

**Clinical trial results:****A Phase Ib/II Study Evaluating the Safety and Efficacy of Obinutuzumab in Combination with Atezolizumab Plus Polatuzumab Vedotin in Patients with Relapsed or Refractory Follicular Lymphoma and Rituximab in Combination with Atezolizumab Plus Polatuzumab Vedotin in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma****Summary**

| | |
|--------------------------|-----------------|
| EudraCT number | 2015-004845-25 |
| Trial protocol | DE PL |
| Global end of trial date | 07 October 2019 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v3 |
| This version publication date | 04 November 2020 |
| First version publication date | 21 September 2019 |
| Version creation reason | |

Trial information**Trial identification**

| | |
|-----------------------|---------|
| Sponsor protocol code | BO29561 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02729896 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, globa.trial_information@roche.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 | 07 October 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 October 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To Evaluate the Safety and Efficacy of Obinutuzumab in Combination with Atezolizumab plus Polatuzumab Vedotin in Patients with Relapsed or Refractory Follicular Lymphoma and Rituximab in Combination with Atezolizumab plus Polatuzumab Vedotin in Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 09 November 2016 |
| 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 | Germany: 11 |
| Country: Number of subjects enrolled | Poland: 14 |
| Country: Number of subjects enrolled | United States: 11 |
| Worldwide total number of subjects | 36 |
| EEA total number of subjects | 25 |

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) | 20 |
| From 65 to 84 years | 15 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

56 patients were screened and 36 patients enrolled and dosed in the study.

Period 1

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

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|---------------------------|
| Arm title | Dose-Escalation FL Cohort |
|------------------|---------------------------|

Arm description:

During the induction treatment Cycle 1 (21-day cycles): participants received obinutuzumab on Days 1, 8, and 15 and Pola on Day 1; Cycles 2-6: participants received 1000 mg of obinutuzumab on Day 1, 1200 mg of Atezo on Day 1, and either 1.4 mg/kilogram (kg) or 1.8 mg/kg of Pola on Day 1. The 1.4 mg/kg dose was cleared and escalated to 1.8 mg/kg which was declared the recommended Phase 2 dose (RP2D). This was followed by obinutuzumab on Day 1 of every other month starting with Month 1 for 24 months, during maintenance treatment for FL participants. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Atezolizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1200 mg

| | |
|--|-----------------|
| Investigational medicinal product name | Obinutuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1000 mg

| | |
|--|---------------------|
| Investigational medicinal product name | Polatuzumab Vedotin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1.4 mg

| | |
|------------------|---------------------|
| Arm title | Expansion FL Cohort |
|------------------|---------------------|

Arm description:

During the induction treatment Cycle 1 (21-day cycles): participants received obinutuzumab on Days 1, 8, and 15 and Pola on Day 1; Cycles 2-6: participants received 1000 mg of obinutuzumab on Day 1, 1200 mg of Atezo on Day 1, and 1.8 mg/kg of Pola (RP2D) on Day 1. This was followed by

obinutuzumab on Day 1 of every other month starting with Month 1 for 24 months, during maintenance treatment for FL participants. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Atezolizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1200 mg

| | |
|--|-----------------|
| Investigational medicinal product name | Obinutuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1000 mg

| | |
|--|---------------------|
| Investigational medicinal product name | Polatuzumab Vedotin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1.8 mg

| | |
|------------------|--|
| Arm title | Safety Run-in and Expansion DLBCL Cohort |
|------------------|--|

Arm description:

For DLBCL, during the induction treatment Cycles 1-6 (21-day cycles): participants received a 375 mg/m² IV of rituximab on Day 1 and on Day 1 of every other month during consolidation. Participants also received a 1.8 mg/kg IV of Pola on Day 1. Cycles 2-6: participants received 1200 mg of Atezo on Day 1. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Atezolizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1200 mg

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

Dosage and administration details:

375 mg/m²

| | |
|--|---------------------|
| Investigational medicinal product name | Polatuzumab Vedotin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1.4 mg or 1.8 mg

| Number of subjects in period 1 | Dose-Escalation FL Cohort | Expansion FL Cohort | Safety Run-in and Expansion DLBCL Cohort |
|---------------------------------------|---------------------------|---------------------|--|
| | | | |
| Started | 3 | 10 | 23 |
| Completed | 1 | 1 | 1 |
| Not completed | 2 | 9 | 22 |
| Physician decision | 1 | 2 | 3 |
| Withdrawal By Subject | 1 | - | 3 |
| Death | - | 2 | 13 |
| Progressive Disease | - | 1 | - |
| Not Specified | - | 2 | - |
| Lost to follow-up | - | 2 | 3 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Dose-Escalation FL Cohort |
|-----------------------|---------------------------|

Reporting group description:

During the induction treatment Cycle 1 (21-day cycles): participants received obinutuzumab on Days 1, 8, and 15 and Pola on Day 1; Cycles 2-6: participants received 1000 mg of obinutuzumab on Day 1, 1200 mg of Atezo on Day 1, and either 1.4 mg/kilogram (kg) or 1.8 mg/kg of Pola on Day 1. The 1.4 mg/kg dose was cleared and escalated to 1.8 mg/kg which was declared the recommended Phase 2 dose (RP2D). This was followed by obinutuzumab on Day 1 of every other month starting with Month 1 for 24 months, during maintenance treatment for FL participants. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

| | |
|-----------------------|---------------------|
| Reporting group title | Expansion FL Cohort |
|-----------------------|---------------------|

Reporting group description:

During the induction treatment Cycle 1 (21-day cycles): participants received obinutuzumab on Days 1, 8, and 15 and Pola on Day 1; Cycles 2-6: participants received 1000 mg of obinutuzumab on Day 1, 1200 mg of Atezo on Day 1, and 1.8 mg/kg of Pola (RP2D) on Day 1. This was followed by obinutuzumab on Day 1 of every other month starting with Month 1 for 24 months, during maintenance treatment for FL participants. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

| | |
|-----------------------|--|
| Reporting group title | Safety Run-in and Expansion DLBCL Cohort |
|-----------------------|--|

Reporting group description:

