



Clinical trial results:

Phase II multicenter clinical trial to evaluate the efficacy and safety of ibrutinib in combination with rituximab, gemcitabine, oxaliplatin, and dexamethasone followed by ibrutinib as maintenance treatment in patients with refractory or relapsed non-treatment-resistant diffuse large B-cell lymphoma no candidates to receive a ASCT

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2015-005390-21 |
| Trial protocol | ES |
| Global end of trial date | 19 January 2021 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 13 February 2022 |
| First version publication date | 13 February 2022 |

Trial information

Trial identification

| | |
|-----------------------|--------------------|
| Sponsor protocol code | IBDCL-GELTAMO-2015 |
|-----------------------|--------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02692248 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | GELTAMO |
| Sponsor organisation address | C. de Fortuny, 51, Madrid, Spain, 28010 |
| Public contact | Angel Cedillo, SecretarIa Cientifica GELTAMO, +34 913195780, sc@geltamo.com |
| Scientific contact | Angel Cedillo, SecretarIa Cientifica GELTAMO, +34 913195780, sc@geltamo.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 | 17 November 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 January 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of the combination (IR-GEMOX-dexa) as salvage treatment in patients with relapsing or refractory non-GCB-type DLBCL, in terms of overall response rate (ORR).

Protection of trial subjects:

Study drug administration should be permanently discontinued in the event of toxicity lasting longer than 21 days, unless the center investigators consider that the benefit of continuing ibrutinib treatment outweighs the risk.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 01 March 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Spain: 64 |
| Worldwide total number of subjects | 64 |
| EEA total number of subjects | 64 |

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) | 64 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Initially 72 patients from 15 different hospitals were registered, 8 patients could not be considered analyzable since they were screening failures.

Finally the analyzed population has 64 patients

Pre-assignment

Screening details:

Initially 72 patients from 15 different hospitals were registered, 8 patients could not be considered analyzable since they were screening failures.

Finally the analyzed population has 64 patients

Period 1

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

Arms

| | |
|-----------|--------------------|
| Arm title | Full data analysis |
|-----------|--------------------|

Arm description:

Subjects will receive Ibrutinib (Ib) with R-GEMOX-Dexa followed by Ib maintenance according to:

Induction phase:

Rituximab (R) 375 mg/m² IV day 1 during 4 cycles; Gemcitabine (Gem) 1000 mg/m² IV (30-minute infusion) on day 1 or 2, 4 cycles every 14 days; Oxaliplatin (Ox) 100 mg/m² on day 1 or 2 (after Gem adm.) 4 cycles every 14 days; Dex: 20 mg orally or IV on day 1 and orally on days 2-3, 4 cycles every 14 days; Ib 560 mg daily for 14 days.

Responding patients will receive 2 (if CR) or 4 (if PR) additional cycles every 14 days. Patients with SD and ABC profile will receive 4 additional cycles.

Maintenance phase: Responding patients will receive Ib 560 mg daily - Continuous cycles until a maximum of 2 years, disease progression or unacceptable toxicity.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Responsible person designated by the sponsor |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

Subjects will receive Ibrutinib (Ib) with R-GEMOX-Dexa followed by Ib maintenance according to:

Induction phase:

Rituximab (R) 375 mg/m² IV day 1 during 4 cycles; Gemcitabine (Gem) 1000 mg/m² IV (30-minute infusion) on day 1 or 2, 4 cycles every 14 days; Oxaliplatin (Ox) 100 mg/m² on day 1 or 2 (after Gem adm.) 4 cycles every 14 days; Dex: 20 mg orally or IV on day 1 and orally on days 2-3, 4 cycles every 14 days; Ib 560 mg daily for 14 days.

Responding patients will receive 2 (if CR) or 4 (if PR) additional cycles every 14 days. Patients with SD and ABC profile will receive 4 additional cycles.

Maintenance phase: Responding patients will receive Ib 560 mg daily - Continuous cycles until a maximum of 2 years, disease progression or unacceptable toxicity.

| Number of subjects in period 1 | Full data analysis |
|---------------------------------------|--------------------|
| Started | 64 |
| Completed | 64 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Full data analysis |
|-----------------------|--------------------|

Reporting group description: -

| Reporting group values | Full data analysis | Total | |
|--------------------------------------|--------------------|-------|--|
| Number of subjects | 64 | 64 | |
| Age categorical | | | |
| Units: Subjects | | | |
| >18 | 64 | 64 | |
| Age continuous | | | |
| Units: years | | | |
| median | 62.57 | | |
| standard deviation | ± 14.56 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 26 | 26 | |
| Male | 38 | 38 | |
| ECOG-PS | | | |
| Units: Subjects | | | |
| ECOG 0 | 23 | 23 | |
| ECOG 1 | 31 | 31 | |
| ECOG 2 | 10 | 10 | |
| Diagnosis | | | |
| Units: Subjects | | | |
| DLBCL without specification | 60 | 60 | |
| DLBCL rich in T lymphocytes | 3 | 3 | |
| Follicular lymphoma | 1 | 1 | |
| International prognostic index (IPI) | | | |
| Units: Subjects | | | |
| 0-1 | 6 | 6 | |
| 2-3 | 43 | 43 | |
| 4-5 | 13 | 13 | |
| Unk | 2 | 2 | |
| Disease stage at diagnosis | | | |
| Units: Subjects | | | |
| Stage I | 1 | 1 | |
| Stage II | 9 | 9 | |
| Stage III | 5 | 5 | |
| Stage IV | 46 | 46 | |
| Unk | 3 | 3 | |
| LDH levels | | | |
| Units: Subjects | | | |
| Normal | 20 | 20 | |
| Elevated | 42 | 42 | |
| Unk | 2 | 2 | |

| | | | |
|------------------------------------|--------|---|--|
| Previous lines of treatment | | | |
| Units: Previous lines of treatment | | | |
| median | 2 | | |
| full range (min-max) | 1 to 5 | - | |

Subject analysis sets

| | |
|----------------------------|--------------------|
| Subject analysis set title | Full data analysis |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects will receive Ibrutinib (Ib) with R-GEMOX-Dexa followed by Ib maintenance according to:

Induction phase:

Rituximab (R) 375 mg/m² IV day 1 during 4 cycles; Gemcitabine (Gem) 1000 mg/m² IV (30-minute infusion) on day 1 or 2, 4 cycles every 14 days; Oxaliplatin (Ox) 100 mg/m² on day 1 or 2 (after Gem adm.) 4 cycles every 14 days; Dex: 20 mg orally or IV on day 1 and orally on days 2-3, 4 cycles every 14 days; Ib 560 mg daily for 14 days.

Responding patients will receive 2 (if CR) or 4 (if PR) additional cycles every 14 days. Patients with SD and ABC profile will receive 4 additional cycles.

Maintenance phase: Responding patients will receive Ib 560 mg daily - Continuous cycles until a maximum of 2 years, disease progression or unacceptable toxicity.

| Reporting group values | Full data analysis | | |
|--------------------------------------|--------------------|--|--|
| Number of subjects | 64 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| >18 | 64 | | |
| Age continuous | | | |
| Units: years | | | |
| median | 62.57 | | |
| standard deviation | ± 14.56 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 26 | | |
| Male | 38 | | |
| ECOG-PS | | | |
| Units: Subjects | | | |
| ECOG 0 | 23 | | |
| ECOG 1 | 31 | | |
| ECOG 2 | 10 | | |
| Diagnosis | | | |
| Units: Subjects | | | |
| DLBCL without specification | 60 | | |
| DLBCL rich in T lymphocytes | 3 | | |
| Follicular lymphoma | 1 | | |
| International prognostic index (IPI) | | | |
| Units: Subjects | | | |
| 0-1 | 6 | | |
| 2-3 | 43 | | |
| 4-5 | 13 | | |
| Unk | 2 | | |
| Disease stage at diagnosis | | | |
| Units: Subjects | | | |
| Stage I | 1 | | |

| | | | |
|------------------------------------|--------|--|--|
| Stage II | 9 | | |
| Stage III | 5 | | |
| Stage IV | 46 | | |
| Unk | 3 | | |
| LDH levels | | | |
| Units: Subjects | | | |
| Normal | 20 | | |
| Elevated | 42 | | |
| Unk | 2 | | |
| Previous lines of treatment | | | |
| Units: Previous lines of treatment | | | |
| median | 2 | | |
| full range (min-max) | 1 to 5 | | |

End points

End points reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Full data analysis |
|-----------------------|--------------------|

Reporting group description:

Subjects will receive Ibrutinib (Ib) with R-GEMOX-Dexa followed by Ib maintenance according to:

Induction phase:

Rituximab (R) 375 mg/m² IV day 1 during 4 cycles; Gemcitabine (Gem) 1000 mg/m² IV (30-minute infusion) on day 1 or 2, 4 cycles every 14 days; Oxaliplatin (Ox) 100 mg/m² on day 1 or 2 (after Gem adm.) 4 cycles every 14 days; Dex: 20 mg orally or IV on day 1 and orally on days 2-3, 4 cycles every 14 days; Ib 560 mg daily for 14 days.

Responding patients will receive 2 (if CR) or 4 (if PR) additional cycles every 14 days. Patients with SD and ABC profile will receive 4 additional cycles.

Maintenance phase: Responding patients will receive Ib 560 mg daily - Continuous cycles until a maximum of 2 years, disease progression or unacceptable toxicity.

| | |
|----------------------------|--------------------|
| Subject analysis set title | Full data analysis |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects will receive Ibrutinib (Ib) with R-GEMOX-Dexa followed by Ib maintenance according to:

Induction phase:

Rituximab (R) 375 mg/m² IV day 1 during 4 cycles; Gemcitabine (Gem) 1000 mg/m² IV (30-minute infusion) on day 1 or 2, 4 cycles every 14 days; Oxaliplatin (Ox) 100 mg/m² on day 1 or 2 (after Gem adm.) 4 cycles every 14 days; Dex: 20 mg orally or IV on day 1 and orally on days 2-3, 4 cycles every 14 days; Ib 560 mg daily for 14 days.

Responding patients will receive 2 (if CR) or 4 (if PR) additional cycles every 14 days. Patients with SD and ABC profile will receive 4 additional cycles.

Maintenance phase: Responding patients will receive Ib 560 mg daily - Continuous cycles until a maximum of 2 years, disease progression or unacceptable toxicity.

Primary: Overall Response (OR) Rate (Complete Remission + Partial Response)

| | |
|-----------------|---|
| End point title | Overall Response (OR) Rate (Complete Remission + Partial Response) ^[1] |
|-----------------|---|

End point description:

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

End point timeframe:

Treatment responses will be evaluated 30 days after end of study treatment which can be occurred after 2 years and 4 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 is a single arm trial

| | | | | |
|---|--------------------|--|--|--|
| End point values | Full data analysis | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 64 | | | |
| Units: Percentage of patients presented CR+PR | 36 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: CR Rate During Induction and Maintenance Phases.

| | |
|---|--|
| End point title | CR Rate During Induction and Maintenance Phases. |
| End point description: Complete treatment responses evaluation during 21-35 days after initiation of 6 or 8 cycle of study treatment (depend of treatment responses obtained from cycle 4) and 30 days after end of study treatment which can be occurred after 2 years and 4 months | |
| End point type | Secondary |
| End point timeframe: 2 years | |

| | | | | |
|--|--------------------|--|--|--|
| End point values | Full data analysis | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 64 | | | |
| Units: percentage of the patients presented CR | 25 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Response duration

| | |
|--|-------------------|
| End point title | Response duration |
| End point description: Response duration defined as the time from the documentation of tumor response to disease progression or death, in the event of no documented recurrence, or start of a new anti - lymphoma treatment because of refractory or persistent disease. | |
| End point type | Secondary |
| End point timeframe: Response duration will be evaluated at any time during the study when tumor response is documented or after end of study treatment which can be occurred after 2 years and 4 months. | |

| | | | | |
|-------------------------------|--------------------|--|--|--|
| End point values | Full data analysis | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 64 | | | |
| Units: months | | | | |
| median (full range (min-max)) | 6.5 (0.0 to 38.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

| | |
|-----------------|---------------------------|
| End point title | Progression Free Survival |
|-----------------|---------------------------|

End point description:

Progression free survival defined as the time between start of treatment and the first documentation of recurrence, progression, or death in the event of no documented recurrence, or start of a new anti - lymphoma treatment, due a refractory or persistent disease

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

End point timeframe:

Progression free survival will be evaluated at any time during the study when first documentation of recurrence, progression, or death or after end of study treatment which can be occurred after 2 years and 4 months

| End point values | Full data analysis | | | |
|----------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 64 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.1 (2.2 to 6.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free Survival

| | |
|-----------------|---------------------|
| End point title | Event-free Survival |
|-----------------|---------------------|

End point description:

Event-free survival defined as the time between start of treatment and the first documentation of adverse events and serious adverse events graded according to NCI CTCAE v4.0

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

End point timeframe:

2 years

| End point values | Full data analysis | | | |
|----------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 63 ^[2] | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.03 (2.5 to 5.6) | | | |

Notes:

[2] - pts with new neoplasia, not required new therapeutic strategy and was not considered as an EFS event

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

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

End point description:

Overall survival is defined as the time between the start of treatment and death from any cause. Patients that are withdrawn from the trial or lost of follow-up, will be censored with the date of last contact. Patients who are still alive at the end of the study will be censored at that time.

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

End point timeframe:

2 years

| End point values | Full data analysis | | | |
|----------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 64 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 11.67 (7 to 16.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Tolerability of Ibrutinib in Combination Rituximab, Gemcitabine, Oxaliplatin and Dexamethasone

| | |
|-----------------|---|
| End point title | Safety and Tolerability of Ibrutinib in Combination Rituximab, Gemcitabine, Oxaliplatin and Dexamethasone |
|-----------------|---|

End point description:

Safety and tolerability will be assessed during any phase of study treatment and 30 days after end of study treatment which can be occurred after 2 years and 4 months and will be classified according to the Common Toxicity CNC.

Unit: Percentage of patients that present AE related to the treatment

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

End point timeframe:

2 years

| End point values | Full data analysis | | | |
|---|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 64 | | | |
| Units: Percentage of patients that present AE | 55 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Deberán registrarse en el CRD todos los acontecimientos adversos ocurridos durante la realización del ensayo clínico (en el caso de AAG desde la firma del consentimiento informado) y hasta 30 días después de la última dosis de la medicación del estudio.

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

Dictionary used

| | |
|--------------------|-----------|
| Dictionary name | NCI-CTCAE |
| Dictionary version | 4.03 |

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | All patients |
|-----------------------|--------------|

Reporting group description: -

| Serious adverse events | All patients | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 33 / 64 (51.56%) | | |
| number of deaths (all causes) | 46 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Renal tumor grade 4 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumor lysis syndrome - Grade 4 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| fracture grade 3 | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hip fracture grade 3 | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Patient took expired medication grade Unknown | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Subarachnoid hemorrhage - Grade 2 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Heart failure - Grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericardial tamponade - Grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericarditis - Grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Akathisia Grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|----------------|--|--|
| Confusion grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischemic attacks - Grade 2 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anemia - Grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia - Grade 2 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia - Grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hematoma - Grade 2 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Back pain grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| fatigue grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| fever grade 1 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| fever grade 2 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| fever grade 3 | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Flu like symptoms grade 2 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Clinical deterioration Grade 5 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malaise Grade 5 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea grade 2 | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea grade 3 | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysphagia grade 2 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting grade 2 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure grade 3 | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure grade 5 | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Partial Respiratory failure grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Herpes zoster grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| candidiasis grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung infection grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung infection grade 5 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock grade 5 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| upper respiratory infection grade 3 | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory infection grade 5 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection grade 3 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection grade 4 | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | All patients | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 63 / 64 (98.44%) | | |
| Nervous system disorders | | | |
| Paresthesia | | | |
| subjects affected / exposed | 8 / 64 (12.50%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Anemia | | | |
| subjects affected / exposed | 14 / 64 (21.88%) | | |
| occurrences (all) | 0 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 22 / 64 (34.38%) | | |
| occurrences (all) | 0 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 39 / 64 (60.94%) | | |
| occurrences (all) | 0 | | |

| | | | |
|--|-----------------------|--|--|
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 10 / 64 (15.63%) 0 | | |
| Hypomagnesemia subjects affected / exposed occurrences (all) | 4 / 64 (6.25%) 0 | | |
| General disorders and administration site conditions | | | |
| Nausea subjects affected / exposed occurrences (all) | 14 / 64 (21.88%) 0 | | |
| Fatigue subjects affected / exposed occurrences (all) | 7 / 64 (10.94%) 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 20 / 64 (31.25%) 0 | | |
| Vomiting subjects affected / exposed occurrences (all) | 6 / 64 (9.38%) 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 02 April 2016 | Modification of the title of the trial due to a typographical error. |
| 31 January 2017 | Modifications corresponding to the Patient Information and Informed Consent, as a result of the update of the safety aspects reflected in the new edition of the IB of IBRUTINIB and the IBRUTINIB data sheet. |
| 19 September 2020 | Change of the principal investigator of the study at a Hospital and safety changes included in the new IB of Ibrutinib that apply to HIP-CI. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported