End point description:

Duration of response (DOR) was defined as the time (in days) from the date of the first observed tumor response of CR or PR (whichever was noted earlier) to first subsequent disease progression (either first progressive disease [PD], first clinical progression or first adverse event [AE] associated with clinical disease progression) or death caused by disease progression, if this death occurred before progression was documented. All deaths were considered as 'caused by disease progression' except deaths with the reason "other" or "AE not related to disease progression." "99999" denotes value can't be estimated.

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

End point timeframe:

Baseline up to approximately 6 years

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part A arms.

| End point values | Part A: Indolent NHL/CLL | Part A: Aggressive NHL | | |
|----------------------------------|--------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 ^[21] | 15 ^[22] | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 189 (56 to 574) | 190 (112 to 99999) | | |

Notes:

[21] - PPS

[22] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: DOR Based on Investigator Assessment-Part B

| | |
|-----------------|---|
| End point title | DOR Based on Investigator Assessment-Part B ^[23] |
|-----------------|---|

End point description:

Duration of response (DOR) was defined as the time (in days) from the date of the first observed tumor response of CR or PR (whichever was noted earlier) to first subsequent disease progression (either first progressive disease [PD], first clinical progression or first adverse event [AE] associated with clinical disease progression) or death caused by disease progression, if this death occurred before progression was documented. All deaths were considered as 'caused by disease progression' except deaths with the reason "other" or "AE not related to disease progression.

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

End point timeframe:

Baseline up to approximately 10 years

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

| End point values | Part B: Indolent NHL | | | |
|----------------------------------|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 78 ^[24] | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 11.5 (9.2 to 16.1) | | | |

Notes:

[24] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: PFS Based on Investigator Assessment-Part A

| | |
|-----------------|---|
| End point title | PFS Based on Investigator Assessment-Part A ^[25] |
|-----------------|---|

End point description:

PFS was defined as the time (in days) from the date of the first treatment to the date of first observed PD (radiological or clinical, or first AE associated with clinical PD, whichever was earlier) or death due to any cause (if death occurred before progression was documented).

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

End point timeframe:

Baseline up to approximately 6 years

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part A arms.

| End point values | Part A: Indolent NHL/CLL | Part A: Aggressive NHL | | |
|----------------------------------|--------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 ^[26] | 51 ^[27] | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 224 (172 to 419) | 70 (47 to 115) | | |

Notes:

[26] - FAS

[27] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: PFS Based on Independent Review-Part B

| | |
|---|--|
| End point title | PFS Based on Independent Review-Part B ^[28] |
| End point description: | |
| PFS was defined as the time (in days) from the date of the first treatment to the date of first observed PD (radiological or clinical, or first AE associated with clinical PD, whichever was earlier) or death due to any cause (if death occurred before progression was documented). | |
| End point type | Secondary |

End point timeframe:

Baseline up to approximately 10 years

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

| End point values | Part B: Indolent NHL | | | |
|----------------------------------|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 142 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 11.3 (8.1 to 17.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) Based on Independent Review-Part A

| | |
|-----------------|--|
| End point title | Progression Free Survival (PFS) Based on Independent Review- |
|-----------------|--|

End point description:

PFS was defined as the time (in days) from the date of the first treatment to the date of first observed PD (radiological or clinical, or first AE associated with clinical PD, whichever was earlier) or death due to any cause (if death occurred before progression was documented).

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

End point timeframe:

Baseline up to approximately 6 years

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part A arms.

| End point values | Part A: Indolent NHL/CLL | Part A: Aggressive NHL | | |
|----------------------------------|--------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 ^[30] | 51 ^[31] | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 223 (147 to 546) | 70 (47 to 115) | | |

Notes:

[30] - FAS

[31] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: PFS Based on Investigator Assessment-Part B

| | |
|-----------------|---|
| End point title | PFS Based on Investigator Assessment-Part B ^[32] |
|-----------------|---|

End point description:

PFS was defined as the time (in days) from the date of the first treatment to the date of first observed PD (radiological or clinical, or first AE associated with clinical PD, whichever was earlier) or death due to any cause (if death occurred before progression was documented).