For DLBCL, during the induction treatment Cycles 1-6 (21-day cycles): participants received a 375 mg/m² IV of rituximab on Day 1 and on Day 1 of every other month during consolidation. Participants also received a 1.8 mg/kg IV of Pola on Day 1. Cycles 2-6: participants received 1200 mg of Atezo on Day 1. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

| Reporting group values | Dose-Escalation FL Cohort | Expansion FL Cohort | Safety Run-in and Expansion DLBCL Cohort |
|---|---------------------------|---------------------|--|
| Number of subjects | 3 | 10 | 23 |
| Age Categorical Units: Subjects | | | |
| <=18 years | 0 | 0 | 0 |
| Between 18 and 65 years | 2 | 6 | 12 |
| >=65 years | 1 | 4 | 11 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 52.3 | 57.7 | 64.3 |
| standard deviation | ± 13.6 | ± 11.7 | ± 15.3 |
| Sex: Female, Male Units: Subjects | | | |
| Female | 0 | 4 | 9 |
| Male | 3 | 6 | 14 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Hispanic or Latino | 0 | 1 | 3 |
| Not Hispanic or Latino | 3 | 9 | 18 |
| Unknown | 0 | 0 | 2 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Other | 0 | 1 | 2 |

| | | | |
|-------|---|---|----|
| White | 3 | 9 | 21 |
|-------|---|---|----|

| Reporting group values | Total | | |
|---|-------|--|--|
| Number of subjects | 36 | | |
| Age Categorical Units: Subjects | | | |
| <=18 years | 0 | | |
| Between 18 and 65 years | 20 | | |
| >=65 years | 16 | | |
| Age Continuous Units: Years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male Units: Subjects | | | |
| Female | 13 | | |
| Male | 23 | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Hispanic or Latino | 4 | | |
| Not Hispanic or Latino | 30 | | |
| Unknown | 2 | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Other | 3 | | |
| White | 33 | | |

End points

End points reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Dose-Escalation FL Cohort |
|-----------------------|---------------------------|

Reporting group description:

During the induction treatment Cycle 1 (21-day cycles): participants received obinutuzumab on Days 1, 8, and 15 and Pola on Day 1; Cycles 2-6: participants received 1000 mg of obinutuzumab on Day 1, 1200 mg of Atezo on Day 1, and either 1.4 mg/kilogram (kg) or 1.8 mg/kg of Pola on Day 1. The 1.4 mg/kg dose was cleared and escalated to 1.8 mg/kg which was declared the recommended Phase 2 dose (RP2D). This was followed by obinutuzumab on Day 1 of every other month starting with Month 1 for 24 months, during maintenance treatment for FL participants. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

| | |
|-----------------------|---------------------|
| Reporting group title | Expansion FL Cohort |
|-----------------------|---------------------|

Reporting group description:

During the induction treatment Cycle 1 (21-day cycles): participants received obinutuzumab on Days 1, 8, and 15 and Pola on Day 1; Cycles 2-6: participants received 1000 mg of obinutuzumab on Day 1, 1200 mg of Atezo on Day 1, and 1.8 mg/kg of Pola (RP2D) on Day 1. This was followed by obinutuzumab on Day 1 of every other month starting with Month 1 for 24 months, during maintenance treatment for FL participants. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

| | |
|-----------------------|--|
| Reporting group title | Safety Run-in and Expansion DLBCL Cohort |
|-----------------------|--|

Reporting group description:

For DLBCL, during the induction treatment Cycles 1-6 (21-day cycles): participants received a 375 mg/m² IV of rituximab on Day 1 and on Day 1 of every other month during consolidation. Participants also received a 1.8 mg/kg IV of Pola on Day 1. Cycles 2-6: participants received 1200 mg of Atezo on Day 1. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

Primary: Percentage of Participants with CR at EOI, as Determined by the investigator on the Basis of Positron Emission Tomography and Computed Tomography (PET-CT) Scan

| | |
|-----------------|--|
| End point title | Percentage of Participants with CR at EOI, as Determined by the investigator on the Basis of Positron Emission Tomography and Computed Tomography (PET-CT) Scan ^[1] |
|-----------------|--|

End point description:

Tumor response assessment was performed by the investigator according to modified Lugano classification using PET/CT scan. CR was defined as a score of 1 (no uptake above background), 2 (uptake \leq mediastinum), or 3 (uptake $<$ mediastinum but \leq liver) with or without a residual mass on PET 5-PS, for lymph nodes and extralymphatic sites; no new lesions; no evidence of FDG-avid disease in bone marrow; and normal/IHC-negative bone marrow morphology. 90% confidence interval (CI) for percentage of responders was calculated using Clopper-Pearson method. All PET evaluable 1L FL and 1L DLBCL patients with at least one dose of atezolizumab were included in efficacy population.

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

End point timeframe:

Within 6 to 8 weeks after Day 1 of Cycle 6 (up to approximately 6 months)

Notes:

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

Justification: This endpoint is only reporting the percentage of participants

| End point values | Dose-Escalation FL Cohort | Expansion FL Cohort | Safety Run-in and Expansion DLBCL Cohort | |
|-----------------------------------|---------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 7 | 16 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 33.33 | 14.30 | 12.5 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with CR at EOI, as Determined by Investigator on the Basis of CT Scans Alone

| | |
|-----------------|---|
| End point title | Percentage of Participants with CR at EOI, as Determined by Investigator on the Basis of CT Scans Alone |
|-----------------|---|

End point description:

Tumor response assessment was performed by investigator according to modified Lugano classification using computed tomography (CT) scan. OR: a response of CR or PR. CR: Target nodes/nodal masses regressed to ≤ 1.5 cm in LDi; no extralymphatic sites of disease; organ enlargement regressed to normal; no new lesions; normal/IHC-negative bone marrow morphology. All CT evaluable 1L FL and 1L DLBCL patients with at least one dose of atezolizumab were included in efficacy population.

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

End point timeframe:

Within 6 to 8 weeks after Day 1 of Cycle 6 (up to approximately 6 months)

| End point values | Dose-Escalation FL Cohort | Expansion FL Cohort | Safety Run-in and Expansion DLBCL Cohort | |
|-----------------------------------|---------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 7 | 16 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 0.00 | 57.14 | 12.50 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Objective Response (CR + PR) at EOI, as Determined by the Investigator on the Basis of PET-CT Scans

| | |
|-----------------|---|
| End point title | Percentage of Participants with Objective Response (CR + PR) at EOI, as Determined by the Investigator on the Basis of PET-CT Scans |
|-----------------|---|

End point description:

Tumor response assessment was performed by investigator according to modified Lugano classification using PET/CT scan. OR: a response of CR or PR. CR: a score of 1 (no uptake above background), 2 (uptake \leq mediastinum), or 3 (uptake $<$ mediastinum but \leq liver) with or without a residual mass on PET 5-PS, for lymph nodes & extralymphatic sites; no new lesions; no evidence of FDG-avid disease in

bone marrow; and normal/IHC-negative bone marrow morphology. PR with a score 4 (uptake moderately greater than [$>$] liver) or 5 (uptake markedly $>$ liver and/or new lesions) with reduced uptake compared with baseline and residual mass(es) of any size on PET 5-PS for lymph nodes and extralymphatic sites; no new lesions; and reduced residual uptake in bone marrow compared with baseline. All PET evaluable 1L FL and 1L DLBCL patients with at least one dose of atezolizumab were included in efficacy population

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

End point timeframe:

Within 6 to 8 weeks after Day 1 of Cycle 6 (up to approximately 6 months)

| End point values | Dose-Escalation FL Cohort | Expansion FL Cohort | Safety Run-in and Expansion DLBCL Cohort | |
|-----------------------------------|---------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 7 | 16 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 33.33 | 57.14 | 25.00 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Objective Response (CR + PR) at EOI, as Determined by the Investigator on the Basis of CT Scans Alone

| | |
|-----------------|---|
| End point title | Percentage of Participants with Objective Response (CR + PR) at EOI, as Determined by the Investigator on the Basis of CT Scans Alone |
|-----------------|---|

End point description:

Tumor response assessment was performed by investigator according to modified Lugano classification using CT scan. OR: a response of CR or PR. CR: Target nodes/nodal masses regressed to ≤ 1.5 cm in LDi; no extralymphatic sites of disease; organ enlargement regressed to normal; no new lesions; normal/IHC-negative bone marrow morphology. PR with ≥ 50 percent decrease in SPD of up to six target measurable nodes and extranodal sites, a 5 mm x 5 mm default value when lesions were too small, 0 x0 mm value when lesions were no longer visible, actual measurements were used for nodes greater than 5 mm x 5 mm for lymph nodes & extralymphatic sites; absent/normal, regression for non-measured lesion; spleen enlargement regression by > 50 percent; no new lesions; reduced residual uptake in bone marrow compared to baseline. All CT evaluable 1L FL and 1L DLBCL patients with at least one dose of atezolizumab were included in efficacy population.

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

End point timeframe:

Within 6 to 8 weeks after Day 1 of Cycle 6 (up to approximately 6 months)

| End point values | Dose-Escalation FL Cohort | Expansion FL Cohort | Safety Run-in and Expansion DLBCL Cohort | |
|-----------------------------------|---------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 7 | 16 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 33.33 | 57.14 | 25.00 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Best Response of CR or PR during the Study, as Determined by the Investigator on the Basis of CT Scans Alone

| | |
|-----------------|--|
| End point title | Percentage of Participants with Best Response of CR or PR during the Study, as Determined by the Investigator on the Basis of CT Scans Alone |
|-----------------|--|

End point description:

Tumor response assessment was performed by investigator according to modified Lugano classification using CT scan. OR: a response of CR or PR. CR: Target nodes/nodal masses regressed to ≤ 1.5 cm in LDi; no extralymphatic sites of disease; organ enlargement regressed to normal; no new lesions; normal/IHC-negative bone marrow morphology. PR with ≥ 50 percent decrease in SPD of up to six target measurable nodes and extranodal sites, a 5 mm x 5 mm default value when lesions were too small, 0 x0 mm value when lesions were no longer visible, actual measurements were used for nodes greater than 5 mm x 5 mm for lymph nodes & extralymphatic sites; absent/normal, regression for non-measured lesion; spleen enlargement regression by > 50 percent; no new lesions; reduced residual uptake in bone marrow compared to baseline. All CT evaluable 1L FL and 1L DLBCL patients with at least one dose of atezolizumab were included in efficacy population.

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

End point timeframe:

Baseline up to 35 months

| End point values | Dose-Escalation FL Cohort | Expansion FL Cohort | Safety Run-in and Expansion DLBCL Cohort | |
|---|---------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 7 | 16 | |
| Units: Percentage of participants number (not applicable) | | | | |
| Complete response | 33.3 | 14.3 | 12.5 | |
| Partial response | 0 | 42.9 | 12.5 | |
| Stable disease | 33.3 | 14.3 | 6.3 | |
| Progressive disease | 33.3 | 14.3 | 31.3 | |
| Not available | 0 | 14.3 | 37.5 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events and Serious Adverse Events

| | |
|-----------------|--|
| End point title | Percentage of Participants with Adverse Events and Serious |
|-----------------|--|

End point description:

An AE was any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with the treatment. An adverse event was therefore any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Grading was completed according to the CTCAE, version 4.0 for severity and tumor flare reactions were graded according to NCI CTCAE v3.0.

End point type Secondary

End point timeframe:

Baseline up to 35 months

| End point values | Dose-Escalation FL Cohort | Expansion FL Cohort | Safety Run-in and Expansion DLBCL Cohort | |
|-----------------------------|---------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 10 | 21 | |
| Units: Participants | | | | |
| number (not applicable) | 100.00 | 100.00 | 81.00 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Obinutuzumab Concentration

End point title Serum Obinutuzumab Concentration^[2]

End point description:

pre-dose (0 hr), 30 min after EOI on Day 1 Cycle 1; pre-dose (within 5 hr), 30 min after EOI on Day 1 of Cycles 2, 4, 6; maintenance phase: pre-dose (within 5 hr) on Day 1 of Months 1, 7, 13, 19; anytime during treatment discontinuation visit, 120 days after the last dose, and 1 year after the last dose up to approximately 4 years (1 cycle=21 days; infusion rate: starts with 50 mg/hr and decreases every 30 min to maximum of 400 mg/hr). 99999 represents the upper limit of confidence interval was not estimable due to the low number of subjects within events.

End point type Secondary

End point timeframe:

Pre-dose (0 hr) up to 35 months

Notes:

[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: Only arms treated with Obinutuzumab were included in this endpoint

| End point values | Dose-Escalation FL Cohort | Expansion FL Cohort | | |
|--|---------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 10 | | |
| Units: mcg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Induction cycle 1 Day 1 Pre-dose (N=3, 10) | 99999 (± 99999) | 99999 (± 99999) | | |

| | | | | |
|---|---------------|----------------|--|--|
| Induction cycle 1 Day 1 Post-dose (N=3, 10) | 308 (± 41.6) | 295 (± 171) | | |
| Induction cycle 2 Day 1 Pre-dose (N=3, 10) | 351 (± 81.3) | 403 (± 143) | | |
| Induction cycle 2 Day 1 Post-dose (N=3, 10) | 616 (± 115) | 672 (± 130) | | |
| Induction cycle 4 Day 1 Pre-dose (N=3, 10) | 433 (± 322) | 311 (± 177) | | |
| Induction cycle 4 Day 1 Post-dose (N=3, 18) | 583 (± 189) | 619 (± 160) | | |
| Induction cycle 6 Day 1 Pre-dose (N=3, 9) | 288 (± 123) | 308 (± 194) | | |
| Induction cycle 6 Day 1 Post-dose (N=3, 8) | 514 (± 121) | 605 (± 161) | | |
| Maintenance Month 1 Day 1 Pre-dose (N=1, 6) | 221 (± 99999) | 171 (± 131) | | |
| Maintenance Month 7 Pre-dose (N=2, 6) | 90.4 (± 58.8) | 83.8 (± 59.6) | | |
| Maintenance Month 13 Pre-dose (N=2, 2) | 78.8 (± 42.8) | 158 (± 1.41) | | |
| Drug completion or early discontinuation (N=0, 1) | 0 (± 0) | 37.2 (± 99999) | | |
| PK and Immunogenicity follow up (N=2, 3) | 110 (± 120) | 15.4 (± 3.20) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Rituximab Concentration

| | |
|--|--|
| End point title | Serum Rituximab Concentration ^[3] |
| End point description: pre-dose (0 hr), 30 min after EOI on Day 1 Cycle 1; pre-dose (within 5 hr) on Day 1 of Cycles 2, 4; pre-dose (within 5 hr), 30 min after EOI on Day 1 of Cycle 6; anytime during treatment discontinuation visit, 120 days after the last dose, and 1 year after the last dose up to approximately 4 years (1 cycle=21 days; infusion rate: starts with 50 mg/hr and increases every 30 min to maximum of 400 mg/hr) | |
| End point type | Secondary |
| End point timeframe: Pre-dose (0 hr) up to 35 months | |

Notes:

[3] - 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: Only arms treated with Rituximab were included in this endpoint

| End point values | Safety Run-in and Expansion DLBCL Cohort | | | |
|--|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: mcg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Induction Cycle 1 Day 1 Pre-dose (N=9) | 30.4 (± 28.8) | | | |
| Induction Cycle 1 Day 1 Post-dose (N=19) | 197 (± 56.9) | | | |
| Induction Cycle 2 Day 1 Pre-dose (N=17) | 43.5 (± 28.7) | | | |

| | | | | |
|--|---------------|--|--|--|
| Induction Cycle 4 Day 1 Pre-dose (N=10) | 84.8 (± 35.7) | | | |
| Induction Cycle 6 Day 1 Pre-dose (N=13) | 101 (± 45.5) | | | |
| Induction Cycle 6 Day 1 Post-dose (N=12) | 239 (± 42.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Atezo Concentration

| | |
|---|---------------------------|
| End point title | Serum Atezo Concentration |
| End point description: pre-dose (within 5 hr), 30 min after EOI on Day 1 of Cycles 2, 3, 4; pre-dose (within 5 hr) on Day 1 of Cycle 6; maintenance phase: pre-dose (within 5 hr) on Day 1 of Month 1; 30 min after EOI on Day 2 of Month 1; pre-dose (within 5 hr) on Day 1 of Month 4, 7, 13, 19; anytime during treatment discontinuation visit, 120 days after the last dose, and 1-2 years after the last dose up to approximately 4 years (1 cycle=21 days; infusion rate: starts with 60 min and decreases to 30 min). 99999 represents the upper limit of confidence interval was not estimable due to the low number of subjects within events. | |
| End point type | Secondary |
| End point timeframe: Pre-dose (0 hr) up to 35 months | |

| End point values | Dose-Escalation FL Cohort | Expansion FL Cohort | Safety Run-in and Expansion DLBCL Cohort | |
|---|---------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 10 | 21 | |
| Units: mcg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Induction Cycle 2 Day 1 Pre-dose (N=3, 10, 18) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | |
| Induction Cycle 2 Day 1 Post-dose (N=3, 10, 18) | 332 (± 56.7) | 365 (± 80.7) | 355 (± 78.8) | |
| Induction Cycle 3 Day 1 Pre-dose (N=3, 9, 14) | 86.9 (± 28.8) | 78.7 (± 18.4) | 79.7 (± 30.6) | |
| Induction Cycle 4 Day 1 Pre-dose (N=3, 7, 9) | 139 (± 33.1) | 125 (± 47.3) | 139 (± 56.4) | |
| Induction Cycle 4 Day 1 Post-dose (N=3, 6, 8) | 462 (± 82.0) | 450 (± 136) | 489 (± 131) | |
| Induction Cycle 6 Day 1 Pre-dose (N=3, 6, 8) | 194 (± 67.7) | 181 (± 112) | 180 (± 90.6) | |
| Maintenance Month 1 Day 1 Pre-dose (N=2, 4, 0) | 100 (± 66.0) | 70.7 (± 55.5) | 0 (± 0) | |
| Maintenance Month 1 Day 2 Post-dose (N=3, 4, 0) | 577 (± 144) | 473 (± 177) | 0 (± 0) | |
| Maintenance Month 4 Pre-dose (N=3, 3, 0) | 240 (± 101) | 140 (± 141) | 0 (± 0) | |
| Maintenance Month 7 Pre-dose (N=2, 2, 0) | 226 (± 134) | 221 (± 90.5) | 0 (± 0) | |

| | | | | |
|--|---------------|---------------|----------------|--|
| Maintenance Month 13 Pre-dose (N=2, 0, 0) | 106 (± 83.0) | 0 (± 0) | 0 (± 0) | |
| Drug completion or early discontinuation (N=0,1,2) | 0 (± 0) | 127 (± 99999) | 93.0 (± 14.2) | |
| Consolidation Month 1 Day 1 Pre-dose (N=0, 0, 4) | 0 (± 0) | 0 (± 0) | 132 (± 43.3) | |
| Consolidation Month 1 Day 2 Post-dose (N=0, 0, 3) | 0 (± 0) | 0 (± 0) | 503 (± 214) | |
| PK and Immunogenicity followup 120D (N=2, 3, 2) | 61.4 (± 60.3) | 16.8 (± 26.8) | 19.9 (± 0.778) | |
| PK and Immunogenicity followup 1 Year (N=0, 2, 0) | 0 (± 0) | 0 (± 0) | 0 (± 0) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Pola Concentration

| | |
|------------------------|---|
| End point title | Serum Pola Concentration |
| End point description: | pre-dose (0 hr) on Day 1 Cycle 1; pre-dose (within 5 hr) on Day 1 of Cycles 2, 4; maintenance phase: pre-dose (within 5 hr) on Day 1 of Months 1; anytime during treatment discontinuation visit, 120 days after the last dose, and 1 year after the last dose up to approximately 4 years (1 cycle=21 days; infusion rate: starts with 90 min and decreases to 30 min). 99999 represents the upper limit of confidence interval was not estimable due to the low number of subjects within events. |
| End point type | Secondary |
| End point timeframe: | Pre-dose (0 hr) up to 35 months |

| End point values | Dose-Escalation FL Cohort | Expansion FL Cohort | Safety Run-in and Expansion DLBCL Cohort | |
|--|---------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 10 | 21 | |
| Units: mcg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Pre Day 120 Follow-up (N=0, 1, 1) | 0 (± 0) | 0.136 (± 99999) | 2.91 (± 99999) | |
| Induction Cycle 1 Day 1 Pre-dose (N=0, 1, 1) | 0 (± 0) | 0.847 (± 99999) | 35.9 (± 99999) | |
| Induction Cycle 2 Day 1 Pre-dose (N=3, 8, 17) | 2.54 (± 0.918) | 2.62 (± 1.22) | 3.37 (± 3.60) | |
| Induction Cycle 4 Day 1 Pre-dose (N=3, 9, 12) | 4.73 (± 2.10) | 4.27 (± 1.63) | 4.92 (± 2.65) | |
| Maintenance Month 1 Day 1 Pre-dose (N=2, 3, 0) | 1.30 (± 0.696) | 1.63 (± 1.75) | 0 (± 0) | |
| Drug completion or early discontinuation (N=0,0,2) | 0 (± 0) | 0 (± 0) | 0.716 (± 0.200) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Human Anti-Human Antibodies (HAHAs) to Obinutuzumab

| | |
|-----------------|--|
| End point title | Percentage of Participants with Human Anti-Human Antibodies (HAHAs) to Obinutuzumab ^[4] |
|-----------------|--|

End point description:

Pre-dose (0 hr) on Day 1 of Cycle 1, 6, anytime during treatment discontinuation visit, 120 days after the last dose, and 1 year after the last dose up to approximately 4 years (1 cycle=21 days; infusion rate: starts with 50 mg/hr and increased every 30 min to maximum of 400 mg/hr)

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

End point timeframe:

Baseline up to 35 months

Notes:

[4] - 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: Only arms treated with Obinutuzumab were included in this endpoint

| End point values | Dose-Escalation FL Cohort | Expansion FL Cohort | | |
|-----------------------------------|---------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 10 | | |
| Units: Percentage of participants | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Human Anti-Chimeric Antibodies (HACAs) to Rituximab

| | |
|-----------------|--|
| End point title | Percentage of Participants with Human Anti-Chimeric Antibodies (HACAs) to Rituximab ^[5] |
|-----------------|--|

End point description:

Pre-dose (0 hr) on Day 1 of Cycle 1, 2, 4, 6, anytime during treatment discontinuation visit, 120 days after the last dose, and 1 year after the last dose up to approximately 4 years (1 cycle=21 days; infusion rate: starts with 50 mg/hr and increased every 30 min to maximum of 400 mg/hr)

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

End point timeframe:

Baseline to 35 months

Notes:

[5] - 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: Only arms treated with Rituximab were included in this endpoint

| End point values | Safety Run-in and Expansion DLBCL Cohort | | | |
|--|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Baseline, positive (N=18) | 5.6 | | | |
| Baseline, negative (N=18) | 94.4 | | | |
| Induction Cycle 2 Day 1, positive (N=18) | 5.6 | | | |
| Induction Cycle 2 Day 1, negative (N=18) | 94.4 | | | |
| Induction Cycle 4 Day 1 (N=12) | 100 | | | |
| Induction Cycle 6 Day 1 (N=13) | 100 | | | |
| Study drug completion (N=1) | 100 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Anti-Therapeutic Antibodies (ATAs) to Atezo

| | |
|------------------------|---|
| End point title | Percentage of Participants with Anti-Therapeutic Antibodies (ATAs) to Atezo |
| End point description: | Pre-dose (0 hr) on Day 1 of Cycle 2, 3, 4, 6, Month 1, 4, 7, 13 and 19, anytime during treatment discontinuation visit, 120 days after the last dose, and 1 year after the last dose up to approximately 4 years (1 cycle=21 days; infusion rate: starts with 60 min and decreases to 30 min) |
| End point type | Secondary |
| End point timeframe: | Baseline to 35 months |

| End point values | Dose-Escalation FL Cohort | Expansion FL Cohort | Safety Run-in and Expansion DLBCL Cohort | |
|--|---------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 10 | 21 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Induction, Cycle 2 Day 1, positive (N=3, 10, 1) | 0 | 0 | 5.3 | |
| Induction, Cycle 2 Day 1, negative (N=3, 10, 18) | 0 | 0 | 94.7 | |
| Induction, Cycle 3 Day 1, positive (N=3, 10, 1) | 0 | 0 | 7.1 | |
| Induction, Cycle 3 Day 1, negative (N=3, 10, 13) | 0 | 0 | 92.9 | |
| Induction, Cycle 4 Day 1, negative (N=3, 10, 9) | 0 | 0 | 100.0 | |

| | | | | |
|--|---|---|-------|--|
| Induction, Cycle 6 Day 1, negative (N=3, 10, 7) | 0 | 0 | 100.0 | |
| Consolidation Month 1 Day 1, negative (N=3, 10, 4) | 0 | 0 | 100.0 | |
| Study drug completion, negative (N=3, 10, 2) | 0 | 0 | 100.0 | |
| PK Immuno. Follow up (120D), negative (N=3, 10, 2) | 0 | 0 | 100.0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with ATAs to Pola

| | |
|--|--|
| End point title | Percentage of Participants with ATAs to Pola |
| End point description: | |
| Pre-dose (0 hr) on Day 1 of Cycle 1, 2, 4, anytime during treatment discontinuation visit, 120 days after the last dose, and 1 year after the last dose up to approximately 4 years (1 cycle=21 days; infusion rate: starts with 90 min and decreases to 30 min) | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to 35 months | |

| End point values | Dose-Escalation FL Cohort | Expansion FL Cohort | Safety Run-in and Expansion DLBCL Cohort | |
|-----------------------------------|---------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 10 | 21 | |
| Units: Percentage of participants | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization up to 35 months

Adverse event reporting additional description:

All adverse events that occurred on or after the first dose of study treatment are summarized by mapped term, appropriate thesaurus levels, and National Cancer Institute Common Terminology Criteria (NCI CTCAE) v4.0 grade. All-Cause Mortality is reported for the ITT population.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Dose-Escalation FL Cohort |
|-----------------------|---------------------------|

Reporting group description:

During the induction treatment Cycle 1 (21-day cycles): participants received obinutuzumab on Days 1, 8, and 15 and Pola on Day 1; Cycles 2-6: participants received 1000 mg of obinutuzumab on Day 1, 1200 mg of Atezo on Day 1, and either 1.4 mg/kilogram (kg) or 1.8 mg/kg of Pola on Day 1. The 1.4 mg/kg dose was cleared and escalated to 1.8 mg/kg which was declared the recommended Phase 2 dose (RP2D). This was followed by obinutuzumab on Day 1 of every other month starting with Month 1 for 24 months, during maintenance treatment for FL participants. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

| | |
|-----------------------|--|
| Reporting group title | Safety Run-in and Expansion DLBCL Cohort |
|-----------------------|--|

Reporting group description:

For DLBCL, during the induction treatment Cycles 1-6 (21-day cycles): participants received a 375 mg/m² IV of rituximab on Day 1 and on Day 1 of every other month during consolidation. Participants also received a 1.8 mg/kg IV of Pola on Day 1. Cycles 2-6: participants received 1200 mg of Atezo on Day 1. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

| | |
|-----------------------|---------------------|
| Reporting group title | Expansion FL Cohort |
|-----------------------|---------------------|

Reporting group description:

During the induction treatment Cycle 1 (21-day cycles): participants received obinutuzumab on Days 1, 8, and 15 and Pola on Day 1; Cycles 2-6: participants received 1000 mg of obinutuzumab on Day 1, 1200 mg of Atezo on Day 1, and 1.8 mg/kg of Pola (RP2D) on Day 1. This was followed by obinutuzumab on Day 1 of every other month starting with Month 1 for 24 months, during maintenance treatment for FL participants. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

| Serious adverse events | Dose-Escalation FL Cohort | Safety Run-in and Expansion DLBCL Cohort | Expansion FL Cohort |
|---|---------------------------|--|---------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 23 (8.70%) | 4 / 10 (40.00%) |
| number of deaths (all causes) | 0 | 13 | 2 |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| C-REACTIVE PROTEIN INCREASED | | | |

| | | | |
|---|---------------|----------------|-----------------|
| subjects affected / exposed ^[1] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| GUILLAIN-BARRE SYNDROME | | | |
| subjects affected / exposed ^[2] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LETHARGY | | | |
| subjects affected / exposed ^[3] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 0 / 10 (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 |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed ^[4] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FEBRILE NEUTROPENIA | | | |
| subjects affected / exposed ^[5] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 2 / 10 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| DEATH | | | |
| subjects affected / exposed ^[6] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| PYREXIA | | | |
| subjects affected / exposed ^[7] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| 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 ^[8] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 0 / 10 (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 ^[9] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed ^[10] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 0 / 10 (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 |
| PNEUMONITIS | | | |
| subjects affected / exposed ^[11] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| DERMATITIS | | | |
| subjects affected / exposed ^[12] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ERYTHEMA | | | |
| subjects affected / exposed ^[13] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| BRONCHOPULMONARY ASPERGILLOSIS | | | |
| subjects affected / exposed ^[14] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| ERYSIPELAS | | | |

| | | | |
|---|---------------|----------------|-----------------|
| subjects affected / exposed ^[15] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SEPSIS | | | |
| subjects affected / exposed ^[16] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 0 / 10 (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 |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[12] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[13] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[14] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[15] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[16] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

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

| Non-serious adverse events | Dose-Escalation FL Cohort | Safety Run-in and Expansion DLBCL Cohort | Expansion FL Cohort |
|---|---------------------------|--|----------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 3 / 3 (100.00%) | 15 / 23 (65.22%) | 10 / 10 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) BASAL CELL CARCINOMA subjects affected / exposed ^[17] occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 21 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| Vascular disorders HYPERTENSION subjects affected / exposed ^[18] occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| THROMBOSIS subjects affected / exposed ^[19] occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| General disorders and administration site conditions CHEST PAIN subjects affected / exposed ^[20] occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| FACE OEDEMA | | | |

| | | | |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed ^[21] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| FATIGUE | | | |
| subjects affected / exposed ^[22] | 2 / 3 (66.67%) | 1 / 21 (4.76%) | 3 / 10 (30.00%) |
| occurrences (all) | 2 | 1 | 3 |
| INFLUENZA LIKE ILLNESS | | | |
| subjects affected / exposed ^[23] | 1 / 3 (33.33%) | 0 / 21 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| INFUSION SITE EXTRAVASATION | | | |
| subjects affected / exposed ^[24] | 1 / 3 (33.33%) | 0 / 21 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| OEDEMA | | | |
| subjects affected / exposed ^[25] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed ^[26] | 0 / 3 (0.00%) | 5 / 21 (23.81%) | 3 / 10 (30.00%) |
| occurrences (all) | 0 | 5 | 3 |
| PERIPHERAL SWELLING | | | |
| subjects affected / exposed ^[27] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 1 | 3 |
| PYREXIA | | | |
| subjects affected / exposed ^[28] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 4 / 10 (40.00%) |
| occurrences (all) | 0 | 0 | 6 |
| Respiratory, thoracic and mediastinal disorders | | | |
| COUGH | | | |
| subjects affected / exposed ^[29] | 0 / 3 (0.00%) | 2 / 21 (9.52%) | 2 / 10 (20.00%) |
| occurrences (all) | 0 | 3 | 3 |
| DYSPNOEA | | | |
| subjects affected / exposed ^[30] | 0 / 3 (0.00%) | 2 / 21 (9.52%) | 0 / 10 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| DYSPNOEA EXERTIONAL | | | |
| subjects affected / exposed ^[31] | 0 / 3 (0.00%) | 2 / 21 (9.52%) | 0 / 10 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| HICCUPS | | | |

| | | | |
|--|----------------|----------------|-----------------|
| subjects affected / exposed ^[32] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| LARYNGEAL OEDEMA | | | |
| subjects affected / exposed ^[33] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed ^[34] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 2 |
| PULMONARY THROMBOSIS | | | |
| subjects affected / exposed ^[35] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Psychiatric disorders | | | |
| DEPRESSION | | | |
| subjects affected / exposed ^[36] | 1 / 3 (33.33%) | 1 / 21 (4.76%) | 0 / 10 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| INSOMNIA | | | |
| subjects affected / exposed ^[37] | 1 / 3 (33.33%) | 0 / 21 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| ANXIETY | | | |
| subjects affected / exposed ^[38] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Investigations | | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed ^[39] | 1 / 3 (33.33%) | 0 / 21 (0.00%) | 2 / 10 (20.00%) |
| occurrences (all) | 1 | 0 | 2 |
| BLOOD CREATININE INCREASED | | | |
| subjects affected / exposed ^[40] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 2 / 10 (20.00%) |
| occurrences (all) | 0 | 0 | 2 |
| BLOOD LACTATE DEHYDROGENASE INCREASED | | | |
| subjects affected / exposed ^[41] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 1 | 1 |
| C-REACTIVE PROTEIN INCREASED | | | |
| subjects affected / exposed ^[42] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 2 / 10 (20.00%) |
| occurrences (all) | 0 | 0 | 5 |
| GAMMA-GLUTAMYLTRANSFERASE INCREASED | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed ^[43] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| LIPASE INCREASED | | | |
| subjects affected / exposed ^[44] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 1 | 1 |
| NEUTROPHIL COUNT DECREASED | | | |
| subjects affected / exposed ^[45] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 2 |
| PROCALCITONIN INCREASED | | | |
| subjects affected / exposed ^[46] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| THYROXINE DECREASED | | | |
| subjects affected / exposed ^[47] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| TRI-IODOTHYRONINE DECREASED | | | |
| subjects affected / exposed ^[48] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| WEIGHT DECREASED | | | |
| subjects affected / exposed ^[49] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 4 / 10 (40.00%) |
| occurrences (all) | 0 | 0 | 4 |
| WHITE BLOOD CELL COUNT DECREASED | | | |
| subjects affected / exposed ^[50] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| INFUSION RELATED REACTION | | | |
| subjects affected / exposed ^[51] | 1 / 3 (33.33%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Cardiac disorders | | | |
| SINUS TACHYCARDIA | | | |
| subjects affected / exposed ^[52] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| DIZZINESS | | | |
| subjects affected / exposed ^[53] | 0 / 3 (0.00%) | 2 / 21 (9.52%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 2 | 1 |
| FACIAL PARALYSIS | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed ^[54] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| HEADACHE | | | |
| subjects affected / exposed ^[55] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 1 | 2 |
| HYPOAESTHESIA | | | |
| subjects affected / exposed ^[56] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 1 | 2 |
| NEUROPATHY PERIPHERAL | | | |
| subjects affected / exposed ^[57] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 2 |
| PARAESTHESIA | | | |
| subjects affected / exposed ^[58] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 2 |
| POLYNEUROPATHY | | | |
| subjects affected / exposed ^[59] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed ^[60] | 0 / 3 (0.00%) | 2 / 21 (9.52%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 2 | 1 |
| ANAEMIA FOLATE DEFICIENCY | | | |
| subjects affected / exposed ^[61] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| LEUKOPENIA | | | |
| subjects affected / exposed ^[62] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 2 / 10 (20.00%) |
| occurrences (all) | 0 | 1 | 5 |
| NEUTROPENIA | | | |
| subjects affected / exposed ^[63] | 1 / 3 (33.33%) | 3 / 21 (14.29%) | 4 / 10 (40.00%) |
| occurrences (all) | 1 | 4 | 7 |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed ^[64] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 4 / 10 (40.00%) |
| occurrences (all) | 0 | 0 | 5 |
| Eye disorders | | | |
| DRY EYE | | | |

| | | | |
|---|---------------|----------------|-----------------|
| subjects affected / exposed ^[65] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 2 / 10 (20.00%) |
| occurrences (all) | 0 | 1 | 2 |
| GLAUCOMA | | | |
| subjects affected / exposed ^[66] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| SCLERITIS | | | |
| subjects affected / exposed ^[67] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| CATARACT NUCLEAR | | | |
| subjects affected / exposed ^[68] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| VITREOUS DEGENERATION | | | |
| subjects affected / exposed ^[69] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed ^[70] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 1 | 2 |
| CONSTIPATION | | | |
| subjects affected / exposed ^[71] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| DIARRHOEA | | | |
| subjects affected / exposed ^[72] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 3 / 10 (30.00%) |
| occurrences (all) | 0 | 0 | 3 |
| DRY MOUTH | | | |
| subjects affected / exposed ^[73] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 1 | 1 |
| DYSPEPSIA | | | |
| subjects affected / exposed ^[74] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| GASTROESOPHAGEAL REFLUX DISEASE | | | |
| subjects affected / exposed ^[75] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| STOMATITIS | | | |

| | | | |
|---|---------------------|---------------------|----------------------|
| subjects affected / exposed ^[76] occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| VOMITING subjects affected / exposed ^[77] occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Skin and subcutaneous tissue disorders NIGHT SWEATS subjects affected / exposed ^[78] occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| RASH subjects affected / exposed ^[79] occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 10 (10.00%) 4 |
| Renal and urinary disorders ACUTE KIDNEY INJURY subjects affected / exposed ^[80] occurrences (all) | 0 / 3 (0.00%) 0 | 2 / 21 (9.52%) 3 | 0 / 10 (0.00%) 0 |
| Endocrine disorders AUTOIMMUNE THYROIDITIS subjects affected / exposed ^[81] occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| HYPOTHYROIDISM subjects affected / exposed ^[82] occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed ^[83] occurrences (all) | 0 / 3 (0.00%) 0 | 2 / 21 (9.52%) 2 | 0 / 10 (0.00%) 0 |
| BACK PAIN subjects affected / exposed ^[84] occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| BONE PAIN subjects affected / exposed ^[85] occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 21 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| MUSCULOSKELETAL PAIN subjects affected / exposed ^[86] occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 10 (10.00%) 1 |

| | | | |
|---|----------------|----------------|-----------------|
| SACROILIITIS | | | |
| subjects affected / exposed ^[87] | 1 / 3 (33.33%) | 0 / 21 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| TENDONITIS | | | |
| subjects affected / exposed ^[88] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| BACTERAEMIA | | | |
| subjects affected / exposed ^[89] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 2 |
| BACTERIAL INFECTION | | | |
| subjects affected / exposed ^[90] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| BRONCHOPULMONARY ASPERGILLOSIS | | | |
| subjects affected / exposed ^[91] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| CONJUNCTIVITIS | | | |
| subjects affected / exposed ^[92] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 1 | 1 |
| CYTOMEGALOVIRUS INFECTION | | | |
| subjects affected / exposed ^[93] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| LARYNGITIS | | | |
| subjects affected / exposed ^[94] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed ^[95] | 1 / 3 (33.33%) | 0 / 21 (0.00%) | 2 / 10 (20.00%) |
| occurrences (all) | 2 | 0 | 2 |
| ORAL FUNGAL INFECTION | | | |
| subjects affected / exposed ^[96] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 2 |
| PELVIC ABSCESS | | | |
| subjects affected / exposed ^[97] | 1 / 3 (33.33%) | 0 / 21 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| PNEUMONIA | | | |

| | | | |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed ^[98] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 1 | 1 |
| RHINITIS | | | |
| subjects affected / exposed ^[99] | 1 / 3 (33.33%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 4 | 0 | 1 |
| SINUSITIS | | | |
| subjects affected / exposed ^[100] | 2 / 3 (66.67%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 2 | 0 | 1 |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed ^[101] | 0 / 3 (0.00%) | 3 / 21 (14.29%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 3 | 2 |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed ^[102] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 2 |
| VIRAL INFECTION | | | |
| subjects affected / exposed ^[103] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| VIRAL UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed ^[104] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| ACUTE SINUSITIS | | | |
| subjects affected / exposed ^[105] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| CONJUNCTIVITIS VIRAL | | | |
| subjects affected / exposed ^[106] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed ^[107] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 3 / 10 (30.00%) |
| occurrences (all) | 0 | 1 | 3 |
| FLUID RETENTION | | | |
| subjects affected / exposed ^[108] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| HYPERGLYCAEMIA | | | |

| | | | |
|--|---------------|----------------|-----------------|
| subjects affected / exposed ^[109] | 0 / 3 (0.00%) | 0 / 21 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| HYPOALBUMINAEMIA | | | |
| subjects affected / exposed ^[110] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 1 | 1 |
| HYPOKALAEMIA | | | |
| subjects affected / exposed ^[111] | 0 / 3 (0.00%) | 1 / 21 (4.76%) | 3 / 10 (30.00%) |
| occurrences (all) | 0 | 1 | 3 |

Notes:

[17] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[18] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[19] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[20] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[21] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[22] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[23] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[24] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[25] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[26] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[108] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[109] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[110] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[111] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 14 January 2016 | Version 2: The protocol has been revised to update the DLT window and to clarify inclusion/exclusion and stopping criteria. Additional minor changes have been made to improve clarity and consistency. |
| 28 June 2016 | Version 3: The inclusion criterion on contraception requirements for women of childbearing potential has been revised to include the duration of contraception for atezolizumab and polatuzumab vedotin. Enrollment rules into the dose escalation phase have been updated, for patients' safety considerations. A sequential enrollment instead of a parallel enrollment will be used for each of the two dosing groups, |
| 17 November 2016 | Version 4: "Immune-mediated" was revised to "immune-related" when referring to adverse events. Cut-off date for Atezolizumab was changed to 15 December 2016. The title has been revised. Study treatment has been modified to include Rituximab (R00452294) in combination with atezolizumab plus polatuzumab vedotin in patients with relapsed or refractory diffuse large B-cell lymphoma. |
| 04 May 2017 | Version 5: The protocol has been modified to prohibit use of the term "sudden death" on the Adverse Event eCRF, unless it is combined with the presumed cause of death. Language has been added to clarify that the Sponsor will review all protocol deviations, and clarification has been added that prospective requests to deviate from the protocol are not allowed. |
| 21 December 2017 | Version 6: Clinical Data) has been updated with the most recent efficacy and safety results from Study GO29383. Aligned the protocol with the current atezolizumab Investigator's Brochure, Version 10. A few exclusion criteria updated. |
| 01 May 2018 | Version 7: The study design and treatment schedule has been revised to reflect discontinuation of atezolizumab in patients still receiving study treatment. In addition, the post-induction (rituximab + atezolizumab consolidation) treatment phase has been removed from the treatment schedule (rituximab + atezolizumab + polatuzumab vedotin [R+Atezo+Pola] treatment group) of patients with RR DLBCL. |
| 07 November 2018 | Version 8: Lists of risks for atezolizumab-associated adverse events were revised to include nephritis. Regular Internal Monitoring Committee assessments stopped taking place as no new safety signals identified. Language was changed allowing patients still under treatment to enter the extension study. Medical Monitor information was updated. Survival follow-up period for assessment of new anti-lymphoma treatment re-added. PK sampling one year after last dose for polatuzumab vedotin was removed. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A safety signal was observed during the study in two patients in the R/R FL cohort. As a result, enrollment was permanently discontinued and atezolizumab was discontinued for all patients still receiving study treatment.

Notes: