# Clinical trial results:
# A Multicentric, Open-Label, Single Arm Study of Obinutuzumab Short Duration Infusion (SDI) in Patients with Previously Untreated Advanced Follicular Lymphoma

## Summary

| | |
|---|---|
| EudraCT number | 2018-003255-38 |
| Trial protocol | NL DE |
| Global end of trial date | |

### Results information

| | |
|---|---|
| Result version number | v2 |
| This version publication date | 05 September 2021 |
| First version publication date | 04 August 2021 |
| Version creation reason | • Correction of full data set<br>Updates to end points based on comments received from the NIH |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | MO40597 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03817853 |
| 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, global.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 | Interim |
| Date of interim/final analysis | 04 August 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 04 August 2020 |
| Global end of trial reached? | No |

Notes:

## General information about the trial

Main objective of the trial:

This open-label, single arm study evaluated the safety of obinutuzumab administered as a short duration infusion (SDI; target 90-minute infusion) during cycle 2 and from cycle 2 onwards in combination with chemotherapy in participants with previously untreated advanced follicular lymphoma (FL).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 26 February 2019 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 3 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Brazil: 19 |
| Country: Number of subjects enrolled | Japan: 27 |
| Country: Number of subjects enrolled | United States: 13 |
| Country: Number of subjects enrolled | Germany: 11 |
| Country: Number of subjects enrolled | Netherlands: 6 |
| Country: Number of subjects enrolled | Spain: 28 |
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Worldwide total number of subjects | 113 |
| EEA total number of subjects | 45 |

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) | 69 |
| From 65 to 84 years | 43 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at 35 sites across 7 countries.

### Pre-assignment

Screening details:

Of the all participants population (114 participants), one participant did not receive the study treatment, thus the safety-evaluable population included 113 participants.

### Period 1

| | |
|---|---|
| Period 1 title | Induction Phase |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | All Participants |

Arm description:

Participants were enrolled in an induction phase and received 6-8 cycles of obinutuzumab, combined with 6 or 8 cycles of standard chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone [CHOP - 21-day cycle) or bendamustine (28-day cycle), or cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone [CVP - 21-day cycle]). Participants received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. The investigator was free to choose the chemotherapy for each participant.

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

Dosage and administration details:

Obinutuzumab was administered as a 1000 mg IV infusion on Day 1, 8 and 15 during Cycle 1, and on Day 1 of subsequent cycles, for 6-8 cycles. Each cycle is 21 or 28 days long depending on the chemotherapy regimen allocated.

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

Dosage and administration details:

Bendamustine was administered on Days 1 and 2 for Cycles 1–6 at a dose of 90 mg/m2/day, for six 28-day cycles.

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

Dosage and administration details:

Cyclophosphamide 750 milligrams per square metre (mg/m^2), administered intravenously (IV) on Day 1 of each 21-day cycle, for six cycles for CHOP treatment or eight cycles for CVP treatment.

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

| | |
|---|---|
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Doxorubicin 50 mg/m^2 IV, administered on Day 1 of each 21-day cycle, for six cycles.

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

Dosage and administration details:

Prednisone 100 mg (or equivalent prednisolone or methylprednisolone), administered orally on Days 1-5 of each 21-day cycle, for six cycles for CHOP treatment or eight cycles for CVP treatment.

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

Dosage and administration details:

Vincristine 1.4 mg/m^2 (maximum 2 mg) IV, administered on Day 1 of each 21-day cycle, for six cycles for CHOP treatment or eight cycles for CVP treatment.

| **Number of subjects in period 1** | All Participants |
|---|---|
| Started | 113 |
| Completed | 62 |
| Not completed | 51 |
| Physician decision | 2 |
| Consent withdrawn by subject | 3 |
| Adverse Event | 5 |
| Progressive Disease | 4 |
| Other Continuing on Study | 34 |
| Various reasons | 3 |

## Period 2

| | |
|---|---|
| Period 2 title | Maintenance |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| **Arm title** | Maintenance |
|---|---|

Arm description:

Participants who achieved a partial response (PR) or complete response (CR) following the induction phase received obinutuzumab maintenance therapy. 1000 mg of obinutuzumab as single agent was administered as an SDI every 8 weeks (+ or - 10 days) for 2 years or until disease progression).

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

Dosage and administration details:

1000 mg of obinutuzumab was administered as an SDI every 8 weeks (+ or - 10 days) for 2 years or until disease progression).

| **Number of subjects in period 2[1]** | Maintenance |
|---|---|
| Started | 56 |
| Started Follow Up | 17 |
| Completed Follow-up | 11 |
| Completed | 0 |
| Not completed | 56 |
| Consent withdrawn by subject | 1 |
| Adverse Event | 1 |
| Death | 1 |
| Progressive Disease | 1 |
| Continuing on study | 52 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Some participants will have completed the treatment of a phase, but not yet had the first treatment of the next phase.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | All Participants |

Reporting group description:

Participants were enrolled in an induction phase and received 6-8 cycles of obinutuzumab, combined with 6 or 8 cycles of standard chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone [CHOP - 21-day cycle) or bendamustine (28-day cycle), or cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone [CVP - 21-day cycle]). Participants received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. The investigator was free to choose the chemotherapy for each participant.

| Reporting group values | All Participants | Total | |
|---|---|---|---|
| Number of subjects | 113 | 113 | |
| Age Categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 69 | 69 | |
| From 65-84 years | 43 | 43 | |
| 85 years and over | 1 | 1 | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 58.9 | | |
| standard deviation | ± 12.7 | - | |
| Sex: Female, Male<br>Units: Subjects | | | |
| Male | 57 | 57 | |
| Female | 56 | 56 | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 33 | 33 | |
| Not Hispanic or Latino | 80 | 80 | |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| Asian | 27 | 27 | |
| White | 82 | 82 | |
| Other | 2 | 2 | |
| Multiple | 2 | 2 | |

## End points

### End points reporting groups

| Reporting group title | All Participants |
|---|---|

Reporting group description:

Participants were enrolled in an induction phase and received 6-8 cycles of obinutuzumab, combined with 6 or 8 cycles of standard chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone [CHOP - 21-day cycle) or bendamustine (28-day cycle), or cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone [CVP - 21-day cycle]). Participants received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. The investigator was free to choose the chemotherapy for each participant.

| Reporting group title | Maintenance |
|---|---|

Reporting group description:

Participants who achieved a partial response (PR) or complete response (CR) following the induction phase received obinutuzumab maintenance therapy. 1000 mg of obinutuzumab as single agent was administered as an SDI every 8 weeks (+ or - 10 days) for 2 years or until disease progression).

| Subject analysis set title | Short duration infusion population |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

This population included all enrolled participants who did not experience a Grade 3 or 4 IRR during Cycle 1 (i.e. at any of the 3 Cycle 1 infusions) and received obinutuzumab as an SDI at Cycle 2.

| Subject analysis set title | Follow-up |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

Participants with stable disease (SD) or progressive disease (PD) as best response after induction therapy discontinued study treatment and underwent a safety follow-up visit at 3 months (90 days (+ or - 10 days)). All participants were followed up at 3 months (90 days (+ or - 10 days)) from the time of the last dose of study treatment.

### Primary: Percentage of Grade >=3 Infusion-Related Reactions (IRRs) During Cycle 2 in Patients Who Had Previously Received Obinutuzumab at the Standard Infusion Rate During Cycle 1 Without Experiencing a Grade 3 or 4 IRR

| End point title | Percentage of Grade >=3 Infusion-Related Reactions (IRRs) During Cycle 2 in Patients Who Had Previously Received Obinutuzumab at the Standard Infusion Rate During Cycle 1 Without Experiencing a Grade 3 or 4 IRR[1] |
|---|---|

End point description:

IRRs were defined as all adverse events (AEs) that occurred during or within 24 hours from the end of study treatment infusion and were judged as related to infusion of study treatment components by the investigator. The Short Duration Infusion (SDI) population included all enrolled particpants who did not experience a Grade 3 or 4 IRR during cycle 1 (i.e. at any of the three Cycle 1 infusions), received obinutuzumab given at the standard rate only during Cycle 1, and received obinutuzumab as an SDI at cycle 2.

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

End point timeframe:

Within 24 hours from the end of study treatment infusion of Day 1 in Cycle 2 (1 cycle: 21 or 28 days depending on the chemotherapy selected)

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 presented with a point estimate and a 95% confidence interval according to Clopper&Pearson

| End point values | Short duration infusion population | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 97 | | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 0 (0.00 to 3.73) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Adverse Events (AEs)

| End point title | Percentage of Participants With Adverse Events (AEs) |
|---|---|

End point description:

An AE was defined as any untoward medical occurrence in a clinical investigation participant who was administered a pharmaceutical product, regardless of causal attribution. An AE 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. Pre-existing conditions which worsened during the study, recurrence of an intermittent medical condition, deterioration in a laboratory value or other clinical test or were related to a protocol-mandated intervention were also considered AEs. Grading was completed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. The safety population included all participants who received at least one dose of obinutuzumab.

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

End point timeframe:

Baseline up to clinical cut off date (up to approximately 1.5 years)

| End point values | All Participants | Maintenance | Follow-up | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 113 | 56 | 17 | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 99.1 | 41.1 | 35.3 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of IRRs Regardless of Grade by Cycle

| End point title | Percentage of IRRs Regardless of Grade by Cycle |
|---|---|

End point description:

IRRs were defined as all adverse events (AEs) that occurred during or within 24 hours from the end of study treatment infusion and were judged as related to infusion of study treatment components by the investigator. The safety population included all participants who received at least one dose of obinutuzumab.

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

End point timeframe:

Within 24 hours from the end of study treatment infusion in all cycles, including maintenance ((1 cycle: 21 or 28 days depending on the chemotherapy selected); up to approximately 2.5 years)

| End point values | All Participants | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 113 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Cycle 1 Day 1 (n=113) | 49.6 | | | |
| Cycle 1 Day 2 (n=51) | 7.8 | | | |
| Cycle 1 Day 8 (n=112) | 4.5 | | | |
| Cycle 1 Day 15 (n=111) | 4.5 | | | |
| Cycle 2 (n=110) | 11.8 | | | |
| Cycle 3 (n=108) | 8.3 | | | |
| Cycle 4 (n=103) | 4.9 | | | |
| Cycle 5 (n=97) | 6.2 | | | |
| Cycle 6 (n=84) | 3.6 | | | |
| Cycle 7 (n=45) | 4.4 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to IRR From Infusion to Onset of the IRR During Cycle 2

| End point title | Time to IRR From Infusion to Onset of the IRR During Cycle 2 |
|---|---|

End point description:

Time to IRR (of any grade) in Cycle 2 was defined as the time from the start of infusion (i.e., start date/time of infusion of the first component of study treatment) in Cycle 2 to the onset of the IRR (of any grade) during Cycle 2. The SDI population included all enrolled particpants who did not experience a Grade 3 or 4 IRR during cycle 1 (i.e. at any of the three Cycle 1 infusions), received obinutuzumab given at the standard rate only during Cycle 1, and received obinutuzumab as an SDI at cycle 2. For this outcome measure, only one participant was analyzed. 9999999 = Standard deviation (SD) is not available because only 1 participant had the time to IRR recorded and the SD for one value is not defined.

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

End point timeframe:

From infusion to onset of IRR during Cycle 2 (1 cycle: 21 or 28 days depending on the chemotherapy selected)

| End point values | Short duration infusion population | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 97 | | | |
| Units: Hours | | | | |
| arithmetic mean (standard deviation) | 11.800 (± 9999999) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration (In Minutes) of Obinutuzumab Administration by Cycle

| End point title | Duration (In Minutes) of Obinutuzumab Administration by Cycle |
|---|---|

End point description:

The duration of obinutuzumab administration (in minutes) by cycle was defined as the difference between the end time and the start time of obinutuzumab administration. The safety population included all participants who received at least one dose of obinutuzumab.

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

End point timeframe:

All cycles including maintenance (1 cycle: 21 or 28 days depending on the chemotherapy selected; up to approximately 2.5 years)

| End point values | All Participants | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 113 | | | |
| Units: Minutes | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle(C) 1 Day(D) 1 (n=100) | 295.96 (± 147.87) | | | |
| C1D8 (n=107) | 215.97 (± 46.99) | | | |
| C1D15 (n=103) | 207.52 (± 35.85) | | | |
| C2 (n=104) | 101.48 (± 20.56) | | | |
| C3 (n=101) | 102.97 (± 65.58) | | | |
| C4 (n=97) | 98.33 (± 10.24) | | | |
| C5 (n=92) | 98.26 (± 17.59) | | | |
| C6 (n=83) | 99.49 (± 12.86) | | | |
| C7 (n=43) | 99.56 (± 14.68) | | | |
| C8 (n=39) | 94.54 (± 10.69) | | | |
| Maintenance Week 1 (n=54) | 101.48 (± 21.01) | | | |

| | | | | |
|---|---|---|---|---|
| Maintenance Week 9 (n=33) | 97.21 (± 11.13) | | | |
| Maintenance Week 17 (n=22) | 97.64 (± 7.40) | | | |
| Maintenance Week 25 (n=12) | 93.83 (± 3.16) | | | |
| Maintenance Week 33 (n=6) | 92.50 (± 2.74) | | | |
| Maintenance Week 41 (n=2) | 90.00 (± 0.00) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Type of Grade >=3 IRRs Associated with the obinutuzumab Administered as an SDI by Cycle

| End point title | Type of Grade >=3 IRRs Associated with the obinutuzumab Administered as an SDI by Cycle |
|---|---|

End point description:

The safety population included all participants who received at least one dose of obinutuzumab. Only 1 participant had a Grade >=3 IRR, with 3 symptoms in Cycle 5. Weight increased was a grade 1 symptom belonging to the grade 3 IRRs.

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

End point timeframe:

All cycles including maintenance (1 cycle: 21 or 28 days depending on the chemotherapy selected; up to approximately 2.5 years)

| **End point values** | All Participants | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 97 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Cycle (C) 5- Hypertension (n=1) | 33.3 | | | |
| C5 - Renal failure (n=1) | 33.3 | | | |
| C5 - Weight increased (n=1) | 33.3 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Grade >=3 IRRs Associated with the obinutuzumab Administered as an SDI by Cycle

| End point title | Duration of Grade >=3 IRRs Associated with the obinutuzumab Administered as an SDI by Cycle |
|---|---|

End point description:

The duration, in minutes, of IRRs during all cycles, where obinutuzumab was administered as an SDI. The safety population included all participants who received at least one dose of obinutuzumab. For this outcome measure, only one participant was analyzed. 9999999 = SD is not available because only 1 participant had the duration of IRR recorded and the SD for one value is not defined.

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

End point timeframe:

All cycles including maintenance (1 cycle: 21 or 28 days depending on the chemotherapy selected; up to approximately 2.5 years)

| **End point values** | All Participants | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1 | | | |
| Units: Minutes | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 5 | 165.0 (± 9999999) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Objective Response Rate (ORR) at the End of Induction (EOI) Therapy

| End point title | Objective Response Rate (ORR) at the End of Induction (EOI) Therapy |
|---|---|

End point description:

ORR at EOI therapy was defined as the percentage of particpants with either a CR, CR unconfirmed or PR at the EOI visit, as determined by the investigator and according to the guidelines used at the site. The safety population included all participants who received at least one dose of obinutuzumab.

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

End point timeframe:

Baseline up to end of induction therapy (up to approximately 6 months)

| **End point values** | All Participants | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 68 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Complete Response (n=49) | 72.1 | | | |
| Partial Response (n=13) | 19.1 | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to clinical cut off date (up to approximately 1.5 years)

Adverse event reporting additional description:

An AE was defined as any untoward medical occurrence in a clinical investigation participant who was administered a pharmaceutical product, regardless of causal attribution. Grading was completed according to the CTCAE, version 5.0.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Follow-up |

Reporting group description:

Participants with stable disease (SD) or progressive disease (PD) as best response after induction therapy discontinued study treatment and underwent a safety follow-up visit at 3 months (90 days (+ or - 10 days)). All participants were followed up at 3 months (90 days (+ or - 10 days)) from the time of the last dose of study treatment.

| | |
|---|---|
| Reporting group title | All Participants |

Reporting group description:

Participants were enrolled in an induction phase and received 6-8 cycles of obinutuzumab, combined with 6 or 8 cycles of standard chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone [CHOP - 21-day cycle) or bendamustine (28-day cycle), or cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone [CVP - 21-day cycle]). Participants received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. The investigator was free to choose the chemotherapy for each participant.

| | |
|---|---|
| Reporting group title | Maintenance |

Reporting group description:

Participants who achieved a partial response (PR) or complete response (CR) following the induction phase received obinutuzumab maintenance therapy. 1000 mg of obinutuzumab as single agent was administered as an SDI every 8 weeks (+ or - 10 days) for 2 years or until disease progression).

| Serious adverse events | Follow-up | All Participants | Maintenance |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 21 / 113 (18.58%) | 4 / 56 (7.14%) |
| number of deaths (all causes) | 1 | 2 | 1 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bowen's disease | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 113 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Double hit lymphoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 |
| Metastatic bronchial carcinoma | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 |
| Injury, poisoning and procedural complications | | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 113 (0.00%) | 0 / 56 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 arrest | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 113 (0.00%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cardiorenal syndrome | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 5 / 113 (4.42%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 113 (1.77%) | 0 / 56 (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 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 |
| Chills | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 |
| Malaise | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 |
| Gastrointestinal disorders | | | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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, thoracic and mediastinal disorders | | | |
| Pneumonia aspiration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 113 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 113 (0.00%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 |
| Herpes zoster disseminated | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 113 (0.00%) | 0 / 56 (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 |

| | | | |
|---|---|---|---|
| Influenza | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 | 0 / 17 (0.00%) | 3 / 113 (2.65%) | 2 / 56 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 113 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 113 (0.88%) | 0 / 56 (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 | | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 113 (0.00%) | 0 / 56 (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 |

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

| **Non-serious adverse events** | Follow-up | All Participants | Maintenance |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 111 / 113 (98.23%) | 15 / 56 (26.79%) |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 8 / 113 (7.08%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 9 | 0 |

| | | | |
|---|---|---|---|
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 10 / 113 (8.85%) | 3 / 56 (5.36%) |
| occurrences (all) | 0 | 10 | 3 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 17 / 113 (15.04%) | 1 / 56 (1.79%) |
| occurrences (all) | 0 | 18 | 1 |
| Malaise | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 12 / 113 (10.62%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 15 | 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 8 / 113 (7.08%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 8 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 14 / 113 (12.39%) | 1 / 56 (1.79%) |
| occurrences (all) | 0 | 16 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 7 / 113 (6.19%) | 2 / 56 (3.57%) |
| occurrences (all) | 0 | 7 | 2 |
| Hiccups | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 6 / 113 (5.31%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 8 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 17 / 113 (15.04%) | 1 / 56 (1.79%) |
| occurrences (all) | 1 | 17 | 1 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 11 / 113 (9.73%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 13 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 7 / 113 (6.19%) | 2 / 56 (3.57%) |
| occurrences (all) | 0 | 7 | 2 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---|---|---|
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 67 / 113 (59.29%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 126 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 7 / 113 (6.19%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 7 | 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 19 / 113 (16.81%) | 1 / 56 (1.79%) |
| occurrences (all) | 0 | 20 | 1 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 18 / 113 (15.93%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 19 | 0 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 9 / 113 (7.96%) | 1 / 56 (1.79%) |
| occurrences (all) | 0 | 13 | 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 20 / 113 (17.70%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 23 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 15 / 113 (13.27%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 28 | 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 22 / 113 (19.47%) | 1 / 56 (1.79%) |
| occurrences (all) | 0 | 33 | 1 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 63 / 113 (55.75%) | 2 / 56 (3.57%) |
| occurrences (all) | 1 | 104 | 3 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 17 / 113 (15.04%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 23 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 10 / 113 (8.85%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 12 | 0 |
| Abdominal pain upper | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 17 (0.00%) | 8 / 113 (7.08%) | 1 / 56 (1.79%) |
| occurrences (all) | 0 | 9 | 1 |
| Constipation | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 39 / 113 (34.51%) | 2 / 56 (3.57%) |
| occurrences (all) | 0 | 42 | 2 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 12 / 113 (10.62%) | 1 / 56 (1.79%) |
| occurrences (all) | 0 | 14 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 7 / 113 (6.19%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 7 | 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 45 / 113 (39.82%) | 4 / 56 (7.14%) |
| occurrences (all) | 0 | 60 | 4 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 13 / 113 (11.50%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 15 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 14 / 113 (12.39%) | 0 / 56 (0.00%) |
| occurrences (all) | 1 | 14 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 6 / 113 (5.31%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 7 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 14 / 113 (12.39%) | 1 / 56 (1.79%) |
| occurrences (all) | 0 | 17 | 1 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 11 / 113 (9.73%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 14 | 0 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 7 / 113 (6.19%) | 0 / 56 (0.00%) |
| occurrences (all) | 1 | 7 | 0 |
| Urinary tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 17 (5.88%) | 3 / 113 (2.65%) | 1 / 56 (1.79%) |
| occurrences (all) | 1 | 3 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 7 / 113 (6.19%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 7 | 0 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 6 / 113 (5.31%) | 0 / 56 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 17 October 2018 | This amendment was created to clarify that participants with prior radiotherapy for FL were excluded from the study; clarification that rescreening of participants was possible at any time; the guidance on the use of premedication before obinutuzumab infusion to reduce the risk of IRRs in participants was updated; additional guidance was provided on hepatitis B reactiviation management; clarification was added that the assessment of LVEF was only required for participants who received obinutuzumab with CHOP chemotherapy; assessments of B symptoms at the end-of-infusion, during maintenance, and at the end-of maintenance was not required and that it was only mandatory at screening; clarifications were added to state the assessments of weight at follow-up and response assessments at screening were not required; clarification that hepatitis B virus DNA PCR testing would be performed every 3-4 weeks for participants with prior HBV infection of who are carriers of HBV; the study title was updated to change "Gazyva" to "obinutuzumab" since the trade name differs depending on the country. |
| 06 December 2018 | This protocol was amended to state that the addition to the steroid premedication, participants would also receive premedication with an anti-histamine and antipyretic before the first cycle of obinutuzumab given as an SDI. |
| 12 September 2019 | The protocol was amended to allow participants who experienced a first Grade 3 IRR during SDI dosing to continue to receive SDI dosing during their current and next infusion. The statistical analysis plan was updated to include earlier reporting of the efficacy data at the EOI therapy. Clarification that the SDI population was used for the analysis of the secondary safety endpoint and the primary endpoint analysis. Exclusion criteria was updated to exclude participants with known HTLV-1 infection. Updates to the inclusion criteria allowed participants treated with corticosteroids for reasons other than chemotherapy and premedication to reduce the risk of IRRs as long as the dose didn't exceed 30 mg/day and to clarify that the frequency and period of DNA testing in participants with occult or prior HBV infection and with undetectable HBV DNA would be at least every 3 months for willing participants. The secondary safety endpoint was revised to clarify that it included IRRs linked to any study treatment. The following was clarified: participants who began a prohibited therapy would discontinue the study treatment and the end of induction or end of maintenance visit was performed before any new therapy was started, that 'study treatment' referred to obinutuzumab and chemotherapy during induction and obinutuzumab alone during maintenance, that Beta-2 microglobulin testing would be conducted at screening and EOI, the infusion rates at which obinutuzumab would be restarted following IRRs; premedication that would be given for IRRs, participants with a Grade 4 IRR during induction would discontinue study treatment (and not discontinue the study). This amendment also included additional guidance on when maintenance therapy began, managing suspected anaphylactic reactions, how often to assess vital signs, on tumor and bone marrow assessments and how participant and provided-reported outcome instruments would be administered, the timing of assessments and follow-up period. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported