Obinutuzumab versus Rituximab in transplant-eligible Mantle cell lymphoma patients.

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clémentine Sarkozy (Institut Curie, Hematology department, France) Mary Callanan (CHU Dijon-INSERM 1231, France) Catherine Thieblemont (AP-HP, Hôpital Saint-Louis, Hemato-oncologie, DMU DHI,F-75010 Paris, France, France) Lucie Obéric (Department of Hematology, Institut universitaire du cancer Toulouse- Oncopole, France) Barbara Burroni (Cochin Hospital, Assistance Publique des Hôpitaux de Paris, France) Krimo Bouabdallah (CHU de Bordeaux, France) Gandhi Damaj (Normandy University, Hematology Institute, France) Benoit Tessoulin (Nantes University Hospital, France) Vincent Ribrag (Institut Gustave Roussy, France) Roch HOUOt (CHU Rennes, University of Rennes, France) Franck Morschhauser (University of Lille, France) Samuel Griolet (LYSARC, Statistics, Pierre-Benite, France) Clémentine Joubert (Lymphoma Academic Research Organisation, France) Victoria Cacheux (Clermont-Ferrand Univeristy Hospital, France) vincent delwail (Oncology hematology and cell therapy chu poitiers france, France) Violaine Safar (Hospices Civils de Lyon, France) Remy Gressin (chu michallon, France) Morgane CHEMINANT (Hôpital Necker, APHP, France) Marie-Helene Delfau-Larue (APHP, GH MONDOR, UPEC university, INSERM U955, France) Olivier Hermine (Necker Hospital, AP-HP. Centre Paris-Cité University, France) Elizabeth Macintyre (Hopital Necker, Université de Paris, France) Steven Le Gouill (Institut Curie, France)

Abstract:
Obinutuzumab (O) and Rituximab (R) are two CD antibodies that have never been compared in a prospective randomised trial in mantle cell lymphoma (MCL). Herein, we report the long-term outcome of the LYMA-101 (NCT02896582) trial, in which newly diagnosed MCL patients were treated with chemotherapy plus O before transplantation followed by O maintenance (O group). We then compared these patients to those treated with the same treatment design with Rituximab instead of O (R group) (NCT00921414). A propensity score matching (PSM) was used to compare the two populations (O vs R groups) in terms of MRD at the end of induction (EOI), PFS and OS. In LYMA-101, the estimated five-year PFS and OS since inclusion (n=85) were 83.4% (95%CI: 73.5-89.8%) and 86.9% (95%CI: 77.6-92.5%), respectively. At EOI, patients treated in the O group had more frequent bone marrow MRD negativity than those treated in the R group (83.1% vs 63.4% Chi2 p=0.007). The PSM resulted in 2 sets of 82 patients with comparable characteristics at inclusion. From treatment initiation, the O group had a longer estimated five-year PFS (p=0.029; 82.8% versus 66.6%, HR 1.99, IC95 1.05-3.76) and OS (p=0.039; 86.4% versus 71.4% (HR 2.08, IC95 1.01-4.16) compared to the R group. Causes of death were comparable in the 2 groups, the most common cause being lymphoma. Obinutuzumab prior to transplantation and in maintenance provides better disease control and enhances PFS and OS, as compared to Rituximab in transplant-eligible MCL patients.

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Clémentine Sarkozy[1,2], Mary Callanan[3], Catherine Thieblemont[4], Lucie Oberic[5], Barbara Burroni[6], Krimo Bouabdallah[7], Gandhi Damaj[8], Benoit Tessoulin[9], Vincent Ribrag[10], Roch Houot[11], Franck Morschhauser[12], Samuel Griolet[13], Clémentine Joubert[13], Victoria Cacheux[14], Vincent Delwail[15], Violaine Safar[16], Remy Gressin[17], Morgane Cheminant[18], Marie-Hélène Delfau-Larue[19], Olivier Hermine[18], Elizabeth Macintyre[20], and Steven Le Gouill[1,2]

1-Service d'hématologie, Institut Curie, Saint Cloud, France ; Université de Versailles Saint-Quentin (UVSQ), France
2-Laboratoire d'Imagerie Translationnelle en Oncologie (LITO), U1288 Inserm/Institut Curie centre de recherche, France
3-University of Burgundy, Institut national de recherche médicale (INSERM) U1231, Unit for innovation in genetics and epigenetics in oncology, University Hospital, Dijon, France
4-Service d'hématologie, Hôpital Saint Louis, APHP, Paris, France
5-Service d'hématologie, Institut Universitaire du Cancer Toulouse, Oncopole, Toulouse, France
6-Service d'anatomopathologie, Hôpital Cochin, APHP, Paris, France
7-Service d'hématologie, CHU de Bordeaux, Bordeaux, France
8-Service d'hématologie, CHU de Caen, Caen, France
9-Service d'hématologie, CHU Nantes, France
10-Département d'hématologie, Institut Gustave Roussy, Villejuif, France
11-Service d'hématologie, CHU Rennes, Rennes, France
12-Department of Hematology, Claude Huriez hospital, University Lille, EA 7365, Research Group on Injectable Forms and Associated Technologies, Lille, France, France.
13-LYSARC, Centre Hospitalier Lyon-Sud, 69310 Pierre-Bénite, France.
14-Service d'hématologie, CHU de Clermont Ferrand, France.
15-Service d'hématologie, Hôpital Poitiers, Poitiers, France
16-Service d'hématologie, Hôpital Lyon Sud, Pierre Bénite, France
17-Service d'hématologie, CHU Grenoble, Paris, France
18-INSERM U1163, University of Paris and department of clinical hematology, Necker University Hospital, Paris, France
19-INSERM U955 équipe 9, Institut Mondor de Recherche Biomédicale, Department of Immunology, Hopital Henri Mondor, Creteil, France
20-Université Paris Descartes Sorbonne Cité, Institut Necker-Enfants Malades (INEM), INSERM U1151, Laboratory of Onco-Haematology, Assistance Publique-Hôpitaux de Paris, Hôpital Necker Enfants-Malades, Paris, Paris, France

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Corresponding author:

Steven Le Gouill, Institut Curie, Saint Cloud, France.

Steven.legouill@curie.fr, 35 rue Dailly, 92180 Saint Cloud France

Data sharing statement: Data will be made available and shared by request and emails to the corresponding author.

Key points:

Obinutuzumab can safely be used in combination with chemotherapy and in maintenance after ASCT as frontline therapy in MCL patients.

Obinutuzumab provides better disease control than Rituximab without additional toxicity in MCL.