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

End point timeframe:

Baseline up to approximately 10 years

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

| End point values | Part B: Indolent NHL | | | |
|----------------------------------|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 142 ^[33] | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 10.8 (7.2 to 12.8) | | | |

Notes:

[33] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Cancer Therapy – Lymphoma Lymphoma Subscale (FACT-Lym LymS) at Week 16 - Part B

| | |
|-----------------|--|
| End point title | Functional Assessment of Cancer Therapy – Lymphoma Lymphoma Subscale (FACT-Lym LymS) at Week 16 - Part B ^[34] |
|-----------------|--|

End point description:

HRQoL assessment was used to describe development of patients with copanlisib by using FACT-Lym questionnaire assessment tool. It contains 42 items (questions) covering HRQoL, common lymphoma symptoms and treatment side-effects. The FACT - General (FACT-G) questionnaire contains 27 items covering 4 core HRQoL subscales: Physical Wellbeing (7 items), Social/Family Wellbeing (7), Emotional Wellbeing (6), and Functional Wellbeing (7). The FACT-Lym also includes an Additional Concerns subscale (15 items) (FACT-Lym LymS), addressing issues typically experienced by lymphoma patients. Some of the issues covered include pain, itching, night sweats, trouble sleeping, fatigue and trouble concentrating. FACT-Lym also asks patients about lumps and swelling, fevers, infections, weight, appetite, emotional stability and treatment. Score range for the FACT-Lym LymS was 0 - 60, higher score represent less symptoms. Here in below table "n" signifies evaluable participants for the respective category.

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

End point timeframe:

Baseline up to week 16

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

| | | | | |
|---------------------------------------|-------------------------|--|--|--|
| End point values | Part B: Indolent NHL | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 141 ^[35] | | | |
| Units: units on a scale | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Baseline | 46.50 (40.50 to 52.00) | | | |
| Value at Week 16 | 49.00 (42.00 to 54.00) | | | |

Notes:

[35] - FAS; Baseline N=132; Week 16 N=141

Statistical analyses

No statistical analyses for this end point

Secondary: OS-Part B

| | |
|-----------------|---------------------------|
| End point title | OS-Part B ^[36] |
|-----------------|---------------------------|

End point description:

OS was defined as the time (in days) from the date of first administration of study treatment to death due to any cause. "99999" denotes value can't be estimated.

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

End point timeframe:

Baseline up to approximately 10 years

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

| End point values | Part B: Indolent NHL | | | |
|----------------------------------|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 142 ^[37] | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 59.1 (36.5 to 99999) | | | |

Notes:

[37] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)-Part A

| | |
|--|--|
| End point title | Overall Survival (OS)-Part A ^[38] |
| End point description: | |
| OS was defined as the time (in days) from the date of first administration of study treatment to death due to any cause. "99999" denotes value can't be estimated. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to approximately 6 years | |

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part A arms.

| End point values | Part A: Indolent NHL/CLL | Part A: Aggressive NHL | | |
|----------------------------------|--------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 ^[39] | 51 ^[40] | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 657 (391 to 99999) | 211 (140 to 399) | | |

Notes:

[39] - FAS

[40] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) total score at Week 16 - Part B

| | |
|-----------------|---|
| End point title | Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) total score at Week 16 - Part B ^[41] |
|-----------------|---|

End point description:

HRQoL assessment was used to describe development of patients with copanlisib by using FACT-Lym questionnaire assessment tool. It contains 42 items (questions) covering HRQoL, common lymphoma symptoms and treatment side-effects. The FACT - General (FACT-G) questionnaire contains 27 items covering 4 core HRQoL subscales: Physical Wellbeing (7 items), Social/Family Wellbeing (7), Emotional Wellbeing (6), and Functional Wellbeing (7). The FACT-Lym also includes an Additional Concerns subscale (15 items) (FACT-Lym LymS), addressing issues typically experienced by lymphoma patients. Some of the issues covered include pain, itching, night sweats, trouble sleeping, fatigue and trouble concentrating. FACT-Lym also asks patients about lumps and swelling, fevers, infections, weight, appetite, emotional stability and treatment. FACT-Lym total score range was 0-168, higher score indicates better HRQoL. Here, in the below table "n" signifies evaluable participants for the respective category.

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

End point timeframe:

Baseline up to week 16

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

| | | | | |
|---------------------------------------|------------------------------|--|--|--|
| End point values | Part B: Indolent NHL | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 141 ^[42] | | | |
| Units: units on a scale | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Baseline | 127.50 (113.75 to 145.75) | | | |
| Value at Week 16 | 130.83 (113.33 to 146.50) | | | |

Notes:

[42] - FAS; Baseline N=132; Week 16 N=141

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After the first study intervention up to 35 days after the end of study intervention, Part A: approximately 6 years. Part B: approximately 10 years.

Adverse event reporting additional description:

Adverse event reporting for the deaths (all causes) considers all deaths that occurred at any time during the study before the last contact, Part A: approximately 6 years. Part B: approximately 10 years.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 26.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | Part A: Indolent NHL/CLL |
|-----------------------|--------------------------|

Reporting group description:

Participants with indolent Non-Hodgkin's lymphoma/Chronic lymphocytic leukemia [iNHL/CLL] received copanlisib 0.8 milligram per kilogram (mg/kg), maximum 65 mg, intravenous (IV) infusion dosing over 1 hour in 100 milliliter (mL) normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas by Cheson et al. 1999, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.

| | |
|-----------------------|----------------------|
| Reporting group title | Part B: Indolent NHL |
|-----------------------|----------------------|

Reporting group description:

Subjects with indolent B-cell NHL received copanlisib fixed 60 mg or 0.8 mg/kg, IV infusion dosing over 1 hour in 100 mL normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Revised Response Criteria for Malignant Lymphoma by Cheson et al., 2007, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.

| | |
|-----------------------|------------------------|
| Reporting group title | Part A: Aggressive NHL |
|-----------------------|------------------------|

Reporting group description:

Participants with aggressive NHL (aNHL) received copanlisib 0.8 mg/kg, maximum 65 mg, IV infusion dosing over 1 hour in 100 mL normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas by Cheson et al. 1999, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.

| Serious adverse events | Part A: Indolent NHL/CLL | Part B: Indolent NHL | Part A: Aggressive NHL |
|---|--------------------------|----------------------|------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 33 (48.48%) | 81 / 142 (57.04%) | 31 / 51 (60.78%) |
| number of deaths (all causes) | 21 | 75 | 39 |
| number of deaths resulting from adverse events | 3 | 6 | 7 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour compression | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|----------------|
| Porocarcinoma | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 0 / 51 (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 |
| Tumour flare | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic lymphocytic leukaemia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Deep vein thrombosis | | | |

| | | | |
|--|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 0 / 51 (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 |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Superficial vein thrombosis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Surgical and medical procedures | | | |
| Preoperative care | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 142 (1.41%) | 4 / 51 (7.84%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 9 / 142 (6.34%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 9 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|----------------|
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Reproductive system and breast disorders | | | |
| Scrotal swelling | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 6 / 142 (4.23%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 8 / 8 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 0 / 51 (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 |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 142 (1.41%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 0 / 51 (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 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| Organising pneumonia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 142 (1.41%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary congestion | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Disorientation | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 | | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 142 (1.41%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Biliary-vascular fistula | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Afferent loop syndrome | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|----------------|
| Aortic valve incompetence | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 142 (1.41%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Seizure | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Syncope | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 0 / 51 (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 | 1 / 33 (3.03%) | 3 / 142 (2.11%) | 2 / 51 (3.92%) |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 0 / 51 (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 |
| Thrombotic thrombocytopenic purpura | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Autoimmune haemolytic anaemia | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 0 / 51 (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 |

| | | | |
|---|----------------|-----------------|----------------|
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 4 / 142 (2.82%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Colitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 4 / 142 (2.82%) | 3 / 51 (5.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 4 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 2 / 51 (3.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|----------------|
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Melaena | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 0 / 51 (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 |
| Nausea | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 142 (1.41%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 2 / 51 (3.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 0 / 51 (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 |
| Hepatobiliary disorders | | | |

| | | | |
|---|----------------|-----------------|----------------|
| Gallbladder obstruction | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 142 (1.41%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 0 / 51 (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 |
| Dermatitis exfoliative generalised | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 142 (1.41%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 142 (1.41%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|----------------|
| Renal failure | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Psoriatic arthropathy | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 142 (1.41%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Groin pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Back pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 2 / 51 (3.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 0 / 51 (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 |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |

| | | | |
|---|-----------------|-------------------|----------------|
| Cellulitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Progressive multifocal leukoencephalopathy | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Pneumonia viral | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 33 (12.12%) | 20 / 142 (14.08%) | 4 / 51 (7.84%) |
| occurrences causally related to treatment / all | 2 / 4 | 20 / 25 | 5 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 1 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 2 / 51 (3.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 3 / 51 (5.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Influenza | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 0 / 51 (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 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Cryptococcosis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 142 (1.41%) | 2 / 51 (3.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 142 (1.41%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Urinary tract infection | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Rectal abscess | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis aspergillus | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronavirus infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Klebsiella bacteraemia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Pneumonia fungal | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 142 (1.41%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 142 (1.41%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Systemic infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Varicella zoster pneumonia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 142 (0.70%) | 0 / 51 (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 |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 142 (1.41%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 142 (0.00%) | 0 / 51 (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 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 33 (3.03%) | 7 / 142 (4.93%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 9 / 9 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Part A: Indolent NHL/CLL | Part B: Indolent NHL | Part A: Aggressive NHL |
|---|--------------------------|----------------------|------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 33 / 33 (100.00%) | 138 / 142 (97.18%) | 50 / 51 (98.04%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 23 / 33 (69.70%) | 42 / 142 (29.58%) | 24 / 51 (47.06%) |
| occurrences (all) | 94 | 330 | 82 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 16 / 33 (48.48%) | 36 / 142 (25.35%) | 14 / 51 (27.45%) |
| occurrences (all) | 20 | 41 | 15 |
| Chills | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 12 / 142 (8.45%) | 1 / 51 (1.96%) |
| occurrences (all) | 2 | 13 | 1 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 142 (1.41%) | 3 / 51 (5.88%) |
| occurrences (all) | 1 | 2 | 4 |
| Influenza like illness | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 6 / 142 (4.23%) | 2 / 51 (3.92%) |
| occurrences (all) | 2 | 6 | 2 |
| Asthenia | | | |
| subjects affected / exposed | 8 / 33 (24.24%) | 11 / 142 (7.75%) | 6 / 51 (11.76%) |
| occurrences (all) | 13 | 14 | 6 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 4 / 33 (12.12%) | 10 / 142 (7.04%) | 6 / 51 (11.76%) |
| occurrences (all) | 5 | 17 | 8 |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 12 / 142 (8.45%) | 2 / 51 (3.92%) |
| occurrences (all) | 7 | 14 | 2 |

| | | | |
|---|------------------------|-------------------------|-----------------------|
| Pyrexia subjects affected / exposed occurrences (all) | 10 / 33 (30.30%) 14 | 35 / 142 (24.65%) 54 | 8 / 51 (15.69%) 22 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | 4 / 142 (2.82%) 5 | 2 / 51 (3.92%) 3 |
| Productive cough subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 3 | 10 / 142 (7.04%) 12 | 3 / 51 (5.88%) 3 |
| Nasal congestion subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 3 | 4 / 142 (2.82%) 5 | 0 / 51 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 4 | 0 / 142 (0.00%) 0 | 3 / 51 (5.88%) 3 |
| Dyspnoea exertional subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 3 | 4 / 142 (2.82%) 4 | 1 / 51 (1.96%) 1 |
| Dyspnoea subjects affected / exposed occurrences (all) | 4 / 33 (12.12%) 4 | 11 / 142 (7.75%) 11 | 4 / 51 (7.84%) 4 |
| Cough subjects affected / exposed occurrences (all) | 7 / 33 (21.21%) 13 | 27 / 142 (19.01%) 45 | 6 / 51 (11.76%) 6 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | 15 / 142 (10.56%) 20 | 2 / 51 (3.92%) 2 |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 8 / 142 (5.63%) 8 | 3 / 51 (5.88%) 3 |
| Anxiety subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 4 / 142 (2.82%) 5 | 3 / 51 (5.88%) 3 |
| Investigations | | | |

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|---|----------------------|------------------------|---------------------|
| Blood creatinine increased subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | 6 / 142 (4.23%) 6 | 4 / 51 (7.84%) 5 |
| Blood glucose increased subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 5 | 2 / 142 (1.41%) 42 | 0 / 51 (0.00%) 0 |
| Eosinophil count increased subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | 0 / 142 (0.00%) 0 | 1 / 51 (1.96%) 1 |
| Lipase increased subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 4 | 8 / 142 (5.63%) 9 | 2 / 51 (3.92%) 2 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 15 | 7 / 142 (4.93%) 19 | 1 / 51 (1.96%) 2 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 5 / 33 (15.15%) 5 | 13 / 142 (9.15%) 16 | 4 / 51 (7.84%) 4 |
| Weight decreased subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 9 / 142 (6.34%) 9 | 2 / 51 (3.92%) 2 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | 8 / 142 (5.63%) 8 | 0 / 51 (0.00%) 0 |
| Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | 2 / 142 (1.41%) 2 | 0 / 51 (0.00%) 0 |
| Nervous system disorders Taste disorder subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | 1 / 142 (0.70%) 1 | 1 / 51 (1.96%) 1 |
| Somnolence subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | 0 / 142 (0.00%) 0 | 0 / 51 (0.00%) 0 |
| Paraesthesia | | | |

| | | | |
|---|------------------------|--------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 3 | 4 / 142 (2.82%) 5 | 1 / 51 (1.96%) 1 |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | 6 / 142 (4.23%) 6 | 3 / 51 (5.88%) 3 |
| Headache subjects affected / exposed occurrences (all) | 7 / 33 (21.21%) 9 | 14 / 142 (9.86%) 22 | 9 / 51 (17.65%) 12 |
| Dizziness subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 4 | 4 / 142 (2.82%) 5 | 3 / 51 (5.88%) 4 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 11 / 33 (33.33%) 21 | 27 / 142 (19.01%) 43 | 12 / 51 (23.53%) 13 |
| Lymphopenia subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 8 / 142 (5.63%) 16 | 0 / 51 (0.00%) 0 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 3 | 21 / 142 (14.79%) 30 | 3 / 51 (5.88%) 3 |
| Neutropenia subjects affected / exposed occurrences (all) | 9 / 33 (27.27%) 12 | 40 / 142 (28.17%) 117 | 15 / 51 (29.41%) 25 |
| Ear and labyrinth disorders | | | |
| Vertigo subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | 0 / 142 (0.00%) 0 | 1 / 51 (1.96%) 1 |
| Gastrointestinal disorders | | | |
| Dry mouth subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 3 | 1 / 142 (0.70%) 1 | 3 / 51 (5.88%) 3 |
| Diarrhoea subjects affected / exposed occurrences (all) | 13 / 33 (39.39%) 65 | 51 / 142 (35.92%) 98 | 21 / 51 (41.18%) 39 |
| Constipation | | | |

| | | | |
|--|------------------|-------------------|------------------|
| subjects affected / exposed | 5 / 33 (15.15%) | 18 / 142 (12.68%) | 8 / 51 (15.69%) |
| occurrences (all) | 7 | 21 | 11 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 11 / 142 (7.75%) | 3 / 51 (5.88%) |
| occurrences (all) | 4 | 16 | 3 |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 33 (12.12%) | 10 / 142 (7.04%) | 1 / 51 (1.96%) |
| occurrences (all) | 6 | 10 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 5 / 142 (3.52%) | 2 / 51 (3.92%) |
| occurrences (all) | 2 | 5 | 2 |
| Vomiting | | | |
| subjects affected / exposed | 5 / 33 (15.15%) | 20 / 142 (14.08%) | 5 / 51 (9.80%) |
| occurrences (all) | 10 | 25 | 7 |
| Stomatitis | | | |
| subjects affected / exposed | 4 / 33 (12.12%) | 14 / 142 (9.86%) | 4 / 51 (7.84%) |
| occurrences (all) | 6 | 24 | 4 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 3 / 142 (2.11%) | 3 / 51 (5.88%) |
| occurrences (all) | 0 | 3 | 3 |
| Nausea | | | |
| subjects affected / exposed | 10 / 33 (30.30%) | 33 / 142 (23.24%) | 18 / 51 (35.29%) |
| occurrences (all) | 17 | 45 | 22 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 7 / 142 (4.93%) | 3 / 51 (5.88%) |
| occurrences (all) | 1 | 10 | 3 |
| Rash | | | |
| subjects affected / exposed | 5 / 33 (15.15%) | 14 / 142 (9.86%) | 6 / 51 (11.76%) |
| occurrences (all) | 6 | 31 | 8 |
| Pruritus | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 14 / 142 (9.86%) | 3 / 51 (5.88%) |
| occurrences (all) | 3 | 37 | 5 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 142 (0.00%) | 1 / 51 (1.96%) |
| occurrences (all) | 2 | 0 | 1 |

| | | | |
|--|-----------------------|-------------------------|---------------------|
| Erythema subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 3 | 2 / 142 (1.41%) 3 | 3 / 51 (5.88%) 3 |
| Eczema subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 4 | 4 / 142 (2.82%) 10 | 2 / 51 (3.92%) 2 |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | 2 / 142 (1.41%) 2 | 0 / 51 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) | 7 / 33 (21.21%) 10 | 12 / 142 (8.45%) 17 | 3 / 51 (5.88%) 5 |
| Back pain subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 4 | 14 / 142 (9.86%) 22 | 4 / 51 (7.84%) 4 |
| Arthralgia subjects affected / exposed occurrences (all) | 5 / 33 (15.15%) 6 | 14 / 142 (9.86%) 15 | 5 / 51 (9.80%) 5 |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 4 / 33 (12.12%) 10 | 16 / 142 (11.27%) 22 | 5 / 51 (9.80%) 8 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 4 / 33 (12.12%) 4 | 6 / 142 (4.23%) 9 | 1 / 51 (1.96%) 2 |
| Cystitis subjects affected / exposed occurrences (all) | 4 / 33 (12.12%) 5 | 1 / 142 (0.70%) 1 | 1 / 51 (1.96%) 1 |
| Herpes zoster subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | 3 / 142 (2.11%) 4 | 1 / 51 (1.96%) 1 |
| Lower respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | 4 / 142 (2.82%) 5 | 3 / 51 (5.88%) 6 |

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|------------------------------------|------------------|-------------------|------------------|
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 9 / 142 (6.34%) | 2 / 51 (3.92%) |
| occurrences (all) | 2 | 16 | 2 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 6 / 142 (4.23%) | 3 / 51 (5.88%) |
| occurrences (all) | 0 | 7 | 3 |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 12 / 142 (8.45%) | 2 / 51 (3.92%) |
| occurrences (all) | 3 | 14 | 2 |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 9 / 142 (6.34%) | 1 / 51 (1.96%) |
| occurrences (all) | 1 | 13 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 10 / 142 (7.04%) | 2 / 51 (3.92%) |
| occurrences (all) | 1 | 13 | 4 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 22 / 142 (15.49%) | 2 / 51 (3.92%) |
| occurrences (all) | 2 | 45 | 2 |
| Urinary tract infection | | | |
| subjects affected / exposed | 6 / 33 (18.18%) | 7 / 142 (4.93%) | 7 / 51 (13.73%) |
| occurrences (all) | 6 | 10 | 7 |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 9 / 142 (6.34%) | 2 / 51 (3.92%) |
| occurrences (all) | 2 | 13 | 2 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 33 (15.15%) | 15 / 142 (10.56%) | 7 / 51 (13.73%) |
| occurrences (all) | 6 | 15 | 8 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 4 / 142 (2.82%) | 4 / 51 (7.84%) |
| occurrences (all) | 2 | 10 | 4 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 21 / 33 (63.64%) | 71 / 142 (50.00%) | 27 / 51 (52.94%) |
| occurrences (all) | 88 | 515 | 55 |
| Hypokalaemia | | | |

| | | | |
|-----------------------------|----------------|------------------|----------------|
| subjects affected / exposed | 2 / 33 (6.06%) | 11 / 142 (7.75%) | 5 / 51 (9.80%) |
| occurrences (all) | 3 | 11 | 5 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 10 / 142 (7.04%) | 2 / 51 (3.92%) |
| occurrences (all) | 1 | 11 | 3 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 15 January 2013 | Amendment 2: Inclusion criteria: the wording of the inclusion criterion applicable for patients with aggressive NHL was slightly changed to clarify that patients who failed first line chemo /immunotherapy but who were not eligible for a high dose regimen followed by transplant were considered suitable for the study even if they had undergone only one previous treatment. Introduction of mandatory collection of archival tumor tissue for biomarker analysis. Introduction of the ECG sub-study at the request of Food and Drug Administration (FDA). Exclusion criteria: Patients affected by central nervous system lymphoma involvement were excluded from the study. Clarification of the requirement to perform CT/MRI to all suspected sites of disease. Clarification of the tumor response evaluation criteria: CT/MRI was to be required at EOT if a patient discontinued due to progressive disease in order to radiologically assess such progression. Imaging was not required if progressive disease was radiologically evaluated within previous 4 weeks. Inclusion of interstitial lung disease and pneumonitis as AEs of special safety interest based on recently available data from Phase I studies. |
| 28 March 2013 | Amendment 3: Introduction of study Part B: New cohort (extension cohort) of patients with FL was added (further changes related only to study Part B are not listed below). Introduction of mandatory collection of fresh biopsies from patients with aggressive lymphoma. Introduction of the possibility to re-screen patients. Replacement criteria: Patients whose participation was terminated due to disease progression before the first evaluable post-baseline tumor evaluation could be replaced. Specification of validity of signed informed consent: It was clarified that the maximum allowed interval between signing of informed consent and start of treatment was 28 days. Inclusion and exclusion criteria: patients with transformed indolent lymphoma must have received at least 2 prior chemotherapy- and/or immunotherapy-based regimens. The measurable lesion must not have been previously irradiated. Inclusion criterion related to alkaline phosphatase was removed. Exclusion criterion related to dehydration was removed. Open biopsy was excluded within the previous 7 days before start of study medication. Wording of the exclusion criterion referring to pheochromocytoma was clarified. Changes in the laboratory analyses: Bands were removed as a parameter for differential white blood cell count and turbidity was added to the urinalysis parameters. Urea could now be measured alternatively to BUN (blood urea nitrogen) if BUN was not routinely measured at the site. Additional PK sampling was added for patients participating in the ECG sub-study. |

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| 17 February 2014 | Amendment 4: following modifications applicable to study Part A: It was specified that the end of the safety follow-up would take place 35 days after the last study drug administration. Inclusion criteria: An additional T-cell histotype was added to the inclusion criteria for patients with aggressive NHL and a previously existing histotype was further specified according to the World Health Organization (WHO) classification. Exclusion criteria: The requirement for laboratory screening for hepatitis B and C to be carried out up to 28 days before starting the study drug administration was added. Text was included which only allowed the use of short acting insulin for the treatment of transient hyperglycemia and not permitting prophylactic administration of short acting insulin prior to copanlisib infusion. Dose modification guidance was clarified in case of skin toxicity (since some rash events were reported in Part A of the study) and non-infectious pneumonitis. Additional assessments were included for hepatitis to be performed 28 days prior to the first administration of study drug to be consistent with the protocol's exclusion criteria regarding known history of chronic hepatitis B or C. Statistical analysis text regarding additional aggressive NHL patients was amended. Data for these patients was to be analyzed separately from the patients in the primary analysis, i.e., 16 weeks after the last of these patients started treatment. In addition, these patients were to be analyzed in separate FAS (full analysis set), SAF (safety analysis set) and PPS (per protocol set) analysis sets. Definition of duration of response (DOR) was amended to state that duration of response is defined as the time from the date of first observed tumor response (CR or PR) until first subsequent disease progression or until death "due to any cause". In addition, unconfirmed responses were also to be included in the analysis. |
| 04 July 2014 | Amendment 5: following modifications applicable to study Part A: Collection of tumor tissue was clarified: For patients with aggressive NHL, fresh tissue was mandatory. For all patients: If the patient has undergone a fresh biopsy for any reason and archival tumor tissue is not available, fresh biopsy is sufficient for central pathology review and biomarker analysis. The text describing conditions for withdrawal from study treatment was clarified to reduce occurrence of screening failures. In addition, withdrawal criterion for drug-induced pancreatitis was added. It was clarified that phenytoin, carbamazepine and phenobarbital were prohibited medications. Text regarding AEs of special safety interest was clarified. Unspecific interstitial lung disease (ILD) was removed as it had not been observed within the copanlisib program. All observed cases of ILD were likely attributable to non-infectious pneumonitis, which remained as an AE of special safety interest. |
| 25 August 2015 | Amendment 7: It introduced changes to the Part B integrated protocol, Part A integrated protocol remained unchanged, except for two administrative changes. |
| 20 October 2015 | Amendment 8: The amendment introduced changes to the Part B integrated protocol. The Part A integrated protocol remained unchanged. |
| 18 July 2016 | Amendment 9: following modifications applicable to study Part A: Enhanced monitoring of respiratory symptoms. Added monitoring guidelines for opportunistic infection prophylaxis. |
| 11 April 2017 | Amendment 10: following modifications applicable to study Part A: Extended the possibility to collect tumor assessment data for beyond 3 years. Identified a new Sponsor's Medical Expert. |
| 21 November 2017 | Amendment 11: Replacement of 80 mg vials with 60 mg vials. |
| 31 January 2019 | Amendment 13: Extend the study from 3 to 4 years after the last patient started study treatment. |
| 02 March 2022 | Amendment 14: Extend the study up to 4 years after the last patient has completed study treatment. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported