2. SYNOPSIS

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Obinutuzumab (GA101)		
Name of Active Ingredient: Obinutuzumab (GA101)		

Title of Study:

A randomized Phase III study using a PET-driven strategy and comparing GA101 versus rituximab in combination with a chemotherapy delivered every 14 days (ACVBP or CHOP) in DLBCL CD20+ lymphoma untreated patients from 18 to 60 years presenting with 1 or more adverse prognostic factors of the age-adjusted IPI.

Coordinating Investigator: Pr. Steven Le Gouill, Service d'Hématologie, CHU de Nantes – Hôtel Dieu, Nantes, France.

Co-coordinating Investigator: Dr. Olivier Casasnovas, Service d'Hématologie, CHU de Dijon, Dijon, France.

Study site(s) and countries:

99 actives study centers from France and Belgium.

Publications (reference):

Le Gouill S, Ghesquières H, Oberic L, Morschhauser F, Tilly H, Ribrag V, Lamy T, Thieblemont C, Maisonneuve H, Gressin R, Bouhabdallah K, Haioun C, Damaj G, Fornecker L, Bouhabdallah R, Feugier P, Sibon D, Cartron G, Bonnet C, André M, Chartier L, Ruminy P, Kraeber-Bodéré F, Bodet-Milin C, Berriolo-Riedinger A, Brière J, Jais JP, Molina TJ, Itti E, Casasnovas RO. Obinutuzumab vs rituximab for advanced DLBCL: a PET-guided and randomized phase 3 study by LYSA. Blood. 2021 Apr 29;137(17):2307-2320. [doi: 10.1182/blood.2020008750. PMID: 33211799].

Studied period (years): Date first subject first visit: 20 Sep 2012 Date last subject completed: 30 Jul 2015 Data cutoff date: 31 Dec 2017	**Phase of development:** 3

Trial registry number(s):

ClinicalTrials.gov identifier: NCT01659099

EudraCT number: 2011-005851-15

Objectives:

Primary: To demonstrate an improvement in Event Free Survival (EFS) at 2-years in patients with previously untreated CD20+ DLBCL patients aged 18 to 60 years with adverse prognostic factors (aa-IPI 1-3) treated with GA101 plus chemotherapy compared with Rituximab plus chemotherapy in a PET-driven strategy. Events for EFS were defined as PET positivity according to ΔSUVmax criteria after 2 or 4 induction cycles as defined by RAC (Response Assessment Committee based on central PET review), progression or relapse according to Cheson 2007, modification of planned treatment out of progression (including radiotherapy) or death of any cause.

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Secondary: To evaluate:

- Early metabolic response rate according to PET after 2 and 4 cycles
- Overall Response Rate and Best Overall Response after 4 cycles and at end of treatment according to Cheson 2007 (CR and PR) criteria based both an RAC assessment for PET 4 and investigator assessment for EoT PET
- Overall Response rate and Best Overall Response after 4 cycles and at end of treatment according to Cheson 1999 (CR, CRu and PR) criteria, based on investigator assessment.
- Safety of the two antibodies (Rituximab vs GA101) and of the two chemotherapy regimen in the whole population and in the two arms of treatment (R-ACVBP14 vs GA101-ACVBP14 and R-CHOP14 vs GA101-CHOP14)
- Duration of response, progression-free survival and overall survival in the whole population, in the two inductive arms (R-Chemo14 vs GA101-Chemo14)

Methodology:

This study was a multicenter, randomized phase III trial.

Patients were recruited over 3 years and followed until 3 years after the last patient completed study treatment. The phases of this study included:

- Induction treatment phase
- Consolidation treatment phase
- Follow-up phase

Transplant-eligible patients (18-60yrs) with untreated aged-adjusted international prognostic index (aa-IPI) ≥1 DLBCL were randomized (1:1) between GA101 (1g iv) or Rituximab (375mg/m2 iv). Patients were stratified by aa-IPI (1 vs 2-3) and chemotherapy regimen (ACVBP or CHOP).

Consolidation treatment was determined according to response assessed by centrally reviewed interim semi-quantitative PET. Responders after cycle 2 and 4 (PET2-/PET4-) received planned immunochemotherapy consolidation. Responders only after cycle 4 (PET2+/4-) received high-dose methotrexate plus autologous hematopoietic stem-cell transplantation.

All subjects were to be followed in the Follow-up Phase for PFS and OS with clinic visits every 6 months for at least 3 years from the last dose of study drug (for any patient).

Number of subjects (planned, enrolled, and analyzed):

Planned: 670 subjects (335 by treatment arm)
Enrolled: 670 subjects
Analyzed: 227 and 197 patients with complete planned consolidation respectively in arm GA101 and in arm Rituximab.

Diagnosis and main criteria for inclusion:

Eligible patients were 18 to 60 years old with newly diagnosed untreated histologically proven CD20+ DLBCL (2008 WHO classification), aaIPI≥1, at least one hypermetabolic lesion at baseline PET,

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eligibility for ASCT and had a life expectancy of ≥3 months. Patients not previously diagnosed with indolent lymphoma and presenting a DLBCL with small cell infiltration in bone marrow or lymph node at diagnosis were also eligible. Patients were required to have normal liver, renal and hematological functions unless abnormalities were related to DLBCL. Patients with altered cardiac function or uncontrolled diabetes mellitus interfering with normal application of protocol treatment were not eligible for inclusion. Patients presenting a central nervous system involvement at diagnosis were excluded.

Test product, dose, and mode of administration:

Except GA101, all drugs composing the regimens of the study were registered and were available at the hospital pharmacy. They were to be used according to summary of product characteristics.

GA101 was provided by F. Hoffmann-La Roche Ltd, Basel – Switzerland.

Reconstituted GA101 drug product intended for IV infusion is prepared by dilution of the drug product into an infusion bag containing 0.9% sodium chloride, to the final drug concentration of 4 mg/mL.

Duration of treatment:

The duration of the treatment period was from 16 to 24 weeks for 8 cycles to 12 cycles of chemotherapy.

Criteria for evaluation:

Responses during induction were assessed by PET and use of Cheson 2007 criteria. All eligible patients had a baseline PET scan (PET0). PET2 was scheduled 2 weeks after the second cycle and PET4 was scheduled 2 weeks after completion of induction chemotherapy (four cycles). Interpretations of PET2 and PET4 were based on the ΔSUVmax method, and all PET images were centrally reviewed by three expert reviewers. The Deauville 5-point scale, with grades 1,2,3 classified as negative and grades 4,5 classified as positive, was used for patients whose PET0 SUVmax was <10, or interim with SUVmax>5 and ΔSUVmax>66% for PET2 or ΔSUVmax>70% for PET4.

Statistical methods:

Intent To Treat Set (ITT)

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

Efficacy Set (ES)

The ES included 617 patients, 311 in the GA101 arm and 306 in the Rituximab arm.

Per Protocol Set (PPS)

The PP set included 594 patients, 296 in the GA101 arm and 298 in the Rituximab arm. Among the 76 patients with major protocol violations, 40 were in the GA101 arm and 36 in the Rituximab arm.

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Safety Set (SS)

The safety set included all patients having received at least one dose of GA101 (N=332) or Rituximab (N=331). Patients were analyzed according to the treatment received.

SUMMARY – CONCLUSION

Study Disposition

From September 20, 2012, to July 30, 2015, 670 patients (ITT set) were enrolled and randomly assigned to receive either standard treatment with Rituximab (n=334) or experimental treatment with GA101 (n=336).

Among the 670 enrolled patients, 339 patients received at least one cycle of CHOP (with GA101 in 169 cases and Rituximab in 170 cases) and 324 received at least one cycle of ACVBP (with GA101 in 163 cases and Rituximab in 161 cases), constituting the safety population. Three hundred and twelve patients out of 336 (93%) and 312 out of 334 (93%) completed induction treatment in the GA101 and Rituximab arms, respectively.

PET2 and 4 were performed in 302 (90%) and 297 (88%) out of 336 patients in the GA101 arm and 302 (90%) and 289 (86.5%) out of 334 patients in the Rituximab arm. 401 out of 581 patients (69%) were PET2-/4- of whom 398 (99.3%) received the planned immunochemotherapy. Eighty seven out of 581 (15%) patients were PET2+/PET4- of whom 74 (85%) received the planned consolidation therapy followed by ASCT. Ninety three out of 581 patients (16%) had positive PET4 of whom 91 (97.8%) received salvage therapy. In all, 227 patients (68%) completed the planned treatment in the GA101 arm (including 124 patients (73%) with CHOP and 103 (63%) with ACVBP) and 197 (59%) in the Rituximab arm (including 109 patients (64%) with CHOP and 88 (55%) with ACVBP.

Efficacy Results

There was no benefit of GA101 compared to Rituximab for any of the endpoints examined, except for the Overall Response Rate after 4 cycles according to Cheson 2007 criteria.

Safety Results

In general, AEs seemed to be manageable in both arms. Severe hematological events (grade 3 and 4), serious infections and SAEs with outcome of death appeared to be slightly more frequently reported in the GA101 arm. More AEs were assessed as related to GA101 than Rituximab, and also more AEs were attributed to ACVBP than CHOP by investigators (who were not blinded). Overall, the safety profile was as expected in this setting.

Conclusions

The GAINED trial demonstrates that GA101 does not provide better EFS than Rituximab in combination

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with chemotherapy delivered every 14 days for treatment-naïve young patients with IPI≥1 DLBCL. PFS and OS are similar in both arms. Analysis of subgroups does not show a subset of patients who may benefit from GA101 rather than Rituximab.

The GALLIUM14 study demonstrated that, in newly diagnosed follicular lymphoma patients, GA101 plus chemotherapy followed by an GA101 maintenance significantly improves PFS compared to the same treatment with Rituximab. In contrast, the GOYA trial fails to show superiority of GA101 over Rituximab in treatment naïve DLBCL patients >18yrs. The two antibodies, in combination with CHOP, show similar 3-year PFS (median follow-up of 29 months): 70% in the GA101 arm versus 67% in the Rituximab arm. The present trial addresses the same question as the GOYA trial, but it looks at a different population and uses a different consolidation treatment strategy based on interim PET results. Indeed, patients enrolled in GAINED are all <60yrs and transplant-eligible at diagnosis while in GOYA the median age was 62 years with more than half of the patients IPI low/intermediate. The GOYA trial compared 8 Rituximab vs 10 GA101 infusions associated to CHOP21 while GAINED compares Rituximab vs GA101 in young patients with advanced disease who had double negative interim PET (69%). These last patients are those who received complete planned antibodies infusions. The GAINED and GOYA trials use different endpoints, EFS and PFS respectively. The PET-driven design of the GAINED trial led to the choice of EFS, with PET positivity results after 2 and 4 courses considered as events. Despite all these discrepancies, both trials reach the same conclusion that GA101 and Rituximab are equivalent in the treatment of DLBCL regardless of age, IPI score, COO, treatment intensity and use of PET-driven strategy.

The GAINED study provides interesting additional findings. The 2 and 4-year PFS in the whole cohort are 83.1% (95%CI 80–85.8) and 78.1% (95%CI 74.6–81.2) respectively. These results are the best published so far in young patients with aaIPI≥1. The PET-driven strategy could help explain these good outcomes. Indeed, Interim PET identifies the DLBCL patients less sensitive to chemotherapy, those at high risk of early relapse or progression. A post Hoc analysis of the LNH07-3B study shows that ΔSUVmax improves the prognosis value of interim PET after cycles 2 and 4 compared to visual analysis. In the present study, ΔSUVmax is used prospectively in order to interpret interim PET and to discriminate patients with different outcomes. The PETAL study which uses the ΔSUVmax method with the same 66% cut-off after 2 cycles of immunochemotherapy, demonstrates that DLBCL patients have significantly better outcomes when ΔSUVMax>66%. It is interesting to compare the efficacy of the consolidation strategy applied to PET2+ patients in the PETAL and GAINED trials. In the present trial, PET2+/PET4- patients (15%) were allocated to ASCT while in PETAL, PET2+ patients were randomized between continuing treatment with R-CHOP and a Burkitt-like regimen. PETAL demonstrates that the Burkitt-like experimental chemotherapy is not superior to R-CHOP and confirms that PET2 positivity is an independent prognostic marker. In view of this, PET2+/PET4- patients underwent ASCT and their outcomes are identical to PET2-/PET4- patients. This suggests that ASCT

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may overcome the bad prognostic value of PET2 positivity in the subset of patients achieving a good response after 4 cycles of induction, but the lack of randomization regarding treatment consolidation for PET2+/PET4- patients does not allow formal conclusion in favor of ASCT consolidation. Our results also suggest that interim PET assessment (PET2 plus PET4) accurately stratifies patients into 3 risk groups with PET4 positive patients being those with the poorer outcome, despite salvage treatment. These last patients require new therapy options and should be candidate for innovative strategies. CAR T-cells have been recently approved for relapse refractory DLBCL and could be an interesting option for PET4+ patients who can be identified earlier, thanks to PET2 response assessment using ΔSUVmax. In contrast, PET2-/PET4- high aaIPI score patients (nearly 70% of patients) experience prolonged response duration (4-year PFS=83.1% and OS=90.2%). This raises the question of therapeutic reduction. Indeed, low risk IPI PET2 negative young DLBCL patients could be cured with only 4 cycles of chemotherapy instead of 6 cycles of R-CHOP19 .

CHOP remains the most widely used regimen in DLBCL and the reference polychemotherapy in clinical trials. Other more intensive polychemotherapy regimens are used in daily practice, such as DA-EPOCH or ACVBP. ACVBP demonstrated superiority over CHOP in aaIPI=1 patients. In the GAINED study, patients treated with ACVBP have a lower rate of PET2 positivity which, thanks to the PET-driven strategy, diminishes the number of patients referred to autograft and/or salvage therapy. Toxicity of ACVBP regimen is superior to CHOP and the present study shows that ACVBP enhances neither PFS nor OS compared to R-CHOP (including for patients with aaIPI=1). Recent phase III studies added new molecules (bortezomib/ibrutinib/lenalidomide) in combination with R-CHOP, but none demonstrated superiority over R-CHOP. This highlights the need to better decipher the DLBCL molecular heterogeneity background in order to set up new personalized biology-driven therapies. PET-driven strategy is among those new tools which could help tailor personalized approaches in future trials. Indeed, baseline total metabolic volume and interim-PET results added to longitudinal analysis of ctDNA could provide an interesting multi-parameters approach capable of refining the prediction of early response to treatment.

In conclusion, GA101 does not provide outcome benefits compared to Rituximab in the first-line treatment of young DLBCL patients with advanced disease. A PET-driven approach based on ΔSUVmax criteria enables early identification of patients with high risk of relapse for whom innovative therapeutic solutions are needed.

Date of the report: 25 Nov 2020.