Abstract: (244 w)

Obinutuzumab (O) and Rituximab (R) are two CD antibodies that have never been compared in a prospective randomised trial in mantle cell lymphoma (MCL). Herein, we report the long-term outcome of the LYMA-101 (NCT02896582) trial, in which newly diagnosed MCL patients were treated with chemotherapy plus O before transplantation followed by O maintenance (O group). We then compared these patients to those treated with the same treatment design with Rituximab instead of O (R group) (NCT00921414). A propensity score matching (PSM) was used to compare the two populations (O vs R groups) in terms of MRD at the end of induction (EOI), PFS and OS. In LYMA-101, the estimated five-year PFS and OS since inclusion (n=85) were 83.4% (95%CI: 73.5-89.8%) and 86.9% (95%CI: 77.6-92.5%), respectively. At EOI, patients treated in the O group had more frequent bone marrow MRD negativity than those treated in the R group (83.1% vs 63.4% Chi2 p=0.007). The PSM resulted in 2 sets of 82 patients with comparable characteristics at inclusion. From treatment initiation, the O group had a longer estimated five-year PFS (p=0.029; 82.8% versus 66.6%, HR 1.99, IC95 1.05-3.76) and OS (p=0.039; 86.4% versus 71.4% (HR 2.08, IC95 1.01-4.16) compared to the R group. Causes of death were comparable in the 2 groups, the most common cause being lymphoma. Obinutuzumab prior to transplantation and in maintenance provides better disease control and enhances PFS and OS, as compared to Rituximab in transplant-eligible MCL patients.

Introduction:

Mantle cell lymphoma (MCL) is an aggressive B-cell malignancy in which therapeutic innovation has led to significant improvements in outcome over the past 20 years. Rituximab-containing high-dose cytarabine chemotherapy regimens followed by autologous stem-cell transplantation (ASCT) and rituximab maintenance (RM) is the standard of care(1) in transplant-eligible patients. We recently reported that 78% of transplanted patients are alive and remain free of disease at 7 years. However, MCL patients experiencing a progressive disease or early relapse within 2 years from treatment initiation (so-called POD24) (2) or relapsing after maintenance(3) both represent unmet medical needs. Bruton tyrosine kinase inhibitor (BTKi) targeted therapies and CAR-T cell approaches have demonstrated high efficacy in relapse MCL. The addition of Ibrutinib to standard frontline chemotherapy has also recently shown promising results (4). The emergence of new targeted therapies and immunotherapy and CD20 Ab maintenance have thus deeply modified MCL patient outcomes.

Obinutuzumab is a glycoengineered, type 2, anti-CD20 monoclonal antibody designed to improve antibody-dependent cell-mediated cytotoxicity compared to rituximab. Obinutuzumab is approved for follicular lymphoma (FL) (5). Conversely, Obinutuzumab (O) failed to demonstrate its superiority in diffuse large B cell lymphoma (DLBCL) (6). *In-vitro* data suggest that O provides better anti-mantle cell leukaemia activity than Rituximab (7). The Lyma-101 phase II trial investigated the activity of Obinutuzumab plus DHAP (O-DHAP) followed by ASCT and O maintenance (OM) (8). However, no head-to-head trial comparing O versus R in MCL has been performed so far and is unlikely to happen, given the rarity of the disease and the current therapeutic landscape.

Thus, the question of the best CD20 antibody in MCL remains open while it has been demonstrated that RM prolongs OS in both young and elderly patients(1,9). We performed an indirect comparison of O vs R in first line MCL patients.

Methods:

Inclusion criteria and study design:

All patients enrolled in the Lyma and lyma-101 trials (NCT00921414, NCT02896582)) were eligible for the present work. Inclusion and exclusion criteria were similar in both trials and have been previously reported (1,8). These two trials enrolled transplant-eligible patients aged 18 to 65 years with newly diagnosed untreated MCL. Trial designs are presented in supplementary figure 1. Briefly, patients received four courses of anti-CD20 plus DHAP regimen followed by ASCT. In the phase III LYMA study (n=299), 240 patients were randomised between R maintenance (RM) or observation (120 patients in each arm) (1). In the phase II Lyma-101 study (n=86), Obinutuzumab was used, treatment design was similar, and all patients received maintenance. The timing of CT evaluation was identical in both studies, during and after the maintenance phase.

These two prospective trials were performed according to the principles of the Declaration of Helsinki, and the protocols were approved by ethics committees.

Statistical analysis:

The statistical analysis plan was divided into two parts. We first updated the lyma-101 trial, then compared O vs R using a PSM analysis. The results of this last analysis were challenged by a Stabilised Inverse probability of treatment weighting analysis.

- *Final analysis of the LYMA-101 protocol:*

We first updated the outcome of patients enrolled in the LyMa-101 trial. Time-to-event survival curves were estimated with the Kaplan-Meier method. PFS was defined as the time from inclusion into the study to the first observation of documented disease progression or death due to any cause. If a subject had not progressed or died, PFS was censored at the time of the last visit with adequate assessment. OS was measured from the date of inclusion to the date of death from any cause. Living patients were censored at their last contact date.

- *Maintenance on demand in LYMA-101:*

MRD (quantitative PCR for clonal immunoglobulin gene, as previously reported(8)) was monitored during the maintenance period, at month 6, 12, 18, 24, 30 and 36. After the end of maintenance, an “on demand” maintenance period started, with O on-demand administration in case of MRD positivity. During this on-demand period, MRD was assessed at M3, 6, 9, 12, 15, 18, 21, 24, 27, 30 after the end of OM.

- *Propensity score matching for O versus R comparison:*

The aim of PSM was to balance covariates between the Lyma and Lyma-101 protocols to account for all possible measured confounding variables (10). Clinical characteristics at

inclusion (sex; Ann Arbor stage; MIPI score; B symptoms; presence of a blastoid variant; and/or presence of bulky disease) were used for PSM to compare ORR (Cheson 1999) and BM MRD negativity rate amongst responders at EOI, between Lyma and Lyma-101 patients. To compare the efficacy of RM versus OM, a second matching process, relying on the same characteristics plus EOI BM MRD negativity within patients initiating maintenance, was performed. Of note, in LYMA-101 2 patients were not eligible for matching (1 due to consent withdrawn and 1 due to missing data) and in LYMA, 3 patients were not eligible: 1 due to consent withdrawn and 2 due to missing data.

To compare the efficacy of O versus R for PFS and OS from treatment initiation, half of the 59 non-randomised patients in Lyma (N=29) were randomly allocated to the RM arm to create a pseudo-population with outcome data from inclusion (so-called Lyma-ITT; n=149 patients of whom 29 non-randomised and 120 randomised) in an RM intention to treat fashion (RM-ITT). A PSM based on the initial characteristics was then performed between the Lyma-ITT population (N=149) and all the Lyma-101 (N=86) patients.

Another statistical approach using the stabilised inverse probability of treatment weighting (sIPTW) was also performed to confirm or refute the PSM results (10). In IPTW, weights are assigned to patients based on the inverse probability of receiving one treatment or the other as estimated by the propensity score. For each treatment, the stabilised IPTW is calculated as the inverse of the propensity score associated with the treatment multiplied by the marginal probability of receiving the treatment.

After matching, the balance between populations and pseudo-populations was checked using standardised mean differences (SMD).

Time-to-event endpoints in the different groups were compared with the use of log-rank tests and Cox proportional-hazards regression. Patients who were lost to follow-up (e.g., all the patients for whom an outcome was not updated for >1 year at the time of the final analysis) who did not have a PFS event, had their data censored at the time of their last visit. The incidence of progression or lymphoma-related death within 24 months from treatment initiation (POD24 events) was compared within the O and R groups, using the PSM-matched population of Lyma-ITT and Lyma-101.

These two prospective trials were performed according to the principles of the Declaration of Helsinki, and the protocols were approved by ethics committees.

Results:

Final results of LYMA-101(8): The 5-year PFS and OS estimates were 83.4% (95% CI: 73.5-89.9%) and 86.9% (95% CI: 77.6-92.5%), respectively (**figure 1B**). Twelve patients died. Causes of death were MCL in five cases (42%), COVID in three cases (25%, during OM), myocardial infarction in one case, related to second-line treatment for one case, and unknown for two cases, without disease progression. Seventy-four patients presented at least an AE of grade 3 or higher (total 809 AEs). 52.3% of AEs occurred during induction, 31% during ASCT and 16.7% were reported during OM (**table 1 and supplementary table 2A**). Of note, as an exploratory analysis, treatment with Oxaliplatin within the induction regimen had no impact on PFS as compared to treatment with Caroplatine/Cisplatine, with a 5 years PFS of 79% (IC95: 63.5-88.5) versus 87.9% (IC95: 73.3-94.8) for patients treated with Oxaliplatin versus Caroplatine/Cisplatine respectively (p=0.38, HR=0.631 (IC95: 0.224-1.780) (supplementary figure 2).

Forty out of 86 included patients (46.5%) had premature treatment discontinuation (mean time since inclusion: 16.2 months, median 10.4 months), 57.5% during the OM phase (N=23). The majority were due to AE (N=25, 62.5%) and 5 were due to progressive disease (12.5%) **(supplementary table 2**).

MRD analysis during maintenance and maintenance on demand in LYMA-101:

During OM phase, all evaluable patients reached MRD negativity at M6, M12, M24, M30, M36 and only one patient had a positive MRD at M18 (1/48 evaluable patients, 2.4%). During the OM on demand phase (ie after the end of the 3 years of OM planned in the protocol), positive MRD results (greater than 10-4) were detected in 5 patients. MRD positive time points were M15, 18, 21, 24 and 30 (no positive sample detected at M3-6-9-12). OM was then re-started (ie on demand) for 4 of these patients, resulting in a negativation of MRD results in 3 of them. The patient with a persistent MRD remained in clinical CR and under OM.

Comparisons between Rituximab and Obinutuzumab at induction. 84/86 and 296/299 patients included in the Lyma-101 and Lyma protocols were eligible for matching, respectively (See **supplementary figure 1**). Matching based on propensity score resulted in a total population of 252 patients eligible for response comparison (so-called PS set), of whom 168 were treated with R-DHAP and 84 with O-DHAP (**table 2**). After matching, the absolute SMD values were less than 0.1 for all matching covariates (**supplementary table 3**). ORR were 90.5% *versus* 91.7% for PSM patients treated with R-DHAP and O-DHAP, respectively (**table 3**). The incidence of primary refractory disease (i.e., stable or progressive disease) was higher in the R group: 5.6% versus 1.3% in the O group. Of note, in LYMA-101, 10 patients

were classified in PR and not CR due to the absence of BM biopsy at the end of induction (all were in CR according to PET). EOI MRD negativity assessed in BM was superior with O (83.1% vs 63.4%, Chi-2, p=0.007) and blood (95.3% vs 72.9%, Chi-2, p<0.001) (**table 3**). Similar findings were observed using the stabilised IPTW approach (**supplementary table 4A, B and C**). In a sensitivity analysis, we performed a PSM using the same clinical variables and ki67 (data available for 214 patients in LYMA and 68 patients in LYMA-101). The matching resulted in 2 groups of 68 patients with consistent results with regards to ORR and MRD negativity at end of induction (supplementary table 5A-D).

Comparisons between Rituximab and Obinutuzumab for maintenance: Seventy-eight out of 120 patients who initiated RM and 59 out of 69 who initiated OM were assessed for MRD before maintenance. PSM resulted in 2 sets of 43 patients (**table 4A**, **supplementary table 6**). No difference was observed in post-ASCT PFS (p=0.5) or OS (p=0.9) between the R and O groups (**figure 2A and B**). The stabilised IPTW approach led to similar results (**supplementary table 7 and** supplementary **figure 3**).

PFS and OS Comparisons between Rituximab and Obinutuzumab calculated from treatment initiation. The matching between Lyma-ITT with the Lyma-101 populations (see methods and supplementary figure 1C) resulted in 2 groups of 82 patients (namely O and R-ITT groups, **table 4B**). Patients treated in the O group presented a prolonged PFS (p=0.029) and OS (p=0.039). The estimated 5-year PFS and OS for O-ITT vs R-ITT were 82.8% versus 66.6% (HR 1.99, IC95 1.05-3.76) and 86.4% versus 71.4% (HR 2.08, IC95 1.01-4.16; **figure 2C and D**), respectively. The stabilised IPTW approach gave similar results, although OS was not statistically significant (**supplementary table 8**, **supplementary figure 4A and 4B**). Finally, the incidence of POD24 events (progression or lymphoma-related death) was 19.5% for R-treated patients versus 7.2% in the O arm.

Safety and cause of death comparisons between Rituximab and Obinutuzumab. Per protocol, maintenance durations were identical (29 months for RM and 29.4 months for OM). The incidence of grade 3-4 neutropenia during maintenance was also comparable (44.2% in RM versus 37.6% in OM), as was the rate of grade 3-5 infection (12.5% versus 15.9% in RM versus OM respectively). The rate of premature maintenance discontinuation was identical with 30.8% in R and 33% in O who stopped maintenance before 3 years (**supplementary table 9**). Reasons for discontinuation were AE in 15/37 (40.5%) *versus* 14/23 (61%) and progression in 10/37 (27%) *versus* 3/23 (13%) in the RM versus OM groups, respectively. The rate of grade 3-4 infusion related reaction (IRR) during induction tended to be higher in LYMA-101 as compared to LYMA (4.7% versus 0.7%). The median treatment intervals

between R or G-DHAP cycles were identical (21 days) such as the relative dose intensity of Rituximab and Obinutuzumab during induction (mean 97.4% (SD 5.4), median 98.6% and mean 92.1% (SD 16.33), median 100% for R and O respectively). Incidences of POD24 (progression or lymphoma-related death during the first 2 years of treatment) were 19.5% for R-treated patients versus 7.2% for those treated with O.

Overall, lymphoma was the leading cause of death in both the Lyma and Lyma-101 protocols (42% in O and 53% in R). The rate of infectious deaths with O (N=3, 25% of all deaths) tended to be higher than with R (8% of all deaths), but importantly, all infectious deaths in Lyma-101 (O-treated patients) were COVID-related, whereas the Lyma trial was conducted before the pandemic (**supplementary table 10**). Finally, as an exploratory analysis, responding patients relapsing after OM had a similar OS-2 compared to those relapsing after RM (supplementary figure 5).

Discussion:

The final LYMA-101 phase II trial analysis confirms that Obinutuzumab provides long-term disease control and a high MRD negativity rate. Indeed, we show superiority of O versus R in terms of MRD negativity at EOI, reduction of the incidence of early relapse (POD24) and longer PFS and OS. The predominant benefice of O at end of induction in term of BM MRD negativity and the lack of significant difference in post-ASCT, suggest that O provides better quality of response than R which is mainly due to induction.

CD20 antibodies have various anti-lymphoma mechanisms of action, leading to varying efficacy according to lymphoma type. While O has demonstrated its superiority compared to R in FL(11), no difference was reported in DLBCL(6). In MCL, the question of the best CD20 antibody has never been addressed and probably never will be. However, it is a question of great value because CD20 maintenance has been the only frontline treatment that has enhanced OS for both young and elderly patients so far. In the present update of the Lyma-101 trial, the 5-year PFS and OS are 83.4% and 86.9% respectively, which compares favourably to studies conducted in the same transplant-eligible MCL populations (4,12,13). We observe a lower incidence in POD24 events for patients treated with O as compared to R, which is in line with results reported in FL (14), and this seems to translate into early relapse reduction and may prolong OS. In the present work use of oxaliplatin in LYMA-101 did not translate to a longer disease control. This might be due to the use of O during induction that could have erased this gain (15). The safety profile of R and O during treatment appears to be similar, as reported in FL (11). O based strategy led to a few more discontinuations due to AE

(including IR during induction) than with R, this did not convert into an excess in toxic deaths in LYMA-101 compared to LYMA. Infection-related deaths in the LYMA-101 study where all patients received O-DHAP and OM were all COVID-related, suggesting that the benefit/risk balance for CD20 maintenance should probably be carefully addressed for patients at a high risk of severe infections. Overall, our study supports the use of O-based therapy rather than R-based in MCL, but it has some limitations. Indeed, it is a comparison between two trials that were not designed to be compared and some parameters such as Ki67 and p53 status could not be included due to missing data. The fact that data were prospectively collected, follow-up performed in clinical prospective, and the use of a PSM, should limit the bias between the 2 groups. Finally, the designs of the two-trial are not perfectly comparable given that MRD was a primary endpoint in LYMA-101, while it was exploratory in LYMA with an on-demand maintenance after 3 years. However, despite discrepancies between the two studies regarding maintenance, our results support the benefice of O vs R during the induction phase, but not during maintenance.

In the two trials that we compared for the present work, ASCT was used to consolidate response at end of induction. Recently, the emergence of new therapies in MCL has started to challenge the benefit of ASCT. The initial results of the TRIANGLE trial(4) conducted by the EMCL network, suggest that adding BTKi to chemotherapy could avoid the need for ASCT. Moreover, combinations of targeted therapies challenge the use of standard chemotherapy including for treatment-naïve patients, like in CLL. Indeed, the Ibrutinib, Venetoclax (V) plus O (16) or the Acalabrutib VR(17), Zanubrutinib VO combinations have shown very promising response rates with MRD negativity rates greater than 90% when used frontline, including for high-risk patients presenting with p53 abnormalities (18). These triplet chemo-free treatments are currently compared to standard chemotherapy in phase II or III randomised trials in the elderly MCL population (ISRCTN11038174 and NCT04002297). It is interesting to note that all these studies include anti-CD20 antibodies with or without maintenance which underlines that anti-CD20 Abs remain pivotal for the treatment of MCL patients and thus the question of the best anti-CD20 remains of great value including in the chemo-free era. The present work, in addition to *in vivo/vitro* models, supports O as the most effective CD20 Ab in MCL (7).

In conclusion, Obinutuzumab might be considered as the anti-CD20 of choice during induction and maintenance in MCL as Obinutuzumab enhances the response rate at the molecular level and prolong PFS and OS without jeopardizing safety. This will require further investigations.

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Author contribution:

All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

All the authors performed the literature search and reviewed the manuscript.

CS, SLG, OH and MC designed the study.

CS, MC, CT, MO, BB, B, GD, BT, VR, RH, FM, VC, VD, VS, RG, MC, MHD, OH, EM and SLG performed data collection.

CS, SLG, SG, CJ, MHD, MC and EM analysed and interpreted the data.

CS; SLG, OH, EM and MC wrote the manuscript, all the authors edited and agreed to submission.

Conflict of interest:

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The authors declare no relevant COI with the study results.

COI of each authors are available on Blood website.

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Table 1: Patients with grade 3 or higher adverse events in LYMA-101 trial.

N=85 patients treated	Grade 3 Patients N=6	Grade 4 Patients N=74	Grade 5 Patients N=2
Patients with at least one AE	**6 (7.1%)**	**74 (87.1%)**	**2 (2.4%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**4 (4.7%)**	**65 (76.5%)**	**0 (0.0%)**
ANAEMIA	2 (2.4%)	43 (50.6%)	0 (0.0%)
NEUTROPENIA	1 (1.2%)	43 (50.6%)	0 (0.0%)
THROMBOCYTOPENIA	1 (1.2%)	40 (47.1%)	0 (0.0%)
LEUKOPENIA	0 (0.0%)	16 (18.8%)	0 (0.0%)
FEBRILE NEUTROPENIA	0 (0.0%)	15 (17.6%)	0 (0.0%)
LYMPHOPENIA	0 (0.0%)	14 (16.5%)	0 (0.0%)
FEBRILE BONE MARROW APLASIA	2 (2.4%)	7 (8.2%)	0 (0.0%)
INFECTIONS AND INFESTATIONS	**2 (2.4%)**	**45 (52.9%)**	**1 (1.2%)**
PNEUMONIA	0 (0.0%)	6 (7.1%)	0 (0.0%)
COVID-19	0 (0.0%)	4 (4.7%)	0 (0.0%)
ESCHERICHIA SEPSIS	0 (0.0%)	4 (4.7%)	0 (0.0%)
HUMAN HERPESVIRUS 6 INFECTION	0 (0.0%)	4 (4.7%)	0 (0.0%)
SINUSITIS	0 (0.0%)	4 (4.7%)	0 (0.0%)
BRONCHITIS	0 (0.0%)	3 (3.5%)	0 (0.0%)
COVID-19 PNEUMONIA	0 (0.0%)	2 (2.4%)	1 (1.2%)
SEPSIS	0 (0.0%)	3 (3.5%)	0 (0.0%)
DEVICE-RELATED INFECTION	0 (0.0%)	2 (2.4%)	0 (0.0%)
HEPATITIS E	0 (0.0%)	2 (2.4%)	0 (0.0%)
INFLUENZA	0 (0.0%)	2 (2.4%)	0 (0.0%)
PNEUMONIA HAEMOPHILUS	0 (0.0%)	2 (2.4%)	0 (0.0%)
POST-ACUTE COVID-19 SYNDROME	0 (0.0%)	2 (2.4%)	0 (0.0%)
STAPHYLOCOCCAL INFECTION	0 (0.0%)	2 (2.4%)	0 (0.0%)
STAPHYLOCOCCAL SEPSIS	0 (0.0%)	2 (2.4%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	**2 (2.4%)**	**38 (44.7%)**	**0 (0.0%)**
STOMATITIS	1 (1.2%)	23 (27.1%)	0 (0.0%)
DIARRHOEA	1 (1.2%)	9 (10.6%)	0 (0.0%)
COLITIS	1 (1.2%)	7 (8.2%)	0 (0.0%)
NAUSEA	0 (0.0%)	6 (7.1%)	0 (0.0%)
VOMITING	0 (0.0%)	3 (3.5%)	0 (0.0%)
RECTAL HAEMORRHAGE	0 (0.0%)	2 (2.4%)	0 (0.0%)
INVESTIGATIONS	**1 (1.2%)**	**39 (45.9%)**	**0 (0.0%)**
PLATELET COUNT DECREASED	1 (1.2%)	28 (32.9%)	0 (0.0%)
NEUTROPHIL COUNT DECREASED	1 (1.2%)	21 (24.7%)	0 (0.0%)
LYMPHOCYTE COUNT DECREASED	0 (0.0%)	16 (18.8%)	0 (0.0%)
WHITE BLOOD CELL COUNT DECREASED	0 (0.0%)	14 (16.5%)	0 (0.0%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	0 (0.0%)	3 (3.5%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**1 (1.2%)**	**11 (12.9%)**	**0 (0.0%)**
LUNG DISORDER	0 (0.0%)	3 (3.5%)	0 (0.0%)
PLEURAL EFFUSION	0 (0.0%)	2 (2.4%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	**0 (0.0%)**	**11 (12.9%)**	**0 (0.0%)**
HYPOKALAEMIA	0 (0.0%)	3 (3.5%)	0 (0.0%)
TUMOUR LYSIS SYNDROME	0 (0.0%)	3 (3.5%)	0 (0.0%)
DECREASED APPETITE	0 (0.0%)	2 (2.4%)	0 (0.0%)
HYPERGLYCAEMIA	0 (0.0%)	2 (2.4%)	0 (0.0%)
HYPONATRAEMIA	0 (0.0%)	2 (2.4%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**1 (1.2%)**	**9 (10.6%)**	**0 (0.0%)**
PYREXIA	0 (0.0%)	7 (8.2%)	0 (0.0%)
GENERAL PHYSICAL HEALTH DETERIORATION	0 (0.0%)	2 (2.4%)	0 (0.0%)
HEPATOBILIARY DISORDERS	**1 (1.2%)**	**6 (7.1%)**	**0 (0.0%)**
HEPATIC CYTOLYSIS	1 (1.2%)	5 (5.9%)	0 (0.0%)
CHOLESTASIS	0 (0.0%)	3 (3.5%)	0 (0.0%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**0 (0.0%)**	**7 (8.2%)**	**0 (0.0%)**
PROSTATE CANCER	0 (0.0%)	2 (2.4%)	0 (0.0%)
CARDIAC DISORDERS	**0 (0.0%)**	**4 (4.7%)**	**1 (1.2%)**
MYOCARDIAL INFARCTION	0 (0.0%)	0 (0.0%)	1 (1.2%)
NERVOUS SYSTEM DISORDERS	**0 (0.0%)**	**5 (5.9%)**	**0 (0.0%)**
PRESYNCOPE	0 (0.0%)	2 (2.4%)	0 (0.0%)
RENAL AND URINARY DISORDERS	**1 (1.2%)**	**4 (4.7%)**	**0 (0.0%)**
RENAL FAILURE	0 (0.0%)	2 (2.4%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**0 (0.0%)**	**4 (4.7%)**	**0 (0.0%)**
INFUSION-RELATED REACTION	0 (0.0%)	4 (4.7%)	0 (0.0%)
IMMUNE SYSTEM DISORDERS	**0 (0.0%)**	**3 (3.5%)**	**0 (0.0%)**
HYPOGAMMAGLOBULINAEMIA	0 (0.0%)	2 (2.4%)	0 (0.0%)
PSYCHIATRIC DISORDERS	**0 (0.0%)**	**3 (3.5%)**	**0 (0.0%)**
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**0 (0.0%)**	**3 (3.5%)**	**0 (0.0%)**
VASCULAR DISORDERS	**1 (1.2%)**	**2 (2.4%)**	**0 (0.0%)**

Grade 3 or higher AEs with at least 2 instances are reported by worse grade for the 85 patients treated in LYMA-101.

Table 2: Baseline characteristics of LYMA and LYMA-101 treated patients, before and after PSM.

Set	Before matching (PS set)		After PSM (Matching set)		Fisher Test after PSM*
N	**LYMA, N=296**	**LYMA-101, N=84**	**LYMA, N=168**	**LYMA-101, N=84**	
Sex:					P=1
- Male	234 (79%)	61 (73%)	121 (72%)	61 (72%)	
- Female	62 (21%)	23 (27%)	47 (28%)	23 (27%)	
MIPI risk group					P=1
- Low	157 (53%)	46 (55%)	89 (53%)	46 (54%)	
- Intermediate	82 (28%)	24 (28%)	50 (30%)	24 (29%)	
- High	57 (19%)	14 (17%)	29 (17%)	14 (17%)	
Ann Arbor Stage:					P=0.2
- II	18 (6%)	2 (3%)	1 (1%)	2 (2%)	
- III	30 (10%)	6 (7%)	21 (12%)	6 (7%)	
- IV	248 (84%)	76 (90%)	146 (87%)	76 (91%)	
B symptoms:					P=0.7
- No	209 (71%)	68 (81%)	139 (83%)	68 (81%)	
- Yes	87 (29%)	16 (19%)	29 (17%)	16 (19%)	
Blastoid Variant:					P=0.7
- No	261 (88%)	70 (83%)	143 (85%)	70 (83%)	
- Yes	35 (12%)	14 (17%)	25 (15%)	14 (17%)	

In this analysis, 296 and 84 patients in the R and O groups were matched based on clinical data at inclusion, resulting in 168 and 84 PSM patients in the R and O groups respectively. Of note, 5 patients (3 in LYMA and 2 in LYMA-101) were excluded from this analysis, due to missing data (N=3 with no MIPI group assessment available) or consent withdrawn (N=2).

*Fisher test is done between matched population

Table 3: Response rate and Minimal residual disease (MRD) after propensity score matching (PSM) matching, in R versus O group-treated patients.

Response, Cheson	R-DHAP (LYMA), N=168	O-DHAP (LYMA-101), N=84	
ORR	152 (90.5%)	77 (91.7%)	
PR	24 (14.9%)	26 (33.3%)*	
CR/uCR	65/63 (79.5%)	51 (65.4%)	
Stable disease	6 (3.7%)	0	
Progressive disease	3 (1.9%)	1 (1.3%)	
Not performed	7	6	
MRD*: BM**	**R-DHAP (LYMA), N=93/152 responders**	**O-DHAP (LYMA-101), N=65/77 responders**	
Negative	59 (63.4%)	54 (83.1%)	CHi2**, 0.007
Positive	16	2	
PNQ	18	9	
Not performed	59 (-)	12	
MRD*: Blood**	**R-DHAP (LYMA), N=96/152 responders**	**O-DHAP (LYMA-101), N=64/77 responders**	
Negative	70 (72.9%)	61 (95.3%)	CHi2**, <0.001
Positive	7	0	
PNQ	19	3	
Not performed	56	13	

*Including 10 scored as PR due to bone marrow biopsies not being performed at the end of induction. 21/26 in PET metabolic CR.

BM: bone marrow. PNQ: positive not quantifiable.

**Chi2 between negative vs other.

***MRD assessed within responding patients (PR and CR).

Table 4A: Baseline characteristics of LYMA-101 and LYMA maintenance populations before and after PSM.

Population	Before matching, PS set		After PSM, Matching set		Test Fisher After PSM
N	LYMA, N=78	LYMA-101, N=59	R-Group, N=43	O-Group, N=43	
Sex:					0.59
- Male	62 (79.5%)	41 (69.5%)	33 (76.7%)	36 (83.7%)	
- Female	16 (20.5%)	18 (30.5%)	10 (23.3%)	7 (16.3%)	
MIPI risk group					0.74
- Low	43 (55.1%)	37 (62.7%)	26 (60.5%)	28 (65.1%)	
- Intermediate	23 (29.5%)	14 (23.7%)	9 (20.9%)	10 (23.3%)	
- High	12 (15.4%)	8 (13.6%)	8 (18.6%)	5 (11.6%)	
Ann Arbor Stage:					1
- II	3 (3.8%)	0 (0%)	-	-	
- III	7 (9%)	4 (6.8%)	4 (9.3%)	4 (9.3%)	
- IV	68 (87.2%)	55 (93.2%)	39 (90.7%)	39 (90.7%)	
B symptoms:					0.8
- No	51 (65.4%)	46 (78%)	31 (72.1%)	33 (76.7%)	
- Yes	27 (34.6%)	13 (22%)	12 (27.9%)	10 (23.3%)	
Blastoid Variant:					1
- No	72 (92.3%)	48 (81.4%)	35 (88.4%)	38 (88.4%)	
- Yes	6 (7.7%)	11 (18.6%)	5 (11.6%)	5 (11.6%)	
End of induction					1
- MRD neg	47 (60.3%)	48 (81.4%)	34 (79.1%)	33 (76.7%)	
- PNQ	22 (28.2%)	9 (15.3%)	7 (16.3%)	8 (18.6%)	
- Positive	9 (11.5%)	2 (3.4%)	2 (4.7%)	2 (4.7%)	

In this analysis, 78 and 59 patients in the R and O groups were matched based on baseline characteristics and end-of-induction MRD negativity, resulting in 2 groups of 43 each.

The Fisher test as performed between matched populations.

EOI: end of induction; MRD: minimal residual disease.

Table 4B: Baseline characteristics of LYMA-101 and LYMA-ITT (reattribution of non-randomised patient) populations, before and after PSM.

Population	Before matching (PS set)		After PSM (Matching set)		Fisher Test after PSM
N	LYMA, N=148*	LYMA-101, N=84	R-Group, N=82	O-Group, N=82	
Sex: - Male - Female	 115 (77.7%) 33 (22.3%)	 61 (73%) 23 (27%)	 62 (75.6%) 20 (24.4%)	 59 (72%) 23 (28%)	P=0.72
MIPI risk group - Low - Intermediate - High	 79 (53.4%) 842 (28.4%) 27 (18.2%)	 46 (55%) 24 (28%) 14 (17%)	 42 (51.2%) 24 (29.3%) 16 (19.5%)	 44 (53.7%) 24 (29.3%) 14 (17.1%)	P=0.93
Ann Arbor Stage: - II - III - IV	 9 (6.1%) 15 (10.1%) 124 (83.8%)	 2 (3%) 6 (7%) 76 (90%)	 2 (2.4%) 7 (8.5%) 73 (89%)	 2 (2.4%) 6 (7.3%) 74 (90.2%)	P=1
B symptoms: - No - Yes	 103 (69.6%) 45 (30.4%)	 68 (81%) 16 (19%)	 67 (81.7%) 15 (18.3%)	 66 (80.5%) 16 (19.5%)	P=1
Blastoid Variant: - No - Yes	 129 (87.2%) 19 (12.8%)	 70 (83%) 14 (17%)	 70 (85.4%) 12 (14.6%)	 70 (85.4%) 12 (14.6%)	P=1

In this analysis, 148 and 84 patients in the R and O groups were matched based on baseline characteristics, resulting in 82 patients in each group. Survival curves were drawn from inclusion. Out of the 149 LYMA-ITT patients, 1 patient withdrew his consent, leading to 148 patients analysed. Out of the 86 patients included in LYMA-101, 1 withdrew his consent and 1 had missing data for matching.

ITT: Intention to treat.

*120 randomised and 28 non-randomised

The Fisher test as performed between matched populations.

Figures legends:

Figure 1A and 1B: Progression-free and overall survival since inclusion in the LYMA-101 protocol, for the N=85 treated patients.

Figure 2: R versus O outcome comparison after matching

A and B: Propensity score Matched comparison of post-ASCT Progression-free (A) and overall survival (B) for patients treated in the R versus the O group.

In this analysis, 78 and 59 responding patients in the R and O groups were matched based on propensity score, including MRD data, resulting in 43 patients in each group. Survival curves were drawn from post-ASCT or maintenance initiation.

C and D: Propensity score Matched comparison of Progression-free (C) and overall survival (D) from inclusion for patients treated in the R versus theO group.

In this analysis, 148 and 84 patients in the R and O groups were matched based on propensity score, resulting in 82 patients in each group. Survival curves were drawn from inclusion.

Figure 1

Figure 1A

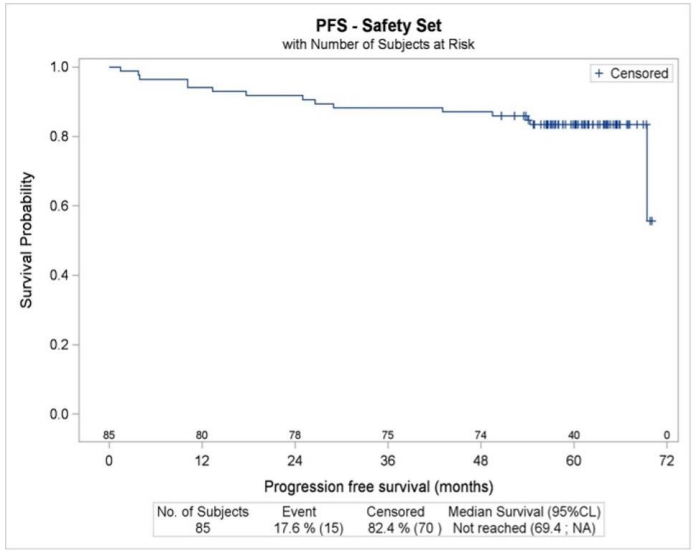


Figure 1B

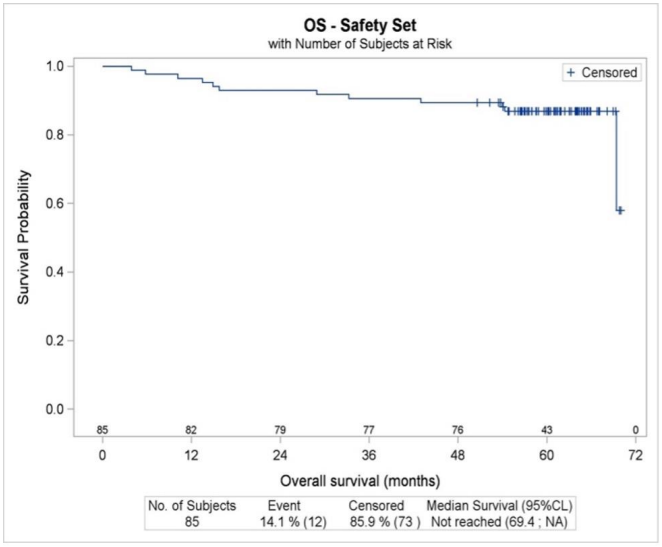


Figure 2A

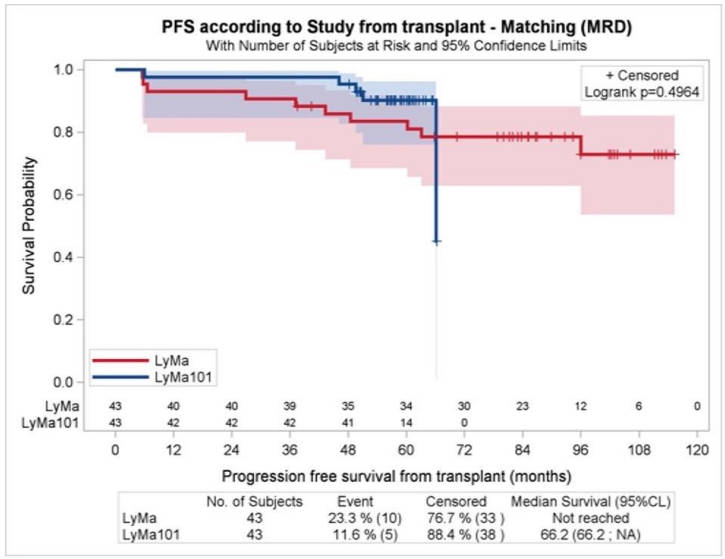


Figure 2B

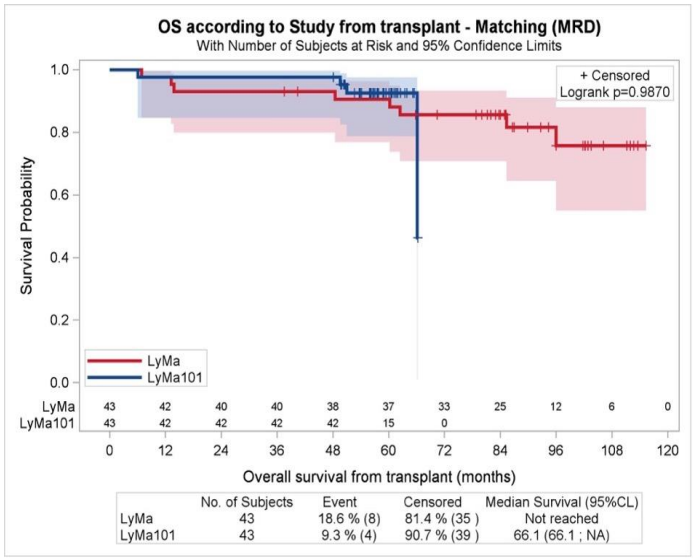


Figure 2C

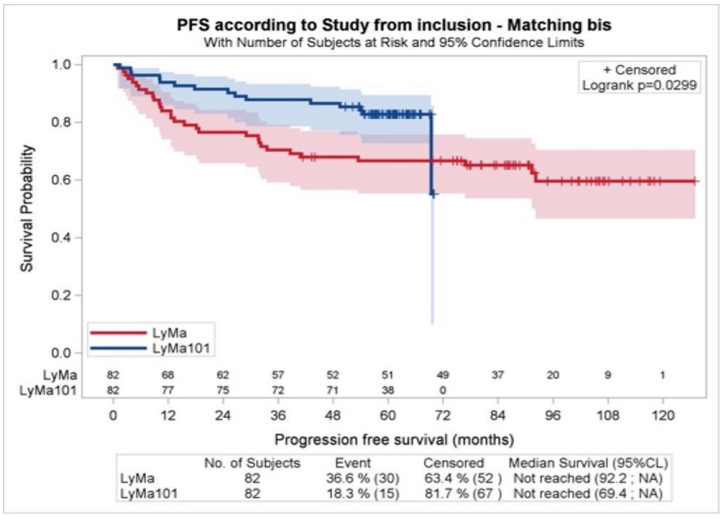
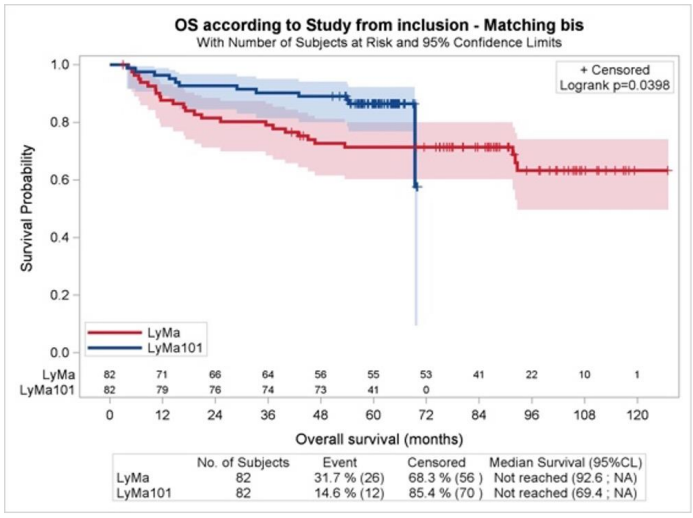
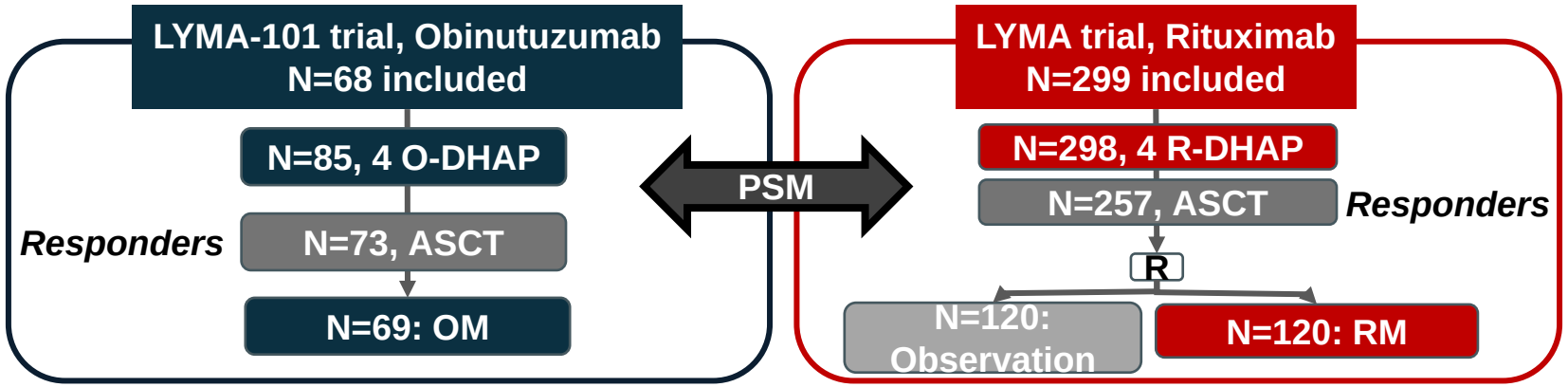


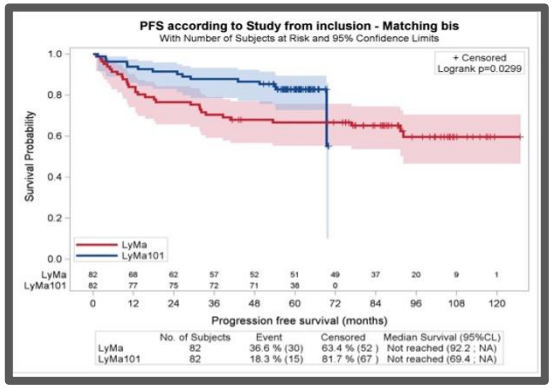
Figure 2D

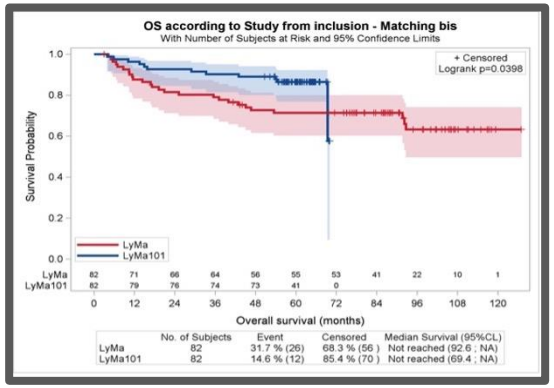


Obinutuzumab versus Rituximab in first line transplant eligible MCL



- Deeper response with O *vs* R based induction: End of induction BM MRD-: **83.1%** vs **64.4%**
- Prolonged disease control with O *vs* R-DHAP, ASCT and maintenance





Obinutuzumab provides deeper MRD response leading to prolonged PFS and OS in first line MCL, without significant excess of toxicity.