

**Clinical trial results:**

A RANDOMIZED PHASE III STUDY USING A PET-DRIVEN STRATEGY AND COMPARING GA101 OR RITUXIMAB IN COMBINATION WITH A CHEMOTHERAPY DELIVERED EVERY 14 DAYS (ACVBP OR CHOP) IN DLBCL CD20+ LYMPHOMA UNTREATED PATIENTS FROM 18 TO 60 PRESENTING WITH 1 OR MORE ADVERSE PROGNOSTIC FACTORS OF THE AGE-ADJUSTED IPI

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2011-005851-15 |
| Trial protocol | BE |
| Global end of trial date | 31 December 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 15 December 2022 |
| First version publication date | 15 December 2022 |

Trial information**Trial identification**

| | |
|-----------------------|--------|
| Sponsor protocol code | GAINED |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01659099 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | LYSARC |
| Sponsor organisation address | CH LYON SUD BATIMENT 2D, PIERRE BENITE, France, 69495 |
| Public contact | Project Management, LYSARC, 33 472669333, gained@lysarc.org |
| Scientific contact | Coordinating investigator, Pr Steven Le Gouill, 33 240083271, gained@lysarc.org |

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 | 31 December 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 December 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate an improvement of the 2-year Event Free Survival (EFS) in DLBCL CD20+ patients aged from 18 to 60 years with 1 to 3 adverse prognostic factors of the aa-IPI treated with GA101 or Rituximab in combination with ACVBP14 or CHOP14 in a PET-driven strategy.

Protection of trial subjects:

DSMC

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 20 September 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Belgium: 40 |
| Country: Number of subjects enrolled | France: 630 |
| Worldwide total number of subjects | 670 |
| EEA total number of subjects | 670 |

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) | 670 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

From September 20, 2012, to July 30, 2015,
France
Belgium

Pre-assignment

Screening details:

Patients provided informed consent before any non-routine screening tests or evaluations were conducted. The inclusion and exclusion criteria were assessed during the screening period. Patients must have continued to meet all eligibility criteria on day 1 cycle 1 of induction treatment.

Period 1

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

Arms

| | |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Obinutuzumab |

Arm description:

Obinutuzumab + Chemo (CHOP or ACVP)

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

Dosage and administration details:

Standard use

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

Dosage and administration details:

Standard use

| | |
|------------------|-----------|
| Arm title | Rituximab |
|------------------|-----------|

Arm description:

Rituximab + Chemo (CHOP or ACVP)

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | CHOP |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

| | |
|--|-----------------|
| Dosage and administration details: | |
| Standard use | |
| Investigational medicinal product name | ACVBP |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Standard use | |

| Number of subjects in period 1 | Obinutuzumab | Rituximab |
|--------------------------------|--------------|-----------|
| Started | 336 | 334 |
| Completed | 312 | 312 |
| Not completed | 24 | 22 |
| Consent withdrawn by subject | - | 2 |
| Adverse event, non-fatal | 8 | 7 |
| Death | 2 | 1 |
| concurrent illness | 1 | 1 |
| Progression | 2 | 1 |
| Untreated | 4 | 3 |
| other | 5 | 2 |
| Protocol deviation | 2 | 5 |

| | |
|------------------------------|-------------------------|
| Period 2 | |
| Period 2 title | Consolidation |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

| | |
|------------------------------|--------------|
| Arms | |
| Are arms mutually exclusive? | Yes |
| Arm title | Obinutuzumab |

Arm description:

Obinutuzumab + MTX/VP/Ifosfamide/Arac/CHOP if PET 2 neg / PET 4 neg

MTX+BEAM + ASCT if PET 2 pos / PET 4 neg

Salvage therapy if PET 4 pos

| | |
|--|-------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | MTX/VP/Ifosfamide/Arac/CHOP/R |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:
standard use

| | |
|--|-----------------------------|
| Arm title | Rituximab |
| Arm description: Rituximab + MTX/VP/Ifosfamide/Arac/CHOP if PET 2 neg / PET 4 neg MTX+BEAM + ASCT if PET 2 pos / PET 4 neg Salvage therapy if PET 4 pos | |
| Arm type | Active comparator |
| Investigational medicinal product name | MTX/VP/Ifosfamide/Arac/CHOP |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:
standard use

| Number of subjects in period 2 | Obinutuzumab | Rituximab |
|---------------------------------------|--------------|-----------|
| Started | 312 | 312 |
| Completed | 227 | 197 |
| Not completed | 85 | 115 |
| Consent withdrawn by subject | - | 1 |
| missing PET | 20 | 23 |
| Adverse event, non-fatal | 15 | 16 |
| concurrent illness | 1 | - |
| PET4+ | 37 | 56 |
| Progression | - | 2 |
| other | 6 | 11 |
| Protocol deviation | 4 | 6 |
| Lack of efficacy | 2 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Obinutuzumab |
|-----------------------|--------------|

Reporting group description:

Obinutuzumab + Chemo (CHOP or ACVP)

| | |
|-----------------------|-----------|
| Reporting group title | Rituximab |
|-----------------------|-----------|

Reporting group description:

Rituximab + Chemo (CHOP or ACVP)

| Reporting group values | Obinutuzumab | Rituximab | Total |
|--|--------------|-----------|-------|
| Number of subjects | 336 | 334 | 670 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 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) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 49 | 48 | |
| full range (min-max) | 19 to 60 | 18 to 61 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 133 | 164 | 297 |
| Male | 203 | 170 | 373 |

Subject analysis sets

| | |
|----------------------------|-----|
| Subject analysis set title | ITT |
|----------------------------|-----|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

The ITT set included 670 patients, 336 in the GA101 arm and 334 in the Rituximab arm.

| Reporting group values | ITT | | |
|--|-----|--|--|
| Number of subjects | 670 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |

| | | | |
|---|----------------|--|--|
| Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years median full range (min-max) | 48 18 to 61 | | |
| Gender categorical Units: Subjects | | | |
| Female Male | 297 373 | | |

End points

End points reporting groups

| | |
|---|--------------------|
| Reporting group title | Obinutuzumab |
| Reporting group description: Obinutuzumab + Chemo (CHOP or ACVP) | |
| Reporting group title | Rituximab |
| Reporting group description: Rituximab + Chemo (CHOP or ACVP) | |
| Reporting group title | Obinutuzumab |
| Reporting group description: Obinutuzumab + MTX/VP/Ifosfamide/Arac/CHOP if PET 2 neg / PET 4 neg MTX+BEAM + ASCT if PET 2 pos / PET 4 neg Salvage therapy if PET 4 pos | |
| Reporting group title | Rituximab |
| Reporting group description: Rituximab + MTX/VP/Ifosfamide/Arac/CHOP if PET 2 neg / PET 4 neg MTX+BEAM + ASCT if PET 2 pos / PET 4 neg Salvage therapy if PET 4 pos | |
| Subject analysis set title | ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT set included 670 patients, 336 in the GA101 arm and 334 in the Rituximab arm. | |

Primary: EFS

| | |
|---|---------|
| End point title | EFS |
| End point description: Progression, Death, PET positivity after central review after 2 and/or 4 cycles were considered as an event | |
| End point type | Primary |
| End point timeframe: 2y -EFS | |

| End point values | Obinutuzumab | Rituximab | | |
|---|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 227 | 197 | | |
| Units: percent of patient with no event | | | | |
| number (confidence interval 95%) | 59.8 (54.3 to 64.8) | 56.6 (51.1 to 61.8) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------------|
| Statistical analysis title | Comparison Obinutuzumab vs Rituximab |
| Comparison groups | Obinutuzumab v Rituximab |

| | |
|---|------------------------|
| Number of subjects included in analysis | 424 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.123 ^[1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.1 |
| Variability estimate | Standard deviation |

Notes:

[1] - Stratified

Secondary: Early metabolic response rate - 2 cycles

| | |
|------------------------|--|
| End point title | Early metabolic response rate - 2 cycles |
| End point description: | |
| Central review | |
| End point type | Secondary |
| End point timeframe: | |
| 2 cycles | |

| End point values | Obinutuzumab | Rituximab | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 227 | 197 | | |
| Units: percent of negative PET-2 | | | | |
| number (not applicable) | 73.5 | 68.2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response rate Cheson 2007

| | |
|-------------------------------|-----------------------------------|
| End point title | Overall Response rate Cheson 2007 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 4 cycles and end of treatment | |

| End point values | Obinutuzumab | Rituximab | Obinutuzumab | Rituximab |
|----------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 312 | 312 | 227 | 197 |
| Units: percent of CR+PR | | | | |
| number (confidence interval 95%) | 90.1 (86.2 to 93.1) | 84.2 (79.7 to 88.1) | 86.2 (81.9 to 89.8) | 85.3 (80.9 to 89.0) |

Statistical analyses

| Statistical analysis title | Comparison of ORR - 4 cycles |
|---|------------------------------|
| Comparison groups | Obinutuzumab v Rituximab |
| Number of subjects included in analysis | 624 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | = 0.018 ^[3] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[2] - Stratified on AA-IPI and chemotherapy

[3] - 4 cycles

| Statistical analysis title | Comparison of ORR - End of treatment |
|---|--------------------------------------|
| Comparison groups | Obinutuzumab v Rituximab |
| Number of subjects included in analysis | 424 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[4] |
| P-value | = 0.836 |
| Method | Cochran-Mantel-Haenszel |

Notes:

[4] - Stratified on AA-IPI and chemotherapy

Secondary: Overall Response rate Cheson 1999

| End point title | Overall Response rate Cheson 1999 |
|-------------------------------|-----------------------------------|
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 4 cycles and end of treatment | |

| End point values | Obinutuzumab | Rituximab | Obinutuzumab | Rituximab |
|----------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 312 | 312 | 227 | 197 |
| Units: Percent of PR+CR | | | | |
| number (confidence interval 95%) | 73.4 (68.1 to 78.2) | 71.4 (66.0 to 76.3) | 80.6 (75.8 to 84.8) | 77.1 (72.1 to 81.6) |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | Comparison ORR - 4 cycles |
| Comparison groups | Obinutuzumab v Rituximab |
| Number of subjects included in analysis | 624 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.551 ^[5] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[5] - Stratified on AA-IPI and chemotherapy

| | |
|---|-----------------------------------|
| Statistical analysis title | Comparison ORR - End of treatment |
| Comparison groups | Obinutuzumab v Rituximab |
| Number of subjects included in analysis | 424 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.368 ^[6] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[6] - Stratified on AA-IPI and chemotherapy

Secondary: Duration of response

| | |
|------------------------|----------------------|
| End point title | Duration of response |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 2 years | |

| | | | | |
|----------------------------------|---------------------|---------------------|--|--|
| End point values | Obinutuzumab | Rituximab | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 227 | 197 | | |
| Units: percent of non event | | | | |
| number (confidence interval 95%) | 87.4 (83.1 to 90.7) | 86.8 (82.3 to 90.2) | | |

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Comparison |
| Comparison groups | Rituximab v Obinutuzumab |
| Number of subjects included in analysis | 424 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.984 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.652 |
| upper limit | 1.484 |
| Variability estimate | Standard deviation |

Secondary: Progression-free survival

| | |
|------------------------|---------------------------|
| End point title | Progression-free survival |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 2 years | |

| | | | | |
|----------------------------------|---------------------|---------------------|--|--|
| End point values | Obinutuzumab | Rituximab | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 227 | 197 | | |
| Units: Percent | | | | |
| number (confidence interval 95%) | 83.2 (78.7 to 86.8) | 83.0 (78.5 to 86.7) | | |

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Comparison of PFS |
| Comparison groups | Obinutuzumab v Rituximab |
| Number of subjects included in analysis | 424 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.028 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.735 |
| upper limit | 1.436 |

| | |
|----------------------|--------------------|
| Variability estimate | Standard deviation |
|----------------------|--------------------|

Secondary: Overall survival

| | |
|------------------------|------------------|
| End point title | Overall survival |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 2 years | |

| End point values | Obinutuzumab | Rituximab | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 227 | 197 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 90.7 (87.0 to 93.4) | 91.8 (88.1 to 94.3) | | |

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Comparison of OS |
| Comparison groups | Rituximab v Obinutuzumab |
| Number of subjects included in analysis | 424 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.959 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 1.507 |
| Variability estimate | Standard deviation |

Secondary: Early metabolic response rate - 4 cycles

| | |
|------------------------|--|
| End point title | Early metabolic response rate - 4 cycles |
| End point description: | |
| Central review | |
| End point type | Secondary |
| End point timeframe: | |
| 4 cycles | |

| End point values | Obinutuzumab | Rituximab | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 227 | 197 | | |
| Units: percent of negative PET-4 | | | | |
| number (not applicable) | 87.5 | 80.6 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

28 days after end of treatment

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Obinutuzumab |
|-----------------------|--------------|

Reporting group description: -

| | |
|-----------------------|-----------|
| Reporting group title | Rituximab |
|-----------------------|-----------|

Reporting group description: -

| Serious adverse events | Obinutuzumab | Rituximab | |
|--|--------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 142 / 336 (42.26%) | 223 / 331 (67.37%) | |
| number of deaths (all causes) | 34 | 36 | |
| number of deaths resulting from adverse events | 8 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | | | |
| subjects affected / exposed | 3 / 336 (0.89%) | 6 / 331 (1.81%) | |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 6 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | |
| Vascular disorders VASCULAR DISORDERS | | | |
| subjects affected / exposed | 2 / 336 (0.60%) | 6 / 331 (1.81%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures SURGICAL AND MEDICAL PROCEDURES | | | |
| subjects affected / exposed | 1 / 336 (0.30%) | 0 / 331 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |

| | | | |
|--|------------------|------------------|--|
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| subjects affected / exposed | 24 / 336 (7.14%) | 25 / 331 (7.55%) | |
| occurrences causally related to treatment / all | 25 / 33 | 25 / 31 | |
| deaths causally related to treatment / all | 2 / 2 | 0 / 0 | |
| Immune system disorders IMMUNE SYSTEM DISORDERS | | | |
| subjects affected / exposed | 1 / 336 (0.30%) | 1 / 331 (0.30%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| subjects affected / exposed | 16 / 336 (4.76%) | 15 / 331 (4.53%) | |
| occurrences causally related to treatment / all | 10 / 16 | 13 / 19 | |
| deaths causally related to treatment / all | 2 / 2 | 0 / 1 | |
| Psychiatric disorders PSYCHIATRIC DISORDERS | | | |
| subjects affected / exposed | 1 / 336 (0.30%) | 0 / 331 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations INVESTIGATIONS | | | |
| subjects affected / exposed | 2 / 336 (0.60%) | 3 / 331 (0.91%) | |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | |
| subjects affected / exposed | 22 / 336 (6.55%) | 9 / 331 (2.72%) | |
| occurrences causally related to treatment / all | 6 / 22 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders CARDIAC DISORDERS | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 5 / 336 (1.49%) | 5 / 331 (1.51%) | |
| occurrences causally related to treatment / all | 1 / 5 | 4 / 6 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Nervous system disorders | | | |
| NERVOUS SYSTEM DISORDERS | | | |
| subjects affected / exposed | 4 / 336 (1.19%) | 13 / 331 (3.93%) | |
| occurrences causally related to treatment / all | 1 / 4 | 3 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Blood and lymphatic system disorders | | | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| subjects affected / exposed | 16 / 336 (4.76%) | 9 / 331 (2.72%) | |
| occurrences causally related to treatment / all | 17 / 18 | 12 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| GASTROINTESTINAL DISORDERS | | | |
| subjects affected / exposed | 25 / 336 (7.44%) | 22 / 331 (6.65%) | |
| occurrences causally related to treatment / all | 20 / 30 | 26 / 31 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| HEPATOBIILIARY DISORDERS | | | |
| subjects affected / exposed | 2 / 336 (0.60%) | 2 / 331 (0.60%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| subjects affected / exposed | 5 / 336 (1.49%) | 2 / 331 (0.60%) | |
| occurrences causally related to treatment / all | 5 / 5 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| RENAL AND URINARY DISORDERS | | | |
| subjects affected / exposed | 11 / 336 (3.27%) | 8 / 331 (2.42%) | |
| occurrences causally related to treatment / all | 3 / 12 | 3 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |

| | | | |
|---|-------------------|-------------------|--|
| ENDOCRINE DISORDERS | | | |
| subjects affected / exposed | 1 / 336 (0.30%) | 0 / 331 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| subjects affected / exposed | 3 / 336 (0.89%) | 2 / 331 (0.60%) | |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| INFECTIOUS AND INFESTATIONS | | | |
| subjects affected / exposed | 61 / 336 (18.15%) | 36 / 331 (10.88%) | |
| occurrences causally related to treatment / all | 77 / 86 | 37 / 46 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| METABOLISM AND NUTRITION DISORDERS | | | |
| subjects affected / exposed | 6 / 336 (1.79%) | 7 / 331 (2.11%) | |
| occurrences causally related to treatment / all | 4 / 6 | 4 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Obinutuzumab | Rituximab | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 325 / 336 (96.73%) | 307 / 331 (92.75%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | | | |
| subjects affected / exposed | 3 / 336 (0.89%) | 7 / 331 (2.11%) | |
| occurrences (all) | 3 | 7 | |
| Vascular disorders | | | |
| VASCULAR DISORDERS | | | |
| subjects affected / exposed | 10 / 336 (2.98%) | 10 / 331 (3.02%) | |
| occurrences (all) | 11 | 11 | |
| Surgical and medical procedures | | | |

| | | | |
|---|---------------------------------------|---------------------------------------|--|
| <p>SURGICAL AND MEDICAL PROCEDURES</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 336 (0.30%)</p> <p>1</p> | <p>0 / 331 (0.00%)</p> <p>0</p> | |
| <p>General disorders and administration site conditions</p> <p>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>9 / 336 (2.68%)</p> <p>10</p> | <p>10 / 331 (3.02%)</p> <p>10</p> | |
| <p>Immune system disorders</p> <p>IMMUNE SYSTEM DISORDERS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 336 (0.89%)</p> <p>3</p> | <p>2 / 331 (0.60%)</p> <p>2</p> | |
| <p>Reproductive system and breast disorders</p> <p>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 336 (0.30%)</p> <p>1</p> | <p>0 / 331 (0.00%)</p> <p>0</p> | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>22 / 336 (6.55%)</p> <p>23</p> | <p>27 / 331 (8.16%)</p> <p>39</p> | |
| <p>Psychiatric disorders</p> <p>PSYCHIATRIC DISORDERS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 336 (0.60%)</p> <p>7</p> | <p>3 / 331 (0.91%)</p> <p>3</p> | |
| <p>Investigations</p> <p>INVESTIGATIONS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>118 / 336 (35.12%)</p> <p>1365</p> | <p>124 / 331 (37.46%)</p> <p>1176</p> | |
| <p>Injury, poisoning and procedural complications</p> <p>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>67 / 336 (19.94%)</p> <p>69</p> | <p>26 / 331 (7.85%)</p> <p>29</p> | |
| <p>Cardiac disorders</p> <p>CARDIAC DISORDERS</p> | | | |

| | | | |
|---|----------------------------|----------------------------|--|
| subjects affected / exposed occurrences (all) | 7 / 336 (2.08%) 7 | 8 / 331 (2.42%) 11 | |
| Nervous system disorders NERVOUS SYSTEM DISORDERS subjects affected / exposed occurrences (all) | 21 / 336 (6.25%) 25 | 34 / 331 (10.27%) 48 | |
| Blood and lymphatic system disorders BLOOD AND LYMPHATIC SYSTEM DISORDERS subjects affected / exposed occurrences (all) | 303 / 336 (90.18%) 2746 | 291 / 331 (87.92%) 2445 | |
| Ear and labyrinth disorders EAR AND LABYRINTH DISORDERS subjects affected / exposed occurrences (all) | 1 / 336 (0.30%) 1 | 2 / 331 (0.60%) 3 | |
| Eye disorders EYE DISORDERS subjects affected / exposed occurrences (all) | 2 / 336 (0.60%) 2 | 1 / 331 (0.30%) 1 | |
| Gastrointestinal disorders GASTROINTESTINAL DISORDERS subjects affected / exposed occurrences (all) | 54 / 336 (16.07%) 100 | 48 / 331 (14.50%) 90 | |
| Hepatobiliary disorders HEPATOBIILIARY DISORDERS subjects affected / exposed occurrences (all) | 6 / 336 (1.79%) 7 | 5 / 331 (1.51%) 5 | |
| Skin and subcutaneous tissue disorders SKIN AND SUBCUTANEOUS TISSUE DISORDERS subjects affected / exposed occurrences (all) | 13 / 336 (3.87%) 13 | 8 / 331 (2.42%) 11 | |
| Renal and urinary disorders RENAL AND URINARY DISORDERS subjects affected / exposed occurrences (all) | 13 / 336 (3.87%) 15 | 9 / 331 (2.72%) 9 | |
| Endocrine disorders ENDOCRINE DISORDERS | | | |

| | | | |
|---|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 336 (0.30%) 1 | 0 / 331 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS subjects affected / exposed occurrences (all) | 8 / 336 (2.38%) 17 | 7 / 331 (2.11%) 11 | |
| Infections and infestations INFECTIOUS AND INFESTATIONS subjects affected / exposed occurrences (all) | 122 / 336 (36.31%) 196 | 118 / 331 (35.65%) 194 | |
| Metabolism and nutrition disorders METABOLISM AND NUTRITION DISORDERS subjects affected / exposed occurrences (all) | 30 / 336 (8.93%) 96 | 30 / 331 (9.06%) 78 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 11 June 2012 | Request for modifications from the ANSM of the initial protocol before the start of the study (the main modification was to precise the principal objective paragraph). |
| 10 August 2012 | <ul style="list-style-type: none">• "GELARC" replaced by "LYSARC"; "GELA" replaced by "LYSA" reflecting change to names of these organizations;• Suppression of certain evaluations and extension of the deadline for carrying out certain evaluations: vital signs before day 1 of each cycle and each evaluation, and complete blood cells count at Day 7 and 10 of each cycle• Addition of a new rule for SAE reporting: SAE linked to scheduled hospitalizations before patient randomization into the study should not be reported• Addition of a jugal epithelial cells sample for genomic study |
| 30 October 2012 | <ul style="list-style-type: none">• This amendment follows the letter from the ANSM dated October 17, 2012, concerning a case of progressive multifocal leukoencephalopathy (PML) reported in a patient who was treated with GA101 (GA101).• Patients with a history of PML will not be included in the study. The exclusion criterion "Prior history of Progressive Multifocal Leukoencephalopathy (PML)" is added.• A neurological examination must be carried out during each clinical examination, during the treatment phase as well as during the follow-up phase, in order to detect any neurological signs suggestive of potential PML.• Information on what to do in case of suspected PML: symptoms, diagnosis, what to do with the administration of anti CD20. In the event of symptoms suggestive of PML, investigations must be carried out: consultation with a neurologist, brain MRI, search for the JC virus in the cerebrospinal fluid, etc. Treatment with Rituximab or GA101 should be suspended during investigations, and definitively stopped if the diagnosis of PML is confirmed. |
| 12 December 2012 | Change of tubes used for biological studies. Analysis of samples collected for the first patients included revealed that the stability of blood cells in EDTA tubes was not compatible with the achievement of standardized NFP. It was decided to keep the number of tubes taken per patient, i.e. 4 tubes, but to distribute these tubes as follows: <ul style="list-style-type: none">- 2 EDTA tubes for genetic study- 2 heparin tubes for standardized NFP. |

| | |
|------------------|---|
| 17 June 2013 | Following the shortage of vindesine, possibility of replacing vindesine by vincristine for patients treated with ACVBP chemotherapy. In this study, the centers use CHOP or ACVBP as chemotherapy, according to their habits. This choice is valid for all patients in the same center and cannot be modified, the randomization being stratified on the choice of chemotherapy. Vindesine, a component of ACVBP, was out of stock worldwide (laboratory release dated June 7, 2013). This substitution should only take place in the event of a complete shortage of the stock of vindesine (dosage: D1 and D5 vincristine 0.7 mg / m ² without exceeding 1 mg total dose by injection, which makes a total dose of 1.4mg / m ² per cycle of ACVBP without exceeding 2 mg total dose). |
| 28 July 2014 | <ul style="list-style-type: none"> • Recommendations have been put in place to alert investigators on the increased toxicity of GA101 and the potential risks of severe infection: contraception until 18 months after last dose of GA101 instead of 12 months, changes in management of hematological toxicities, GA101 dose adjustments. • Addition and modification of blood and bone marrow samples for further biological analyzes. |
| 10 February 2015 | Following the announcement by the ANSM, on November 24, 2014, of the global shortage of BCNU (Carmustine), a drug forming part of the BEAM multidrug therapy (Carmustine, Etoposide, Cytarabine, Melphalan), proposal for 2 alternative conditioning regimes: <ul style="list-style-type: none"> - Benda-EAM polychemotherapy (Bendamustine, Etoposide, Cytarabine, Melphalan) - BAM polychemotherapy (Busulfan, Cytarabine, Melphalan) |
| 24 November 2015 | Modification of the schedule of intermediate and final analyzes. Intermediate analysis n°3 after treatment phase of all patients and final analysis performed after the onset of 345 events |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33211799>